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The prognostic value of interleukin 6 in multiple chronic diseases and all-cause death: The Multi-Ethnic Study of Atherosclerosis (MESA)

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HIGHLIGHTS

- We evaluated the prognostic value of IL6 in a contemporary cohort.
- IL6 levels were strongly associated with ASCVD events, HF and mortality, particularly among statins users.
- In statin users, associations remained strong adjusting for risk factors and hsCRP.
- IL6 did not improve CHD prediction beyond traditional risk factors.
- IL6 improved the prediction of incident HF, stroke, and all-cause death among statin users.

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ABSTRACT

Background and aims: We aimed to evaluate the associations and prognostic value of interleukin-6 (IL6) for the prediction of atherosclerotic cardiovascular disease (ASCVD) events, heart failure (HF), and other chronic diseases in a large, multi-ethnic, contemporary population.

Methods: We included 6617 participants from the Multi-Ethnic Study of Atherosclerosis (5640 non-users, 977 users of statins at baseline). Main outcomes were hard ASCVD events and HF; secondary outcomes included all-cause death, atrial fibrillation, venous thromboembolism and cancer.

Results: Median follow-up was 13.2 years. Strong associations were observed in Cox regression analyses between higher IL6 levels and ASCVD events, HF, and mortality, particularly among statins users. In the latter, associations remained strong after adjusting for traditional risk factors and other inflammation biomarkers (e.g., risk

Abbreviations: ACC/AHA, American College of Cardiology/American Heart Association; ACEIs, angiotensin-converting-enzyme inhibitor(s); AF, atrial fibrillation; ARBs, angiotensin II receptor blocker(s); ASCVD, atherosclerotic cardiovascular disease events; CANTOS, Canakinumab Anti-inflammatory Thrombosis Outcomes Study; CHD, coronary heart disease; ESC, European Society of Cardiology; HF, heart failure; ICD-9, International Classification of Diseases, Ninth Revision; MESA, Multi-Ethnic Study of Atherosclerosis; NSAIDs, non-steroidal anti-inflammatory drug(s); VTE, venous thromboembolism

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factor, hsCRP-adjusted hazard ratio for incident HF comparing 3rd *vs.* 1st IL6 tertiles: 3.55, 95% CI 1.23–10.27). Although IL6 did not improve CHD prediction beyond traditional risk factors, among statin users it improved the prediction of stroke (improvement in the C statistic +0.018), incident HF (+0.028, the largest C statistic increase across all study outcomes), and all-cause death (+0.017).

Conclusions: IL6 is strongly and independently associated with ASCVD events, HF, and all-cause mortality, particularly among statin users. Although the prognostic value of IL6 is limited for the prediction of CHD events, it may have a role for the prediction of stroke, HF and all-cause death in asymptomatic statin users. Larger studies are needed to replicate these findings.

1. Introduction

Chronic inflammation and its biomarkers may have roles in the genesis [1–8], prediction [9], and management [10,11] of atherosclerotic cardiovascular disease (ASCVD) and other chronic diseases. The recent Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS) [10,11] has renewed attention on the potential role that measures of inflammation might have for identifying responders to the ASCVD and cancer-reducing properties of novel (anti-inflammatory or biologic) therapies.

While initial interest focused on high sensitivity C-reactive protein (hsCRP), which is currently the most widely used biomarker of subclinical inflammation, its prognostic value has been shown to be limited for the prediction of ASCVD events [9,12,13]. Whether this poor performance is the consequence of an actual lack of additional prognostic information of the inflammatory pathway, or of limitations of hsCRP as a measure of inflammation [12,14,15], is currently unknown.

Interleukin 6 (IL6) is a more upstream mediator of the inflammatory pathway [16,17] (closer, for example, to interleukin 1 beta [IL1B], the therapeutic target in CANTOS [10,11]). IL6 is associated with the acute immune response [18] and chronic inflammation [19]. However, as of now, the pathophysiological role of IL6 across the spectrum of common chronic cardiovascular diseases is less understood. Also, the prognostic value of IL6 for the prediction of ASCVD events is poorly understood, and the American College of Cardiology/American Heart Association (ACC/AHA) and the European Society of Cardiology (ESC) risk assessment guidelines [20,21] do not provide any recommendation for its potential clinical use.

The purpose of our study was to fill these evidence gaps, by characterizing the associations and prognostic value of IL6 for the prediction of ASCVD events in a large, multi-ethnic population, including non-users and users of statins (which are known to affect levels of IL6 [22]) who were followed for more than 13 years. In addition, we also evaluated the associations and predictive value of IL6 for incident heart failure (HF), for which hsCRP has shown promising results [13]. Other secondary outcomes evaluated were atrial fibrillation (AF), venous thromboembolism (VTE), cancer, and death, in all of which chronic inflammation is considered to play a relevant pathogenic role [5–7].

2. Materials and methods

2.1. Study design and study population

The Multi-Ethnic Study of Atherosclerosis (MESA) is a NHLBI-funded, community-based, multi-center cohort study that recruited 6814 apparently healthy, cardiovascular asymptomatic adults from 4 racial/ethnic groups (Non-Hispanic Whites, African Americans, Hispanics, and Chinese Americans) living in the US [23]. Participants were recruited between 2000 and 2002 from 6 urban areas (New York [NY], Baltimore [MD], Chicago [IL], Los Angeles [CA], Twin Cities [MI] and Winston-Salem [NC]), and since then have been followed for events at least yearly for up to 15 years. Details of the study methods have been published by Bild and colleagues [23], and further information can be found on the study website (https://www.mesa-nhlbi.org).

For the present analysis, we excluded participants in whom IL6 levels had not been measured at baseline (MESA Visit 1), as well as those with missing follow-up information (Supplemental Fig. 1). Two subgroups were defined based on the absence/presence of statin use at baseline, as statins are known to affect levels of IL6 [22].

Additionally, a sensitivity analysis subpopulation was defined, comprising individuals free of fever and acute infections at baseline, and not taking medications known to affect levels of inflammatory biomarkers, including statins, other lipid-lowering agents, aspirin, medications for diabetes, non-steroidal anti-inflammatory drugs (NSAIDs), cyclo-oxygenase-2 (COX-2) inhibitors, steroids, betablockers, angiotensin-converting-enzyme inhibitors (ACEIs), and angiotensin II receptor blockers (ARBs) [22,24].

2.2. Research ethics

The MESA was approved by the institutional ethics review committees of each of the 6 study sites, and conforms to the ethical guidelines of the 1975 Declaration of Helsinki. In addition, the protocol of the present analysis was approved by the local ethics in research committee at the Bellvitge University Hospital, Barcelona (Spain). All participants provided written informed consent before study entry.

2.3. Measurement of baseline IL6 levels

Levels of IL6 were measured in MESA Visit 1 from blood samples, using an ultrasensitive ELISA (Quantikine HS Human IL6 Immunoassay; R&D Systems, Minneapolis, MN, USA) and quantified in pg/mL. The analytical coefficient of variation was 6.3% (detection level 0.04 pg/mL).

2.4. Event ascertainment

Full details on the event ascertainment methods used in MESA are available online (https://www.mesa-nhlbi.org) and have been described elsewhere. All events were adjudicated by a committee of experts. The primary outcomes were hard coronary heart disease (CHD) events (defined as the composite of non-fatal myocardial infarction, death from CHD, or resuscitated cardiac arrest), stroke, hard ASCVD events (defined as the composite of hard CHD events, stroke, other atherosclerotic death, or other cardiovascular death), and incident HF. In MESA, HF was defined by the simultaneous presence of the following items: symptoms suggestive of HF (e.g., shortness of breath or edema), a physician diagnosis of HF, and use of medical treatments for HF.

In secondary analyses, we also evaluated the following clinically relevant outcomes: AF, VTE, cancer, and all-cause mortality. AF was either self-reported by study participants or identified via hospital record review based on the presence of specific International Classification of Diseases, 9th Revision (ICD-9) diagnosis codes. VTE and cancer were identified exclusively based on identification of specific ICD-9 codes from hospitalization data (Supplemental Table 1). Mortality was ascertained using information from the National Death Index, as well as contacting the participant's next of kin.

2.4.1. Assessment of relevant covariates

MESA participants provided detailed information at the baseline