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ORIGINAL ARTICLE

Association of Elevated Plasma Homocysteine Level with Restenosis and Clinical Outcomes After Percutaneous Coronary Interventions: a Systemic Review and Meta-analysis

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Abstract

Purpose We conducted this systemic review and meta-analysis to investigate the association between elevated plasma homocysteine (Hcy) levels and recurrent restenosis and clinical outcomes after percutaneous coronary intervention (PCI).

Methods PubMed, EMBASE, and Web of Science were systematically searched prior to May 2018. Studies evaluating the association between plasma Hcy levels and the occurrence of restenosis, major adverse cardiac events (MACE), all-cause mortality, cardiac death, non-fatal myocardial infarction (MI), and target lesion revascularization were identified.

Results A total of 19 articles with 4340 participants were identified. Higher Hcy levels were not associated with an increased risk of restenosis (relative risk (RR) = 1.10, 95% CI 0.90–1.33). Hcy levels in the restenosis group were not significantly higher than in the non-restenosis group (weighted mean difference = 0.70, 95% CI − 0.23–1.63). Subgroup analysis revealed that higher Hcy levels were not associated with restenosis after stenting but appeared to increase the risk of restenosis after angioplasty. Elevated Hcy levels increased the risk of all-cause mortality by an average of 3.19-fold (RR = 3.19, 95% CI 1.90–5.34, $P = 0.000$), the risk of MACE by 1.51-fold (RR = 1.51, 95% CI 1.23–1.85, $P = 0.000$), and the risk of cardiac death by 2.76-fold (RR = 2.76, 95% CI 1.44–5.32, $P = 0.000$) but appeared not to increase the risk of non-fatal MI (RR = 1.36, 95% CI 0.89–2.09).

Conclusions Our meta-analysis suggests that although there is no clear association between higher Hcy levels and restenosis following stent implantation, higher Hcy levels appeared to increase the risk of restenosis after coronary angioplasty and also increased the risk of all-cause mortality, MACE, and cardiac death after PCI.

Registration Details The protocol of this meta-analysis was registered on PROSPERO (CRD42018096466). (http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018096466).

Keywords Homocysteine · Restenosis · Percutaneous coronary intervention · Meta-analysis

Introduction

Homocysteine (Hcy), a sulfur-containing amino acid, is mainly derived through methionine (Met) metabolism, rather than directly from food, in human beings. It subsequently undergoes metabolism through two major pathways: remethylation to Met or trans-sulfuration to cysteine [1]. In addition to mutations in genes encoding enzymes in Hcy metabolic pathways, elevated levels of Hcy are also attributed to vitamin deficiencies, excessive Met intake, pregnancy, the use of certain medications, and other factors [1, 2]. As has been extensively documented, higher levels of Hcy are closely correlated with coronary heart diseases, atrial fibrillation, stroke, arterial stiffness, and other cardiovascular diseases (CADs) [3–6]. Hcy, as a novel and modifiable risk-factor, has now been given considerable attention for the management of CAD.

Percutaneous coronary intervention (PCI) is an indispensable alternative to bypass surgery in the treatment of coronary artery disease. However, the prevalent application and beneficial value of PCI have been greatly hindered by the occurrence of restenosis. Restenosis is a complicated

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pathophysiological process, for which the underlying mechanisms have not been well defined, and it is speculated to involve elastic recoil, vascular remodeling, and neointimal hyperplasia [7]. Several studies have suggested that Hcy might contribute to restenosis after PCI by causing endothelial injuries, thrombus formation, the proliferation of smooth muscle cells, and the synthesis of collagen [8–10]. Clinical trials have reported conflicting results regarding the association between Hcy levels and restenosis and clinical outcomes after PCIs, and we aimed to further explore this association through a meta-analysis.

Methods

Our study has been registered, and the protocol can be accessed at http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018096466 (Registration number: CRD42018096466). This review was performed following PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) guidelines [11].

The literature retrieval was conducted using PubMed, EMBASE, and Web of Science databases prior to May 2018 for potentially relevant articles, with no language restrictions.

The search strategies in PubMed were presented as follows: ((“Percutaneous Coronary Intervention”[Mesh]) OR (Percutaneous Coronary Revascularization [Title/Abstract]) OR (Stents [Mesh]) OR (stent [Title/Abstract]) OR (stenting [Title/Abstract]) OR (Angioplasty, Balloon [Mesh]) OR (Dilation, Transluminal Arterial [Title/Abstract]) OR (Arterial Dilation, Transluminal [Title/Abstract]) OR (Arterial Dilations, Transluminal [Title/Abstract]) OR (Dilations, Transluminal Arterial [Title/Abstract]) OR (Transluminal Arterial Dilation [Title/Abstract]) OR (Transluminal Arterial Dilations [Title/Abstract]) OR (Balloon Angioplasty [Title/Abstract]) OR (Angioplasty [Title/Abstract]) OR (“Atherectomy”[Mesh]) OR (Atherectomies [Title/Abstract])) **AND** ((“Homocysteine”[Mesh]) OR (2-amino-4-mercaptobutyric acid [Title/Abstract]) OR (2 amino 4 mercaptobutyric acid [Title/Abstract]) OR (Homocysteine, L-Isomer [Title/Abstract]) OR (L-Isomer Homocysteine [Title/Abstract]) OR (S-Adenosylhomocysteine [Title/Abstract])).

The inclusion criteria were the following: (1) observational studies investigating the relationship between plasma Hcy levels and the occurrence of restenosis, composite primary end points, major adverse cardiac events (MACEs), all-cause mortality, cardiac death, non-fatal myocardial infarction (MI), and target lesion revascularization (TLR) after PCI, and (2) data were available for meta-analysis.

The exclusion criteria were the following: (1) case reports, reviews, meeting abstracts, and editorials; (2) studies that were conducted in a particular population, e.g., patients with diabetes mellitus or undergoing dialysis; and (3) studies evaluating Hcy-lowering therapy and clinical outcomes.

Two reviewers (Zhipeng Zhang and Changqiang Yang) independently extracted the relevant information regarding the first author, year of publication, country or area, study type, duration of follow-up, sample size, Hcy assay method, study end point, cases, and total numbers of the experimental and control groups. All disagreements were settled through discussion. In addition, we sent requests to corresponding authors for missing data via e-mail.

The study quality was evaluated by the Newcastle–Ottawa Scale (NOS) [12]. Newcastle–Ottawa Scale comprises three sections: population selection (four items), comparability (one item), and outcome (three items). Each of the items can be given one score except for comparability which can be given a maximum of two scores. Studies with a total score < 7 were considered “low quality.”

All statistical analysis was performed using STATA MP 14.0 (Stata Corp LP, College Station, TX, USA). A P value of less than 0.05 was considered to indicate statistical significance. Relative risks (RRs) and 95% CIs of the higher Hcy category versus the lower Hcy category were calculated and pooled using a fixed or random effects model. For continuous variables, such as Hcy levels, weighted mean difference (WMD) was used as the measurement. Heterogeneity across studies was quantified using the χ^2 test and the I^2 statistic. An I^2 value of less than 25%, 50%, and 75% was considered to indicate a low, moderate, and high risk of heterogeneity, respectively. If heterogeneity was significant, subgroup analysis and meta-regression were performed to detect the potential sources. Funnel plots and the Egger test were performed to detect potential publication bias.

Results

A total of 773 articles were identified from the initial retrieval (PubMed = 89, EMBASE = 381, Web of Science = 303). Finally, 19 articles with 4340 participants were included in the meta-analysis following the inclusion and exclusion criteria [13–31]. The details of the screening process are presented in Fig. 1.

The study characteristics are displayed in Table 1. Among the 19 studies, seven (36.8%) were performed in Asia, seven (36.8%) in Europe, four (21.1%) in North America, and one (5.3%) in New Zealand. All were cohort studies published between 2000 and 2017. Six studies measured Hcy levels through a fluorescence polarization immunoassay, ten studies through high-performance liquid chromatography with fluorescence detection, one used an Alfresa Auto Hcy Kit, and another two studies did not declare the exact methods used. Of the 19 studies, most excluded patients with renal

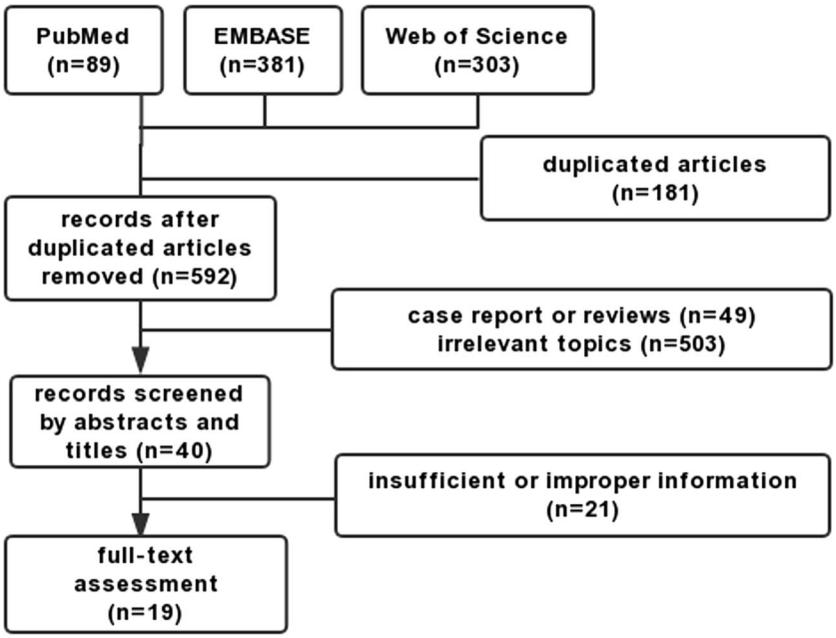

Fig. 1 The flow chart of the meta-analysis

dysfunction, and seven studies did not report any information about creatinine.

Nine studies [14, 16–19, 21, 25–27] involving 3296 patients reported the impact of higher Hcy levels on the occurrence of restenosis after PCI. As shown in Fig. 2, higher Hcy levels appeared to not be associated with a greater risk of restenosis (RR = 1.10, 95% CI 0.90–1.33). The heterogeneity across studies was almost significant ($I^2 = 49.1\%$, $P = 0.047$). We performed a subgroup analysis using available information concerning whether all participants received stent implantation ("angioplasty" = all participants received angioplasty only; "combination" = some participants received angioplasty only and some received angioplasty plus stent implantation, the particular proportions were not available; "stent" = all participants received stent implantation). The results suggest that heterogeneity in the stent subgroup was insignificant ($I^2 = 0.0\%$, $P = 0.761$). Considering that the cutoff points of higher versus lower Hcy levels were different across the studies, we conducted a meta-regression analysis taking the cutoff points as a covariate. The results suggested that the cutoff points could not explain the heterogeneity (adjusted R-squared = − 34.68%, $t = -0.22$, $P = 0.832$); namely, the different cutoff points did not influence the total effects. There was no publication bias, as assessed using Egger's test ($t = 0.12$, $P = 0.905$).

Eleven studies [15, 17–22, 24, 28, 29, 31] evaluated the differences in Hcy levels between a restenosis group and a non-restenosis group. Of the remaining 11 studies with 1887 participants, the overall WMD was 0.70 μmol/l (95% CI − 0.23–1.63) with a significant heterogeneity ($I^2 = 73.2\%$, $P = 0.000$). We also performed a subgroup analysis using the available information on whether all participants received stent implantation (as mentioned above). The results revealed that the heterogeneity in the angioplasty and stent subgroups was negligible ($I^2 = 0.0\%$, $P = 0.413$ vs $I^2 = 0.0\%$, $P = 0.518$, respectively), as shown in Fig. 3. The differences in Hcy levels between the restenosis and non-restenosis group were significant in the angioplasty subgroup (WMD = 2.33 μmol/l, 95% CI 1.35–3.31) but not in the stent subgroup (WMD = − 0.35 μmol/l, 95% CI − 0.93–0.24). Publication bias was not detected using Egger's test ($t = 0.69$, $P = 0.505$).

Of the 19 studies, five [14, 16, 25, 30, 32] reported the impact of Hcy levels (higher versus lower) on all-cause mortality. Among the 3337 patients, 166 events occurred in the higher Hcy group and 156 in the lower Hcy group. The pooled RR was 3.19 (95% CI 1.90–5.34, $P = 0.000$) with heterogeneity ($I^2 = 55.6\%$, $P = 0.061$).

Among the 4135 participants [14, 16, 23, 25, 26, 32], MACE was seen in 15.2% ($n = 381$) of subjects in the lower Hcy category and 21.9% ($n = 358$) in the higher Hcy category. The results suggest that elevated Hcy levels increase the risk of MACE after PCI (RR = 1.51, 95% CI 1.23–1.85, $P = 0.000$) with low heterogeneity across the studies ($I^2 = 39.3\%$, $P = 0.144$).

Four [14, 16, 25, 26] studies involving 2682 participants assessed the impact of Hcy levels on cardiac death. A total of 56 cardiac deaths occurred in the higher Hcy group and 36 in the lower Hcy group. As shown in Fig. 4, higher Hcy levels increased the risk of cardiac death by approximately 2.76-fold compared with lower Hcy levels (RR = 2.76, 95% CI 1.44–5.32, $P = 0.000$). The heterogeneity was insignificant ($I^2 = 24.3\%$, $P = 0.260$).

Five studies [14, 16, 25, 26, 32] investigated the relationship between higher Hcy levels and non-fatal MI. Among the

Table 1 Basic characteristics of the included studies

Study	Year	Country/area	Design	Age/range mean (SD)	Sample size	Follow-up period	End point	Comparison
Yi Ma	2013	China	Cohort	46–71	805	30 days	All-cause mortality; MACE	Hcy (μmol/l): < 15.0 μmol/l vs ≥ 15.0 μmol/l
G. Schnyder	2002	USA	Cohort	50–73	205	20 ± 13 weeks	Restenosis; all-cause mortality; MACE	Restenosis vs non-restenosis; Hcy (μmol/l): < 9.0 μmol/l vs ≥ 9.0 μmol/l
Paolo Ortolani	2004	Italy	Cohort	65.3 ± 10.7	196	17.8 ± 7.5 months	Restenosis; all-cause mortality; MACE	Hcy (μmol/l): < 17.0 μmol/l vs ≥ 17.0 μmol/l
Israel Hodish	2002	Israel	Cohort	44–74	55	1 years	Restenosis	Restenosis vs non-restenosis; Hcy (μmol/l): < 11.0 μmol/l vs ≥ 11.0 μmol/l
Nithi Mahanonda	2001	Thailand	Cohort	48.98–73.82	100	6 months	Restenosis	Restenosis vs non-restenosis; Hcy (μmol/l): < 12.0 μmol/l vs ≥ 12.0 μmol/l, < 15.0 μmol/l vs ≥ 15.0 μmol/l
Hiroyuki Morita	2000	Japan	Cohort	62.2 ± 8.9	112	3–6 months	Restenosis	Restenosis vs non-restenosis; Hcy (μmol/l): < 17.1 μmol/l vs ≥ 17.1 μmol/l.
Sirikci, O.	2000	Turkey	Cohort	56 ± 10	146	6.9 ± 3.6 months	Restenosis	Restenosis vs non-restenosis
Werner Koch	2003	Germany	Cohort	53.1–78.9	800	6 months	Restenosis	Restenosis vs non-restenosis; Hcy (μmol/l): < 11.6 μmol/l vs ≥ 11.6 μmol/l.
Steven E.S. Miner	2000	Canada	Cohort	56 ± 10	159	6 months	Restenosis	Restenosis vs non-restenosis
Karl Stangl	2000	Germany	Cohort	54.5–66.2	648	30 days	MACE	Hcy (μmol/l): < 15.0 μmol/l vs ≥ 15.0 μmol/l.
Kumbasar, S. D.	2001	Turkey	Cohort	48.3–67.1	56	6 months	Restenosis	Restenosis vs non-restenosis
Yeh, J. K.	2017	China	Cohort	62 ± 12	1307	58 ± 41 months	All-cause mortality; MACE	Hcy (μmol/l): < 12.0 μmol/l vs ≥ 12.0 μmol/l.
Zairis, M. N.	2002	USA	Cohort	59.3 ± 10	465	22.1 ± 8.3 months	Restenosis; MACE	Hcy (μmol/l): < 13.0 μmol/l vs ≥ 13.0 μmol/l.
Wong, C. K.	2004	New Zealand	Cohort	47.8–71.4	134	6–6.8 months	Restenosis	Hcy (μmol/l): < 13.11 μmol/l vs ≥ 13.11 μmol/l.
Schnyder, G.	2002	USA	Cohort	49–76	504	1 year	All-cause mortality; MACE	Hcy (μmol/l): < 8.6 μmol/l vs ≥ 8.6 μmol/l.
Breuckmann, F.	2006	Germany	Cohort	61 ± 9	143	6 months	Restenosis	Restenosis vs non-restenosis
Jae, Y. C.	2007	Korea	Cohort	35.6 ± 4	121	NK	Restenosis	Restenosis vs non-restenosis
Hassan, A.	2017	Japan	Cohort	66 ± 9	315	10.5 years	All-cause death	Hcy (μmol/l): < 13.5 μmol/l vs ≥ 13.5 μmol/l.
Genser, D.	2002	Austria	Cohort	54.1–68.5	262	6.3 ± 1 months	Restenosis	Restenosis vs non-restenosis

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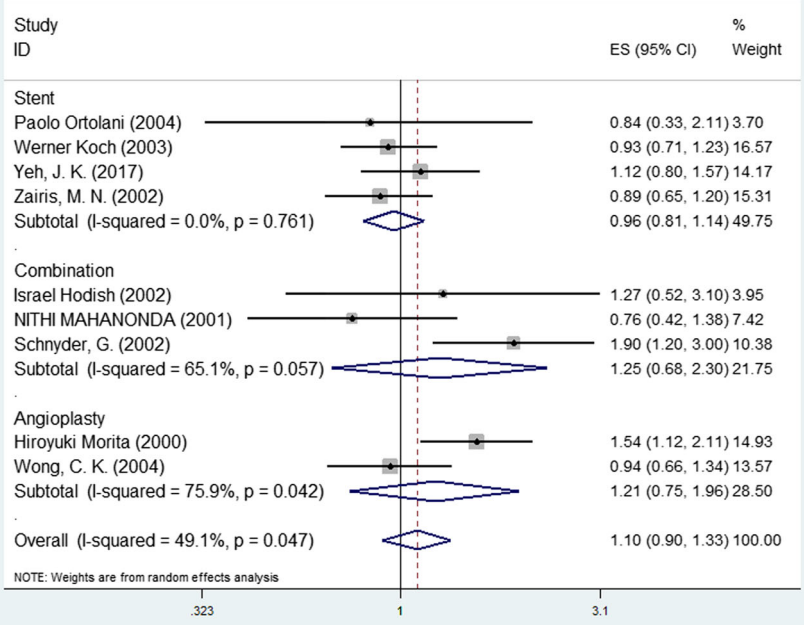

Fig. 2 Meta-analysis of RRs in studies evaluating the link between Hcy levels and restenosis in higher vs lower Hcy categories. RR relative risk, Hcy homocysteine; stent: all subjects in the studies received stent implantation; combination: some subjects in the studies received angioplasty and others received stenting plus angioplasty; angioplasty: all subjects in the studies received angioplasty only

3487 participants, 63 encountered non-fatal MI in the higher Hcy category and 57 in the lower Hcy category. The results suggested that there was no significant link between elevated Hcy and the occurrence of non-fatal MI (RR = 1.36, 95% CI 0.89–2.09). The heterogeneity among studies was low (I^2 = 18.2%, P = 0.299) when a fixed-effects model was used.

Of the 19 studies, only two studies [14, 25] involving 2021 subjects evaluated the link between higher Hcy levels and the incidence of TLR. The incidence of TLR in the lower Hcy category and the higher Hcy category was 9.9% vs 11.1% and 6.6% vs 12.7%, respectively.

Discussion

The findings of the current study are as follows: (1) Overall, elevated Hcy levels have no significant effects on the restenosis rate after PCI. Subgroup analysis suggested that a link between higher Hcy levels and restenosis was not definite after coronary stent implantation. However, higher Hcy levels appeared to increase the risk of restenosis after coronary angioplasty; (2) elevated Hcy levels increased the risk of all-cause mortality by an average of 3.19-fold, the risk of MACE by 1.51-fold, and the risk of cardiac death by 2.76-

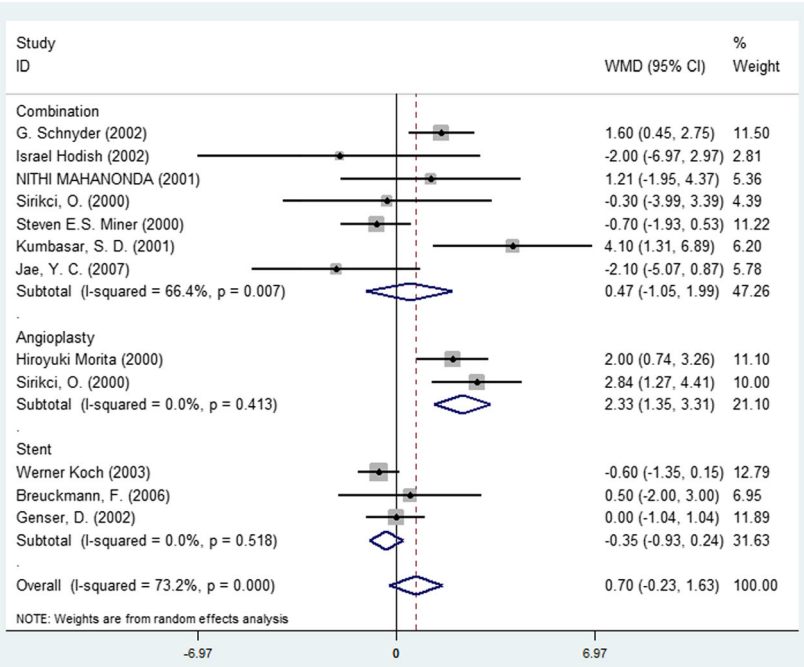

Fig. 3 Meta-analysis of the mean differences in studies evaluating the link between Hcy levels and restenosis in restenosis vs non-restenosis categories. WMD weighted mean difference, Hcy homocysteine

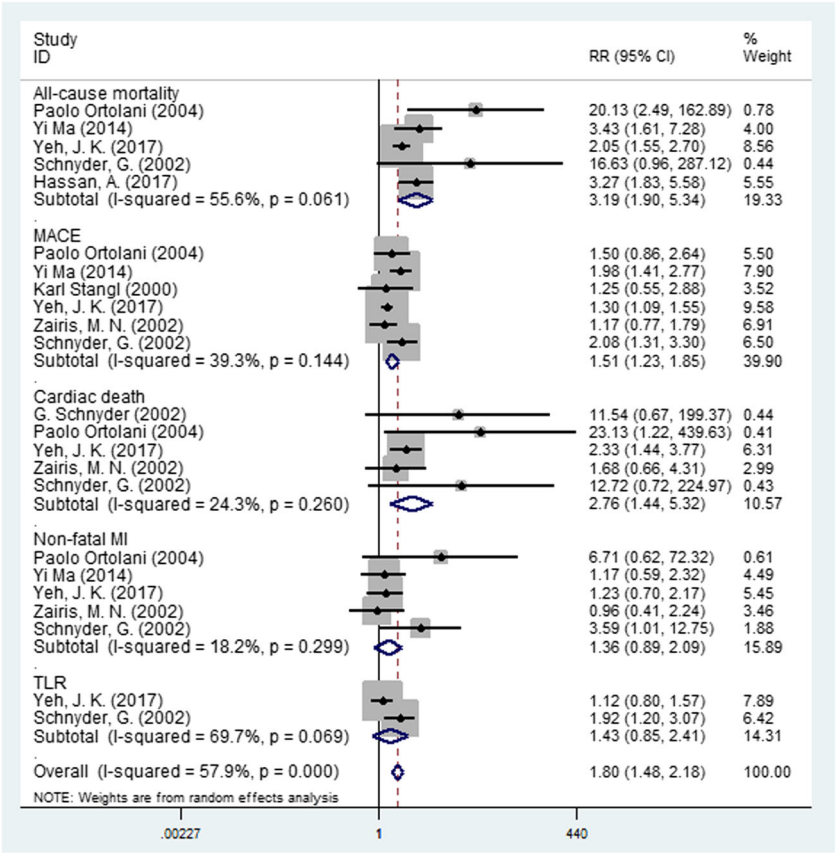

Fig. 4 Meta-analysis of RRs in studies evaluating the link between Hcy levels and the occurrence of all-cause mortality, MACE, cardiac death, non-fatal MI and TLR in higher vs lower Hcy categories. RR relative risk, Hcy homocysteine, MACE major adverse cardiac events, MI myocardial infarction, TLR target lesion revascularization

fold; (3) there appeared to be no significant link between elevated Hcy and the occurrence of non-fatal MI; and (4) the incidence of TLR appeared to be higher in the elevated Hcy category.

Disputes exist regarding whether elevated Hcy levels increase the risk of restenosis after PCI. Hiroyuki M. and colleagues reported a positive correlation in this regard in subjects undergoing coronary angioplasty [18]. Ortolani P. et al. reported that Hcy could not be used as a prognostic indicator for in-stent restenosis in subjects receiving stent implantation [16]. There are also many studies evaluating such a correlation by recruiting subjects undergoing a mix of angioplasty and stent implantation, that is, some participants in the study received angioplasty and others received stent implantation. In the current meta-analysis, we found a negative association between Hcy levels and restenosis after PCI with modest heterogeneity. We therefore performed a meta-regression analysis by including publication year, study area, sample size, and NOS score but failed to find potential sources of heterogeneity. The incidence of restenosis possibly varied in the angioplasty and stent group, and we speculated that the heterogeneity resulted from the proportions of subjects undergoing angioplasty and stent implantation in different studies. Subsequently, we conducted a subgroup analysis by stent, combination and angioplasty with the available extracted information. The results suggested that Hcy levels were not associated with the occurrence of restenosis after stent implantation in the higher vs lower Hcy category and the restenosis vs non-restenosis group. For the angioplasty subgroup, in restenosis vs non-restenosis comparisons, Hcy levels were significantly higher in the restenosis group. In higher vs lower Hcy comparisons, Wong, C. K. et al. reported that higher Hcy levels did not increase the risk of restenosis after angioplasty; however, their study excluded subjects with insulin dependent diabetes (type 1) and only 5% of subjects had non-insulin dependent diabetes (type 2). Moreover, many studies have reported the role of elevated Hcy in the development of diabetes mellitus [33–35] and the exclusion of subjects with diabetes mellitus could possibly reduce the proportion of hyperhomocysteinemic subjects. We determined the proportions of individuals with diabetes mellitus in other studies included in this analysis. The results varied from 16.3 to 40.2% (16.3%, 19.7%, 22%, 30.5%, and 40.2%, respectively). Accordingly, we concluded that elevated Hcy levels appear to increase the risk of restenosis after coronary angioplasty but had no effect for stent implantation.

Experimental results have shown that Hcy increased the expression of monocyte chemotactic protein 1 and interleukin-8, which facilitated the migration and adhesion of monocytes to the endothelium [36]. Hcy was also shown to activate nuclear factor kappa B, a transcription factor that is pivotal in stimulating the production of cytokines, leukocyte adhesion

molecules, chemokines, and hemopoietic growth factors, all of which were demonstrated to participate in vascular inflammation [37]. These inflammatory pathways contribute to atherosclerosis by promoting endothelial dysfunction, oxidative stress, platelet activation, hypercoagulation status, the proliferation of smooth muscle cells, and synthesis of collagen [10, 38]. These pathophysiological processes also correlate closely with vascular remodeling, which is referred to as a permanent change in artery diameter after vascular injury. We speculated that long-term exposure to high Hcy made the vascular wall more prone to vascular remodeling. Vascular remodeling is essential in restenosis, and many factors are involved in this pathophysiological process. Therefore, we speculate that Hcy is a marker of this process, rather than a cause, and elevated Hcy represents a greater possibility of vascular remodeling. The main mechanisms of restenosis after angioplasty are elastic recoil and vascular remodeling. The dominant process in restenosis after stenting is neo-intimal hyperplasia [39, 40]. Stents effectively hinder elastic recoil and vascular remodeling. The role of neo-intimal hyperplasia in the development of restenosis has been reduced with advances in stent technology and the development of P2Y12 inhibitors. Therefore, it is comprehensible that Hcy is not associated with restenosis after stenting.

A dose–response meta-analysis has previously reported a linear trend between Hcy levels and all-cause mortality in the general population and each 5 μmol/l increase in Hcy levels was related to a 1.336-fold risk of all-cause mortality [41]. While many studies have explored the link between Hcy levels and long-term outcomes after PCI, the results are inconsistent and conflicting [16, 23, 26]. Sample sizes, the included population, basic characteristics, assessment methods, and follow-up period varied among these studies. The present meta-analysis indicated that elevated Hcy levels are associated with a higher risk of all-cause mortality, MACE, and cardiac death. The underlying mechanisms have not been clearly elucidated. Studies have suggested a direct relationship between Hcy and multi-vessel lesions and heart failure [14, 42]. We speculate that the link between Hcy and MACE (mainly cardiac death) might be mediated by multi-vessel lesions and heart failure through Hcy-induced endothelial dysfunction, oxidative stress, platelet activation, hypercoagulation status, the proliferation of smooth muscle cells, and collagen synthesis. It is also possible that Hcy is involved in many chronic diseases, such as CAD, cognitive disorders [43], and thrombogenesis [25], which together give rise to the long-term prognosis.

In the past 10 to 15 years, the role of Hcy in CAD has been challenged by many negative results in cohort studies and also randomized controlled studies involving vitamin B complex and folate. Ching-Yu Julius Chen et al. [44] disclosed that Hcy levels were not increased in patients with ST segment elevation myocardial infarction (STEMI), regardless of Killip classifications and they proposed that Hcy was a bystander rather than a causative factor in STEMI. In their study, the mean Hcy concentration was considerably low (8.4 ± 2.2 μmol/l). A study by Bleie Ø et al. [45] revealed that Hcy-reducing therapy did not change the serum concentrations of inflammatory markers of atherosclerosis in patients with stable CAD after a 6-month follow-up (Hcy 11.0 μmol/l at baseline). A meta-analysis of randomized controlled trials [46] suggested that supplementation with B vitamins and folic acid could lower plasma Hcy levels but failed to decrease the risk of cardiovascular diseases and all-cause mortality [44]. However, most patients in these trials had normal or moderately elevated Hcy levels at baseline. Given that mean Hcy levels and genetic backgrounds are diverse in different areas, the effects of Hcy on CAD might be different among populations with varying average Hcy levels. Besides, the significant advances in PCI and drug-eluting stents, together with new anti-platelet drugs, have greatly decreased the occurrence of restenosis and adverse cardiac events and might attenuate the effect of Hcy in CAD. The most appropriate form of intervention in hyperhomocysteinemia still remains to be verified through large-scale randomized trials. Such trials could also help to identify individuals at high risk of developing restenosis after angioplasty and long-term adverse events after PCI.

The current study has some limitations. Firstly, the respective proportions of subjects receiving angioplasty or stenting were not available in certain studies, which confined the stratification analysis and made the total effects analysis less convincing. Secondly, most of the included studies provided only two categories of Hcy levels, and the dose–effect relationship of Hcy and the end point could not be evaluated through a dose–response analysis. Thirdly, the number of studies was not sufficient, and the conclusions need to be verified through more large-scale randomized studies. Fourthly, kidney function and vitamin intake can have a considerable impact on plasma Hcy levels. However, seven of the 19 studies did not provide any information about creatinine and only a few studies mentioned that they excluded patients receiving B complex vitamins, folate-containing supplements, and other drugs that interfere with Hcy levels. Lastly, the cutoff point for higher vs lower Hcy categories was not consistent among studies, and this might have some influence on the total effects, although it is not a potential source of heterogeneity. In fact, people in different areas have various living habits and genetic backgrounds. The mean Hcy levels were diverse, ranging from 6.7 μmol/l in Kuwait to 14 μmol/l in Italy [47, 48]. Therefore, high and low levels were relative, and we pooled the data to find differences in levels of restenosis between higher and lower Hcy groups.

In summary, our meta-analysis suggested that although there is no clear association between higher Hcy levels and restenosis following stent implantation, higher Hcy levels appeared to increase the risk of restenosis after coronary

angioplasty. Elevated Hcy levels also increased the risk of all-cause mortality, MACE, and cardiac death after PCI.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that there is no conflict of interests.

Statement of Human and Animal Rights All procedures involving human participants were performed in accordance with ethical standards of local committee. This article does not contain any studies with human or animal subjects performed by any of the authors.

Informed Consent The informal consent is not required.

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