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Homocysteine has been regarded as a modest independent risk factor for atherosclerotic vascular disease.\(^1\)\(^,\)\(^2\) Although folic acid can reduce homocysteine concentrations substantially, the value of folic acid intervention in primary and secondary prevention in terms of hard clinical end points is still uncertain. Many studies addressing this question are still underway. The results on folic acid intervention in patients undergoing percutaneous coronary intervention are still uncertain. \(^3\) Recently we have reported the results of an open label intervention study with folic acid in a population with stable coronary artery disease while taking stable statin treatment.\(^4\) Within a follow up of 24 (10) months folic acid did not appear to attenuate the risk for recurrent events. Yet longer follow up observations are necessary before definite conclusions can be made. We therefore continued the study after renewed informed consent of the participating patients. We report here the results of the study with a mean (SD) follow up of 42 (10) months. In addition, we analysed the data again according to contemporary definitions of acute coronary syndromes (ACS).\(^3\)

**PATIENTS AND METHODS**

The methods of the study have been previously reported.\(^4\) Briefly, consecutive patients with stable coronary artery disease visiting the outpatient department of the cardiology department were screened for inclusion. The history of patients had to include one of the following: myocardial infarction, significant coronary artery lesions (> 60%) on coronary angiography, percutaneous coronary intervention, or coronary bypass surgery. Patients had to be stable with no invasive vascular procedures scheduled. Patients were eligible when they had been taking statin for at least three months. The main exclusion criteria were age below 18 years, history of low vitamin B12 concentration, treatment for hyperhomocysteinaemia, severe renal failure or any other treatment for renal disease, known hepatic disease, signs and symptoms of severe heart failure (New York Heart Association functional class IV), or any other serious illness that would exclude the patient from follow up of at least three years.

The patients were randomly assigned to receive open label folic acid 0.5 mg once daily or to standard care. In addition, during the study statin treatment was intensified when necessary. At least one of four goals was meticulously pursued: firstly, a decrement of low density lipoprotein (LDL) cholesterol of 30% (compared with concentrations before the initiation of statin treatment); secondly, LDL cholesterol concentration of < 3 mmol/l; thirdly apolipoprotein B concentration of < 1 g/l; and fourthly, a decrement of apolipoprotein B concentrations of 30% compared with persistent statin concentrations. Persistent nicotine use was discouraged at regular intervals. Patients were followed up for a maximum of five years. During the whole study clinical events were carefully registered. Visits for laboratory examinations were planned at three, six, and 12 months and every six months thereafter. The study was conducted in accordance with the Declaration of Helsinki as revised in 1996. This study was performed in a rural area in the vicinity of the city of Goes, called the Bevelanden (province of Zeeland, the Netherlands), from 1998 to 2003. The local ethics committee approved the study protocol before the start of the study. The primary end point was a composite of vascular events. These events were defined as vascular death (sudden death, fatal recurrent ACS, fatal stroke, and other cardiovascular deaths), non-cardiovascular death, recurrent ACS, cerebrovascular accident, and transient ischaemic attack. ACS was defined according to contemporary criteria, which include an increase of troponin of > 0.2 µg/l (with a typical rise and fall) with at least one of the following: ischaemic symptoms, development of pathological Q waves on the ECG, and ECG changes indicative of ischaemia. All clinical events were adjudicated by an independent end point monitoring committee, unaware of treatment arm.

**RESULTS**

A total of 593 patients were enrolled in this study. Of these patients, 300 were randomly assigned to folic acid 0.5 mg once daily and 293 patients served as control group. Baseline data have been previously reported. Mean follow up was 42 (10) months. After inclusion, 24 patients withdrew from the study (12 in each group) but were followed up according to the protocol and were included in the analysis on an intention to treat basis. No patients were lost to follow up. During the course of the study no difference in LDL concentrations between the groups were noted; on average LDL concentrations were 2.6 (0.6) mmol/l.

Clinical cardiovascular events were evenly distributed in both treatment arms. In total, 49 (16.3%) clinical events in

**Figure 1** Cumulative event rate according to random allocation to folic acid treatment (dashed line) and control (solid line). Analysis for cumulative event rate for death, acute coronary syndromes (ACS) or cerebrovascular accident (CVA) or transient ischaemic attack. Probability value is estimated by log rank statistic.
Cholesterol embolisation syndrome

A 68 year old male smoker, who was hypertensive, diabetic, and dyslipidaemic, with renal dysfunction (blood urea nitrogen 19 mg/dl, serum creatinine 1.6 mg/dl) and recent troponin T negative unstable angina, underwent a coronary angiogram. A non-ionic contrast agent (iopamidol) was used. Pre-procedure peripheral pulses were normal with no bruit. The angiogram revealed three vessel disease, and coronary artery bypass graft surgery was advised. Immediately following the angiogram no significant deterioration of renal function was evident. However, the patient presented four weeks later with renal failure (maximum blood urea nitrogen 73 mg/dl, serum creatinine 3.6 mg/dl), livedo reticularis (panel A, arrow), and bilateral persistent lower limb pain with bluish discolouration of toes suggestive of digital gangrene (panels A and B). Peripheral pulses were normal. Doppler of lower limb arteries showed normal flow in major arteries. A diagnosis of cholesterol embolisation syndrome (livedo reticularis and digital gangrene with renal impairment) was made. The patient was managed conservatively.

Cholesterol embolisation syndrome is a systemic disease caused by distal showering of cholesterol crystals after angiography, major vessel surgery, or thrombolysis. The management is supportive. The syndrome may go undetected unless there is monitoring of renal function following invasive procedures.

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