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Correspondence

Use of high-sensitivity CRP to predict first cardiovascular events

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The JUPITER trial¹ is a randomised comparison of rosuvastatin with placebo in 15 000 patients (men aged 55 years or older and women aged 65 years or older) who have normal LDL cholesterol concentrations and mildly raised high-sensitivity C-reactive protein (hsCRP) concentrations, the aim being to investigate whether statin therapy prevents first-ever cardiovascular events.

A prescreening programme in our eight hub sites enrolled 2261 patients and measured a combination of hsCRP and LDL cholesterol on two separate occasions, ultimately resulting in 0·8% of randomisations, most patients having not met the criterion of raised hsCRP on repeated testing.

A second group of 789 patients who had hsCRP and LDL concentrations measured just once resulted in 5·4% of randomisations, with non-eligibility apparently evenly split because of hsCRP and LDL cholesterol. These findings stood in stark contrast to the US experience in unselected patients, for which a 29·3% randomisation rate was reported at the German Investigator Meeting.

Raised hsCRP has been claimed to be stable over long periods of time—ie, more than a decade². This statement contrasts with our clinical observation, which indicates that intraindividual variation within a timeframe of 2–23 weeks occurs in the elderly age-group investigated. A large scatter of intraindividual hsCRP especially in older people was also reported by Maat and colleagues,³ who therefore suggested at least three measurements. By contrast, to be randomised for JUPITER, one raised hsCRP measurement at visit 1 suffices.

In a review, Kushner and colleagues⁴ suggested “multiple possible underlying causes of minor CRP elevation, many sharing the underlying characteristic of a degree of tissue injury or stress”. For example, minor CRP elevations have been associated with age, osteoarthritis, periodontitis, denture-related oral mucosal lesions, second-hand smoke exposure, and air pollution—all clinically relevant for the age-group of patients randomised for JUPITER. Considering the half life of CRP of about 19 h, it is conceivable that fluctuating levels of hsCRP in the elderly just reflect minor degrees of tissue stress at various time points.

Although our clinical observation could be the result of regression to the mean,⁵ it casts doubt on the value of hsCRP to predict first-time cardiovascular events.

The sponsor, the international principal investigator, the German Institute for Drugs and Medicinal Products (BfARM), the European Agency for the Evaluation of Medicinal Products, and the US Food and Drug Administration have been informed of our findings.

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