Utilization of High-Sensitivity C-Reactive Protein Testing in Primary and Secondary ASCVD Prevention

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BACKGROUND

- Inflammation is increasingly recognized as a critical driver of cardiovascular disease (CVD).[1-4]
- The **high-sensitivity C-reactive protein (hs-CRP) assay** is an inexpensive test standardized over 20 years ago that measures small concentrations of CRP, a protein synthesized in response to inflammation.[1-4]
- Hs-CRP's sensitivity is important to accurately quantify levels of CRP associated with the low-grade chronic inflammation of CVD, providing insight into inflammatory risk and supporting therapeutic decision-making to prevent major adverse cardiovascular events (MACE).[5-7]
- In studies of large contemporary patient populations, hs-CRP consistently outperformed LDL-C in the prediction of incident MACE.[8-11]

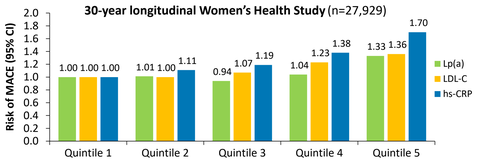


Figure 1. Risk of MACE in US women by measurements' quintiles. Women in the highest quintile of hs-CRP had a 70% increased MACE risk, while women in the highest quintile of LDL-C had a 36% increased risk.[8] MACE included: heart attack, stroke, coronary revascularization, or death from cardiovascular causes.

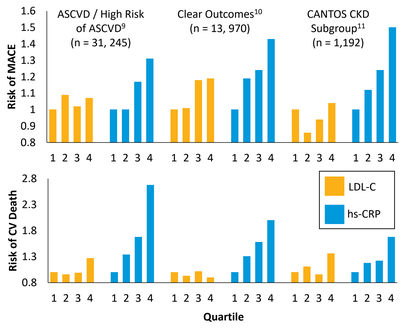


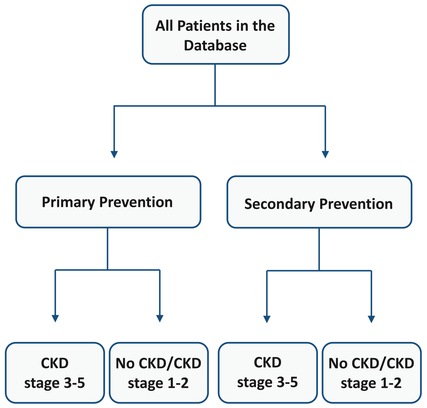
Figure 2. Risk of MACE and CV Death in High-Risk ASCVD, Chronic Kidney Disease (CKD) patients. Analyses of multiple clinical trial populations demonstrated higher risk for MACE and CV death (shown as hazard ratios) for individuals with elevated hs-CRP.[9-11] MACE included myocardial infarction, stroke, coronary revascularization, and cardiovascular (CV) death.

- Hs-CRP has been validated as a cardiovascular risk factor in over 100 clinical studies across diverse populations[12] and incorporated into cardiovascular guidelines in North America, Europe and Japan.[13-16] Yet, the characterization of hs-CRP's use has been limited.

Objective: To characterize the use of hs-CRP in atherosclerotic CVD (ASCVD) primary and secondary prevention settings in the United States (US).

METHODS

- A **retrospective cohort study using real-world evidence** was conducted using US data collected between 1 Jan 2016 and 8 Nov 2023 from the EVERSANA Electronic Health Records Integrated Database.
- Patients who received hs-CRP testing were identified with LOINC codes and known units of mg/L (or able to be unit converted). In the case of multiple hs-CRP measurements, the first eligible one was designated as index.
- **Two analyses were completed:** one in the high-risk primary prevention setting and one in the secondary prevention setting. The patients in each cohort did not overlap.
- The **primary prevention cohort** was defined as patients meeting all these criteria:
  - age 50 years or older
  - diabetes mellitus (DM) OR at least two risk factors (RF) at the time of hs-CRP: hypertension (HTN), hyperlipidemia (HLD) or tobacco use, after 50 years of age
  - no ASCVD anytime before or within 90 days after hs-CRP
- The **secondary prevention cohort** was defined as patients with any ICD-10 code consistent with ASCVD anytime before or within 90 days after hs-CRP. The 90-day time period was established to increase specificity by capturing patients with ASCVD but not yet confirmed due to a diagnosis lag, and/or patients with incomplete data.
- Sub-cohorts of CKD stage 3-5 patients were identified in both prevention settings.
- Sensitivity analyses excluded patients with ICD-10 codes of inflammation, infection and/or malignancy ±180 days of hs-CRP test and/or with hs-CRP values ≥20 mg/L. The 20 mg/L threshold was selected to exclude patients with elevated values resulting from an acute illness, or with levels above those observed clinically for risk stratification.



CKD recorded before or ≤90 days after hs-CRP value

RESULTS

High-Risk Primary Prevention Cohort

Table 1. Patients with hs-CRP testing in the primary prevention cohort.

Patient Populations	Total (n)	CKD Stage 3-5 (n)
All high-risk primary prevention patients	6,500,218	555,257
- Any hs-CRP recorded	20,925 (0.3%)*	2,323 (0.4%)
- Above and no concomitant inflammation, infection and/or malignancy	9,730 (0.1%)	700 (0.1%)
- Above and hs-CRP ≤ 20 mg/L	9,285 (0.1%)	651 (0.1%)

- *In this population (n=20,925), hs-CRP ≥2 mg/L in 61.1%, and ≥3 mg/L in 49.2%.

Secondary Prevention Cohort

Table 2. Patients with hs-CRP testing in the secondary prevention cohort.

Patient Populations	Total (n)	CKD Stage 3-5 (n)
All secondary prevention patients	3,746,209	352,304
- Any hs-CRP recorded	25,550 (0.7%)*	5,931 (1.7%)
- Above and no concomitant inflammation, infection and/or malignancy	7,668 (0.2%)	940 (0.3%)
- Above and hs-CRP ≤ 20 mg/L	7,264 (0.2%)	851 (0.2%)

- *In this population (n=25,550), hs-CRP ≥2 mg/L in 62.3%, and ≥3 mg/L in 52.7%.

Characteristics of Patients with Hs-CRP Values

Table 3. Patient demographics for the primary and secondary prevention cohorts.

Demographics	Primary Prevention (N=20,925)	Secondary Prevention (N=25,550)
Age (Median [IQR])	63.5 [57.5; 69.5]	63.7 [54.7; 70.6]
Sex (%)	F: 55.6; M: 44.4	F: 48.2; M: 51.8
Region (%)	MW: 2.9; NE: 28.3; S: 33.7; W: 32.4; U: 2.7	MW: 3.0; NE: 23.3; S: 32.9; W: 38.8; U: 2.0
Race (%)	Wh: 64.8; B: 5.2; A: 3.7; Other or N/A: 26.3	Wh: 61.3; B: 5.2; A: 4.2; Other or N/A: 29.3
Ethnicity (%)	H: 6.9; Non-H: 46.2; N/A: 46.9	H: 7.3; Non-H: 46.1; N/A: 46.6

A, Asian; B, Black; F, female; H, Hispanic; IQR, inter-quartile range; M, male; MW, Mid-West; NE, North-East; Non-H, Non-Hispanic; S, South; U, Unknown; W, West; Wh, White.

Table 4. Clinical history of patients within the primary and secondary prevention cohorts.

Clinical History	Primary Prevention (N=20,925)	Secondary Prevention (N=25,550)
Coronary Artery Disease *(%)*	-	67.0
Cerebrovascular Disease *(%)*	-	27.8
Peripheral Disease *(%)*	-	37.6
Diabetes *(%)*	43.7	81.4
Hyperlipidemia *(%)*	82.2	37.3
Hypertension *(%)*	74.2	73.7
Obesity *(%)*	73.8	20.1
Tobacco Use *(%)*	28.5	6.1

RESULTS (CONT'D)

Percent of Patients with ≥1 hs-CRP test, by Year, by Cohort (2016-2023)

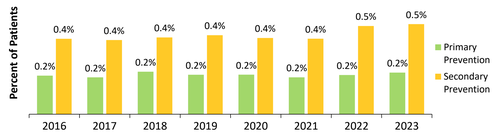


Figure 3. Yearly percentage of patients in each cohort with at least one hs-CRP test. Overall, when assessing hs-CRP utilization between 2016 to 2023 in the primary and secondary prevention cohorts, no meaningful changes were observed from year-to-year. Percent of hs-CRP tests by year were calculated as the number of patients in the primary prevention (green) or secondary prevention (orange) cohorts who had ≥1 hs-CRP test during the calendar year, divided by the total number of patients in the respective cohorts during the calendar year.

CONCLUSIONS

- Despite robust data supporting the association of hs-CRP with cardiovascular risk as well as inclusion of the test in cardiology guidelines, the use of hs-CRP testing in the US in primary and secondary prevention settings was very low.
- Among patients who were tested, the prevalence of systemic inflammatory risk, defined as hs-CRP ≥2 mg/L,[13] was high.
- Enhancing education on the clinical benefits of hs-CRP testing may facilitate tailoring treatment intensity and modality to better align with ASCVD risk profiles.
- It will be important to also understand the potential challenges regarding access to hs-CRP across different laboratories and regions, including laboratory charges and insurance coverage for this assay.

DISCLOSURES

- EdG, YC, and JW are employees of Tourmaline Bio. CWP, JM, VM, JCD, and SG are employees of Atropos Health, contracted by Tourmaline Bio. MDS is supported by institutional grants from Amgen, Arrowhead, Boehringer Ingelheim, 89Bio, Esperion, Novartis, Ionis, Merck, New Amsterdam, and Cleerly; has participated in scientific advisory boards with Amgen, Agepha, Ionis, Novartis, New Amsterdam, and Merck; and has served as a consultant for Ionis, Novartis, Regeneron, Aidoc, Shanghai Pharma Biotherapeutics, Kaneka, Novo Nordisk, Arrowhead, and Tourmaline.

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MORE INFORMATION

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REFERENCES:
1. Ridker P., *JACC* (2018). 2. Rifai et al., *Clin Chem* (1999). 3. Roberts et al., *Clin Chem* (2000). 4. Roberts et al., *Clin Chem* (2001). 5. Conrad et al., *Lancet* (2022). 6. Cai et al., *JAMA Cardiol.* (2018). 7. Kaptoge et al., *Eur. Heart J.* (2014). 8. Ridker et al., *N. Eng. J. Med.* (2024). 9. Ridker et al., *Lancet* (2023). 10. Ridker et al., *Circulation* (2024). 11. Ridker et al., *Eur Heart J.* (2022). 12. Kaptoge et al., *Lancet* (2010). 13. Arnett et al., *Circulation* (2019). 14. Vrints et al., *Eur. Heart J.* (2024). 15. Pearson et al., *Can. J. Cardiol.* (2021). 16. Okamura et al., *J. Atheroscler. Thromb.* (2024).