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REVIEW ARTICLE

Homoarginine in the renal and cardiovascular systems

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Abstract Homoarginine (hArg) is an endogenous, non-proteinogenic amino acid which differs from arginine by an additional methylene (CH_2) group in the backbone. In this brief narrative review, we summarize the current literature on hArg in the renal and cardiovascular systems. Epidemiological studies have identified low hArg levels as an independent risk marker for cardiovascular, cerebrovascular, and renal diseases as well as for mortality. The relatively low correlation of hArg with established cardiovascular risk factors underlines its great potential as an emerging biomarker to improve risk prediction because plasma hArg concentrations might reflect previously unrecognized pathophysiological processes. hArg may be involved in the pathogenesis of various diseases due to its effects on nitric oxide (NO) and energy metabolism. In view of its structural similarities with arginine, it has been proposed that hArg impacts on arginine metabolism and subsequently also on NO synthesis. The key enzyme for hArg synthesis, arginine:glycine amidinotransferase (AGAT), is involved in the synthesis of energy metabolites including guanidinoacetate, the precursor of creatine. Therefore, the involvement of hArg in energy metabolism could partially explain the close association between hArg and cardiovascular diseases such as heart failure. Whether hArg supplementation or modification of key enzymes of hArg metabolism such as AGAT activity is effective for the treatment of chronic diseases remains to be elucidated.

Keywords Homoarginine · AGAT · Cardiovascular · Stroke · Heart failure · Nitric oxide · Mortality

Abbreviations

ADMA	Asymmetric dimethylarginine
AGAT	L-Arginine:glycine amidinotransferase

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AMPK	AMP-activated protein kinase
Arg	L-Arginine
BMI	Body mass index
CKD-MBD	Chronic kidney disease-mineral and bone disease
GAMT	Guanidinoacetate *N*-methyltransferase
GFR	Glomerular filtration rate
GWAS	Genome wide association study
hArg	L-Homoarginine
KO	Knockout
LURIC	Ludwigshafen risk and cardiovascular health
MACE	Major adverse cardiovascular events
NO	Nitric oxide
PAD	Peripheral arterial disease
PRMT	Protein arginine methyltransferase
SD	Standard deviation
SNP	Single-nucleotide polymorphism
WT	Wild-type

Introduction

Homoarginine (hArg) is an endogenous, nonproteinogenic amino acid which differs from arginine by an additional methylene (CH_2) group in the backbone (Meinitzer et al. 2011a). Over the last few years, several epidemiological studies have identified low hArg levels as an independent risk marker for cardiovascular and renal diseases as well as for mortality (Atzler et al. 2015; Drechsler et al. 2013). These findings along with proposed interferences of hArg with arginine (Arg), nitric oxide (NO), and energy metabolism have generated a great interest in hArg as an emerging risk marker and possible drug target. Further research on hArg metabolism and action may extend our knowledge on the involvement of amino acids in the pathophysiology of various chronic diseases (Wu 2009). In this brief narrative review, we summarize the current literature on hArg in the renal and cardiovascular systems.

Homoarginine biosynthesis and metabolism

hArg was successfully synthesized in 1926 and was subsequently identified as a naturally occurring amino acid (Steib 1926; Stevens et al. 1950; Bernstein et al. 2015). In the 1960s, hArg was isolated from different species of Lathyrus (grass pea), including Lathyrus sativus and Lathyrus cicero (Bell 1962; Rao et al. 1963). In Western countries, nutrition is, however, usually a negligible source for hArg (Meinitzer et al. 2011a; Singh 2013). It has further been shown that hArg can be produced from lysine in humans and is present in various body fluids and organs (Ryan et al. 1964; Marescau et al. 1992). In September 2013, two research groups have, independently, published a Genome Wide Association Study (GWAS) of hArg (Choe et al. 2013b; Kleber et al. 2013). Both studies documented that single-nucleotide polymorphisms (SNPs) at the gene for L-arginine:glycine amidinotransferase (AGAT) are the genetic "top hit" for the association with circulating hArg levels, indicating that AGAT is the principal enzyme for endogenous hArg synthesis. In detail, AGAT converts arginine and glycine into guanidinoacetate and ornithine. This finding is of relevance given that guanidinoacetate is a precursor of creatine. In detail, methylation of guanidinoacetate by the enzyme guanidinoacetate *N*-methyltransferase (GAMT) in the liver results in the formation of creatine, which is well known to serve as an energy buffer with high relevance for cardiovascular health. The fact that the major site of AGAT expression is the kidney points toward a strong link between hArg metabolism and kidney function. Significant AGAT expression has also been identified in various other organs such as the muscles, heart, liver, and brain (Cullen et al. 2006). Further genetic loci associated with hArg in GWAS encode the mitochondrial enzymes carbamoyl phosphate synthetase I (CPS1) and alanine-glyoxylate aminotransferase (AGXT2) (Kleber et al. 2013). SNPs of CPS1, the rate limiting enzyme for the hepatic urea cycle, have previously been associated with NO and creatinine concentrations as well as with vascular smooth muscle reactivity and pulmonary hypertension (Kleber et al. 2013; Summar et al. 2010). AGXT2 catalyzes the conversion of glyoxylate to glycine and has been shown to be involved in the regulation of methylarginines, with one study showing that overexpression of AGXT2 protects against asymmetric dimethylarginine (ADMA)-induced suppression of NO synthesis in endothelial cells (Rodionov et al. 2010). With reference to the urea cycle, it is also important to underline that lysine supplementation can increase hArg concentrations because if the first enzyme of the urea cycle (i.e., ornithine transcarbamoylase), uses lysine instead of ornithine, hArg is formed (Meinitzer et al. 2011a; Ryan et al. 1964). Considering that hArg can be converted by the enzyme arginase into lysine and urea, it has been proposed that arginase activity might also modulate circulating hArg concentrations (Jaźwińska-Kozuba et al. 2013). It should also be noted that in a reference population, median (25th, 75th percentile) serum hArg concentrations were 2.63 (2.08; 3.32) μM, thus, ~4–5 times higher compared to ADMA levels (Atzler et al. 2014b), yet 20–40 times lower than serum Arg concentrations.

Homoarginine and cardiovascular risk factors

It has been observed in several, but not all, studies that there is a moderate decline of hArg with advancing age, which may partially be attributed to reduced kidney function (März et al. 2010; Atzler et al. 2014b). Although male gender is a significant cardiovascular risk factor, it has been reported in

most studies that men have significantly higher hArg concentrations when compared with women (März et al. 2010). The reason for this gender disparity is not entirely clear at present, but one study showed that hArg levels are significantly increased in the second and third trimesters of pregnancy (Valtonen et al. 2008). It has been hypothesized that estrogen-induced upregulation of AGAT may contribute to the elevation in hArg during pregnancy (Valtonen et al. 2008; Zhu et al. 2001). Whether a decrease of estrogen in, for example, postmenopausal women contributes to the age-related decline of hArg concentrations deserves further studies. In this context, it is important to note that AGAT expression is also upregulated by other hormones such as growth hormone, thyroxine, and methyltestosterone (McGuire et al. 1980; Hoberman et al. 1948; Jaźwińska-Kozuba et al. 2013).

According to population-based studies and investigations in various different patient cohorts, higher hArg plasma levels are associated with higher body mass index (BMI) (Atzler et al. 2014a; Pilz et al. 2014a; März et al. 2010). These epidemiological findings are supported by reports from AGAT deficient mice that present with a reduced BMI and improved glucose tolerance, and that are protected from the metabolic syndrome (Choe et al. 2013a). In elegant experiments, it has been shown that this phenotype in AGAT deficiency can be attributed to creatine deficiency which in turn leads to increased AMP-activated protein kinase (AMPK) activity. AMPK activation, which is typically a consequence of energy demanding processes such as hypoxia/ischemia or muscle contractions, promotes catabolic and inhibits anabolic processes in glucose and lipid metabolism. In line with this, it has been observed in the Dallas Heart study that a SNP of the AGAT gene is associated with both higher hArg and higher BMI (Atzler et al. 2014a). Case reports of patients with inherited AGAT deficiency showed that this extremely rare disease is clinically characterized by low BMI, muscle weakness, and mental retardation (Edvardson et al. 2010; Ndika et al. 2012; Davids et al. 2012). These patients can, however, be successfully treated with oral creatine supplementation. In view of the link between hArg and BMI, it has been hypothesized that low hArg could indicate some sort of a wasting process. In this context, it should be noted that several, albeit not all studies, have shown a positive association of hArg with serum albumin and hemoglobin (März et al. 2010; Pilz et al. 2014a). Interestingly, one small study comprising patients undergoing bariatric surgery showed that a significant weight reduction of 36 ± 7 kg did not materially alter hArg concentrations (May et al. 2015). These data suggest that changes in BMI are not directly accompanied by changes in hArg levels, but it is still conceivable that hArg (and its metabolism) could be the cause rather than the consequence of obesity or cachexia.

Epidemiological studies on the association between hArg, type 2 diabetes mellitus, and glucose metabolism have shown inconsistent results, and subsequently, it is not clear whether disturbances in glucose metabolism are associated with lower, higher, or unaltered circulating hArg concentrations. Experimental studies suggest that hArg might stimulate insulin secretion in the pancreas and might modulate the effects of insulin (Blachier et al. 1989; Henningsson et al. 1998; Schwegler et al. 1975). By contrast, observations in AGAT-deficient mice showed reduced gluconeogenesis and enhanced glucose tolerance (Choe et al. 2013a). In the same study, it was documented that increased AMPK activity in AGAT-deficient mice reduced blood glucose levels as this kinase is important for glucose uptake into the skeletal muscle and inhibits gluconeogenesis (Choe et al. 2013a). Moreover, hArg concentrations were decreased in children with type 1 diabetes mellitus as compared with healthy controls; though clearly further studies are needed to explore the relationship between hArg and diabetes mellitus (Krebs et al. 2015).

Epidemiological data on the association between hArg and blood lipids are inconsistent, though most of the extant literature did not observe a meaningful association between hArg and blood lipids such as triglycerides, HDL-cholesterol, and LDL-cholesterol (März et al. 2010; Pilz et al. 2014a; Atzler et al. 2014b).

Several epidemiological studies suggest that smoking might be associated with lower hArg concentrations, albeit this was not consistently found in all investigations. A study in 231 healthy male participants has specifically addressed this issue and reported that plasma hArg concentrations were 16.7 % lower in smokers compared with non-smokers (Sobczak et al. 2014). In fitting with this, reduced age-adjusted hArg concentrations in smokers were also reported in a study including male patients with peripheral arterial disease (PAD) (Vogl et al. 2015). Moreover, current smoking was associated with lower hArg concentrations in the population-based Hoorn and Dallas Heart study (van der Zwan et al. 2013; Atzler et al. 2014a).

The association between hArg and blood pressure has been specifically addressed in the Hoorn study in 746 older persons from the general population (van der Zwan et al. 2013). In multivariate-adjusted models, hArg was significantly and positively associated with higher systolic and diastolic blood pressure. In detail, the increase in systolic and diastolic blood pressure (in mmHg [with 95 % CI]) per 1 standard deviation (SD) increment in hArg was 3.90 (2.28–5.52) and 1.83 (0.95–2.72), respectively (van der Zwan et al. 2013). Blood pressure was also positively correlated with hArg concentrations in the Ludwigshafen Risk and Cardiovascular Health (LURIC) study, a cohort study in more than 3000 patients referred to coronary angiography (Pilz et al. 2011b). In addition, diastolic blood pressure was significantly and positively correlated with hArg in primary care patients at cardiovascular risk (Pilz et al. 2014b). Low hArg concentrations have also been linked

to early pre-eclampsia, a disease characterized by arterial hypertension and proteinuria (Khalil et al. 2013). Not all studies observed a positive correlation between hArg and blood pressure but several pathophysiological mechanisms have been proposed regarding the link of hArg and arterial hypertension. It has been hypothesized that hArg reduces NO synthesis from arginine by (1) competition of Arg and hArg for cellular uptake by cationic amino acid transporters (CAT), (2) by trans-stimulation of CAT, which in turn could increase cellular efflux of Arg, and (3) by competition of hArg and Arg for NO synthase (NOS) because hArg is a less efficient substrate for this enzyme (van der Zwan et al. 2013; Moali et al. 1998). On the other hand, hArg may also increase arginine availability and thus NO synthesis by inhibition of arginase. Moreover, hArg may contribute to higher NO levels by serving as a substrate for NOS because hArg, even with its compared to Arg weaker affinity to NOS, can be metabolized to NO and homocitrulline (Meinitzer et al. 2011a). Data in mice suggest that hArg supplementation might even contribute to a more sustained NOS activation compared to arginine supplementation (Atzler et al. 2015). This is in line with experimental data among rats showing significantly lower blood pressure following intravenous hArg infusions along with an increased excretion of urinary nitrate, indicating enhanced NO synthesis (Chen et al. 1993). By contrast, it has also been shown in rat experiments that hArg infusions decreased NO levels and renal medullary blood flow (Kakoki et al. 2004). It is therefore still uncertain whether the proposed interactions of hArg with NO metabolism translate into beneficial or detrimental effects. Another factor with relevance to NO synthesis is ADMA. ADMA is an established cardiovascular risk factor that functions as an endogenous inhibitor of NO synthase (Tsikas et al. 2000; Kielstein et al. 2007) and is formed by methylation of arginine residues in proteins by protein arginine methyltransferases (PRMTs) (Meinitzer et al. 2011b). Formation of creatine from guanidinoacetate by GAMT as well as of ADMA by PRMT both use *S*-adenosylmethionine as the methyl donor, but creatine synthesis utilizes 20–100 times more *S*-adenosylmethionine than PRMT for ADMA synthesis (Kayacelebi et al. 2015). Despite these similarities in chemical structure and metabolism, no meaningful correlation was observed between ADMA and hArg in most studies (Kayacelebi et al. 2015; van der Zwan et al. 2013; März et al. 2010). Nevertheless, considering that ADMA and hArg may act antagonistically on NO synthesis and cardiovascular diseases, it was proposed by Tsikas and Kayacelebi that the hArg/ADMA ratio might serve as a more useful tool in the prediction of cardiovascular risk than these individual parameters alone (Tsikas and Kayacelebi 2014). It has been subsequently shown that cardiovascular diseases, aging, and smoking are associated with lower, and pregnancy with higher hArg/ADMA ratios, but more studies are needed to address this issue (Tsikas and Kayacelebi 2014).

A study in pregnant women observed that hArg is associated with improved endothelial function (i.e., with brachial artery flow-mediated dilation [FMD]), a finding that could putatively be explained by the involvement of hArg in NO metabolism (Valtonen et al. 2008). Along those lines, an inverse correlation was observed in the LURIC study between hArg and markers of endothelial dysfunction (i.e., intercellular adhesion molecule-1 [ICAM-1] and vascular cell adhesion molecule-1 [VCAM-1]) (März et al. 2010). The latter associations could, however, not be replicated in the Dallas Heart study (Atzler et al. 2014a); thus, the association between hArg and endothelial function remains elusive.

Regarding inflammation, most studies have either observed no association or an inverse association between hArg and inflammatory markers such as C-reactive protein (März et al. 2010; Choe et al. 2013b).

hArg concentrations were inversely correlated with the coagulation parameters fibrinogen and D-Dimer in the LURIC study (März et al. 2010). Similar inverse associations of hArg with fibrinogen, β-thrombomodulin, and von Willebrand factor were also reported in a cohort of patients with ischemic stroke (Choe et al. 2013b). In experimental studies, hArg seems to have an inhibitory effect on platelet aggregation (Radomski et al. 1990). Whether the association between hArg and vascular diseases results from an involvement of hArg in the coagulation, remains to be evaluated in forthcoming studies.

Homoarginine and kidney function

Kidney function is closely related to hArg metabolism which can partially be attributed to the fact that the kidney is the major site of AGAT expression (Cullen et al. 2006). To this end, it should be noted that AGAT SNPs emerged as significant predictors of glomerular filtration rate (GFR) in GWAS (Chambers et al. 2010; Kottgen et al. 2009). In line with this, decreased renal AGAT activity has been reported in rabbits with chronic renal failure, and reduced hArg concentrations were found in nephrectomized rats when compared to sham-operated controls (Tofuku et al. 1985; Al Banachaabouchi et al. 2001). Apart from renal AGAT activity, the hArg serum concentration might theoretically be determined by tubular reabsorption of filtered hArg, albeit the studies addressing this issue showed varying results. While one group observed in rats with 42 % nephrectomy an increased urinary excretion of hArg, another group found significantly lower hArg levels in the urine of non-dialyzed CKD patients compared with age-matched controls (Levillain et al. 1995; Marescau et al. 1997). It has

also been shown that hArg at concentrations of 10 mM inhibits arginine uptake into the renal inner medullary collecting duct (Wu et al. 2000). Additional studies are needed to evaluate the potential contributions of decreased AGAT activity and impaired tubular reabsorption to decreased levels of hArg in patients with impaired renal function.

Most, but not all clinical studies have shown that hArg concentrations are reduced in patients with impaired kidney function. The European mild to moderate kidney disease study consisting of 227 CKD patients, who were followed over the course of 7 years with respect to renal outcomes, confirmed a close relationship between hArg and kidney function (Drechsler et al. 2013). In that study, plasma hArg levels were significantly associated with GFR, and low plasma hArg concentrations were identified as a predictor of kidney disease progression and of a primary endpoint defined as doubling of serum creatinine and/or terminal renal failure necessitating renal replacement therapy (Drechsler et al. 2013). Among 168 predialysis CKD patients, there was also a significant correlation between plasma hArg and estimated GFR as well as proteinuria (Ravani et al. 2013). In the latter study, there was an inverse linear relationship between hArg and progression to dialysis after a median follow-up of 4 years. Serum hArg was also associated with estimated GFR in the LURIC study (Tomaschitz et al. 2014). Importantly, in the LURIC study, low serum hArg levels were a stronger predictor of cardiovascular mortality in patients with estimated GFR levels below 60 ml/min per 1.73 m^2 as compared with patients who had a higher estimated GFR, suggesting that kidney function may modify the association between hArg and cardiovascular risk (Tomaschitz et al. 2014). Considering that chronic kidney disease-mineral and bone disease (CKD-MBD) is a significant predictor of adverse outcomes in CKD patients, it is important to note that hArg levels are also associated with parameters of mineral and bone metabolism. It has been well described in experimental studies that hArg (at concentrations of 10 mM) is an inhibitor of bone alkaline phosphatase, which is a known risk factor for adverse outcomes in CKD patients (Magnusson et al. 2002; Drechsler et al. 2011b). In a study comprising 506 female nursing home patients, the investigators confirmed an inverse association between serum hArg and alkaline phosphatase and also reported that low hArg was associated with an increase in several bone markers including parathyroid hormone, and low bone density (Pilz et al. 2013). A relationship between low serum hArg and increased bone turnover has also been described in the LURIC study (Pilz et al. 2012). In addition, patients with primary hyperparathyroidism have significantly lower serum hArg concentrations when compared with matched controls (Tomaschitz et al. 2015). hArg might also play a role in vascular calcification, which is frequently observed in patients with CKD. Experimental studies in rats showed that lysine supplementation, which causes an increase in plasma hArg, ameliorates vascular calcification processes and suppresses parathyroid hormone (Shimomura et al. 2014). In the same study, it has also been shown that 25–100 mM hArg attenuates mineral precipitations in a supersaturated calcium/phosphate solution but does not affect vascular smooth muscle cell apoptosis. However, the effects of hArg itself on the vasculature in CKD remain elusive.

Homoarginine and total mortality

Associations between hArg and total mortality have been examined in several prospective investigations, and the main findings of these studies (fully adjusted/final models) are presented in Table 1. These data are of interest because cardiovascular diseases are the major cause of death in Western societies. The first publication on the association between hArg serum concentrations and mortality was published in 2010 and included data from the LURIC study in 3305 patients referred for coronary angiography and data from the 4D study ("Die Deutsche Diabetes Dialyse Studie") in 1244 patients with type 2 diabetes mellitus receiving maintenance hemodialysis (März et al. 2010). In both studies, low serum hArg was significantly associated with increased mortality despite careful adjustments for a panel of potential confounders. hArg concentrations were significantly lower in the 4D compared with the LURIC study. This indicates that the predictive value of hArg for mortality is evident across a relatively wide range of different plasma levels. In two other studies consisting of 168 predialysis CKD patients as well as 829 renal transplant recipients using data from the Assessment of Lescol in Renal Transplantation (ALERT) study, low plasma hArg concentrations were also associated with increased mortality (Ravani et al. 2013; Drechsler et al. 2015). Results from the Dallas Heart study involving 2290 participants enrolled from the general population showed that every one SD in log-transformed plasma hArg was associated with 18 % reduced mortality in a multivariate adjusted model (Atzler et al. 2014a). In the Hoorn study, a population-based cohort of 606 older individuals residing in the Netherlands, lower plasma hArg, was a strong predictor of premature death and was associated with an increased risk of total mortality, independent of various risk factors (Pilz et al. 2014a). Moreover, in 239 male patients with PAD, low hArg was also associated with increased mortality (Vogl et al. 2015). In that study, hArg significantly improved risk prediction of mortality in addition to established risk factors. In 282 heart failure patients, increasing plasma hArg concentrations were associated with improved survival, and the likelihood ratio test indicated that the addition of hArg to classic cardiovascular risk factors could significantly improve risk

Table 1 Prospective studies on the association between homoarginine and total mortality

References	Population	Country	Age, years	Males (%)	Follow-up, years	No. of subjects	No. of events	Main analysis	Adjusted relative risk (95 % CI)
März et al. (2010)	Patients referred to coronary angiography	Germany	62.7 ± 10.6	70	7.7	3305	766	First vs fourth hArg quartile	2.4 (1.9–3.1)
März et al. (2010)	Diabetic hemodialysis patients	Germany	65.7 ± 8.3	54	4.0	1244	608	First vs fourth hArg quartile	1.6 (1.2–2.0)
Pilz et al. (2014a)	General population	The Netherlands	70.0 ± 6.6	48.7	7.8	606	112	First vs fourth hArg quartile	1.73 (1.05–2.84)
Vogl et al. (2015)	Male PAD patients	Austria	58.0 ± 6.5[a] 62.1 ± 5.0	100	7.0	239	38	Per 0.35 μM hArg	0.59 (0.41–0.84)
Atzler et al. (2014a)	General population	United States	43 (36–52)	44	9.4	2290	218	Per 1 SD log hArg (0.4; antilog = 1.49 μM)	0.82 (0.73–0.92)
Atzler et al. (2013)	Heart failure patients	Germany	55 ± 12	82	3.0	282	85	Per 1 SD log hArg (antilog = 1.55 μM)	0.72 (0.57–0.91)
Choe et al. (2013b)	Stroke patients	UK	NA	NA	7.4	389	229	Per 1 SD log hArg (antilog: 0.215 μM)	0.79 (0.64–0.96)
Pilz et al. (2013)	Nursing home patients	Austria	83.9 ± 6.0	0	2.3	506	119	Per 1 μM hArg	0.60 (0.38–0.95)
Ravani et al. (2013)	Predialysis CKD patients	Italy	70 ± 11	62	4.0	168	103	Per 1 μM hArg	0.37 (0.17–0.81)[b] 0.62 (0.39–0.98)
Drechsler et al. (2015)	Renal transplant recipients	Multi-national study[c]	50 ± 11	65	6.7	829	107	Per 1 μM hArg	0.69 (0.51–0.94)

hArg homoarginine, *PAD* peripheral arterial disease, *CKD* chronic kidney disease, *SD* standard deviation

[a] Upper line shows data for survivors and lower line shows data for nonsurvivors

[b] Upper line shows data for patients with hArg levels <1.375 μM and lower line for patients with hArg levels ≥1.375 μM

[c] Belgium, Denmark, Finland, Germany, Norway, Sweden, Switzerland, UK, and Canada

prediction of mortality (Atzler et al. 2013). Similarly, among 389 stroke patients, increasing plasma hArg concentrations were associated with a decreased mortality risk, but in that study, plasma hArg did not improve risk prediction over classic cardiovascular risk factors (Choe et al. 2013b). An association between low serum hArg and increased mortality was further confirmed in a study in 506 female nursing home patients from Austria (Pilz et al. 2013). We can therefore conclude that independent of classic risk factors low hArg is a significant risk marker for total mortality.

Homoarginine and cardiovascular diseases

The main study results (fully adjusted/final models) on the association between hArg and cardiovascular events are presented in Table 2. In the population-based Dallas Heart study, low plasma hArg was associated with an increased risk of major adverse cardiovascular events (MACE) (Atzler et al. 2014a). In the population-based Hoorn study, low plasma hArg concentrations were also associated with significantly increased risk of cardiovascular mortality but not of cancer mortality (Pilz et al. 2014a). These data might suggest that low hArg concentrations are not simply reflecting a poor overall health outcome, but are specifically related to an adverse cardiovascular outcome. By contrast, hArg was not associated with cardiovascular events in 239 male patients with PAD, but in that study, low hArg was associated with increased risk of cancer mortality (Vogl et al. 2015). There was also no significant association between serum hArg and MACE in renal transplant recipients and in another cohort of patients with PAD (Drechsler et al. 2015; Hafner et al. 2014). In a study in predialysis CKD patients, there was no significant association between plasma hArg and cardiovascular mortality ($p = 0.12$; no further data shown) (Ravani et al. 2013). Low serum hArg was, however, associated with an increased risk of cardiovascular events in patients referred to coronary angiography (LURIC study), diabetic hemodialysis patients (4D study), and stroke patients (März et al. 2010; Choe et al. 2013b). It can therefore be concluded that the majority of the studies observed a significant association between low hArg concentrations and increased risk of cardiovascular events.

While data on cerebrovascular events (e.g., strokes) are further reviewed below, it is important to note that

Table 2 Prospective studies on the association between homoarginine and cardiovascular events

References	Population	Country	Age, years	Males (%)	Follow-up, years	No. of subjects	No. of events	Event type	Main analysis	Adjusted relative risk (95 % CI)
März et al. (2010)	Patients referred to coronary angiography	Germany	62.7 ± 10.6	70	7.7	3281	482	CV mortality	First vs fourth hArg quartile	3.3 (2.4–4.7)
März et al. (2010)	Diabetic hemodialysis patients	Germany	65.7 ± 8.3	54	4.0	1244	307	CV mortality	First vs fourth hArg quartile	1.7 (1.1–2.4)
Pilz et al. (2014a)	General population	The Netherlands	70.0 ± 6.6	48.7	7.8	581	31	CV mortality	First vs upper three hArg quartiles	3.95 (1.89–8.27)
Vogl et al. (2015)	Male PAD patients	Austria	58.2 ± 6.6[a] 59.9 ± 6.1	100	6	239	65	CV events (fatal and nonfatal)	Per 1 µM hArg	1.12 (0.88–1.43)
Atzler et al. (2014a)	General population	United States	43 (36–52)	44	9.4	2983	184	Major adverse cardiovascular events (MACE)	Per 1 SD log hArg (0.4; antilog = 1.49 µM)	0.86 (0.75–0.98)
Choe et al. (2013b)	Stroke patients	Germany	NA	NA	0.08	137	25	Death, stroke, myocardial infarction, and re-hospitalization	Per 1 SD log hArg (0.68; antilog = 1.65 µM)	0.69 (0.50–0.94)
Drechsler et al. (2015)	Renal transplant recipients	Multi-national study[b]	50 ± 11	65	6.7	829	104	MACE	Per 1 µM hArg	0.95 (0.72–1.24)
Hafner et al. (2014)	PAD patients	Austria	64.3 ± 10.2[c] 72.3 ± 9.3	71.6[c] 57.1	8.3	151	49	CV mortality	1.63 (1.24–2.07)[d] 1.43 (1.00–1.84)	NA ($p = 0.05$)

CV cardiovascular, *hArg* homoarginine, *PAD* peripheral arterial disease, *CKD* chronic kideny disease, *SD* standard deviation

[a] Numbers are for patients with no CV event (upper line) vs patients who had CV events (lower line)

[b] Belgium, Denmark, Finland, Germany, Norway, Sweden, Switzerland, UK, and Canada

[c] Numbers are for survivors (upper line) vs patients who died due to CV events (lower line)

[d] hArg concentrations (mean with 95 % CI in µM) in survivors (upper line) vs patients who died due to CV events (lower line)

some investigations reported on hArg in relation to specific cardiovascular events. Two studies observed that low serum hArg is a risk factor for sudden cardiac death, but data are inconsistent regarding the association between hArg and myocardial infarction (Drechsler et al. 2011a, 2015; Pilz et al. 2011b). In the LURIC study, there was a particularly evident association between low serum hArg levels and increased risk of death due to heart failure (Pilz et al. 2011b). Similar data were found in diabetic dialysis patients of the 4D study (Drechsler et al. 2011a). Various cross-sectional studies indicate that low serum hArg is associated with heart failure as evidenced by high natriuretic peptide concentrations and reduced myocardial function (Pilz et al. 2011b, 2014a, b; Vogl et al. 2015; Atzler et al. 2013). Interestingly, a study in patients with takotsubo cardiomyopathy (also known as stress-induced cardiomyopathy or broken-heart syndrome) showed that plasma hArg was significantly reduced in affected patients compared with controls (Kayacelebi et al. 2014). Regarding the close link between AGAT and energy or creatine metabolism, it was hypothesized that low hArg concentrations may reflect low creatine levels and thereby low intracellular energy stores in the failing heart. In this context, it has been shown in mice that elevations of intracellular creatine protect against myocardial infarction (Lygate et al. 2012). The role of intracellular creatine in cardiovascular health is, however, puzzling because it has also been reported that mice with overexpression of the myocardial creatine transporter, and subsequently high intracellular creatine levels develop progressive heart failure (Phillips et al. 2010). Furthermore, the effects of creatine on myocardial function have been questioned by a study showing that creatine-deficient mice have an unaltered maximal exercise capacity and response to chronic myocardial infarction without metabolic abnormalities (Lygate et al. 2013). AGAT might, however, be involved in the pathogenesis of heart failure because AGAT is upregulated in patients with heart failure and returns to normal values during recovery (Cullen et al. 2006). This AGAT upregulation in heart failure could hypothetically be an adaptive mechanism to compensate for myocardial energy deficits, a hypothesis that fits well to the observation that AGAT upregulation is detected in mice with Duchenne muscular dystrophy (McClure et al. 2007). Regarding the link between hArg and heart failure, it is also important to note that pathway analyses suggest that AGAT interacts with mitogen-activated protein kinase-2 (MPKAP2) and interleukin-4 (Hall et al. 2007).

In a case–control study, hArg was, after adjustment for age, CRP, GFR, HDL-cholesterol, and current smoking, inversely associated with symptomatic PAD with an odds ratio (OR) of 0.75 (95 % CI 0.59–0.96; $p = 0.02$) per increase in one SD in ln-hArg (0.35 μM) (Vogl et al. 2015). This association remained significant after additional adjustment for prevalent cardiovascular disease (OR 0.75; 95 % CI: 0.58–0.97; $p = 0.03$), but significance was lost after further adjustment for high sensitive-Troponin T and ln-N-terminal pro-B-type natriuretic peptide (OR 0.84; 95 % CI: 0.66–1.08; $p = 0.18$). In the population-based Dallas Heart study, plasma hArg was inverse and independent of classic cardiovascular risk factors associated with aortic wall thickness but not with aortic plaque burden or coronary artery calcium (Atzler et al. 2014a). Furthermore, in genome wide expression analyses, it was observed that AGAT mRNA expression and protein levels were significantly increased in abdominal aortic aneurysm (AAA) patients compared to controls (Hinterseher et al. 2013).

Homoarginine and stroke

In the LURIC study containing 3305 participants with 9.9 years of follow-up including 991 deaths with 61 fatal strokes, it was firstly shown that higher serum hArg concentrations were independent of established risk factors associated with a significantly reduced risk of fatal strokes (Pilz et al. 2011a). In the same study, those patients with a previous cerebrovascular disease event at baseline had significantly lower serum hArg concentrations compared to those without such an event (Pilz et al. 2011a). In the 4D study in 1244 diabetic dialysis patients, there were 103 strokes (fatal and nonfatal) recorded during a follow-up period of 4 years (Drechsler et al. 2011a). Low serum hArg was significantly associated with a higher stroke risk in crude analyses, but this association diminished toward a nonsignificant trend after adjustment for a panel of cardiovascular risk factors (Drechsler et al. 2011a). In the Leeds Stroke Study, it was further shown in 389 patients with an acute ischemic stroke who were followed for 7.4 years that plasma hArg levels were significantly higher in those who survived compared with those who died during follow-up (Choe et al. 2013b). In the same study cohort, plasma hArg was inversely associated with stroke severity as assessed by the Oxfordshire Community Stroke Project classification. Among 137 patients with ischemic stroke derived from the Harburg Stroke Study, it was shown that after a short-term follow-up of 30 days, plasma hArg concentrations were significantly reduced in patients reaching the primary endpoint of death, nonfatal recurrent stroke, nonfatal myocardial infarction, and rehospitalization compared with those without such an event (Choe et al. 2013b). In the same study, plasma hArg was also inversely associated with the National Institutes of Health Stroke Scale (NIHSS), a tool designed to quantify impairment caused by stroke (Choe et al. 2013b).

Compared with wild-type (WT) littermates, AGAT knockout (KO) mice had larger infarct volumes and worse

neurological deficits following experimental ischemic stroke induced by temporary middle cerebral artery occlusion (Choe et al. 2013b). Pre-treatment of these AGAT KO mice with creatine had no significant effect, but hArg supplementation was associated with a decrease in stroke volume and an improvement of the neurological deficits in AGAT KO mice, GAMT KO mice, and C57BL/6 (WT) mice (Choe et al. 2013b). To evaluate the hypothesis that hArg could exert beneficial effects on strokes by increasing NO, it was further evaluated whether there are differences in neuronal NO, endothelial NOS, inducible NOS, arginase I and II between WT and AGAT KO mice, but no significant differences were observed (Choe et al. 2013b). In general, hArg can be detected in the human brain, and according to the existing literature, both an excess and deficiency of hArg can be detrimental for the central nervous system as extensively reviewed elsewhere (Bernstein et al. 2015).

Conclusions

Clinical studies have shown that low circulating hArg concentrations are an independent risk marker for cardiovascular and renal diseases, as well as mortality. The underlying pathways explaining these associations remain largely undetermined but could be explained, in part, by the notion that hArg metabolism is linked to energy and NO metabolism. Since low hArg concentrations do not just simply reflect a clustering of classic cardiovascular risk factors, it appears that low hArg indicates pathophysiological processes with relevance for major health outcomes that are not completely covered by established risk factors. Therefore, additional studies are urgently required to better clarify the pathophysiological role of hArg in life threatening chronic diseases in an effort to explore the significance of hArg as a potential biomarker for risk prediction along with guiding clinical decision making and to evaluate whether modification of hArg metabolism is a promising drug target for the treatment of chronic diseases.

Conflict of interest The authors declare that they have no conflict of interest.

Ethical standard All studies reported here were approved by the local Ethics Committees.

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