International Journal of Cardiology xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Plasma cystathionine and risk of acute myocardial infarction among patients with coronary heart disease: Results from two independent cohorts☆

Indu Dhar [a,b,*], Gard F.T. Svingen [c], Eva R. Pedersen [c], Barbara DeRatt [d], Arve Ulvik [e], Elin Strand [a], Per M. Ueland [a,e], Kaare H. Bønaa [f], Jesse F. Gregory [d], Ottar K. Nygård [a,b,c]

[a] Department of Clinical Science, University of Bergen, Bergen, Norway
[b] KG Jebsen Centre for Diabetes Research, University of Bergen, Bergen, Norway
[c] Department of Heart Disease, Haukeland University Hospital, Bergen, Norway
[d] Food Science and Human Nutrition Department, University of Florida, Gainesville, FL
[e] Bevital AS, Bergen, Norway
[f] Department of Cancer Research and Molecular Medicine, Norwegian University of Science and Technology, Trondheim, Norway

ARTICLE INFO

Article history:
Received 25 September 2017
Received in revised form 6 April 2018
Accepted 18 April 2018
Available online xxxx

Keywords:
Biological markers
Coronary heart disease
Cystathionine
Glutathione

ABSTRACT

Background: Cystathionine is a thio-ether and a metabolite formed from homocysteine during transsulfuration. Elevated plasma cystathionine levels are reported in patients with cardiovascular disease; however prospective relationships with acute myocardial infarction (AMI) are unknown. We investigated associations between plasma cystathionine and AMI among patients with suspected and/or verified coronary heart disease (CHD).

Methods: Subjects from two independent cohort studies, the Western Norway Coronary Angiography Cohort (WECAC) (3033 patients with stable angina pectoris; 263 events within 4.8 years of median follow-up) and the Norwegian Vitamin Trial (NORVIT) (3670 patients with AMI; 683 events within 3.2 years of median follow-up) were included.

Results: In both cohorts, plasma cystathionine was associated with several traditional CHD risk factors ($P < 0.001$). Comparing the cystathionine quartile 4 to 1, age and gender adjusted hazard ratios (95% confidence intervals) for AMI were 2.08 (1.43–3.03) and 1.41 (1.12–1.76) in WECAC and NORVIT, respectively. Additional adjustment for traditional risk factors slightly attenuated the risk estimates, which were generally stronger in both cohorts among non-smokers, patients with higher age, and lower BMI or PLP status (P-interaction ≤ 0.04). Risk associations also tended to be stronger in patients not treated with B-vitamins. Additionally, in a subset of 80 WECAC patients, plasma cystathionine associated strongly negatively with glutathione, an important antioxidant and positively with lanthionine, a marker of H_2S production ($P < 0.001$).

Conclusions: Plasma cystathionine is associated with increased risk of AMI among patients with either suspected or verified coronary heart disease, and is possibly related to altered redox homeostasis.

1. Introduction

An increased risk of cardiovascular disease (CVD) has been associated with elevated plasma homocysteine (Hcy) levels [1]. However, supplementation with Hcy-lowering B-vitamin therapy did not reveal any beneficial effects on cardiovascular outcomes in secondary prevention trials [2,3]. The thioether containing amino acid cystathionine is produced from Hcy during the transsulfuration, catalyzed by 5′-pyridoxal phosphate-dependent (PLP) cystathionine β-synthase (CBS), a rate-limiting enzyme mainly present in liver, neural and cardiac tissues (Supplemental Fig. 1). Cystathionine is subsequently metabolized by another PLP-dependent enzyme cystathionine γ-lyase (CSE) to α-ketobutyrate and cysteine, the precursor of glutathione (GSH), the major intracellular antioxidant in the body [4,5]. Additionally, the gaseous transmitter hydrogen sulphide (H_2S) is formed through several non-canonical reactions, catalyzed by CBS and CSE and accompanied by synthesis of thioethers lanthionine and homolanthionine, which have been previously used as indirect markers of H_2S biogenesis [6]. The direction of homocysteine into the cystathionine pathway leads to the

☆ All listed authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

* Corresponding author at: Department of Clinical Science, University of Bergen, Laboratory Building, 9th floor, Haukeland University Hospital, Jonas Lies vei 87, Bergen N-5021, Norway.
E-mail address: Indu.Dhar@uib.no. (I. Dhar).

https://doi.org/10.1016/j.ijcard.2018.04.083

loss of methionine (Met), an essential amino acid required for protein synthesis and methylation reactions [5].

The synthesis of cystathionine catalyzed via CBS is regulated by the availability of Met [5,7], and modified by the changes in the redox status of the cell [8]. Notably, experimental evidence suggests that increased flux through CBS exacerbates outcome of stroke [9]. Others have linked genetically induced cystathioninemia to acute lethal myopathy and redox injury [10]. Interestingly, renal disease patients [11], and diabetic subjects with nephropathy [12] had elevated plasma cystathionine concentrations, which were strongly associated with plasma Hcy levels. In addition, elevated plasma cystathionine levels were found in patients with vascular disease [13], and coronary artery disease (CAD) [1]; and increased levels have been suggested to be associated with impaired vascular function in healthy humans subjected to oral Met loading [14].

Collectively, these studies strongly suggest that plasma cystathionine may be associated with atherosclerotic CVD; however, the prospective relation between plasma cystathionine and acute myocardial infarction (AMI) risk in larger populations with long-time follow-up is unknown. We investigated the associations between plasma cystathionine and the risk of subsequent AMI, using data from two large independent cohort studies consisting of patients with either suspected or verified coronary heart disease (CHD).

2. Methods

2.1. Study cohorts

The present study consisted of patients from two large independent cohorts: the Western Norway Coronary Angiography Cohort (WECAC) [15] and the Norwegian Vitamin Trial (NORVIT) [3] and both have been described previously. In brief, WECAC comprised 4164 adult participants who were undergoing elective coronary angiography for suspected stable angina pectoris (SAP) between 2000 and 2004. Of these, 2573 (61.8%) were enrolled in the Western Norway B-vitamin Intervention Trial (WENBIT), a secondary prevention study to investigate the effect of Hcy-lowering B-vitamins on all-cause mortality and cardiovascular events [2]. NORVIT included 3749 patients who were hospitalized with AMI during the time period from 1998 to 2002, and underwent identical study treatment as the patients in WENBIT. Subjects with missing baseline data on plasma cystathionine were excluded, leaving a total of 3033 and 3670 patients in the WECAC and NORVIT eligible for the final analyses, respectively (Fig. 1). In addition, among WECAC patients, 2623 had provided urine samples at baseline.

The study protocol was in accordance with the Declaration of Helsinki, and was approved by the regional ethics committee and the Norwegian Data Inspectorate. Written informed consent was provided by all patients.

2.2. Baseline data

Information about patient's lifestyle and medical history were obtained from self-administered questionnaires, and was validated against hospital records when available [3,15]. In both cohorts, smoking status was defined according to self-reports and plasma cotinine (≥85 nmol/L) at baseline [15]. In the WECAC, diabetes was defined by fasting plasma glucose levels >7 mmol/L or non-fasting glucose >11.1 mmol/L or glycated hemoglobin >6.5% according to the American Diabetes Association guidelines [16]. Left ventricular ejection fraction (LVEF) was determined by ventriculography or echocardiography performed during cardiac catheterization. The angiographic extent of CAD was scored as 0–3 according to the number of significantly stenotic coronary arteries. Among NORVIT patients, we did not have information on plasma glucose or glycated hemoglobin, hence, diabetes was defined according to pre-existing diagnoses. The parameters LVEF, and extent of CAD were not available for the NORVIT study.

2.3. Follow-up and study end points

WECAC patients were followed-up from enrollment throughout the year 2006, whereas patients included in the NORVIT were followed until suffering from first AMI or through December 31, 2004. Information on study outcomes was collected from the Cardiovascular Disease in Norway project (CVDNOR; https://cvdnor.b.uib.no/) [17], recording all patients being discharged with a CVD diagnosis from any Norwegian hospitals during 1994–2009. The primary endpoint was total AMI, including both fatal and non-fatal events, and was classified according to the International Statistical Classification of Disease, Tenth Revision system (ICD-10; codes I21-I22).

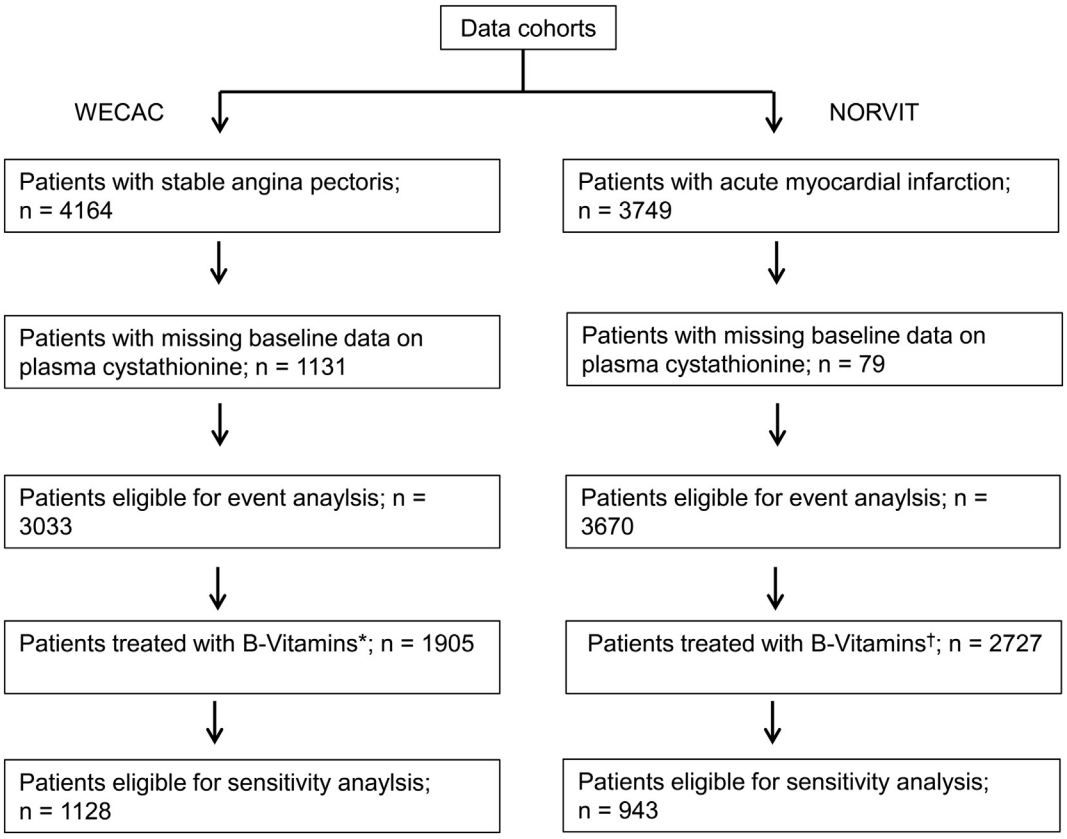

Fig. 1. Flow chat. Flow-diagram showing patient selection from the two study cohorts. NORVIT indicates the Norwegian Vitamin Trial; WECAC, Western Norway Coronary Angiography Cohort. *Excluding patients not randomized to Western Norway B-vitamin Intervention Trial (WENBIT) and group in WENBIT given placebo. †Excluding group given placebo.

Please cite this article as: I. Dhar, et al., Plasma cystathionine and risk of acute myocardial infarction among patients with coronary heart disease: Results from two independ..., Int J Cardiol (2017), https://doi.org/10.1016/j.ijcard.2018.04.083