# hsCRP as a biomarker in ASCVD
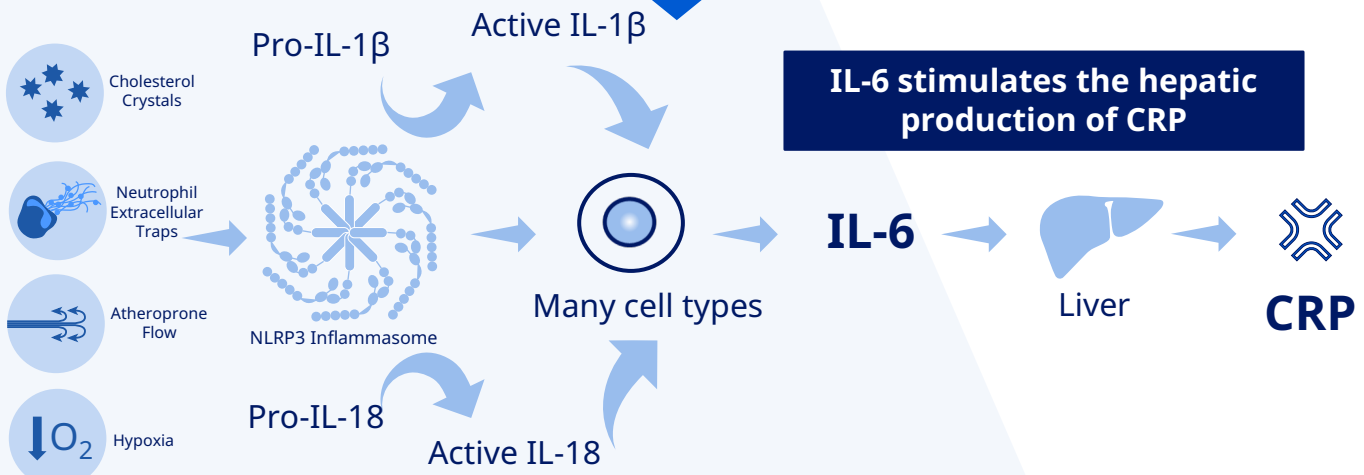
## What is systemic inflammation?

**Systemic inflammation** refers to a sustained activation of the immune system, including release of proinflammatory cytokines such as IL-6

This activation has been suggested to play a key pathophysiological role in several CVDs such as ASCVD (IHD/stroke/PAD), AMI and HF[1,2]

## What is the link between IL-6 and CRP?[3,4]

Cholesterol Crystals

Neutrophil Extracellular Traps

Atheroprone Flow

↓O$_2$ Hypoxia

NLRP3 Inflammasome

Pro-IL-1β → Active IL-1β

Pro-IL-18 → Active IL-18

Many cell types → **IL-6** → Liver → **CRP**

**IL-6 stimulates the hepatic production of CRP**

CRP is an acute phase protein* produced by the liver in response to circulating cytokines such as IL-6, IL-1 and TNF during tissue injury, inflammation or infection[3,5]

## What do CRP and hsCRP levels indicate?

**hsCRP assay**

← – – Appropriate measuring range – – →

Can measure trace amounts of CRP **(1–10 mg/L)** in the blood during a CV risk assessment[6]

| Low CV risk | Moderate CV risk | High CV risk | | | |

**CRP (mg/L)**: 1    3    5    10  //  20    500

Conventional CRP measurement **(>10 mg/L)** is used to find or monitor conditions that cause inflammation (e.g., sepsis, IBD, rheumatoid arthritis)[6–9]

Acute phase reaction due to infections or non-infectious inflammatory conditions

← – – Appropriate measuring range – – →

**Conventional CRP assay**

*Refers to class of proteins whose plasma boncentration increase or decrease in response to inflammation

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# What is the evidence supporting hsCRP as a predictor of CV risk?

**Residual inflammatory risk (RIR)** is defined as **hsCRP levels ≥2 mg/L**, which has been observed in up to 66% of patients with ASCVD in RWE studies[10–14]

- In a combined analysis of the PROMINENT, REDUCE-IT and STRENGTH trials in **statin-treated patients**, RIR was associated with an **increased risk of CV events**, regardless of LDL-C levels[15]
- Similar results were observed in **statin-intolerant patients** from the CLEAR-Outcomes trial[16]

In a CANTOS* sub-study in patients who had a **prior MI and received statin therapy**, achieving **on treatment hsCRP levels <2 mg/L** with the anti-inflammatory IL-1β inhibitor canakinumab was associated with **improved CV outcomes**[17]

# What are the guideline recommendations for hsCRP?

| | |
|---|---|
| **ACC/ AHA**[18,19] | • Measurement of hsCRP is not stipulated in primary prevention<br>• However, if measured, **knowledge of risk-enhancing factors (e.g., hsCRP ≥2.0 mg/L)** can be **particularly useful** in intermediate-risk patients (ASCVD risk of 7.5% to ≤20%) to **determine whether statin treatment is appropriate**) |
| **ESC**[20] | • The routine **collection of urinary or circulating biomarkers** is **not recommended** in primary prevention<br>• New studies confirm that **CRP has limited additional value for risk prediction**<br>• **Cardiac biomarkers are promising** but further work is needed |
| **SMART Risk Score**[21–23] | • The **ESC-endorsed SMART risk score** includes **hsCRP** as a **risk predictor for recurrent CV events** (MI, stroke or CV death) in patients with a history of CV   [Click here to access] |

# What factors should be considered when interpreting hsCRP in the clinic?

hsCRP is generally a reliable predictor of CV risk, but should be interpreted in the context of the patient

**Women have slightly higher hsCRP levels than men,** in study populations with and without ASCVD[24–26]

**Black/African American** patients as well as **Hispanic** and **South Asian** patients have **slightly higher hsCRP** levels than white patients[24,27,28]

*Patients had a history of MI and hsCRP levels ≥2 mg/L at baseline

**References;** 1. Lawler PR et al. *Eur Heart J* 2021;42:113–131; 2. Hansson GK. *N Eng J Med* 2005;352:1685–1695; 3. Ridker PM et al. *Circulation* 2020;141:787–789; 4. Ridker PM. *Circ Res.* 2016;118:145–156; 5. Clyne B et al. *J Emerg Med* 1999;17:1019–1025; 6. FDA. Guidance Document. Available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/review-criteria-assessment-c-reactive-protein-crp-high-sensitivity-c-reactive-protein-HsCRP-and (accessed October 2023); 7. Emery P et al. *Rehumatol Int* 2007;27:793–806; 8. Sproston SR, Ashworth JJ. *Front Immunol* 2018;9:754; 9. University of Rochester Medical Center. Health Encyclopedia: C-Reactive Protein (Blood). Available at: https://www.urmc.rochester.edu/encyclopedia/content.aspx?contenttypeid=167&contentid=c_reactive_protein_serum (accessed December 2023); 10. Pagidipati NJ et al. *Am Heart J* 2018;204:151–155; 11. Carrero JJ et al. *J Am Heart Assoc* 2019;8:e012638; 12. Peikert A et al. *Clin Res Cardiol* 2020;109:315–323; 13 Klingenberg R et al. *Atherosclerosis* 2021;320:31–37; 14. Ahn J-H et al. *JACC Asia* 2022;2:323–337; 15. Ridker PM et al. *Lancet* 2023;401:1293–1301; 16. Ridker PM et al. *Circulation* 2024;149:28–35. 17. Ridker PM et al. *Lancet* 2018;391:319–328; 18. Arnett DK et al. *Circulation* 2019;14011:e596–646; 19. Grundy SM et al. *Circulation* 2019;139:e1082–1143; 20. Visseren FLJ et al. *Eur Heart J* 2021;42:3227–3337; 21. ESC. The SMART Risk Score. Available at: https://www.escardio.org/Education/ESC-Prevention-of-CVD-Programme/Risk-assessment/SMART-Risk-Score (accessed October 2023); 22. Dorresteijn JA et al. *Heart* 2013;99:866–872; 23. U-prevent. Available at: https://uprevent.com/calculators/smartScore (accessed October 2023); 24. Glynn RJ et al. Clin Chem 2009;55:305–312; 25. Sander K et al. Stroke 2007;38:2881–2886; 26. Gijsberts CM et al. Atherosclerosis 2015;241:234–240; 27. Shah T et al. Circ Cardiovasc Genet 2010;3:436–444; 28 Fonseca FA et al. Clinics 2016;71:235–242

ACC, American College of Cardiology; ASCVD, atherosclerotic cardiovascular disease; AHA, American Heart Association; CKD, chronic kidney disease; CRP, C-reactiveA protein;CV, cardiovascular; CVD, cardiovascular disease; ESC, European Society of Cardiology; hsCRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; RIR, residual inflammatory risk; RWE, real-world evidence

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