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Baseline and long-term fibrinogen levels and risk of sudden cardiac death: A new prospective study and meta-analysis

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ABSTRACT

Background: Inflammatory markers such as C-reactive protein (CRP) and interleukin-6 have been linked with an increased risk of sudden cardiac death (SCD), but the relationship between fibrinogen and SCD is uncertain. We aimed to assess the association between fibrinogen and SCD.
Methods: Plasma fibrinogen was measured at baseline in a prospective cohort of 1773 men aged 42–61 years free of heart failure or cardiac arrhythmias, that recorded 131 SCDs during 22 years follow-up. Correction for within-person fibrinogen variability was made using data from repeat measurements taken several years apart.
Results: Fibrinogen was strongly correlated with CRP, weakly correlated with several cardiovascular risk markers, and was log-linearly associated with SCD risk. In analyses adjusted for conventional risk factors, the hazard ratio (HR) (95% CIs) for SCD per 1 standard deviation (SD) higher baseline $\log_e$ fibrinogen was 1.32 (1.11–1.57). The results remained consistent on further adjustment for alcohol consumption, resting heart rate, and circulating lipids 1.30 (1.09–1.56). The corresponding HRs were 1.80 (1.25–2.58) and 1.74 (1.20–2.52) after correction for within-person variability. HRs remained unchanged on further adjustment for CRP and accounting for incident coronary events. In a meta-analysis of three cohort studies, the fully-adjusted relative risks for SCD per 1 SD higher baseline and long-term fibrinogen levels were 1.42 (1.25–1.61) and 2.07 (1.59–2.69) respectively. The associations were similar for non-SCDs in both cohort analysis and the meta-analysis. Addition of plasma fibrinogen to a SCD risk prediction model containing established risk factors did not significantly improve risk discrimination, but improved the net reclassification.
Conclusions: Available data suggest fibrinogen is positively, log-linearly, and independently associated with risk of SCD. Further research is needed to assess the potential relevance of plasma fibrinogen concentrations in SCD prevention.

1. Introduction

Sudden cardiac death (SCD) is a common manifestation of coronary heart disease (CHD) in the general population and is a global public health problem accounting for 15–20% of all deaths [1,2]. Over the past decades, there has been a progressive decline in CHD due to major advances in treatment and preventive measures; in contrast, SCD rates have declined to a lesser extent [3]. Though atherosclerotic cardiovascular disease (CVD) risk factors explain a large proportion of the risk for SCD [4,5] its pathogenesis is still not fully established. This emphasizes the need to better understand the epidemiology of SCD and evaluate the relevance of other potential risk factors.

Inflammation plays a central role in the development and progression of atherothrombosis [6]. Emerging evidence indicates that inflammation may also be linked to the risk of SCD. Cardiac rhythm disturbances (particularly ventricular arrhythmias) are considered to be the leading events behind SCDs, as a result of atherothrombotic occlusion of coronary arteries [7]; and inflammation has also been implicated in the pathogenesis of cardiac arrhythmias [8]. Systemic markers of inflammation such as C-reactive protein (CRP), albumin, and interleukin-6 (IL-6) have been demonstrated to

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be associated with SCD in the general population [9–12]. Fibrinogen, an inflammatory marker, a major coagulation protein in the blood, and an important determinant of blood viscosity and platelet aggregation [13,14], is a risk factor for vascular events [15] and has been demonstrated to be linked to cardiac arrhythmias [16]; however, its association with SCD is uncertain. A number of studies have reported on the association of fibrinogen with SCD in angina patients [17,18], but only two prospective studies have so far reported on the association between baseline plasma fibrinogen levels and SCD risk in apparently healthy participants and their results have been inconsistent. Whereas one study showed a positive association [11], the other study found no association [9], giving rise to uncertainty regarding the nature of the association. Out-of-hospital SCD is an unrecognized yet major contributor to SCDs, however, no study has at yet assessed the association of fibrinogen with out-of-hospital SCDs. Finally, the long-term relevance of fibrinogen to SCD is unknown. This is particularly important, given that fibrinogen has been shown to exhibit high within-person variability [19] as a result of measurement errors, fluctuations due to acute phase reactions, lifestyle changes, and chronic disease [20]. Given the established role of inflammation in the development of CHD, we hypothesized that elevated levels of plasma fibrinogen may be independently associated with an increased risk of SCD in the general population. Against this background, we aimed to evaluate in detail the nature and magnitude of the prospective association of fibrinogen with risk of SCD (in- and out-of-hospital SCDs) in a population-based cohort of 1773 apparently healthy men from eastern Finland. Repeat measurements of fibrinogen were performed 4 and 11 years after the baseline measurements in 959 participants to help quantify within-person variability in fibrinogen levels. To put our results into perspective, we also examined the association of fibrinogen with non-SCD. Finally, to contextualize the associations, we also performed a pooled analysis of the available prospective evidence on the associations.

2. Methods

2.1. Participants

The study population comprised of a representative sample of men living in the city of Kuopio and its surrounding rural communities in eastern Finland. Subjects were participants in the Kuopio Ischaemic Heart Disease (KIHD) risk factor study, a population-based prospective cohort study designed to investigate risk factors for CVD and related outcomes [21]. Of the 3433 randomly selected men who were potentially eligible, 2682 (78%) volunteered to participate in the study. Participants were 42–61 years of age during baseline examinations performed between March 1984 and December 1989. For the present analyses, men with a prevalent history of heart failure or cardiac arrhythmias were excluded leaving a final cohort of 1773 men with non-missing information on plasma fibrinogen, relevant covariates, and SCD outcomes. The Research Ethics Committee of the University of Eastern Finland approved the KIHD study, and each participant gave written informed consent.

2.2. Ascertainment of outcomes

In the KIHD study, participants are under continuous surveillance for the development of new CVD events, including incident cases and deaths [22]. There were no losses to follow-up and all SCDs that occurred from study enrolment through 2012 were included. The sources of information on SCD outcomes were based on a comprehensive review of all available hospital records, wards of health centres, informant interviews, health practitioner questionnaires, medico-legal reports, and death certificate registers. Deaths were coded according to ICD-9 codes or ICD-10 codes. The diagnostic classification of SCDs was based on symptoms, electrocardiographic findings, cardiac enzyme elevations, autopsy findings (80% of all cardiac deaths), and history of CHD together with the clinical history and findings from hospital and paramedic staff. A death was determined to be an SCD when it occurred within 1 h of the onset of an abrupt change in symptoms or within 24 h after the onset of symptoms; including non-witnessed cases when clinical and autopsy findings did not reveal a non-cardiac cause of sudden death or after successful resuscitation from ventricular tachycardia and/or ventricular fibrillation [23]. The witnessed subject was to have been seen alive and symptom free within 1 h before the event. Sudden cardiac deaths that occurred in out-of-hospital conditions were also defined as events that occurred in places that had been reported accurately in hospital documents [23]. Documents were cross-checked in detail by two physicians. Non-SCDs were also carefully documented using standardized criteria. Cardiac deaths that did not lead to death during the following 24 h of the onset of symptoms were considered as non-SCDs. The Independent Events Committee, masked to clinical data, performed classification of deaths.

2.3. Measurement of risk factors

Collection of blood specimens, data on socio-demographics, physical measurements, vascular risk factors, and the measurement of serum lipids and glucose have been described previously [24]. In addition to an overnight fast, participants were instructed to abstain from drinking alcohol for at least three days and from smoking for at least 12 h prior to assessment. Blood samples were taken between 08:00 and 10:00 h following rest in the supine position for 30 min. The serum samples were stored frozen at −80 °C for 0.2–2.5 years. Plasma fibrinogen concentrations were determined in fresh plasma samples with excess thrombin using the Coagulometer KC4 device (Heinrich Amelung GmbH, Lemgo, Germany). The coefficient of variation describing the day-to-day measurement of variability for fibrinogen assays was 5.5 percent. Repeat measurements of fibrinogen were performed 4 years and 11 years after baseline during a 22 year period in a random subset of participants. C-reactive protein (CRP) was measured with an immunometric assay (Immulite High Sensitivity C-Reactive Protein Assay; DPC, Los Angeles, CA, USA). History of diabetes was defined as having a clinical diagnosis of diabetes and regular treatment with diet, oral hypoglycaemic agents or insulin therapy, fasting plasma glucose $\geq$ 7.0 mmol/l, or according to self-reports. Standard resting 12-lead ECG was also recorded. The ECG criterion for left ventricular hypertrophy (LVH) was based on either the Sokolow–Lyon or Romhilt–Estes point score [25–28].

2.4. Statistical analyses

Prospective cohort analyses Values of skewed variables were log-transformed to achieve approximately symmetrical distributions. We performed descriptive analyses summarising the baseline characteristics of the participants. Cross-sectional associations of fibrinogen with various risk markers were assessed using calculated partial correlation coefficients (adjusted for age). All analyses were conducted using Cox proportional hazard models. The proportional hazards assumptions were tested as previously described and satisfied [29]. To quantify and correct for within-person variability in levels of fibrinogen, that is, the