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REVIEW

IL-6 and Cardiovascular Risk: A Narrative Review

Nehal N. Mehta[1] · Emil deGoma[2] · Michael D. Shapiro[3]

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Abstract

Purpose of Review The objective of this narrative review is to summarize data from recently published prospective observational studies that analyze the association between circulating interleukin-6 (IL-6) levels and cardiovascular clinical or imaging endpoints.

Recent Findings Higher levels of IL-6 are associated with a higher risk of cardiovascular death, major adverse cardiovascular events, myocardial infarction, stroke, peripheral artery disease, and heart failure. Imaging studies have also shown an association between IL-6 and carotid intima-media thickness progression, carotid plaque progression, severity, and vulnerability. These observations have been consistent across a wide range of study populations and after adjusting for traditional and emerging risk factors including high-sensitivity C-reactive protein.

Summary Robust epidemiologic evidence supports IL-6 as a central mediator of cardiovascular risk along with human genetic studies and mechanistic experiments. Ongoing clinical studies are testing the therapeutic hypothesis of IL-6 inhibition in patients with atherosclerotic cardiovascular disease or heart failure.

Keywords Interleukin-6 · Inflammation · Cardiovascular outcomes · Risk prediction · Hs-CRP · Atherosclerosis

Introduction

Cardiovascular disease (CVD) remains the leading cause of death in the US [1] and globally [2], highlighting the need for additional therapeutic approaches to address residual risk. Event rates from clinical trials remain high despite optimal medical management, particularly in patients with recurrent events, polyvascular disease, or acute heart failure (HF) (Table 1).

Converging evidence from human genetic [9–13], epidemiological [14, 15], and mechanistic [16, 17], studies as well as results of canakinumab [18, 19] and colchicine [20, 21] trials support the therapeutic potential of IL-6 pathway inhibition to lower the risk of CVD independent of traditional risk factors.

A major cause of CVD is atherosclerosis, which may include acute coronary syndrome (ACS), myocardial infarction (MI), stable or unstable angina, coronary artery disease (CAD), coronary or other arterial revascularization, stroke, transient ischemic attack (TIA), carotid disease, and peripheral artery disease (PAD) [22, 23]. Atherosclerosis is characterized by deposition of apolipoprotein (Apo) B-containing lipoproteins (e.g., the atherogenic lipoproteins principally, low-density lipoprotein cholesterol) in the arterial wall [24]. Subsequent retention, oxidation, aggregation, and engulfment of Apo-B lipoproteins by macrophages within the arterial wall can lead to chronic low-grade inflammation [25]. These inflammatory responses may also be further exacerbated by other conditions and lifestyle factors such as dyslipidemia, hypertension, diabetes, smoking, and physical inactivity [25].

The inflammatory responses underlying CVD progression implicate many immune cell types including macrophages, neutrophils, and lymphocytes, which secrete pro- and anti-inflammatory cytokines [26]. Specifically, inflammatory responses involve a series of complex interactions between different cytokines such as tumor necrosis factor-α (TNF-α), transforming growth factor-β (TGF-β), interferon-γ (IFN-γ), granulocyte colony-stimulating factor (G-CSF),

✉ Emil deGoma
edegoma@tourmalinebio.com

1 The George Washington University School of Medicine, Washington, DC, USA

2 Tourmaline Bio, Inc, New York, NY, USA

3 Wake Forest University School of Medicine, Winston-Salem, NC, USA

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Table 1 Cardiovascular event rates in selected very high-risk patient populations

Patient population	Outcome	Event rate	Reference
Recurrent events	MACE-3	9%/year	Fonarow 2021[3]
	MACE-3 + MALE	9%/year	Colantonio 2019[4]
Polyvascular disease	MACE-4	10%/year (alirocumab arm)	Jukema 2019[5]
	MACE-3 + MALE	10%/year (ticagrelor arm)	Behan 2022[6]
Acute heart failure	Cardiovascular death, heart failure hospitalization or urgent visit	51 events/100 patient-years 18.6% at 6 months (sotagliflozin arm)	Bhatt 2021[7]
	All-cause death or heart failure hospitalization	15.2% at 180 days (highintensity care arm)	Mebazaa 2022[8]

MACE-3 major adverse cardiovascular events, inclusive of cardiovascular death, myocardial infarction, stroke, *MACE*-4, *MACE*-3 + hospitalization for unstable angina, *MALE* major adverse limb events, inclusive of acute limb ischemia, amputation for vascular cause

granulocyte-macrophage colony-stimulating factor (GM-CSF), as well as a variety of interleukins (IL) including IL-1, -2, -4, -6, -7, -10, -12, -13, -17, and −21 [26].

Among the inflammatory mediators, IL-6 is a key contributor to CVD pathophysiology. IL-6 is produced by macrophages, monocytes, endothelial cells, vascular smooth muscle cells, and fibroblasts [26–28], and plays a prominent role in promoting several aspects of atherosclerotic CVD (ASCVD) (Fig. 1).

In response to cholesterol and oxidative stress, proinflammatory cytokines promote further recruitment of immune cells (e.g., macrophages, T-cells, B-cell) and subsequent secretion of additional proinflammatory cytokines such as IL-6, resulting in activation of endothelial cells and expression of cell adhesion molecules [29, 30]. IL-6 is also linked to increased uptake of oxidized LDL by macrophages, contributing to foam cell formation [31].

Furthermore, IL-6 promotes the proliferation and migration of smooth muscle cells, as well as the secretion of extracellular matrix proteins, advancing plaque development [27]. It destabilizes plaques by inducing inflammation, thinning of the fibrous cap, and impairing collagen synthesis, thus making plaques more prone to rupture [31, 32]. This destabilization is further compounded by IL-6-induced expression of tissue factor, leading to a prothrombotic environment [32].

Given this, targeting IL-6 and its downstream pathways may represent a therapeutic strategy for preventing and treating atherosclerosis. To formally test the IL-6 hypothesis,

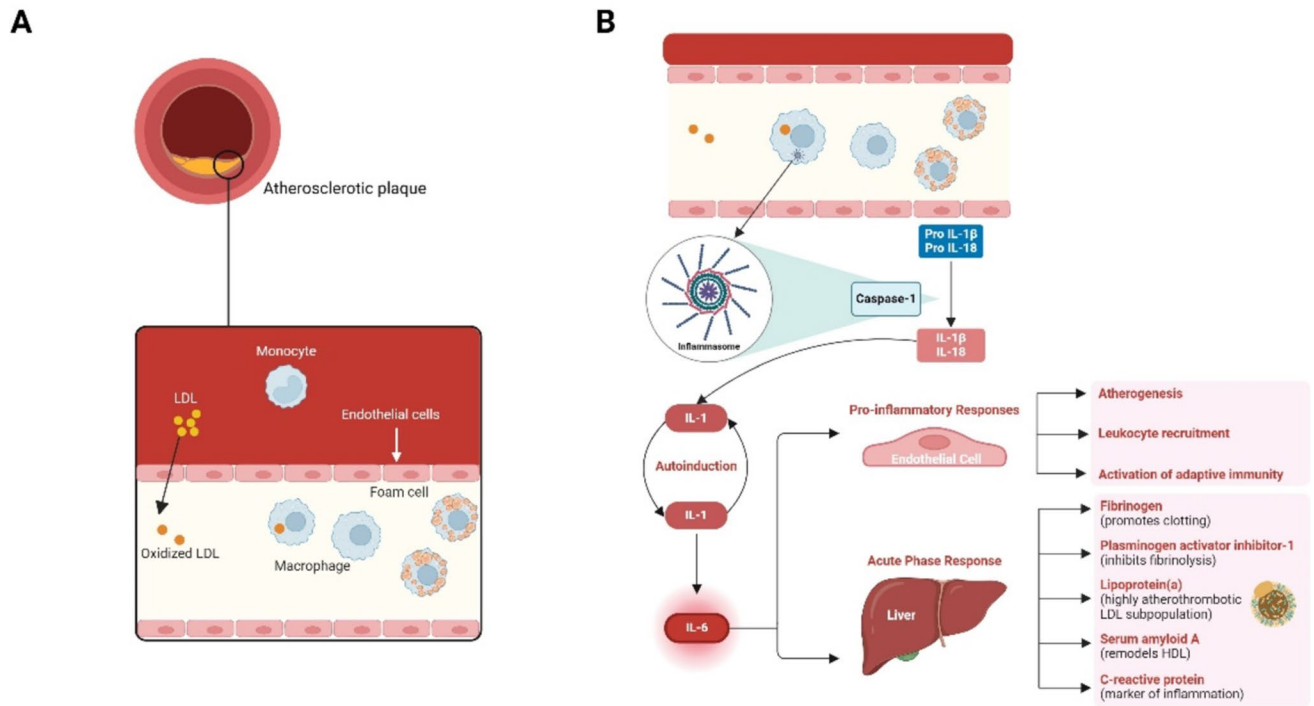

Fig. 1 ASCVD mechanism of disease. Figure created with Biorender.com

well-powered cardiovascular outcome trials are currently ongoing and assessing anti-IL-6 monoclonal antibodies (mAbs) in patients with ASCVD and chronic kidney disease (ZEUS [NCT05021835]), acute myocardial infarction (ARTEMIS [NCT06118281]), HF with preserved ejection fraction (HERMES [NCT05636176]), and end-stage kidney disease (POSIBIL$_6$ESKD [NCT05485961]) (Table 2).

The objective of this narrative review is to summarize data from prospective observational studies published in the past decade that analyze the association between circulating IL-6 levels and cardiovascular clinical or imaging endpoints. A brief historical perspective highlighting earlier landmark studies is presented in Fig. 2.

Methods

To identify relevant studies for inclusion in this narrative review, PubMed was searched for relevant articles from January 1, 2015, through August 15, 2024. Details on the search methodology are provided in the Supplement. Adjusted hazard, relative risk, and odds ratios are reported for each endpoint. Covariates for which analyses were adjusted are reported in the Supplement.

Association of IL-6 Levels with Risk of Cardiovascular Outcomes

The associations between circulating IL-6 levels and cardiovascular death, major adverse cardiovascular events (MACE), MI and other coronary events, stroke, PAD, and HF are summarized in Tables 3, 4, 5, 6, 7 and 8, respectively.

Notably, Ferreira et al. analyzed the Multi-Ethnic Study of Atherosclerosis (MESA) and found IL-6 to be more strongly associated with atherosclerosis, HF, fatal outcomes, and aortic valve calcification compared to high-sensitivity (hs) C-reactive protein (CRP) [44]. IL-6 remained strongly associated with these outcomes independent of hs-CRP, whereas the inverse was not true. High IL-6 levels were associated with increased risk of 3P-MACE (a composite of cardiovascular death, stroke, or MI) regardless of hs-CRP levels, but high hs-CRP levels were associated with higher risk only in conjunction with high IL-6 levels [44].

Further, Ridker et al. reported similar findings based on data from the Cardiovascular Inflammation Reduction Trial (CIRT) [53]. For the endpoint of MACE (a composite of cardiovascular death, nonfatal stroke, and nonfatal MI), multivariable hazard ratios (95% CI; adjusted for age, sex, smoking status, blood pressure, body mass index, total cholesterol, and high-density lipoprotein cholesterol, and stratified on diabetes or metabolic syndrome) for IL-6 were 1.23 (1.10–1.38) and for hs-CRP were 1.12 (1.00-1.26) [53]. This difference was most pronounced with the risk of all-cause mortality: IL-6, 1.35 (1.15–1.59), and hs-CRP, 1.00 (0.85–1.17) [53].

Association of IL-6 Levels with Vascular Imaging Endpoints

Vascular imaging studies have also revealed significant relationships between IL-6 levels and atherosclerosis. The association between circulating IL-6 levels and progression of carotid artery plaque or intima-media thickness assessed by ultrasound are summarized in Table 9. No studies were identified to date that reported association of IL-6 levels and changes in coronary artery plaque burden assessed by coronary CT angiography.

Briefly, Okazaki et al. observed a significant association between average IL-6 levels and long-term progression (nine years) of carotid mean maximal intima-media thickness (mmIMT); this association was independent of baseline mmIMT, age, sex, and other traditional risk factors (e.g., body mass index, diastolic blood pressure, estimated glomerular filtration rate, LDL-C, glycoasylated hemoglobin, use of statins) ($\beta = 0.17$, $P = 0.02$) [72]. Additionally, in the population-based Tromsø Study, Eltoft et al. reported significant associations between IL-6 and plaque progression (defined as an increase in total plaque area [TPA] ≥ 7.8 mm^2) following adjustment for traditional risk factors (OR 1.44, 95% CI 1.12–1.85) [73].

Further, evidence from additional population-based imaging studies has supported IL-6 as a predictor of not only carotid plaque progression but also severity and vulnerability [73, 74]. Data from the Cardiovascular Health Study revealed significant associations between baseline log IL-6 and plaque severity ($\beta = 0.09$, $P = 0.001$), irrespective of other risk factors such as PAD, dyslipidemia, hypertension, history of stroke or TIA, and smoking [74]. Kamtchum-Tatuene et al. also reported a 12% increase in risk for plaque vulnerability per 1 standard deviation (SD) increase in log IL-6 [74]. After five years, each 1 SD increase in log IL-6 levels was also associated with a 24% increase in carotid plaque progression, thereby making IL-6 the topmost contributor to carotid plaque progression following dyslipidemia [74]. Collectively, these findings emphasize the potential importance and utility of IL-6 in predicting carotid plaque severity, vulnerability, and progression.

Comparing IL-6 and hs-CRP as a Biomarker for Cardiovascular risk

CRP has long been established as an informative inflammatory biomarker above and beyond traditional risk factors, largely due to the extensive body of epidemiological evidence demonstrating a significant association between CRP levels and a range of adverse cardiovascular events across

Table 2 Phase 2 and phase 3 randomized, double-blind, placebo-controlled trials of anti-IL-6 monoclonal antibodies for cardiovascular indications

Phase	Anti-IL-6 mAb	Study	*N*	Study Population	Primary Endpoint(s)	Primary Completion (Est.)
2	Pacibekitug (TOUR006) SC quarterly, SC monthly	TRANQUILITY NCT06362759	120	CKD and hs-CRP ≥ 2 mg/L	Change from baseline in hsCRP at Day 90	May 2025
3	Ziltivekimab SC monthly	ZEUS NCT05021835	6,200	ASCVD, CKD, and hsCRP ≥ 2 mg/L	Time to first occurrence of 3-point MACE, a composite endpoint consisting of: CV death, non-fatal MI and non-fatal stroke from randomization to end of study	September 2025
3	Ziltivekimab SC monthly	ATHENA NCT06200207	680	HFpEF and hs-CRP ≥ 2 mg/L	Change in KCCQ-CSS from randomization to Month 12	June 2026
3	Ziltivekimab SC monthly	HERMES NCT05636176	5,600	HFpEF and hs-CRP ≥ 2 mg/L	Time to first occurrence of a composite heart failure endpoint consisting of: CV death, HF hospitalization or urgent HF visit from randomization to end of study	July 2027
3	Ziltivekimab SC loading dose à SC monthly	ARTEMIS NCT06118281	10,000	AMI	Time to first occurrence of 3-point MACE, a composite endpoint consisting of: CV death, non-fatal MI and non-fatal stroke from randomization to end of study	September 2026
3	Clazakizumab IV every 4 weeks	POSIBIL$_6$ESKD NCT05485961	2,310	ESKD, diabetes or ASCVD, and hsCRP ≥ 2 mg/L	Time to first occurrence of CV death or MI	December 2028

AMI acute myocardial infarction, *ASCVD* atherosclerotic cardiovascular disease, *CKD* chronic kidney disease *CV* cardiovascular *ESKD* end-stage kidney disease *HF* heart failure *HFpEF* heart failure with preserved ejection fraction *hs-CRP* high-sensitivity C-reactive protein *KCCQ-CSS* Kansas City Cardiomyopathy Questionnaire Clinical Summary Score, *mAb* monoclonal antibody, *MACE* major adverse cardiovascular event, *RCT* randomized controlled trial

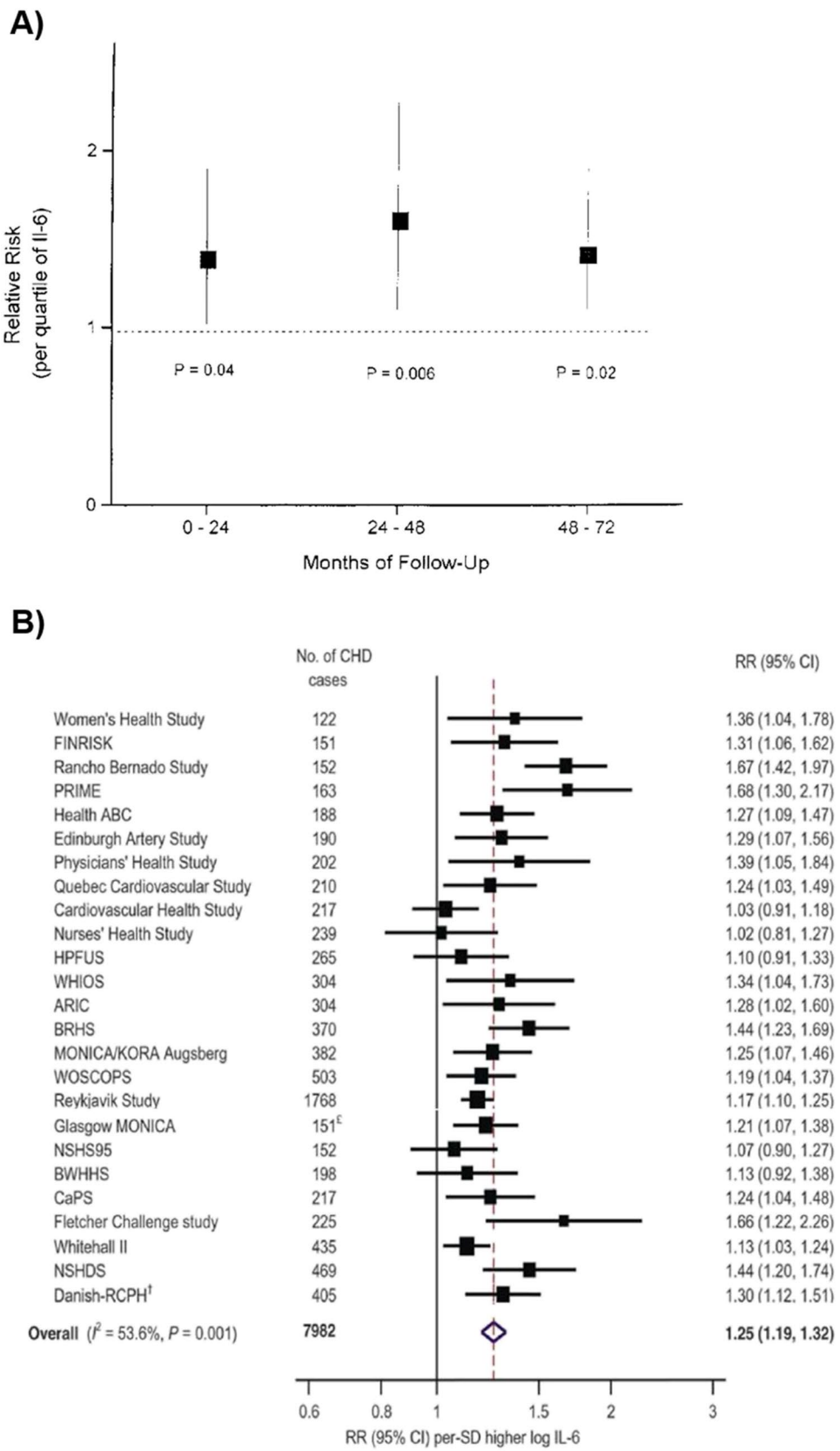

Fig. 2 Landmark epidemiological studies of IL-6 levels and cardiovascular outcomes. **A** The first report of an association between IL-6 and cardiovascular outcomes was published by Ridker at al. [29] in 2000 and showed a 38% increase in risk of myocardial infarction per quartile increase in IL-6. (**B**). A landmark meta-analysis of 29 prospective studies published by Kaptoge et al. [14] in 2014 showed a 25% increased risk of nonfatal myocardial infarction or coronary heart disease death per 1-SD higher level of IL-6

Table 3 Association of IL-6 with cardiovascular death

Publication	Study Type	*N*	Follow-Up Duration (years)	Baseline IL-6 (pg/mL)	Population	Findings
Patterson 2015[34]	Prospective cohort (CaPS)	2,171	15.4[b]	Alive: 1.86[a] CV death: 2.65[a] Non-CV death: 2.72[a]	GP (men)	CV death HR per third of distribution: 1.24 (95% CI 1.08–1.43)[c]
Fanola 2016[35]	RCT (SOLID-TIMI 52)	4,939	2.5[a]	2.02[a]	ACS	CV death HR Q4:Q4: 2.13 (95% CI 1.35–3.36)[d]
Held 2017[36]	RCT (STABILITY)	14,611	3.7[a]	2.1[a]	Stable CHD	CV death Q4:Q1 HR: 2.15 (95% CI 1.53–3.04)[e]
Li 2017[37]	Meta-analysis	9,087	3-15.3	NA	GP	CV death RR highest vs. lowest quantile: 1.69 (95% CI 1.27–2.25)
Singh-Manoux 2017[38]	Prospective cohort (Whitehall II cohort)	6,545	16.7[b]	Alive: 1.38[a] Deceased: 1.84[a]	GP	CV death HR per 1-SD increment: 1.19 (95% CI 1.02–1.39)[f]
Kalsch 2020[39]	Prospective cohort (LURIC)	3,134	9.9[a]	Without CAD: 2.5[a] With CAD: 3.5[a]	Coronary angiography	CV death HR per 1-SD increment: 1.18 (95% CI 1.07–1.31)[g]
Gager 2020[40]	Prospective cohort	322	6[a]	Low: 1.8[b] High: 16.6[b]	ACS	CV death HR ≥ vs. < 3.3 pg/mL: 8.60 (95% CI 1.07–69.32[h]
Li 2021[41]	Meta-analysis	30,289	0.5–6.3	NA	ACS	CV death RR: 1.55 (95% CI 1.06–2.28)
Perez 2021[42]	RCT (ASCEND-HF)	883	0.5	14.1[a]	Acute HF	CV death HR T3:T1: 3.23 (95% CI, 1.18–8.86)[i]
Chen 2023[43]	Meta-analysis	8,370	NA	NA	Hemodialysis or peritoneal dialysis	CV death HR: 1.55 (95% CI 1.20–1.90)
Ferreira 2024[44]	Prospective cohort (MESA)	6,614	14[a]	1.21[a]	GP	CV death HR ≥ vs. < 1.2 pg/mL: 1.88 (95% CI 1.43–2.47)[i]
Khan 2024[45]	Prospective cohort (MESA)	6,622	14[a]	1.21[a]	GP	CV death HR T3:T1: 1.55 (95% CI 1.05–2.30)[k]
Markousis-Mavrogenis 2019[46]	Prospective cohort (BIOSTAT-CHF)	2,329	1.75[a]	5.2[a]	HF	CV death HR per doubling: 1.16 (95% CI 1.09–1.24)[l]
Defilippi 2023[47]	RCT (VICTORIA)	4,652	NA	6.8[a]	HFrEF	CV death HR per 1-SD increment: 1.12 (95% CI 1.04–1.21)[m]
Mooney 2023[48]	Prospective cohort	286	3.2[b]	5.71[a]	Recent HFpEF hospitalization	CV death HR 1-log increment: 1.40 (95% CI 1.10–1.77)[n]
Batra 2021[49]	RCT (STABILITY)	14,611	3.7[a]	Stage 1 CKD: 1.9[a] Stage 2 CKD: 2.0[a] Stage ≥ 3a CKD: 2.5[a]	Chronic coronary syndrome and CKD	CV death HR ≥ vs. < 2.0 pg/mL:[o] Stage 1 CKD 1.54 (95% CI 0.99–2.40); Stage 2 CKD 2.17 (95% CI 1.69–2.79); Stage ≥ 3a CKD 2.24 (95% CI 1.60–3.12)

[a]Median, [b]Mean, [c-o]See supplementary information

ACS acute coronary syndrome, *ASCEND-HF* Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure, *BIOSTAT-CHF* BIOlogy Study to TAilored Treatment in Chronic Heart Failure, *CAD* coronary artery disease, *CaPS* Caerphilly Prospective Study, *CHD* coronary heart disease, *CI* confidence interval, *CKD* chronic kidney disease, *CV* cardiovascular, *GP* general population, *HF* heart failure, *HFpEF* heart failure with preserved ejection fraction, *HFrEF* heart failure with reduced ejection fraction, *HR* hazard ratio, *IL* interleukin, *LURIC* Ludwigshafen Risk and Cardiovascular Health, *MESA* Multi-Ethnic Study of Atherosclerosis, *NA* not available, *Q* quartile, *RCT* randomized controlled trial, *RR* relative risk, *SD* standard deviation, *SOLID-TIMI* Stabilization of pLaques 14 usIng Darapladib-Thrombolysis in Myocardial Infarction, *STABILITY* Stabilization of Atherosclerotic Plaque by Initiation of Darapladib Therapy, *T* tertile,*VICTORIA* Vericiguat Global Study in Subjects with Heart Failure with Reduced Ejection Fraction

Table 4 Association of IL-6 with major adverse cardiovascular events

Publication	Study Type	*N*	Follow-Up Duration (years)	Baseline IL-6 (pg/mL)	Population	Findings
Spoto 2015[50]	Prospective cohort	755	2.6[b]	2.5[a]	CKD	MACE HR ≥ vs. < 2.5 pg/mL: 1.66 (95% CI 1.11–2.49)[c]
Fanola 2016[35]	RCT (SOLID-TIMI 52)	4,939	2.5[a]	2.02[a]	ACS	MACE HR Q4:Q1: 1.57 (95% CI; 1.22–2.03)[d]
Held 2017[36]	RCT (STABILITY)	14,611	3.7[a]	2.1[a]	Stable CHD	MACE HR Q4:Q1: 1.59 (95% CI 1.29–1.97)[e]
Pareek 2017[51]	Prospective cohort (Malmo Preventive Project)	1,324	8.6[a]	Without incident event: 3.30[a] With incident event: 4.04[a]	GP	MACE HR per 1-SD ln: 1.13 (95% CI 1.02–1.25)[f]
Kristono 2020[52]	Prospective cohort	317	1	2.38[a]	Acute MI	MACE OR > vs. ≤ 3.11 pg/mL: 2.18 (95% CI 1.06–4.50)[g]
Ridker 2020[53]	RCT (CIRT)	4,168	≤ 5	2.5[a]	CAD or multivessel coronary disease, and T2D or MetS	MACE HR per quartile: 1.23 (95% CI 1.10–1.38)[h]
Batra 2021[49]	RCT (STABILITY)	14,611	3.7[a]	Stage 1 CKD: 1.9[a] Stage 2 CKD: 2.0[a] Stage ≥ 3a CKD: 2.5[a]	Chronic coronary syndrome and CKD	MACE HR ≥ vs. < 2.0 pg/mL:[i] Stage 1 CKD 1.35 (95% CI 1.02–1.78); Stage 2 CKD 1.57 (95% CI 1.35–1.83); Stage ≥ 3a CKD 1.60 (95% CI 1.28–1.99)
Li 2021[41]	Meta-analysis	30,289	0.3–6.3	NA	ACS	MACE HR: RR 1.29 (95% CI 1.12–1.48)
Barrows 2022[54]	Prospective cohort (CRIC)	3,031	10[a]	1.9[a]	CKD	MACE HR per 1-quintile increase: 1.43 (95% CI 1.36–1.51)[j]
Ferencik 2022[55]	RCT (PROMISE)	1,796	2.1[a]	1.8[a]	Suspected CAD by coronary CTA	MACE HR > vs. ≤ 1.8 pg/mL: 1.92 (95% CI 1.09–3.39)[k]
Koshino 2022[56]	RCT (CANVAS)	3,503	6.1[a]	1.6[a]	T2D with CVD history or multiple CV risk markers	MACE HR per doubling of IL-6: 1.14 (95% CI 1.04–1.24)[l]
Jia 2023[57]	Prospective cohort (ARIC)	5,672	7.2[a]	3.0[a]	GP	MACE HR per 1-log increase: 1.57 (95% CI 1.44–1.72)[m]
McCabe 2023[58]	Meta-analysis	8,420	0.25-10.8[a]	2.0-25.2[a]	IS, TIA	MACE RR Q4:Q1: 1.35 (95% CI 1.09–1.67)[n]
Dirjayanto 2024[59]	Prospective cohort (ICON1)	230	5	2.4[a]	Non-ST elevation ACS	MACE HR: 1.52 (95% CI 0.99–2.34)[o]
Ferreira 2024[44]	Prospective cohort (MESA)	6,614	14[a]	1.21[a]	GP	MACE HR ≥ vs. < 1.2 pg/mL: 1.44 (95% CI 1.25–1.64)[p]
Li 2024[60]	Prospective cohort	290	2	No MACE: 3.36[b] MACE: 5.07[b]	CAS	MACE HR: 1.27 (95% CI 1.12–1.64)[q]

[a]Median, [b]Mean, [c-q]See supplementary information

ACS acute coronary syndrome, *ARIC* Atherosclerosis Risk in Communities, *CAD* coronary artery disease, *CANVAS* Canagliflozin Cardiovascular Assessment Study, *CAS* carotid artery stenosis, *CHD* coronary heart disease, *CI* confidence interval, *CIRT* Cardiovascular Inflammation Reduction Trial, *CKD* chronic kidney disease, *CRIC* Chronic Renal Insufficiency Cohort, *CTA* computed tomography angiography, *CV* cardiovascular, *CVD* cardiovascular disease, *GP* general population, *HR* hazard ratio, *ICON1* Improve Cardiovascular Outcomes in High Risk PatieNts with Acute Coronary Syndrome, *IL* interleukin, *IS* ischemic stroke, *MACE* major adverse cardiovascular events, *MESA* Multi-Ethnic Study of Atherosclerosis, *MetS* metabolic syndrome, *MI* myocardial infarction, *NA* not available, *OR* odds ratio, *PROMISE* PROspective Multicenter Imaging Study for Evaluation of chest pain, *Q* quartile, *RCT* randomized controlled trial, *RR* relative risk, *SD* standard deviation, *SOLID-TIMI* Stabilization of pLaques usIng Darapladib-Thrombolysis in Myocardial Infarction, *STABILITY* Stabilization of Atherosclerotic Plaque by Initiation of Darapladib Therapy, *T2D* type 2 diabetes, *TIA* transient ischemic attack

Table 5 Association of IL-6 with MI and other coronary events

Publication	Study Type	*N*	Follow-Up Duration (years)	Baseline IL-6 (pg/mL)	Population	Findings
Kaptoge 2014[14]	Meta-analysis	7,982	3.7-13.4[a]	NA	GP	Non-fatal MI or CHD death RR per 1-SD increment: 1.25 (95% CI 1.19–1.32)
Held 2017[36]	RCT (STABILITY)	14,611	3.7[a]	2.1[a]	Stable CHD	MI HR Q4:Q1: 1.55 (95% CI 1.16–2.09)[c]
Ridker 2020[53]	RCT (CIRT)	4,168	≤5	2.5[a]	CAD or multivessel coronary disease, and T2D or MetS	MI HR per quartile: 1.20 (95% CI 1.04–1.38)[d]
Batra 2021[49]	RCT (STABILITY)	14,611	3.7[a]	Stage 1 CKD: 1.9[a] Stage 2 CKD: 2.0[a] Stage ≥ 3a CKD: 2.5[a]	Chronic coronary syndrome and CKD	MI HR ≥ vs. < 2.0 pg/mL:[e] Stage 1 CKD 1.37 (95% CI 0.94–1.99); Stage 2 CKD 1.39 (95% CI 1.12–1.72); Stage ≥ 3a CKD 1.26 (95% CI 0.93–1.71)

[a]Median,[b]Mean,[c−e]See supplementary information

CAD coronary artery disease, *CHD* coronary heart disease, *CI* confidence interval, *CIRT* Cardiovascular Inflammation Reduction Trial, *CKD* chronic kidney disease, *GP* general population, *HR* hazard ratio, *IL* interleukin, *MetS* metabolic syndrome, *MI* myocardial infarction, *NA* not available, *RCT* randomized controlled trial, *RR* relative risk, *SD* standard deviation, *STABILITY* Stabilization of Atherosclerotic Plaque by Initiation of Darapladib Therapy, *T2D* type 2 diabetes

diverse populations [75]. A recently published analysis of 27,939 initially healthy women followed for 30 years in the Women's Health Study showed that hs-CRP was highly associated with incident MACE, with the highest quintile exhibiting a HR of 1.70 (95% CI 1.52–1.90), compared with HRs of 1.36 (95% CI 1.23–1.52) and 1.33 (95% CI 1.21–1.47) for LDL-C and Lp(a), respectively [76]. This widespread recognition has elevated CRP as an important biomarker in cardiovascular risk assessment, as evidenced by its incorporation into multiple prevention guidelines [77–79], most recently in the 2024 ESC Guidelines for Chronic Coronary Syndrome [80]. However, despite its clinical utility, CRP is not without its limitations. One of the most significant limitations is its role as a downstream marker in the inflammatory cascade, reflecting systemic inflammation rather than a proximal inflammatory mediator. This has been established by mechanistic experiments and human genetics studies which demonstrated no causal association between genetic variants of CRP and cardiovascular risk [81–83]. IL-6, on the other hand, occupies a more pivotal position in the inflammatory response. As a pro-inflammatory cytokine, IL-6 is integral to the initiation and propagation of inflammatory processes. It not only acts at the early stages of inflammation but also stimulates the secretion of acute-phase proteins such as CRP. This upstream role of IL-6 in the inflammatory pathway suggests that it may provide a more direct and perhaps more clinically meaningful measure of inflammatory activity, particularly in the context of CVD. Importantly, human genetic studies have consistently demonstrated an association between IL-6 pathway inhibition and lower risk of ASCVD [10, 12, 13, 84].

Recent studies have reinforced the significance of IL-6 as a biomarker in cardiovascular risk assessment. Multiple associations have been documented between IL-6 levels and various indicators of atherosclerosis, such as coronary artery calcium (CAC), carotid intima-media thickness (CIMT), and plaque burden [85, 86]. Investigations focusing on vascular imaging outcomes have also demonstrated more robust correlations between IL-6 levels and CIMT than those observed with hs-CRP [72]. CIMT is a well-established surrogate marker for atherosclerosis and cardiovascular risk, and the stronger relationship between IL-6 and CIMT further reinforces the idea that IL-6 may provide a more accurate reflection of underlying vascular inflammation and atherosclerotic burden.

As mentioned, unlike hs-CRP, IL-6 is directly involved in the inflammatory processes that contribute to CVD. Consistent with this framework, recent studies have demonstrated a stronger association of IL-6 compared with hs-CRP for cardiovascular risk, as evidenced by findings from CIRT [53], MESA [44] and CANTOS [19, 87]. In CIRT, the association between IL-6 and MACE was numerically greater than that between hs-CRP and MACE (HR per quartile 1.23 vs. 1.12) [53]. Moreover, high IL-6 levels contributed to risk prediction above and beyond high levels of hs-CRP. Similarly, in MESA, IL-6 was more strongly and consistently associated with adverse cardiovascular outcomes, such as MACE, HF, and all-cause mortality, even when accounting

Table 6 Association of IL-6 with stroke

Publication	Study Type	*N*	Follow-Up Duration (years)	Baseline IL-6 (pg/mL)	Population	Findings
Jenny 2019[61]	Prospective cohort (REGARDS)	30,237	5.4[a]	No stroke: 3.7 Stroke: 4.5	GP	Stroke HR Q4:Q1: 2.0 (95% CI 1.2–3.1)[c]
Papadopoulos 2022[15]	Meta-analysis	27,411	12.4[a]	1.0-4.5[a] 1.2-16.9[b]	GP (9 studies) ≥ 1 vascular risk factor (2 studies)	Stroke RR per 1-SD log increase: 1.19 (95% CI 1.10–1.28)
McCabe 2023[58]	Meta-analysis	8,420	0.25-10.8[b]	2.0-25.2[b]	IS, TIA	Stroke RR Q4:Q1: 1.33 (95% CI 1.08–1.65)[d]
Li 2022[62]	Prospective cohort (CNSR-III)	10,472	1	Male: 2.6 Female: 2.7	AIS, TIA	Stroke HR Q4:Q1: 1.36 (95% CI 1.13–1.64)[e]
Xu 2022[63]	Prospective cohort (CNSR-III)	2,537	1[b]	3.2	AIS, TIA	Stroke HR ≥ vs. < 5.44 pg/mL: 2.05 (95% CI 1.32–3.19)[f]
Held 2017[36]	RCT (STABILITY)	14,611	3.7[b]	2.1[b]	Stable CHD	Stroke HR Q4:Q1: 1.17 (95% CI 0.73–1.87)[g]
Ridker 2020[53]	RCT (CIRT)	4,168	≤ 5	2.5[b]	CAD or multivessel coronary disease, and T2D or MetS	Stroke HR per quartile: 1.17 (95% CI 0.90–1.53)[h]
Batra 2021[49]	RCT (STABILITY)	14,611	3.7[b]	Stage 1 CKD: 1.9[b] Stage 2 CKD: 2.0[b] Stage ≥ 3a CKD: 2.5[b]	Chronic coronary syndrome and CKD	Stroke HR ≥ vs. < 2.0 pg/mL:[i] Stage 1 CKD 0.96 (95% CI 0.47–1.95); Stage 2 CKD 1.39 (95% CI 1.00-1.92); Stage ≥ 3a CKD 1.49 (95% CI 0.90–2.47)
Jia 2023[57]	Prospective cohort (ARIC)	5,672	7.2[b]	3.0[b]	GP	Stroke HR per 1-log increase: 1.15 (95% CI 0.93–1.43)[j]
Dirjayanto 2024[59]	Prospective cohort (ICON1)	230	5	2.4[b]	Non-ST elevation ACS	Stroke/TIA HR: 0.58 (95% CI 0.13–2.56)[k]

[a]Mean, [b]Median, [c-k]See supplementary information

ACS acute coronary syndrome, *AIS* acute ischemic stroke, *ARIC*, Atherosclerosis Risk in Communities, *CAD* coronary artery disease, *CI* confidence interval, *CIRT* Cardiovascular Inflammation Reduction Trial, *CKD* chronic kidney disease, *CNSR-III* Third China National Stroke Registry, *GP* general population, *HR* hazard ratio, *IL* interleukin, *ICON1* Improve Cardiovascular Outcomes in High Risk PatieNts with Acute Coronary Syndrome, *IS*, ischemic stroke, *MetS* metabolic syndrome, *Q* quartile, *RCT* randomized controlled trial, *REGARDS* Reasons for Geographic and Racial Differences in Stroke, *RR* relative risk, *SD* standard deviation, *STABILITY* Stabilization of Atherosclerotic Plaque by Initiation of Darapladib Therapy, *T2D* type 2 diabetes, *TIA* transient ischemic attack

for traditional risk factors and hs-CRP levels [44]. Adding IL-6 to traditional risk models like the Pooled Cohort Equations significantly improves risk reclassification [88], highlighting its potential to enhance cardiovascular risk prediction and help guide more targeted interventions. In joint analysis, when levels of IL-6 and hs-CRP were discordant (e.g., IL-6 ≥ median and hs-CRP < median), risk of MACE tracked with IL-6 (Fig. 3). Finally, on-treatment IL-6 levels were more closely related to cardiovascular event rates than on-treatment hs-CRP levels in the CANTOS trial of canakinumab [19, 87]. Compared to placebo, the MACE HR for lowest tertile IL-6 and the lowest tertile hs-CRP were 0.65 (95% CI 0.53–0.81) and 0.75 (0.66–0.85), respectively, in fully adjusted models [87].

Moreover, McCabe et al. observed that IL-6 exhibited a stronger association with the risk of recurrent stroke compared to hs-CRP, underscoring the potential of IL-6 as a more sensitive biomarker for identifying patients at elevated risk for recurrent cerebrovascular events [58]. The closer ties of IL-6 to the inflammatory pathways directly involved in the pathogenesis of atherosclerosis, along with its stronger associations with clinical outcomes such as recurrent stroke and subclinical measures like CIMT, highlight its greater specificity and sensitivity as a predictor of cardiovascular events. This evidence positions IL-6 as a potentially more reliable and informative marker for guiding preventive strategies and therapeutic interventions in the management of CVD.

Table 7 Association of IL-6 with peripheral artery disease

Publication	Study Type	*N*	Follow-Up Duration (years)	Baseline IL-6 (pg/mL)	Population	Findings
McDermott 2011[64]	Prospective cohort (WALCS II)	368	3	NA	PAD	Greater decline in walking performance (6MWT) with increasing IL-6 levels: lowest tertile for ≥ 75% of study visits − 21.4 ft; highest tertile for ≥ 75% of study visits − 76.8 ft ($P = 0.013$)[c]
Gremmels 2019[65]	Prospective cohort (JUVENTAS)	254	5.6	Event: 8.0[b] No event: 5.8[b]	Severe limb ischemia	Amputation-free survival HR 1.35 (95% CI 1.06–1.71; $p = 0.01$)[d]
Marinho 2022[66]	Prospective cohort (CIRT)	4,248	≤ 5	2.50[a]	CAD, and T2D or MetS	PAD HR Q4:Q1: 2.0[e]

[a]Median, [b]Mean [c−e]See supplementary information

6MWT 6-minute walk test, *CAD* coronary artery disease, *CIRT* Cardiovascular Inflammation Reduction Trial, *HR* hazard ratio, *IL* interleukin, *MetS* metabolic syndrome, *NA* not available, *PAD* peripheral artery disease, *Q* quartile, *T2D* type 2 diabetes, *WALCS II* Walking and Leg Circulation Study II

Despite the promising role of IL-6 in CVD risk prediction, the clinical application of IL-6 as a biomarker faces significant challenges due to the lack of validated assays beyond standard blood concentration measurements. This gap presents a critical opportunity for the development of targeted assays and standardized approaches to timing of sample collection that can more accurately and reliably assess IL-6 levels, potentially enhancing current methods of CVD risk stratification. However, several key obstacles must be addressed to fully harness the potential of IL-6 in clinical practice.

One of the primary challenges in assessing IL-6 is its inherently low and highly variable concentration in the bloodstream. In healthy individuals, IL-6 levels typically range from 4.6 to 5.7 pg/mL on average, with a notable increase observed with advancing age [89]. However, there is considerable variability, with levels ranging from as low as 0 pg/mL to as high as 43.5 pg/mL in some healthy subjects [89]. This contrasts with hs-CRP, where levels are generally stable and typically ≤ 10 mg/L [75]. The variability in IL-6 levels is further compounded by its sensitivity to postprandial, exercise, and diurnal fluctuations [90]. Unlike CRP, which remains relatively stable following food intake, IL-6 levels can significantly increase after meals, making fasting status an important consideration for accurate measurement [91–93]. Likewise, IL-6 may rise acutely in response to exercise, with a lower, but appreciable, secondary increase during the post-exercise recovery phase [94]. Additionally, IL-6 exhibits diurnal variation, with levels generally lowest in the morning and peaking later in the day [35]. These variations can complicate the interpretation of IL-6 levels and require careful consideration of the timing of sample collection. Moreover, the plasma half-life of IL-6 is relatively short, less than six hours, compared to other biomarkers such as hs-CRP, which has a half-life of 18 to 20 h [33, 75]. This short half-life means that IL-6 levels can change rapidly, adding another layer of complexity to its use as a biomarker for chronic conditions like CVD. Standardization of timing, such as obtaining early-morning fasting levels without recent strenuous exercise, may help improve IL-6 assessment for cardiovascular risk.

Despite these challenges, the central role of IL-6 in the inflammatory pathways that drive the initiation, progression, and destabilization of atherosclerotic disease positions it as not only a promising predictive biomarker but also as a potential therapeutic target. Advances in assay development that can overcome the current limitations of IL-6 measurement could lead to more precise and actionable insights into cardiovascular risk, potentially transforming the landscape of preventive cardiology.

Conclusions

Accumulating evidence highlights inflammation as a key driver of CVD. A recent analysis of > 445,000 patients with the 19 most common autoimmune disorders showed a higher risk of a broad spectrum of CVD, including ASCVD, HF, aortic aneurysm, and arrhythmia [95]. Among various inflammatory pathways, the targeting and inhibition of

Table 8 Association of IL-6 with heart failure

Publication	Study Type	*N*	Follow-Up Duration (years)	Baseline IL-6 (pg/mL)	Population	Findings
Fanola 2017[35]	RCT (SOLID-TIMI 52)	4,939	2.5[a]	2.02[a]	ACS	HF hospitalization HR Q4:Q1: 3.1 (95% CI 1.81–5.33)[c]
Held 2017[36]	RCT (STABILITY)	14,611	3.7[a]	2.1[a]	Stable CHD	HF hospitalization HR Q4:Q1: 2.37 (95% CI 1.34–4.18)[d]
He 2017[67]	Prospective cohort (CRIC)	3,557	6.3[b]	Stage 2 CKD: 1.09 Stage 3a CKD: 1.67 Stage 3b CKD: 2.08 Stage 4 CKD: 2.59	CKD	HF HR per 1-log increment: 1.15 (95% CI 1.05–1.25)[e]
de Boer 2018[68]	Prospective cohorts (CHS, FHS, MESA, PREVEND)	22,756	12[a,b]	MESA: 1.2[a] CHS: 1.66[a]	GP	HF HR per 1-SD ln increment: 1.10 (95% CI 1.03–1.16)[f]
Markousis-Mavrogenis 2019[46]	Prospective cohort (BIOSTAT-CHF)	2,329	1.75[a]	5.2[a]	HF	HF hospitalization HR per doubling: 1.01 (95% CI 0.94–1.08)[g]
Albar 2022[69]	Prospective cohort (MESA)	2,610	8.4[a]	No HF: 1.54 HFpEF: 2.20 HFrEF: 1.98	GP	HFpEF HR per doubling: 1.78 (95% CI 1.03–3.08)[h] HFrEF HR per doubling: 0.87 (95% CI 0.45–1.67)[h]
Vasques-Nóvoa 2022[70]	Prospective cohort (EDIFICA)	164	0.5	17.4[a]	Acute HF	HF rehospitalization HR T3:T1: 3.69 (95% CI 1.26–10.8)[i]
Defilippi 2023[47]	RCT (VICTORIA)	4,652	NA	6.8[a]	HFrEF	HF hospitalization HR per 1-SD increment: 1.05 (95% CI 0.98–1.12)[j]
Michou 2023[71]	Prospective cohort (BASEL V)	1,026	1	11.2[a]	Acute HF	HF hospitalization HR 75th vs. 25th percentile 1.00 (95% CI 0.998–1.002)[k]
Mooney 2023[48]	Prospective cohort	286	3.2[b]	5.71[a]	Recent HFpEF hospitalization	HF hospitalization HR 1-log increment: 1.24 (95% CI 1.01–1.51)[l]
Khan 2024[45]	Prospective cohort (MESA)	6,622	14[a]	1.21[a]	GP	Incident HF HR T3:T1: 0.80 (95% CI 0.45–1.45)[m]
Batra 2021[49]	RCT (STABILITY)	14,611	3.7[a]	Stage 1 CKD: 1.9[a] Stage 2 CKD: 2.0[a] Stage ≥ 3a CKD: 2.5[a]	Chronic coronary syndrome and CKD	HF hospitalization HR ≥ vs. < 2.0 pg/mL:[n] Stage 1 CKD 2.02 (95% CI 0.82–4.98); Stage 2 CKD 2.61 (95% CI 1.77–3.86); Stage ≥ 3a CKD 2.52 (95% CI 1.60–3.96)
Koshino 2022[56]	RCT (CANVAS)	3,503	6.1[a]	1.6[a]	T2D with CVD history or multiple CV risk markers	HF hospitalization HR per doubling of IL-6: 1.35 (95% CI 1.16–1.57)[o]
Jia 2023[57]	Prospective cohort (ARIC)	5,672	7.2[a]	3.0[a]	GP	HF hospitalization HR per 1-log increase: 1.82 (95% CI 1.64–2.02)[p]

[a]Median,[b]Mean,[c–p]See supplementary information

ACS acute coronary syndrome, *ARIC* Atherosclerosis Risk in Communities, *BASEL* Basics in Acute Shortness of Breath EvaLuation, *BIOSTAT-CHF* BIOlogy Study to TAilored Treatment in Chronic Heart Failure, *CHD* coronary heart disease, *CHS* Cardiovascular Health Study, *CI* confidence interval, *CKD* chronic kidney disease, *CRIC* Chronic Renal Insufficiency Cohort, *CV* cardiovascular, *CVD* cardiovascular disease, *EDIFICA* Estratificação de Doentes com InsuFIciência Cardíaca Aguda, *FHS* Framingham Heart Study, *GP* general population, *HF* heart failure, *HFpEF* heart failure with preserved ejection fraction, *HFrEF* heart failure with reduced ejection fraction, *HR* hazard ratio, *IL* interleukin, *MESA* Multi-Ethnic Study of Atherosclerosis, *PREVEND* Prevention of Renal and Vascular Endstage Disease, *Q* quartile, *RCT* randomized controlled trial, *SD* standard deviation, *SOLID-TIMI* Stabilization of pLaques usIng Darapladib-Thrombolysis in Myocardial Infarction, *STABILITY* Stabilization of Atherosclerotic Plaque by Initiation of Darapladib Therapy, tertile, *T2D* type 2 diabetes, *VICTORIA* Vericiguat Global Study in Subjects with Heart Failure with Reduced Ejection Fraction

Table 9 Association of IL-6 levels with imaging endpoints

Publication	Study Type	*N*	Baseline IL-6 (pg/mL)	Population	Duration (years)	Imaging method	Findings
Okazaki 2014[72]	Prospective cohort (OSACA2)	210	1.36[b]	CVD or ≥ 1 risk factor: hypertension, diabetes, dyslipidemia, smoking	9	Carotid ultrasound	mmIMT progression β per 1SD increment: 0.17[d]
Eltoft 2018[73]	Case-control (Tromsø Study)	703	No plaques: 2.66[c] Novel plaques: 2.84[c] Stable plaques: 2.80[c] Progression of plaques: 3.58[c]	GP	6	Carotid ultrasound	Plaque progression OR per 1SD increase: 1.44 (95% CI 1.12–1.85)[e]
Kamtchum-Tatuene 2022[74]	Prospective cohort (CHS)	4,334	No plaque progression at 5 years: 1.6[b] With plaque progression at 5 years: 1.6[b]	GP ≥ 65 years	5	Carotid ultrasound	Plaque progression OR per log-IL-6 increment: 1.44 (95% CI 1.23–1.69)[f]

[a]Mean, [b]Median, [c]Geometic mean, [d–f]See supplementary information

CHS Cardiovascular Health Study, *CI* confidence interval, *CVD* cardiovascular disease, *GP* general population, *IL* interleukin, *mmIMT* mean-maximal intima-media thickness, *OR* odds ratio, *OSACA2* Osaka Follow-up Study for Carotid Atherosclerosis part 2, *SD* standard deviation

IL-6 is supported by triangulation from multiple sources of data, including the epidemiological studies summarized herein. Ongoing cardiovascular outcome trials will clarify the potential therapeutic benefit and benefit–risk profile of anti-IL-6 mAbs.

Further research is needed to clarify downstream mechanisms of IL-6 inhibition relevant to CVD and to identify predictive biomarkers that may enrich therapeutic options for patients with greater potential for cardiovascular benefit. Prapiadou et al. reported that CXCL10 (CXC motif chemokine ligand 10) may be a downstream causal

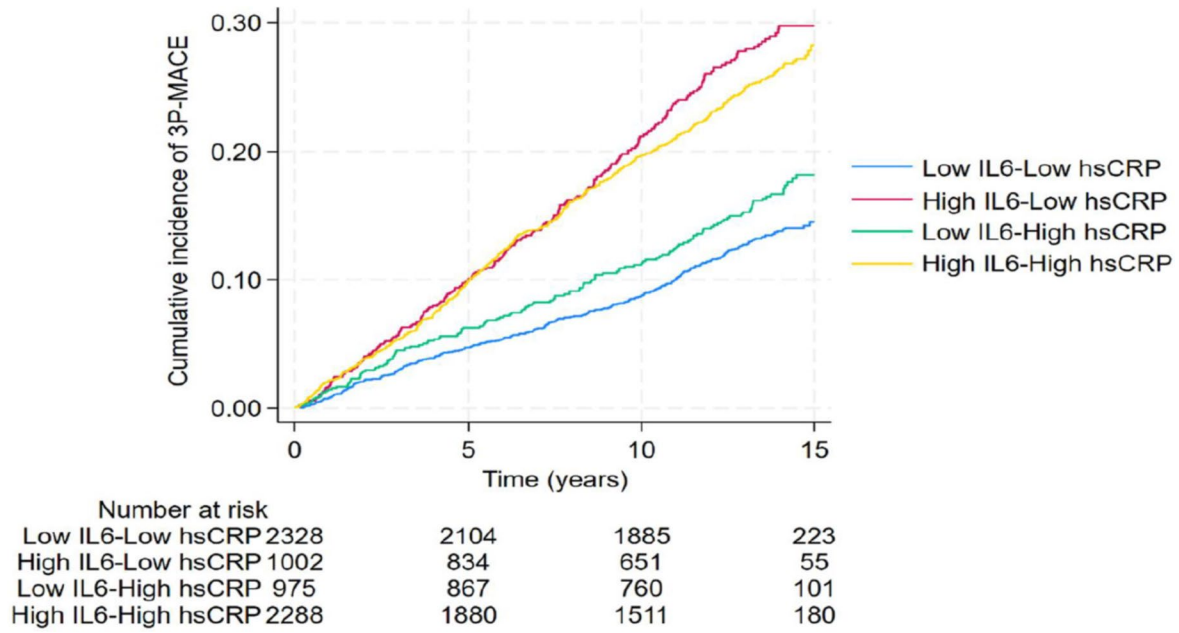

Fig. 3 Patients with high IL-6 experience higher risk of cardiovascular events, irrespective of hs-CRP levels

mediator for IL-6 signaling on ASCVD [96]. Clonal hematopoiesis of indeterminate potential (CHIP), the presence of clonally expanded acquired leukemogenic mutations detectable by sequencing peripheral leukocytes, has been associated with greater MACE reduction with genetically proxied IL-6 pathway inhibition [97] and pharmacological inhibition with the anti-IL-1β mAb canakinumab [98]. Pericoronary fat attenuation index (pFAI), a CT-based measure of coronary inflammation, has been significantly associated with MACE and cardiovascular mortality beyond clinical risk stratification and coronary plaque burden [99]. While ongoing cardiovascular outcome trials rely primarily on hs-CRP, future trials may incorporate IL-6, CHIP, or pFAI as additional or alternative predictive biomarkers to enrich for patients more likely to benefit from targeted anti-inflammatory therapies.

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Declarations

Conflict of Interest NNM has served as a consultant for receiving and received grants/other payments from AbbVie, Celgene, Janssen Pharmaceuticals, Novartis, AMGEN, Astra Zeneca, Abcentra, Tourmaline, Bristol Meyers Squibb, Sun Pharmaceuticals and Celgene. EdG is an employee of Tourmaline Bio, Inc. MDS is supported by institutional grants from Amgen, Arrowhead, Boehringer Ingelheim, 89Bio, Esperion, Novartis, Ionis, Merck, New Amsterdam, and Cleerly. MDS has participated in Scientific Advisory Boards with Amgen, Agepha, Ionis, Novartis, New Amsterdam, and Merck. MDS has also served as a consultant for Ionis, Novartis, Regeneron, Aidoc, Shanghai Pharma Biotherapeutics, Kaneka, Novo Nordisk, Arrowhead, and Tourmaline.

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