

Effect of lipid-lowering and anti-hypertensive drugs on plasma homocysteine levels

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Abstract: Elevated plasma concentrations of homocysteine, a sulfur-containing amino acid, are a risk factor for coronary, cerebral and peripheral artery disease. Next to other factors, drugs used for the prevention or treatment of cardiovascular disease may modulate plasma homocysteine levels. Thus, a drug induced homocysteine increase may counteract the desired cardioprotective effect. The aim is to summarize the current knowledge on the effect of two important classes of drugs, lipid-lowering drugs and anti-hypertensive drugs, on homocysteine metabolism. Among the lipid-lowering drugs, especially the fibric acid derivatives, which are used for treatment of hypertriglyceridemia and low HDL-cholesterol, are associated with an increase of homocysteine by 20%–50%. This increase can be reduced, but not totally avoided by the addition of folic acid, vitamin B12 and B6 to fibrates. HMG-CoA reductase inhibitors (statins) do not influence homocysteine concentrations substantially. The effects of nicotinic acid and n3-fatty acids on the homocysteine concentrations are less clear, more studies are necessary to clarify their influence on homocysteine. Antihypertensive drugs have also been studied with respect to homocysteine metabolism. A homocysteine increase has been shown after treatment with hydrochlorothiazide, a lowering was observed after treatment with β -blockers, but no effect with ACE-inhibitors. The clinical significance of the homocysteine elevation by fibrates and thiazides is not clear. However, individual patients use these drugs for long time, indicating that even moderate increases may be important.

Keywords: homocysteine, fibrates, diuretics, cardiovascular disease

Aim of the review

At present, the meaning of elevated homocysteine concentrations for cardiovascular risk is unclear. Retrospective case-control studies show a clear, strong association of hyperhomocysteinemia and elevated risk, however, in prospective observational studies, the association is less strong (Homocysteine studies collaboration 2002). One reason for this discrepancy can be the influence of the disease on homocysteine concentrations. Indeed, research has shown that a number of drugs frequently given to patients with CVD that might also have an influence on homocysteine.

Therefore, this review will 1) briefly summarize the epidemiological and biochemical evidence of the association between homocysteine and CVD, 2) summarize the effect of lipid-lowering drugs on homocysteine, 3) summarize the effect of anti-hypertensive drugs on homocysteine, and finally, comment on the clinical implications of drug-induced increase of homocysteine.

Link between homocysteine levels and cardiovascular disease

Cardiovascular diseases remain the main cause of mortality in industrialized countries and become increasingly prevalent in developing countries. The risk to develop

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cardiovascular disease is mainly attributable to a number of known risk factors, that are in first instance hyperlipidemia, hypertension, smoking and diabetes mellitus. However, other risk factors must also contribute to cardiovascular disease, as the primary risk factors can not explain all cases of CVD. Among other risk factors, hyperhomocysteinemia was recognized during the last decades as a preventable risk factor present in about 30% of patients with coronary heart disease (Boushey et al 1995) and in 10%–15% of the general population (Nygard et al 1995; Dierkes et al 2001a). The association between elevated homocysteine concentrations and coronary, cerebral or peripheral artery disease was investigated in numerous epidemiological studies with either retrospective or prospective study design. Furthermore, clinical trials are underway or have been closed to investigate whether a lowering of elevated homocysteine concentrations will reduce recurrent cardiovascular disease (Clarke 2005). In addition, a huge number of biochemical studies was performed to investigate the effect of homocysteine on endothelial cells, smooth muscle cells, thrombocytes, or clotting factors.

Epidemiological studies

In order to have an overview on the epidemiological studies conducted on the issue, several meta-analyses have been performed. The first meta-analysis was published more than 10 years ago by Boushey and colleagues (1995), who included 27 studies relating homocysteine to arteriosclerotic vascular disease (Table 1). Most of the following meta-analyses considered more prospective trials that had been published in the meantime, and reported divergent results for retrospective studies compared with prospective studies (Table 1). Overall, retrospective studies show a stronger association of homocysteine and CVD than prospective studies. In addition, the association of homocysteine to stroke seems to be stronger than the association to coronary heart disease. Most meta-analyses calculated the odds ratios for an increase of plasma homocysteine of 5 $\mu\text{mol/L}$. However, it has to be taken into account that the standard deviation of plasma homocysteine measured in healthy populations is in the magnitude of 3–4 $\mu\text{mol/L}$. Therefore, an increase of 5 $\mu\text{mol/L}$ represents a fairly large increase in homocysteine. According to this, it can be concluded, that elevated homocysteine is a significant but modest risk factor for coronary, cerebral, or peripheral artery disease (Wald et al 2002; Homocysteine Studies Collaboration 2002).

Biochemical studies

Homocysteine exerts its atherogenic properties via several mechanisms, which have not been fully elucidated to date.

In vitro studies showed that homocysteine is cytotoxic to endothelial cells, promotes the proliferation of smooth muscle cells, and leads to several interactions with platelets, clotting factors, and lipids (Welch and Loscalzo 1998; Thambyrajah and Townsend 2000; Li et al 2002). In addition, homocysteine can disrupt the folding and processing of newly synthesized proteins in the endoplasmic reticulum (Wilson and Lentz 2005). Homocysteine can also induce oxidative stress and is able to reduce the bioavailability of nitric oxide, mechanisms leading to endothelial dysfunction.

However, since most of the results are derived from in vitro studies using supraphysiological concentrations of homocysteine, their significance to the in vivo processes of atherogenic plaque formation and disruption have to be determined.

Endothelial function

Measurement of endothelial function offers an elegant in vivo method to study an atherogenic effect of a compound, since endothelial vasodilation of the brachial artery correlates well with the function of coronary arteries (Celermajer et al 1992). It was shown in a number of studies that hyperhomocysteinemia impairs endothelial-dependent vasodilation, which is regarded as an early and preclinical sign of atherosclerosis (Tawakol et al 1997; Chambers et al 1999; Thambyrajah et al 2001). Mechanisms leading to endothelial dysfunction by hyperhomocysteinemia depend probably on the generation of reactive oxygen species, decreased bioavailability of nitric oxide (NO) and concurrent elevation of asymmetric dimethylarginine (ADMA), a strong inhibitor of the NO synthase (Nappo et al 1999; Böger et al 2001).

Effects of anti-hyperlipidemic drugs

Hyperlipidemia is the term for a number of conditions of dysregulated lipid metabolism which require different treatment regimens. While the risk associated with elevated total cholesterol and elevated LDL-cholesterol is well investigated, the significance of elevated triglycerides, low HDL-cholesterol or elevated Lp(a) for CVD risk is less clear (Assmann et al 1998; Jeppesen et al 1998). Hypercholesterolemia is a primary risk factor for cardiovascular disease. Large-scale randomized trials have shown that lipid-lowering with HMG-CoA reductase inhibitors (statins) reduce relative risk for cardiovascular events or death both in primary and in secondary prevention (Gotto 2005). Therefore, statins are widely used for the treatment of hypercholesterolemia. Hypertriglyceridemia, however, is less well established as risk factor for cardiovascular disease. Furthermore, results

Table 1 Overview of meta-analyses on homocysteine and CVD since 1995

Year and author	No. of studies Included	No of retrospective/ prospective studies	Main results (OR and 95% CI)
1995 Boushey	27	24 / 3	Hcy + 5 µmol/L: 1.6 (1.4–1.7) Men, CAD 1.8 (1.3–1.9) Women, CAD 1.5 (1.3–1.9) Cerebrovasc.
2000 Moller	12	8 / 4	Hcy > 95th percentile: 3.97 (3.07–5.12) Cerebrovasc.
2000 Cleophas	33	22 / 11	elevated Hcy (no further def.) 1.49 (1.33–1.67) prospective CAD 1.62 (1.50–1.74) retrospect. CAD
2002 Kelly	14	11 / 3	HHcy (binary variable) 1.79 (1.61–2.0) Stroke
2002 Wald	20	– / 16	IHD, 8 Stroke Hcy + 5µmol/L: 1.32 (1.19–1.45) IHD 1.59 (1.29–1.96) Stroke
2002 Ford	38 CHD	26 / 12	Hcy + 5 µmol/L 1.23 (1.07–1.41) prospective 1.70 (1.50–1.93) retrospective
	24 stroke	17 / 7	1.58 (1.35–1.85) prospective 2.16 (1.65–2.82) retrospective
2002 Hcy Studies Collaboration	30	IHD: 15 / 12 Stroke: 5 / 8	Hcy – 25% 0.83 (0.77–0.89) prospective IHD 0.67 (0.62–0.71) retrospect. IHD 0.77 (0.66–0.90) prospective stroke 0.86 (0.73–1.01) retrospect. stroke

Abbreviations: CAD, coronary artery disease; CHD, coronary heart disease; CI, confidence interval; OR, odds ratio; IHD, ischemic heart disease; Hcy, homocysteine; HHcy, hyperhomocysteinemia.

of randomized clinical trials for treatment of hypertriglyceridemia have been less convincing than trials with statins (The BIP study group 2000; The DAIS investigators 2001; The FIELD study 2005). Low HDL-cholesterol is frequently associated with elevated triglycerides. Drugs of choice for the treatment of hypertriglyceridemia and low HDL-cholesterol are the fibrates which act via activating peroxisome proliferation-activated receptors α (PPAR α), nicotinic acid, or derivatives from this compound which act primarily on the adipocytes, and n3-fatty acids. All of these compounds have been investigated with respect on their effect on the homocysteine concentration, which will be summarized within this review.

Fibrates

Fibric acid derivatives (fenofibrate, bezafibrate, ciprofibrate, gemfibrozil) are the drugs of choice for the treatment of hypertriglyceridemia (Fruchart 2001). Upon treatment, plasma triglycerides may be reduced by 30%–60% and cholesterol by 20%–25%, while HDL-cholesterol will be increased (Brown 1987). Fibrates represent synthetic ligands of PPAR α , leading to increased activation of genes involved in lipid metabolism and increased fatty acid metabolism (Fruchart et al 2001).

The effect of fibrates on homocysteine has been investigated both in short-term studies and in long-term epidemiological studies. The long term studies have been designed with the aim of proving the protective effect of fibrates on cardiovascular risk and in subgroups, the effect on homocysteine has been studied in stored samples (Genest et al 2004; Keech et al 2005).

Numerous short-term studies revealed that administration of fenofibrate was associated with an elevation of homocysteine of the magnitude of 40%–50% (Dierkes et al 1999; Landray et al 1999; Giral et al 2001; Bissonnette et al 2001). Ciprofibrate was less often investigated (Harats et al 2001). These studies were all short-term studies lasting for 6–12 weeks. However, re-evaluation of randomized clinical trials with fibric acid derivatives confirmed the homocysteine increase also after longer periods: In the Diabetes Atherosclerosis Intervention Study (DAIS), 418 patients with diabetes mellitus type 2 and mild lipid abnormalities received fenofibrate (n = 207) or placebo (n = 211) for a mean period of 40 months. At baseline and at the end of the study, a coronary angiography was performed (DAIS study group 2001). Homocysteine increased in the fenofibrate group on average by 5.6 ± 6.3 µmol/L and remained unchanged throughout the study in

the placebo group. Increase in homocysteine did not alter results obtained in the angiography (neither mean segment diameter, mean lumen diameter nor % stenosis). The absolute increase in homocysteine was similar over the whole range of baseline homocysteine levels, leading to higher percent increase in those with initially low homocysteine concentrations (Genest et al 2004). Folate and cobalamin were not affected by fenofibrate treatment. In a multinational, randomised controlled trial, the FIELD study (Keech et al 2005), 4895 patients with type 2 diabetes mellitus received 200 mg fenofibrate daily. Fenofibrate did not significantly reduce the risk of the primary outcome of coronary events. The median plasma homocysteine concentration increased about 4 $\mu\text{mol/L}$. There was a slight increase in pulmonary embolism ($p = 0.022$), but whether changes in homocysteine are causal for embolism in this study is unknown.

Administration of bezafibrate also leads to an increase of total homocysteine in short-term studies, as shown by our group (Dierkes et al 1999) and others (Jonkers et al 1999). The homocysteine increase was somewhat lower than the increase observed after fenofibrate, and was about 20%–35%.

Some conflicting data are available on the effect of gemfibrozil on homocysteine. Gemfibrozil differs in some aspects from beza- or fenofibrate, as it does not involve PPAR α activation. In a study of our group, we did not observe any effect of gemfibrozil on plasma homocysteine concentrations in 22 hyperlipidemic men (Westphal 2001). In contrast, a recent re-evaluation of the Lipid Coronary Angiography Trial (LOCAT), a homocysteine increase of 18% was observed in 178 patients treated with gemfibrozil for 16 months while no change of homocysteine was observed in the placebo group ($n = 184$) (Syvanne 2004). Differences between studies are the administered dose of gemfibrozil (900 mg versus 1200 mg), study duration (6 weeks versus 16 months) and sample size ($n = 22$ vs $n = 178$).

In conclusion, it is evident that the elevation of homocysteine by fibric acid derivatives is a class effect which is especially observed after fenofibrate. Mechanisms responsible for this effect may be 1) effects of fibrates on the creatine-creatinine pathway (Hottelart et al 1999, 2002; Broeders et al 2000; Lipscombe and Bargman 2001), 2) the downregulation of the renal cyclo-oxygenase enzyme (COX-2), thus inhibition of synthesis of renal vasodilating prostaglandins (Wilson et al 1995; Yoshinari et al 1998; Khan et al 2002), and 3) a yet unknown effect of PPAR α activation on homocysteine metabolism (Legendre et al 2002; Luc et al 2004).

Concerning creatine-creatinine metabolism, it must be noted that both fenofibrate and bezafibrate cause increases

of serum creatinine concentrations, but obviously not due to an alteration of the glomerular filtration rate (Hottelart et al 1999). Obviously, fenofibrate induces an increased creatine turnover rate. However, an increase in creatine turnover may also cause an increase of homocysteine since the methyl group of creatine is donated by S-adenosylmethionine, rendering S-adenosylhomocysteine and thus homocysteine (Mudd and Poole 1975).

Downregulation of the renal COX-2 enzyme system by PPAR α activation leads to decreased synthesis of vasodilating prostaglandins and may then reduce glomerular filtration rate. The action of these vasodilating prostaglandins is especially important in patients with impaired renal function (Khan et al 2002).

Recently, it has been shown that the homocysteine increasing effect of fibrates depend on the activation of PPAR α in rodents (Legendre et al 2002; Luc et al 2004). Fenofibrate mixed into the diet caused a doubling of homocysteine concentration in wild-type mice, while in PPAR α deficient mice, no change of homocysteine concentrations was observed. In a similar experiment, PPAR α -knock out mice had initially slightly lower homocysteine concentrations than wild-type mice, and there was no increase in homocysteine in the knock-out mice after 2 weeks administration of fenofibrate at a dose of 100 mg/kg. In rats, fenofibrate caused an increase of homocysteine by more than 80% (Legendre et al 2002; Luc et al 2004). In contrast, Stulc et al (2005) did not find any increase in homocysteine after treatment with rosiglitazone. Rosiglitazone, a novel class of antidiabetic drugs, is an agonist of PPAR γ receptors.

At present, there are no data suggesting an effect of fibrates on folate or cobalamin metabolism. In the short-term studies, no effect of fibrates was observed on vitamin levels (Dierkes et al 1999, 2001b; Bissonnette et al 2001; Westphal et al 2001; Milionis et al 2003). Additionally, there was no change in folate or cobalamin levels during the DAIS study (Genest et al 2004). Furthermore, macrocytic anemia or other signs of vitamin deficiency are not associated with long-term treatment with fibrates.

In healthy populations, vitamin supplementation with folic acid and/or cobalamin can reduce circulating homocysteine concentrations effectively by about 25% (Homocysteine Lowering Trialists' Collaboration 1998, 2005). Therefore, addition of vitamins to fenofibrate may be an option to decrease homocysteine concentrations during fibrate treatment. This was investigated in studies using folic acid, vitamin B12 and vitamin B6 in nutritional doses (Dierkes et al 2001b) or using a high dose of folic acid (5–10 mg) (Stulc et al 2001;

Melenovsky et al 2003; Mayer et al 2003, 2005). The uniform result of these studies is that vitamin or folic acid addition to fenofibrate can reduce the increase of plasma homocysteine, but still a small, significant increase of homocysteine can be observed, ranging from 6% to 20%. Other fibrates have not been tested in conjunction with vitamins. Recently, other effects of folic acid added to fenofibrate have been reported: the combination of fenofibrate and folic acid reduced oxidized LDL-cholesterol and von Willebrand factor and thrombomodulin, biochemical markers of endothelial function (Mayer et al 2005). However, these results have been obtained in a small study in 18 volunteers and await confirmation in other studies.

HMG-CoA reductase inhibitors (statins)

Statins are widely used for the prevention of cardiovascular disease through the reduction of total cholesterol and especially LDL-cholesterol. With respect to homocysteine, they have mainly been used as comparison to a fibrate arm during short-term studies (de Lorgeril et al 1999; Melenovsky et al 2002; Sebestjen et al 2004; Milionis et al 2003). No study directly compared different statins. In the prospective AFCAPS/TexCAPS trial, a small reduction of homocysteine during one year of treatment with lovastatin was observed (Ridker et al 2002), however, this finding was statistically significant, but the biological meaning of homocysteine reduction of $-0.4 \mu\text{mol/L}$ may be questioned.

From these and other studies, it can be concluded that statins do not influence homocysteine concentrations significantly. Furthermore, the concurrent administration of statins and vitamins was investigated in a pilot study of the SEARCH trial (MacMahon et al 2000), revealing that there is obviously no effect of the statin component, as the reduction of plasma homocysteine levels was similar in the vitamin group and the vitamin plus statin group.

Nicotinic acid (niacin)

The cholesterol-lowering effect of high doses of nicotinic acid was recognized as early as 1955 (Altschul et al 1955). Nicotinic acid lowers total cholesterol, but is at present re-considered since it is also able to increase the protective HDL-cholesterol concentration (Parhofer 2005). While the physiological dose of the vitamin is about 20 mg per day, the lipid-lowering effect requires administration of 1.5–3 g of nicotinic acid (Knopp 1999). A first analysis in humans whether niacin may also influence homocysteine was made in the Arterial Disease Multiple Intervention Trial (ADMIT). Homocysteine was measured in subgroups treated either

with niacin ($n = 24$) or placebo ($n = 22$). After 18 and 48 weeks of treatment with niacin, average homocysteine levels were 21.1 and 19.9 $\mu\text{mol/L}$ in the niacin group and 11.5 and 11.6 $\mu\text{mol/L}$ in the placebo group, respectively. Unfortunately, no vitamin levels during follow-up were presented (Garg et al 1999). In animal studies, high doses of niacin were associated with lower levels of vitamin B6 and increased homocysteine concentrations (Basu and Mann 1997). Addition of vitamin B6 corrected the hyperhomocysteinemia. Since nicotinic acid is excreted in the methylated form, administration of this drug increases the total methyl demand substantially. Thus, formation of S-adenosylhomocysteine from S-adenosylmethionine is increased. Single cases of drastically increased homocysteine concentrations after niacin administration have been reported (Wang et al 2001). There is no study in humans that considered vitamin B6 during niacin therapy. On the other hand, a recent study which compared the effect of simvastatin or simvastatin plus niacin ($2 \times 1000 \text{ mg/d}$) did not observe a higher frequency of hyperhomocysteinemia in the simvastatin plus niacin group (any homocysteine $> 15 \mu\text{mol/L}$, measured bimonthly for 38 months: 4% in the simvastatin group versus 9% in the combination group, $p = 0.191$). However, this report did not provide means or median values (Zhao et al 2004).

Thus, at present, the effect of niacin on homocysteine and related vitamins in humans is unclear, although there is some evidence that niacin may raise homocysteine. Further studies are needed to clarify this issue, especially when keeping in mind the rising prescription of niacin.

n3-fatty acids

N3-fatty acids in relatively high doses (2–6 g/d) are used in the treatment of severe hypertriglyceridemia. One of the very early studies on homocysteine reported that administration of n3 fatty acids reduces plasma homocysteine (Olszewski and McCully 1993). Since then, a number of studies has been published on this association, however, with conflicting results. There are studies that report an increase of homocysteine after administration of fish oil or pure n3-fatty acids (Bourque et al 2003; Piolot et al 2003), compared with studies that observed no effect on homocysteine (Grundt et al 1999), or even a decrease of homocysteine after administration of fish oil (Olszewski and McCully 1993; Grundt et al 2003; Zeman et al 2006). At a glance, the different results cannot be attributed to differences in study design, fatty acids used or exclusion criteria of study subjects. Thus, the effect of n3-fatty acids on homocysteine cannot be uniformly described at present.

However, it has to be kept in mind that the effects of n3 fatty acid on homocysteine described have been small, ranging from increase by 15%–20% or decrease in the same magnitude. Therefore, chance findings are also likely. In addition, some doubts to the data may be allowed since there is no obvious hypothesis on the mechanism by which n3-fatty acids would alter homocysteine levels. One link may be vitamin B6 which serves as coenzyme both in the homocysteine-transsulfuration pathway but also as cofactor of the d6 desaturase which is involved in PUFA metabolism. Recently, in a rat study an elevated homocysteine concentration was measured in vitamin B6-deficient animals compared with animals with normal vitamin B6. Even more interestingly, significantly higher homocysteine levels were observed in vitamin B6 deficient animals receiving diet high in polyunsaturated fatty acids (PUFA), compared with

vitamin B6 deficient animals receiving a diet with saturated fatty acids (Cabrini et al 2005). It is not known at present, whether these results are also applicable in humans. Unfortunately, studies on PUFA supplementation in humans did not provide vitamin B6 levels at all. Obviously, in rats, homocysteine is closer related to vitamin B6 metabolism than in humans (Basu and Mann 1997). Further studies are necessary to clarify this issue.

Conclusion—lipid lowering drugs

Homocysteine is increased by administration of fibric acid derivatives. Statins do not influence homocysteine levels, while the effect of nicotinic acid and n3-fatty acids is less clear. Concurrent vitamin administration with fibrates can attenuate the homocysteine increase substantially.

Table 2 Effect of fibrates on homocysteine concentration (mean \pm standard deviation, unless otherwise noted)

Study	N	treatment	tHcy before	tHcy after	% change	P
Fenofibrate						
de Lorgeril 1999	29	200 mg/d, 12 weeks	11.4 \pm 3.5	16.6 \pm 5.2	+ 56 %	<0.001
Dierkes 1999	10	200 mg/d, 6 weeks	13.1	20.0	+ 44 (–8 \pm 85) % ^b	^a <0.001
Landray 1999	8	according to renal failure, 8 weeks	15.1	21.8	+ 44 %	^a p = 0.03
Giral 2001	29	200 mg/d, 6 months	12.3 \pm 3.9	16.2 \pm 4.6	+ 32 %	<0.001
Bissonnette 2001	20	200 mg/d, 8 weeks	10.3 \pm 3.3	14.1 \pm 3.8	+ 37 %	<0.001
Dierkes 2001	25	200 mg/d, 6 weeks	10.7	14.0	44 \pm 47 % ^b	^a <0.001
Westphal 2001	22	200 mg/d, 6 weeks	10.7	14.4	+ 35 %	^a <0.001
Stulc 2001	11	200 mg/d, 9 weeks	12.3 \pm 3.2	19.1 \pm 7.2	+ 55 %	<0.001
Melenovsky 2002	15	200 mg/d, 10 weeks	12.4 \pm 2.7	16.9 \pm 3.7	+ 36 %	<0.001
Melenovsky 2003	19	200 mg/d, 65 \pm 18 days	11.5 \pm 3.0	17.5 \pm 6.5	+ 52 %	not provided
Mayer 2003	24	200 mg/d, 3 months	10.0 \pm 2.9	14.2 \pm 2.9	+ 42 %	not provided
Milionis 2003	22	200 mg/d, 12 weeks	10.3 \pm 3.3	14.2 \pm 3.6	+ 38 %	<0.001
Genest 2004	418	200 mg/d, 3 years	11.0 \pm 5.6	16.5 \pm 10.7	+ 55 %	<0.001
DAIS-Study						
Bezafibrate						
Dierkes 1999	10	400 mg/d, 6 weeks	11.9	15.5	+17 (–14–65) % ^b	^a p = 0.02
Jonkers 1999	16	400 mg/d, 6 weeks	11.9 \pm 2.1	14.1 \pm 2.9	+ 18 %	<0.001
Harats 2001	12	400 mg/d, 6 weeks	8.2 \pm 2.3	6.8 \pm 1.4	–17 %	p = 0.22
Ciprofibrate						
Harats 2001	26	100 mg/d, 12 weeks	6.8 \pm 1.8	10.6 \pm 4.3	+ 56 %	<0.0001
Gemfibrozil						
Westphal 2001	22	900 mg/d, 6 weeks	12.9	12.4	–4 %	^a NS
Syv�anne 2004						
LOCAT-Study	395	900 mg/d, 16 months	12.6	14.1	+ 11.9%	^a <0.0001

Notes: ^aMedian; ^bcalculated from individual data.

Abbreviations: ACE inhibitor, angiotensin-converting enzyme inhibitor; BIP, bezafibrate Infarction Prevention; CAD, coronary artery disease; CI, confidence interval; CVD, cardiovascular disease; DAIS, Diabetes Atherosclerosis Intervention Study; FIELD, Fenofibrate Intervention and Event Lowering in Diabetes; GFR, glomerular filtration rate; FA, folic acid; HCT, hydrochlorothiazide; LOCAT, Lipid Coronary Angiography Trial; MTHFR, methylenetetrahydrofolate reductase; PPAR α , peroxisome-proliferation activated receptor alpha; PUFA, polyunsaturated fatty acids; RR, relative risk; homocysteine, total homocysteine.

Anti-hypertensive drugs

Drug treatment strategies to lower blood pressure vary widely throughout the world (Nygard et al 1997). Many studies have recently revealed that homocysteine is positively correlated with blood pressure, especially the systolic component (Nygard et al 1995; Jaques et al 2001; Sutton-Tyrrell et al 1997); however, this association is not evident in other studies (van Guldener 2003). The effects of different antihypertensive agents on plasma homocysteine levels have not been tested extensively. Recent studies have reported associations between diuretic drug therapy for the treatment of hypertension with homocysteine elevations (Nygard et al 1995). Data from the Framingham Offspring Study showed a highly significant positive association between the use of antihypertensive medication and homocysteine concentrations (Jaques et al 2001). Such treatment-associated increases in homocysteine may be a cause for concern if they were to reduce the cardio-protective effects of lowering of blood pressure.

Diuretics

Recent studies have reported that use of diuretics as an antihypertensive drug is associated with increased levels of homocysteine. Morrow and colleagues (1999) analyzed plasma concentrations of homocysteine, vitamins B6 and B12, and RBC folate in 17 hypertensive patients receiving long-term diuretic therapy and 17 hypertensive patients not taking diuretics. The mean serum homocysteine concentration of patients taking diuretics ($17.9 \pm 1.7 \mu\text{mol/L}$) was significantly higher than for patients not taking diuretics ($10.3 \pm 1.0 \mu\text{mol/L}$). The mean RBC folate concentration for patients taking diuretics ($281 \pm 18 \text{ ng/mL}$) was significantly lower than that for patients not taking diuretics ($431 \pm 29 \text{ ng/mL}$). Serum vitamin B6 and vitamin B12 concentrations were not significantly different between the two groups. It has been known for many years that diuretics can cause a depletion of water-soluble vitamins (Montenero

1980), although vitamin deficiency is not a common side effect of long-term diuretic use.

In a small trial of 27 patients assigned to treatment with either hydrochlorothiazide (HCT) or an ACE inhibitor, Westphal et al (2003) measured homocysteine, creatinine, folate, vitamins B6 and B12 before and after 4–6 weeks of treatment. HCT raised homocysteine concentrations by 28%, creatinine by 12% and decreased folate levels non-significantly by 26%. The underlying mechanism for the increase in homocysteine was attributed to a concomitant deterioration of renal function. The magnitude of the increase in homocysteine after HCT may be clinically relevant if this increases cardiovascular risk (Boushey et al 1995) and may counteract the desired cardiovascular protection conferred by lowering blood pressure. The extent to which the changes in homocysteine may explain the discrepant results on risk of coronary heart disease associated with differences in blood pressure mediated by HCT use (Kezdi et al 1992) is unclear. Possible adverse effects of HCT have been chiefly attributed to increases in LDL-cholesterol and glucose or hypokalaemia (Freis 1995), but increases in homocysteine may now be added to this side effect profile of HCT therapy.

Beta blockers

Korkmaz et al (2003) showed in a preliminary study, that metoprolol therapy significantly decreased homocysteine levels both in the first and fifth months of treatment. Two years later, Atar et al (2005) investigated in a prospective study the effects of beta-blocker therapy on homocysteine levels in patients with hypertension. 120 patients with newly diagnosed hypertension were enrolled. All patients received metoprolol succinate 100 mg/day initially. If blood pressure was above normal on the 15th day of follow-up, the metoprolol dosage was doubled. Homocysteine levels decreased significantly by the end of the fourth month when compared with basal values ($13.5 \pm 4.5 \mu\text{mol/L}$ vs $12.4 \pm 4.9 \mu\text{mol/L}$;

Table 3 Lipid-lowering and anti-hypertensive drugs that elevate homocysteine

Drug	Effect on homocysteine	Suggested mechanisms	Evidence from
Fibric acid derivatives	increase of homocysteine: + 40% fenofibrate +20% bezafibrate + 20% gemfibrozil	reduction of glomerular function increased creatin/creatinine metabolism PPAR α -activation	Human studies, cross-sectional and clinical trials mechanistic studies in rodents
Niacin	increase of fasting homocysteine, amount unclear	effect on vitamin B6 metabolism increased methylation demand	Human studies, mechanistic studies in rodents
Diuretics	increase of fasting homocysteine +20% hydrochlorothiazide	decreased glomerular filtration rate	Human studies, cross-sectional and one clinical trial

$p = 0.001$). There was no relation between homocysteine level and blood pressure control. There was a significant decrease in homocysteine levels in the women treated in this study ($p = 0.001$); however, this effect was absent in men ($p = 0.185$). Sharabi et al (1999) studied hypertensive patients with coronary and cerebral atherothrombosis and discovered that homocysteine levels were lower in patients who were taking beta-blockers.

Other anti-hypertensive drugs and conclusion

It is unclear whether other anti-hypertensive drugs, such as ACE inhibitors or calcium-channel blockers influence homocysteine concentrations since their effects have not been widely studied. In summary, most of the available evidence suggests that blood pressure lowering therapy with diuretics is associated with an increase of plasma homocysteine concentrations.

Implications and conclusions: Is drug-induced hyperhomocysteinemia important?

Recently, results of the first randomized clinical trials on homocysteine lowering by vitamins in secondary prevention have been become public (Schnyder et al 2001; Liem et al 2003; Lange et al 2004; Toole et al 2004). Results are, however, not encouraging that lowering homocysteine by vitamins will be effective in reducing cardiovascular morbidity or mortality in secondary prevention. However, even in the VISP study (Toole et al 2004), a high baseline homocysteine concentration was associated with worse outcome. Therefore, at present, the significance of elevated homocysteine due to whatever cause is unclear.

Current evidence shows that a clear, uniform homocysteine increase can be expected in patients treated with fibrates (fenofibrate or bezafibrate) and with thiazides (Table 2).

For these drugs, the increase in homocysteine has been demonstrated in both observational studies and in clinical trials. In the case of fibrates, it was shown that addition of vitamins can reduce the drug induced hyperhomocysteinemia. There is now also a study that suggests beneficial effects of the added folic acid on the endothelium and on anti-oxidative status (Mayer et al 2005). Whether the homocysteine increase is responsible for non-significant results of prospective randomized trials with fenofibrate in secondary prevention can only be speculated at present.

The evidence for a homocysteine increase associated with other lipid lowering drugs is less convincing. The discrepant

results observed for niacin and n-3 fatty acids questions about whether these drugs really influence plasma homocysteine. There is a need for more data on niacin and homocysteine and fish oil and homocysteine, also with respect to vitamin B6, which might be an important confounder that has not been rewarded until now in humans.

It has to be taken into account that the relative risk for cardiovascular events associated with an increase of homocysteine are generally modest (Table 1). Therefore, it does not seem to be justified to discontinue treatment with thiazides or fibrates because of the adverse effects on homocysteine concentrations. Physicians and their patients should be informed about the possibility of combining these drugs with low doses of folic acid, vitamin B12 and B6 in order to enable them to an informed decision.

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