Association of metformin on mortality and cardiovascular events in patients with pre-existing cardiovascular diseases

BACKGROUND Metformin is a first-line drug in type 2 diabetes mellitus (T2DM) treatment, whereas whether metformin reduce all-cause, cardiovascular mortality, and incidence of cardiovascular events in patients with cardiac diseases remains inconclusive.

OBJECTIVES To evaluate the effects of metformin on the mortality and incidence of cardiovascular events in patients with cardiac diseases

METHODS PubMed and Embase were searched up to May 2020 for randomized controlled trials (RCT) (PROSPERO, CRD42020189905). Hazard ratio (HR) with 95% CI was pooled across various trials by a random-effects model.

RESULTS This article enrolled 48 articles (1999-2020) for qualitative synthesis and identified 26 articles (33 studies in total, 61,704 patients) for final quantitative synthesis. Compared with non-metformin control, metformin is associated with reduced all-cause mortality (HR: 0.90; 95% CI: 0.83, 0.98; P = 0.01), cardiovascular mortality (HR: 0.89; 95% CI: 0.85, 0.94; P < 0.0001), incidence of coronary revascularization (HR: 0.79; 95% CI: 0.64, 0.98; P = 0.03), and heart failure (HR: 0.90; 95% CI: 0.87, 0.94; P < 0.0001) in patients with cardiac diseases, whereas metformin is not associated with reduced incidence of myocardial infarction (HR: 0.97; 95% CI: 0.80, 1.17; P = 0.73), angina (HR: 0.29; 95% CI: 0.04, 2.35; P = 0.25), and stroke (HR: 0.95; 95% CI: 0.78, 1.16; P = 0.59).

CONCLUSIONS Metformin reduces all-cause mortality, cardiovascular mortality, incidence of coronary revascularization, and heart failure of patients with cardiac diseases, whereas metformin is not associated with reduced incidence of myocardial infarction, angina, and stroke.

KEY WORDS: Metformin; Mortality; Cardiovascular diseases; Myocardial infarction; Heart

failure；Diabetes

1. Introduction

Cardiovascular disease (CVD) is the major cause of death and imposes an immense health and economic burden globally. The prevalence of CVD (comprising coronary heart disease, heart failure, stroke, and hypertension) in adults ≥20 years of age is 48.0% overall (121.5 million in 2016) and increases with age in both males and females (1). Based on 2016 data, approximately 17.6 million deaths were attributed to CVD globally, a 14.5% increase since 2006 (1). With the aging population, CVD has become a major public health issues for healthcare systems worldwide.

Metformin is a biguanide derivative that is used as the first-line treatment for type 2 diabetes mellitus (T2DM) patients that reduces blood glucose. It was recommended by the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) to treat T2DM since 1957 (2,3). Besides from its efficacy in improving glycemic profile and reducing cardiovascular mortality, metformin does not induce hypoglycemia and/or body weight gains like other antidiabetic drugs (4,5). The incidence of lactic acidosis associated with metformin treatment is low, compared to phenformin and buformin, which were removed from the market in most countries in the late 1970s (6).

Application wise, metformin has been shown to confer protective roles against cancer, CVD, and nervous system disease. Mechanistically, metformin has been shown to reduce blood glucose levels in T2DM which provides vascular protection (7), regulate autophagic flux (8), and regulate AMPK/energetic pathways (9,10). However, it remains elusive as to whether metformin confers cardiovascular protection for cardiac patients. Conflicting reports have shown that metformin treatment for T2DM patients can either reduce (11) or fail to reduce (12,13) all-cause and cardiovascular mortality in patients with pre-existing cardiac diseases. Given single clinical studies

might be underpowered to detect the overall effects, here a meta-analysis of published data was used to evaluate if metformin treatment can reduce all-cause mortality, cardiovascular mortality, and recurrent cardiovascular events.

2. Methods

2.1 Study protocol

This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) of the *Cochrane Handbook for Systematic Reviews of Interventions* (14) (Table S6) and is registered on PROSPERO (CRD42020189905). Data inclusiong, exclusion, and processing were performed in nadherece to the guideline of The Francis A. Countway Library (Harvard University, Cambridge, MA, USA) and Health Information Research Unit (MaMaster University, Hamilton, Canada).

2.2 Search strategy

Two reviewers (Li and Jiang) independently searched the Cochrane Collaboration, PROSPERO, Joanna Briggs Institute (JBI), and INPLASY database to avoid any duplicates in published meta-analyses. Studies up to May 19, 2020 were compiled from PubMed and Embase by using medical subject headings (MeSH), Emtree, and text word with no language limitations (Table S1). Non-English publications analyzed here will be posted on Cochrane TaskExchange (https://taskexchange.cochrane.org/) or other means through voluntary interpreters. Manual search of relevant studies, reviews, comments, editorials, and letters were also performed.

Identified publications were imported into EndNote X9.1 (Clarivate Analytics, Philadelphia, USA), duplicate records and irrelevant literature were removed, and appropriate studies with detailed classification were compiled. In addition, full text and raw data were obtained through

correspondence. Any inconsistency was forwarded to a third reviewer (Ma) for final decision. Publication inclusion criteria is outlined in Table S2.

2.3 Data extraction

Two reviewers (Li and Jiang) independently extracted data from the same set of publications. The following information were extracted: first author, publication year, journal, PubMed ID (PMID) region, study design, types of pre-existing CVD, age, male (%), intervention/control group, sample size, age, male percentage, and follow-up duration. Primary outcomes were defined as all-cause and cardiovascular mortality. Secondary outcomes included myocardial infarction, coronary revascularization, angina, heart failure, and stroke.

2.4 Cohen's kappa coefficient

Cohen’s kappa coefficient (κ) was utilized to measure the inter-rater agreement of enrolled studies (15). Cohen's kappa measures the agreement between two raters who each classify N items into C mutually exclusive categories.

2.5 Summary of effect size

Relative hazard risk (HR) with 95% confidence intervals (CI) of homogenous dichotomous data were calculated. The weight of enrolled studies accounted for by taking into account of the size of treatment group, control group, and total sample size. Z-test was calculated and therapeutic efficacy was deemed significant with a $P < 0.05$ cutoff. No statistical difference was concluded in the event where 95% CI and null line intersected.

2.6 Risk of bias

The risk of bias calculations were performed in accordance to the Cochrane guidelines (16) (Table S4) and Newcastle–Ottawa scale tool (Table S5).

2.7 Heterogeneity analysis

Heterogeneity was assessed using chi-squared test and I^2 test. High heterogeneity was defined with a chi-squared test $P < 0.10$ and $I^2 > 50\%$ (Bubble plot) (17). Subgroup analysis was carried out using categorical moderators, and meta-regression was performed when at least one of the moderator is continuous. Labbe and Galbraith plot were used for intuitive judgment of heterogeneity. Random effect model was used for pooling the effect size.

2.8 Sensitivity and publication bias

Sensitivity analysis was performed data was deemed with high heterogeneity. Analyses included funnel plot, trim-and-fill funnel plot, and contour-enhanced funnel plot to estimate the effect of sensitivity on the interpretation of the results (abscissa means effect size (HR) and ordinate means standard error of HR) (18). Publication bias was accounted for by implementing Begg's funnel plot and Egger's test, and significant publication bias was defined as $P < 0.10$.

2.9 Other methods

Statistical tests were performed using two-tailed t-test and P value < 0.05 was deemed statistically significant. Data were analyzed using STATA 16.0 (Stata Corp, College Station, TX, USA) and Review Manager 5.3 (Nordic Cochrane Center, Copenhagen, Denmark).

3. Results

3.1 Literature search

We did not find any duplicates in meta-analysis topics in the databases used. High agreement value of initial decisions on the inclusion of studies was indicated ($\kappa = 0.825$, 95% CI: 0.728–0.917). A total of 2921 literature were identified during the initial search, after excluding duplicate records (n = 332). Seventy-four articles were retained after title/abstract curation (excluding 2847 records) (Table S3). Thereafter, we read the full text and enrolled 22 articles (containing 35 clinical studies in total) for qualitative synthesis and identified 26 articles (containing 33 clinical studies in total) for final quantitative synthesis (Fig 1).

3.2 Study characteristics

The characteristics of included studies for quantitative (26 articles, 33 studies, 61,704 patients) (18-43) and qualitative analysis (22 articles, 35 studies, 30,479 patients) (44-65) are exhibited in Table 1 and Table 2, respectively. Some articles contain a few of studies themselves, that is to say, one article contains several studies.

For quantitative analysis, studies originated from North America, Europe, Asia, and multiple countries spanning between 1999 and 2020. Twenty-two studies reported the outcome of all-cause mortality (19,20,22,24-32,35,36,38,43,66), 8 studies reported cardiovascular mortality (20,22,28,33,36,39,41,42), 6 studies reported myocardial infarction (22,28,30,32-34), 5 studies reported coronary revascularization (23,28,32,34,37), 1 studies reported angina (33), 6 studies reported heart failure (19,22,30,35,38,39), and 3 studies reported stroke (22,28,33) (Table 1). Information for qualitative analysis can be found in Table 2.

3.3 Risk of bias

Methodological quality score and risk-of-bias assessments of selected articles are summarized in Table S6 and Fig S1, respectively. For RCT, 2 articles had a low risk of bias while 3 articles had a moderate risk. Most studies were categorized as moderate risk due to the lack of random sequence generation and allocation concealment. For cohort studies, 17 articles had a low risk and 4 articles had a high risk.

3.4 All-cause mortality

Pooled analysis of 22 studies (n = 58,271) (19,20,22,24-32,35,36,38,43,66) suggests that metformin is associated with a reduced all-cause mortality (HR: 0.90; 95% CI: 0.83, 0.98; P = 0.01, Fig 2) versus control. Subgroup analysis demonstrated that cohort study, Europe, North America, ≥ 12 months, heart failure, diabetes, and monotherapy are associated with a reduced all-cause mortality (Fig 3, Fig S3-S7). Choropleth map reveals that enrolled studies in Canada, China, Poland, Spain, and USA are associated with a reduced all-cause mortality, whereas in Israel an increased all-cause mortality (Fig 4). The cumulative meta-analysis suggests that the 95% CI is narrower with the increase of year and study size generally (Fig S8-9). Galbraith plot indicates no significant heterogeneity (Fig S10). The meta-regression by Bubble plot also reveals no significant heterogeneity of the year (Fig S11) and study size (Fig S12). Fig S13 and Fig S16 contour-enhanced funnel plot and sensitivity analysis. The Begg's (Fig S14) and Egger's test (Fig S15) revealed no significant publication bias (Begg's: P = 0.602; Egger's: P = 0.822).

3.5 Cardiovascular mortality

Pooled analysis of 8 studies (n = 12,814) (20,22,28,33,36,39,41,42) reveals that metformin

treatment is associated with a reduced cardiovascular mortality (HR: 0.89; 95% CI: 0.85, 0.94; P <0.01, Fig 5) versus control. Subgroup analysis indicates that Europe, ≥12 months, heart failure, and monotherapy are associated with a reduced cardiovascular mortality (Fig 6, Fig S17-21). The cumulative meta-analysis suggests that the 95% CI is narrower with the increase of year and study size generally (Fig S22-23). Galbraith plot indicates no significant heterogeneity (Fig S24). The meta-regression by Bubble plot also reveals no significant heterogeneity of the year (Fig S25) and study size (Fig S26). Fig S27 and Fig S30 contour-enhanced funnel plot and sensitivity analysis. The Begg's (Fig S28) and Egger's test (Fig S29) revealed no significant publication bias (Begg's: P = 0.108; Egger's: P = 0.928).

3.6 Cardiovascular events

Pooled analysis of 6 studies (n = 14,348) (22,28,30,32-34) demonstrates that metformin treatment has no meaningful actions on the incidence of myocardial infarction (HR: 0.97; 95% CI: 0.80, 1.17; P = 0.73, Fig S31) versus control. Subgroup analysis indicates that all subgroups are not statistically significant (Fig S32).

Pooled analysis of 5 studies (n = 2923) (23,28,32,34,37) shows that metformin treatment is associated with a reduced incidence of coronary revascularization (HR: 0.79; 95% CI: 0.64, 0.98; P = 0.03, Fig S33) versus control. The 5 studies were carried out in Spain, China, USA, Netherlands, and UK.

Only one study (33) shown that metformin treatment has no meaningful actions on the incidence of angina (HR: 0.29; 95% CI: 0.04, 2.35; P = 0.25, Fig S34). This work is conducted by Komaru et al in 2020.

Pooled analysis of 6 studies (n = 33,139) (19,22,30,35,38,39) shows that metformin treatment

is associated with a reduced incidence of coronary revascularization (HR: 0.90; 95% CI: 0.87, 0.94; P <0.01, Fig S35) versus control. Subgroup analysis shown that Europe, ≥ 12 months, and existing heart failure, are associated with a reduced incidence of heart failure (Fig S36-Fig S39).

Pooled analysis of 6 studies (n = 4512) (22,28,33) shows that metformin treatment has no meaningful actions on the incidence of stroke (HR: 0.95; 95% CI: 0.78, 1.16; P <0.59, Fig S40) versus control.

4. Discussion

4.1 Main findings

Although introduced for use as a diabetic medication in 1957, metformin remains the cornerstone of diabetic drug management in patients with T2DM, and has identified cardioprotective effects (67). Our results based on 48 articles involving 92,183 patients suggests that metformin reduces all-cause mortality, cardiovascular mortality, incidence of coronary revascularization, and heart failure of patients with cardiac diseases. However, metformin is not associated with reduced incidence of myocardial infarction, angina, and stroke.

4.2 Interpretation

Metformin is the first-line agent for T2DM and an almost all-purpose drug for CVD, neoplasms, neurological diseases, metabolic diseases, etc, evidenced from experiments *in vitro*, *in vivo,* and some clinical studies. Up to Aug 8, 2020, there are 20,590 literature for a preliminary search strategy "Metformin[TIAB]", suggesting the emerging therapeutic effects of it. Our finding is in accordance with previous conclusion and provides strong evidence for the benefits of metformin in mortality and CVD.

Potential mechanisms of the cardioprotective effects of metformin have been well reviewed (mainly in opinion of fundamental research) (6,7,68). Briefly, metformin can lower the cardiovascular risk factors (including hyperglycemia, dyslipidemia, insulin resistance, obesity, and hypertension) to protect against CVD. Metformin can reduce blood glucose and body weight; improve insulin resistance and blood lipid. In addition, metformin directly improves vascular endothelial cell function and increases blood flow (69,70). Our article summarized data from RCT and cohort studies further support the cardiovascular benefits of metformin.

Although 48 articles are enrolled for qualitative analysis, only 22 articles (35 studies in total) met the quantitative criteria which were considered for meta-analysis. Among the pooling cohort, we observed that metformin reduces all-cause mortality, cardiovascular mortality, incidence of coronary revascularization, and heart failure of patients with cardiac diseases, all upper limits of their 95% CI are less than 1 and thereby they have statistical significance. However, we found no statistical benefit of metformin compared to control group, for myocardial infarction, angina, and stroke. The possible reasons might be attributed to the limited number of enrolled studies, e.g. only one study for angina and three studies for stroke.

Our conclusion is also confirmed by previous studies. As shown in Fig 3 and Fig 6, metformin monotherapy is associated with reduced all-cause and cardiovascular mortality whereas combined therapy of metformin is not. Previous study by UK Prospective Diabetes Study (UKPDS) group also demonstrated that metformin in combination with sulphonylurea increases the risk of all-cause mortality and cardiovascular mortality. Pooling conclusion is partly in accordance with Han's work (71).

The conclusion seems to be partly approved or opposed to previous publications. Based on previous studies and hypothesis, the following explanations may address this question. 1) The study

type is different. Previous literature are most animal research or cohort studies. Take melatonin for example, it is a protective drug of cardiovascular effects *in vitro* and *in vivo,* however it has an unfavorable effect in clinical trials (72,73). 2) This study included both cohort and RCT, and make a conclusion based on the pooling evidence. 3) Different eligibility criteria in those meta-analysis articles may result in different enrolled population.

4.3 Strength

Firstly, our meta-analysis was performed by a Cochrane Member and supervised by strict quality control evaluated by Cohen's kappa coefficient ($\kappa = 0.825$, 95% CI: 0.728–0.917). Secondly, this article provides a comprehensive categories of the outcomes: mortality (all-cause, and cardiovascular mortality), myocardial infarction, coronary revascularization, angina, heart failure, and stroke. A systematic review of qualitative studies that offered insufficient data was summarized in Table 2. Thirdly, we used subgroups for Intervention analysis, sub-divided controls in detail. Fourth, we eliminated data of 'Double zero incident' (the events number are 0 in both intervention and control group) per Cochrane Handbook which in previous studies the assumption skews the results.

4.4 Implications

Our result suggests that metformin reduces the all-cause and cardiovascular mortality when it acts as an monotherapy. Though other studies doubt the protective effects of metformin (12,13). Based on our findings, the strong evidence of pooling results, it should be recommended the monotherapy use of metformin for cardiac patients. Compared with other antidiabetics, metformin still should be recommended based on its identified cardiovascular benefits.

To allow better and more informative analysis, we here by recommend several suggestions. Unified criteria for diagnosis and efficacy evaluation need to be standardized for all future trails. Enrollment of prediabetes, T1DM, and non-diabetes for evaluation need to be cautioned as this may introduce bias in analysis. Metformin guidelines would be considerably strengthened and implemented if RCT suggest that the use of metformin monotherapy reduces cardiovascular or all-cause mortality for diabetic patients who do not exhibit hyperglycaemia-induced symptoms. Multi-center, standardized dosage, trial duration, diabetes duration, and ethnicity information will better guide us in using metformin for T2DM management.

4.5 Limitations

Despite our best attempt, we acknowledge there are limitations in our study. Firstly, we do not searched other database e.g. Cochrane Library, ClinicalTrials.gov (74,75). Secondly, this study is a study level rather than a patient-level meta-analysis. We failed to acquire all raw data from the included studies. Thirdly, most excluded studies have unclear/poorly defined risks probably due to unreported random sequence generation and allocation concealment. And some RCT have a small sample size (< 100) and they were conducted at single-centers. Lastly, heterogeneity does exist among the 18 articles. These studies were carried out at three continents (North America, Europe, and Asia) and encompassed different treatment methods, dosage, sample size, and baseline characteristics. We also performed subgroup analysis, meta-regression, Labbe and Galbraith plot for analysis, which explains the origin of heterogeneity and bias.

5. Conclusion

Our results based on 48 articles involving 92,183 patients suggests that metformin reduces

all-cause mortality, cardiovascular mortality, incidence of coronary revascularization, and heart failure of patients with cardiac diseases, whereas metformin is not associated with reduced incidence of myocardial infarction, angina, and stroke. Although further studies are needed to establish the optimal approach to the prevention of mortality and CVD in practice, our findings clearly lend support to the use of metformin in the clinical management of patients with cardiac diseases.

PERSPECTIVES

COMPETENCY IN SYSTEMS-BASED PRACTICE This article enrolled 48 articles (1999-2020) for qualitative synthesis and identified 26 articles (33 studies in total, 61,704 patients) for final quantitative synthesis. Compared with non-metformin control, metformin is associated with reduced all-cause mortality, cardiovascular mortality, incidence of coronary revascularization, and heart failure in patients with cardiac diseases, whereas metformin is not associated with reduced incidence of myocardial infarction, angina, and stroke.

TRANSLATIONAL OUTLOOK Metformin reduces all-cause mortality, cardiovascular mortality, incidence of coronary revascularization, and heart failure of patients with cardiac diseases. Our findings serve as the basis endocrinologist to draft recommendation for metformin use. Although further studies are needed to establish the optimal approach to the prevention of mortality and CVD, our findings, at least in part, clearly lend support to the use of metformin in the clinical management of patients with cardiac diseases.

Figure legends

Fig 1. Search strategy and PICOS according to PRISMA guideline. The flowchart shows the

process of enrolling studies. A total of 2921 literature were identified during the initial search, after excluding duplicate records (n = 332). Seventy-four articles were retained after title/abstract curation (excluding 2847 records) (Table S3). Thereafter, we read the full text and enrolled 22 articles (containing 35 clinical studies in total) for qualitative synthesis and identified 26 articles (containing 33 clinical studies in total) for final quantitative synthesis

Fig 2. All-cause mortality among patients with metformin vs control. Pooled analysis of 22 studies (n = 58,271) suggests that metformin is associated with a reduced all-cause mortality (HR: 0.90; 95% CI: 0.83, 0.98; P = 0.01, Fig 2) versus control.

Fig 3. Subgroup analysis of all-cause mortality among patients with metformin vs control. Subgroup analysis demonstrated that cohort study, Europe, North America, ≥ 12 months, heart failure, diabetes, and monotherapy are associated with a reduced all-cause mortality

Fig 4. Choropleth map of all-cause mortality among patients with metformin vs control. The map reveals that enrolled studies in Canada, China, Poland, Spain, and USA are associated with a reduced all-cause mortality, whereas in Israel an increased all-cause mortality.

Fig 5. Cardiovascular mortality among patients with metformin vs control. Pooled analysis of 8 studies (n = 12,814) reveals that metformin treatment is associated with a reduced all-cause mortality (HR: 0.89; 95% CI: 0.85, 0.94; P <0.01)

Fig 6. Subgroup analysis of cardiovascular mortality among patients with metformin vs control. Subgroup analysis indicates that Europe, ⩾12 months, heart failure, and monotherapy are associated with a reduced cardiovascular mortality

Fig 7. Choropleth map of cardiovascular mortality among patients with metformin vs control. The map reveals that enrolled studies in Spain are associated with a reducedcardiovascular mortality, whereas in other countries in Fig 7 an increased all-cause mortality

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11	Facila et al 2017	J Cardiovasc Med	(25)	Spain	Retrospective cohort study	HF + DM
12	Fisman et al 1999a	Cardiology	(26)	Israel	Retrospective cohort study	MI + T2DM
13	Fisman et al 1999b	Cardiology	(26)	Israel	Retrospective cohort study	MI + T2DM
14	Fisman et al 1999c	Cardiology	(26)	Israel	Retrospective cohort study	MI + T2DM
15	Fisman et al 2001a	Clin Cardiol	(66)	Israel	Retrospective cohort study	CAD+T2DM
16	Fisman et al 2001b	Clin Cardiol	(66)	Israel	Retrospective cohort study	CAD+T2DM
17	Hartman et al 2017	Clin Res Cardiol	(27)	Netherlands	Retrospective cohort study	MI - T2DM
18	Hong et al 2013	Diabetes Care	(28)	China	RCT	CAD + T2D
19	Horsdal et al 2008a	Diabetologia	(29)	Denmark	Retrospective cohort study	MI + T2DM
20	Horsdal et al 2008b	Diabetologia	(29)	Denmark	Retrospective cohort study	MI + T2DM
21	Inzucchi et al 2005	Diabetes Care	(30)	USA	Retrospective cohort study	MI + T2DM
22	Jong et al 2019	Int J Cardiol	(31)	China	Retrospective cohort study	CAD + T2D
23	Kao et al 2004	Am J Cardiol	(32)	USA	Retrospective cohort study	CAD + DM
24	Komaru et al 2020	J Diabetes Complications	(33)	Japan	Retrospective cohort study	CAD + T2D
25	Lexis et al 2014	JAMA	(34)	Netherlands	RCT	MI - T2DM
26	Masoudi et al 2005	Circulation	(35)	USA	Retrospective cohort study	HF + T2DM
27	Mellbin et al 2008	Eur Heart J	(36)	Sweden	RCT	MI + T2DM
28	Preiss et al 2014	Lancet Diabetes Endocrinol	(37)	UK	RCT	CAD - T2D
29	Retwinski et al 2018	Kardiol Pol	(38)	Poland	Retrospective cohort study	HF + T2DM
30	Romero et al 2013	Int J Cardiol	(39)	Spain	Retrospective cohort study	HF + T2DM
31	Sardu et al 2019	Cardiovasc Diabetol	(40)	Italy	Retrospective cohort study	MI + Predia
32	Shah et al 2010	J Card Fail	(41)	USA	Retrospective cohort study	HF + T2DM
33	Zeller et al 2016	Int J Cardiol	(42)	France	Retrospective cohort study	MI + T2DM

Gly, Glyburide; Sulf, Sulfonylureas; Thia, Thiazolidinedione; Nonsen, nonsensitizer; tre, treatment; Gli, Glipizide

10	Biondi-Zoccai et al 2016b	J Cardiovasc Pharmacol	(48)	Italy	Retrospective cohort study	MI + T2DM	66/69
11	Biondi-Zoccai et al 2016c	J Cardiovasc Pharmacol	(48)	Italy	Retrospective cohort study	MI + T2DM	67/69
12	Cacciapuoti et al 1991	Am J Cardiol	(49)	Italy	RCT	CAD + T2DM	55
13	Chang et al 2020	ESC Heart Fail	(50)	China	Retrospective cohort study	HF + T2DM	65
14	Eurich et al 2009	Trials	(51)	Canada	RCT	HF + T2DM	77
15	Eppinga et al 2016	PLoS ONE	(52)	Netherlands	RCT	MI - T2DM	59
16	Evans et al 2010a	Am J Cardiol	(53)	UK	Retrospective cohort study	HF + T2DM	75
17	Evans et al 2010b	Am J Cardiol	(53)	UK	Retrospective cohort study	HF + T2DM	75
18	Jadhav et al 2006a	J Am Coll Cardiol	(54)	UK	RCT	Angina - T2DM	56/58
19	Jørgensen et al 2010a	Cardiovas Diabetol	(55)	Denmark	Retrospective cohort study	MI + DM	69/71
20	Jørgensen et al 2010b	Cardiovas Diabetol	(55)	Denmark	Retrospective cohort study	MI + DM	69/75
21	Jørgensen et al 2010c	Cardiovas Diabetol	(55)	Denmark	Retrospective cohort study	MI + DM	69/75
22	Jørgensen et al 2010d	Cardiovas Diabetol	(55)	Denmark	Retrospective cohort study	MI + DM	69/76
23	Jørgensen et al 2010e	Cardiovas Diabetol	(55)	Denmark	Retrospective cohort study	MI + DM	69/74
24	Jørgensen et al 2010f	Cardiovas Diabetol	(55)	Denmark	Retrospective cohort study	MI + DM	69/76
25	Larsen et al 2019	Eur J Heart Fail	(56)	Denmark	RCT	HF + Prediabetes	68/61
26	Lexis et al 2012	Cardiovasc Drugs Ther	(57)	Netherlands	RCT	MI + T2DM	66/67
27	Liu et al 2017a	Lipids Health Dis	(58)	China	RCT	CAD + T2DM	59/58
28	Liu et al 2017b	Lipids Health Dis	(58)	China	RCT	CAD + T2DM	57/58
29	Lipinski et al 2014	Atherosclerosis	(59)	USA	Retrospective cohort study	CAD + T2DM	64/68
30	Messaoudi et al 2015	Lancet Diabetes Endocrinol	(60)	Netherlands	RCT	CAD – T2DM	65
31	Mohan et al 2019	Eur Heart J	(61)	UK	RCT	CAD – T2DM	65
32	Oktay et al 2017	Anatol J Cardiol	(62)	Turkey	Prospective cohort study	MI + T2DM	59/61
33	Wong et al 2012	Eur J Heart Fail	(63)	UK	RCT	HF + Prediabetes	64/68
34	Zhao et al 2011	Cardiovasc Ther	(64)	China	Retrospective cohort study	MI + DM	62/65
35	Zhao et al 2019	Med Sci Monit	(65)	China	RCT	Stroke + T2DM	58

Gliben, glibenclamide; Glime, Glimepiride; Glip, Glipizide; Glic, Gliclazide; Tolbu, Tolbutamide; No-tre, No-treatment; Lirag, Liraglutide;

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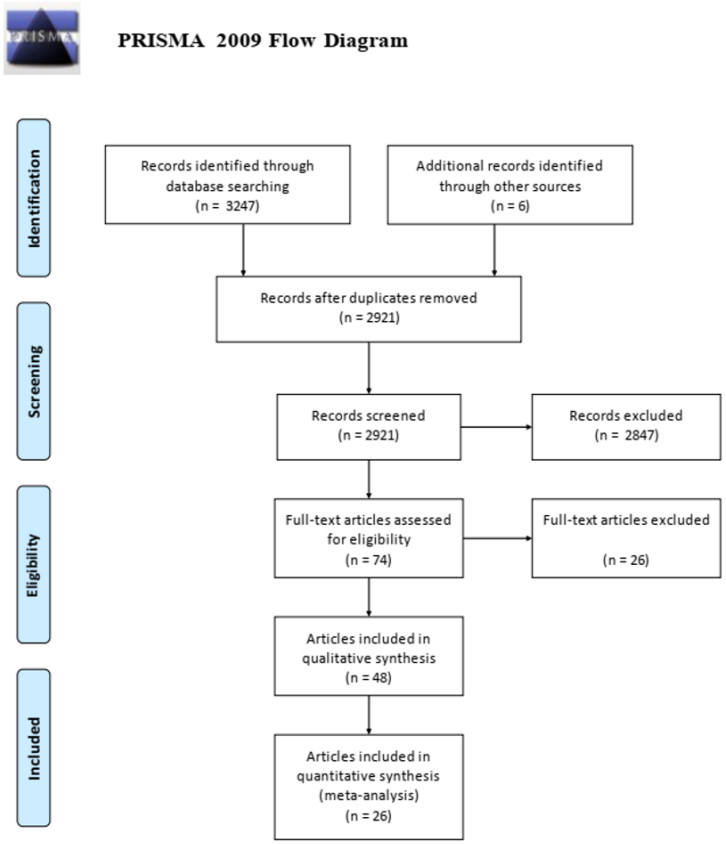
Fig 1. Search strategy and PICOS according to PRISMA guideline.



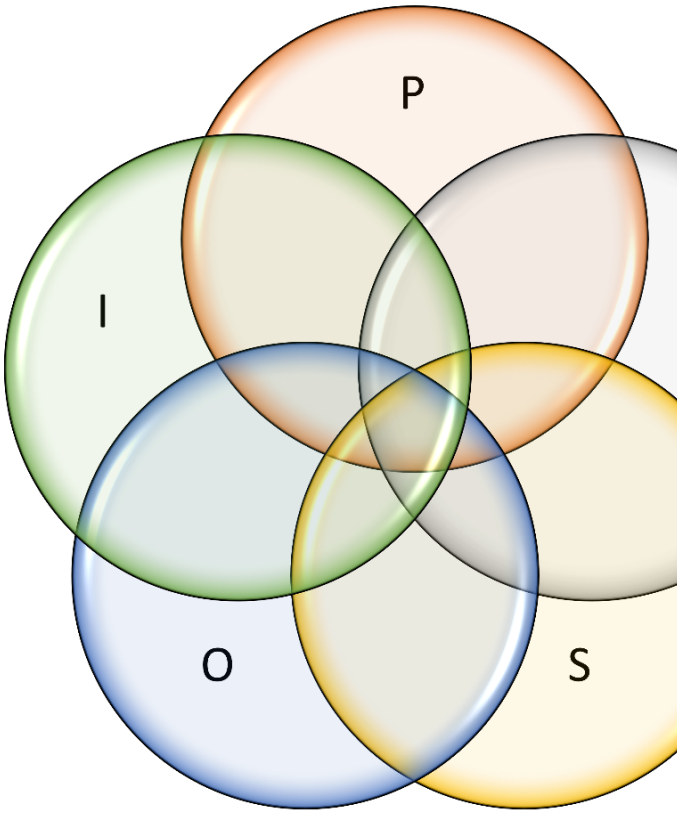


Fig 2. All-cause mortality among patients with metformin vs control.

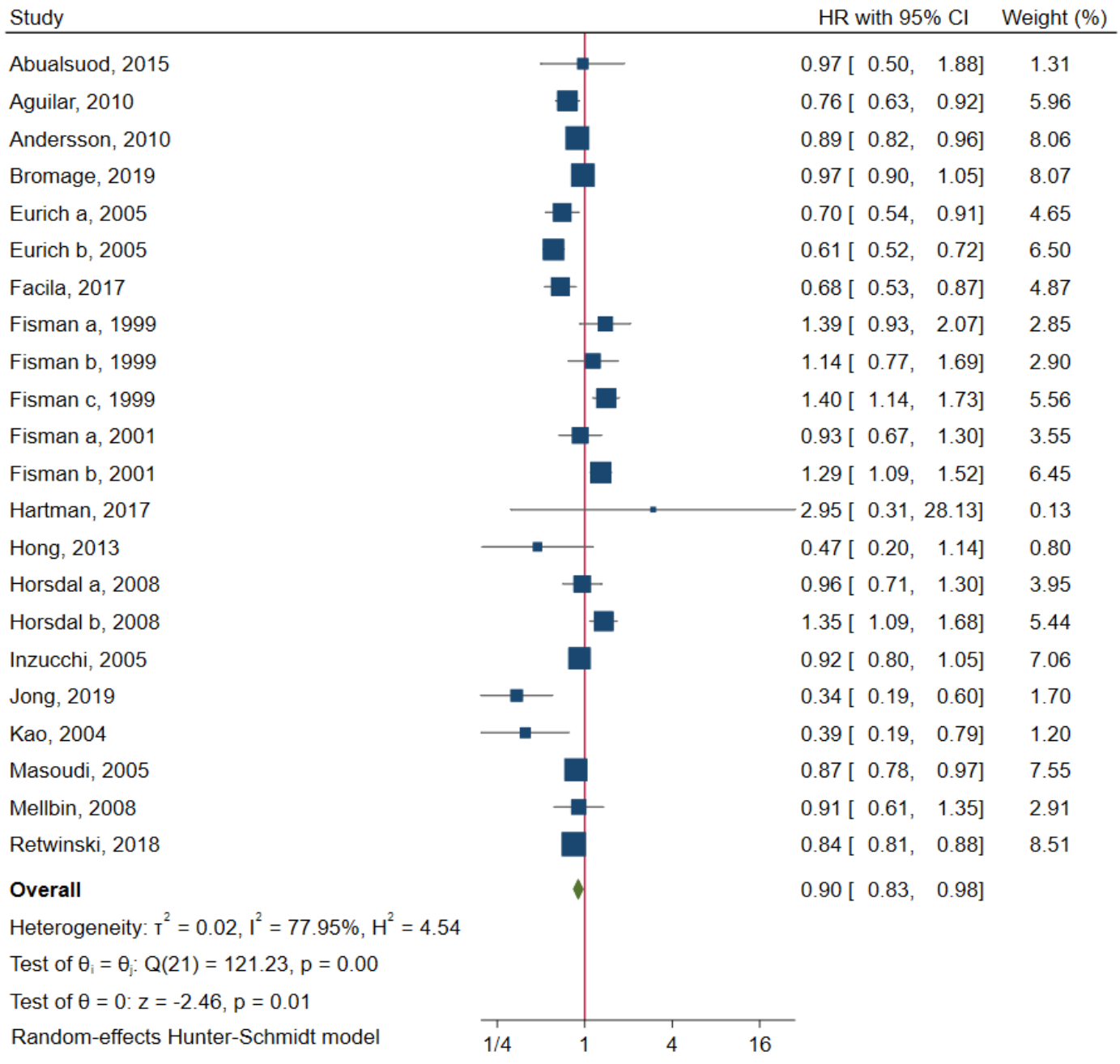


Fig 3. Subgroup analysis of all-cause mortality among patients with metformin vs control.

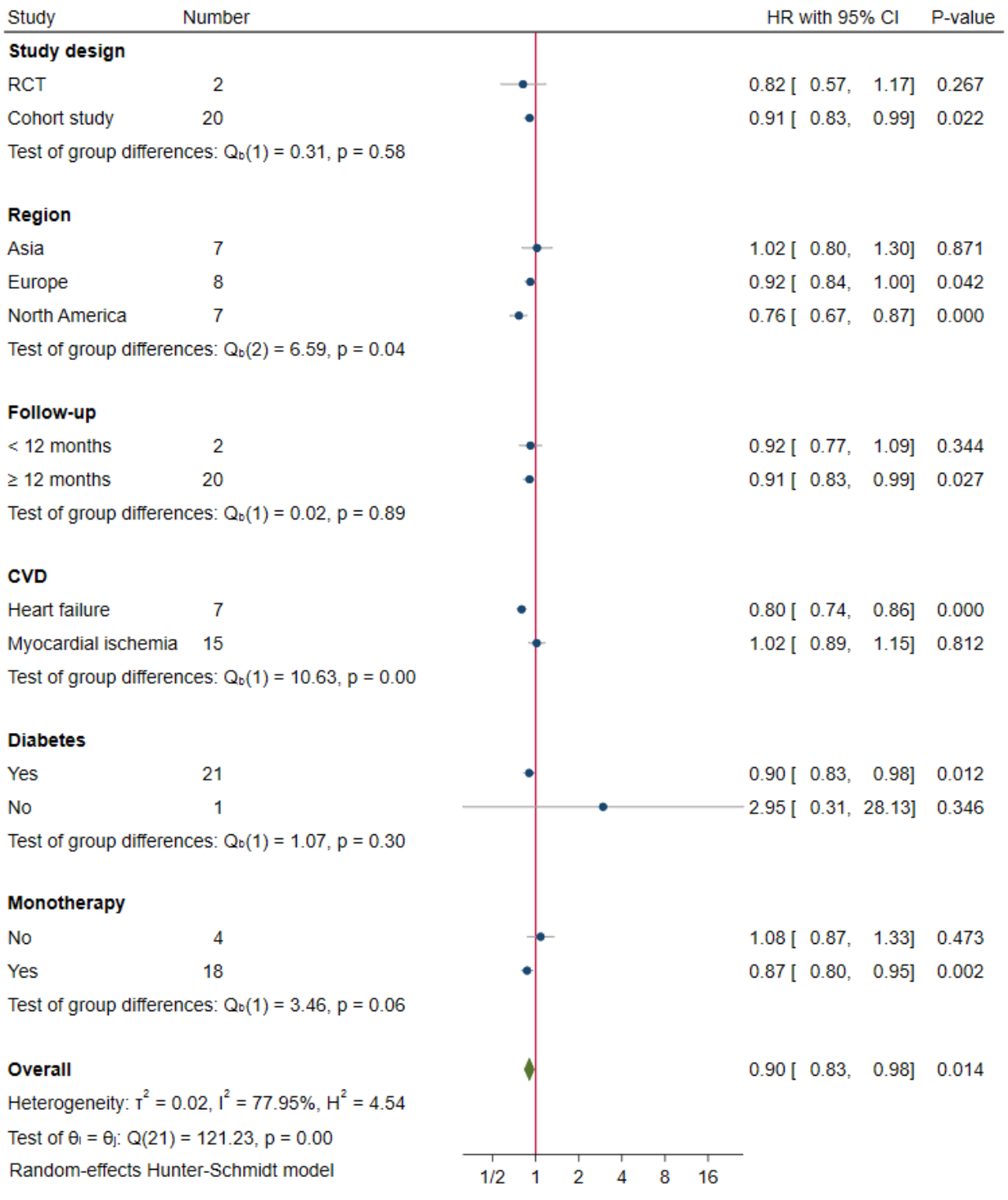


Fig 4. Choropleth map of all-cause mortality among patients with metformin vs control.

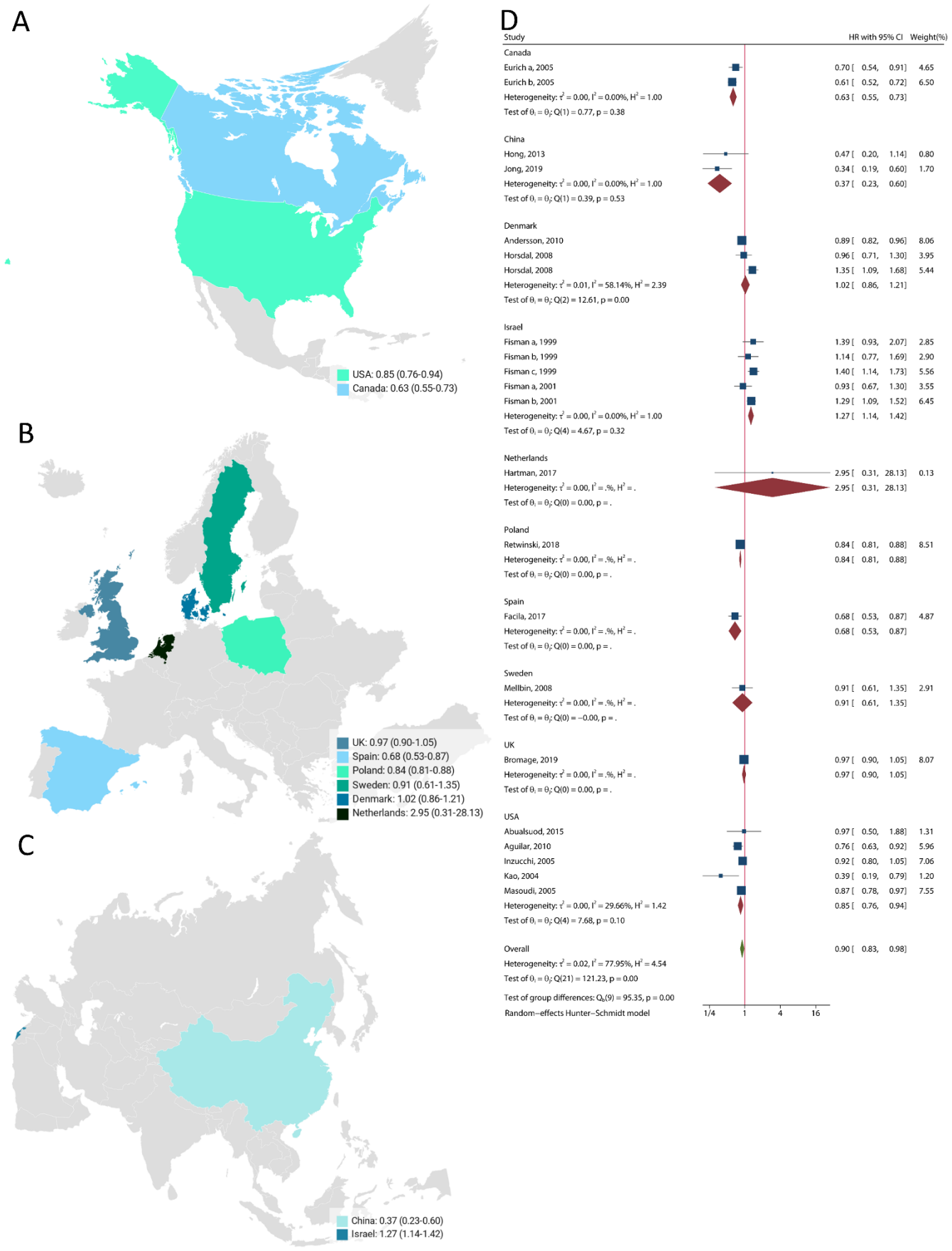


Fig 5. Cardiovascular mortality among patients with metformin vs control.

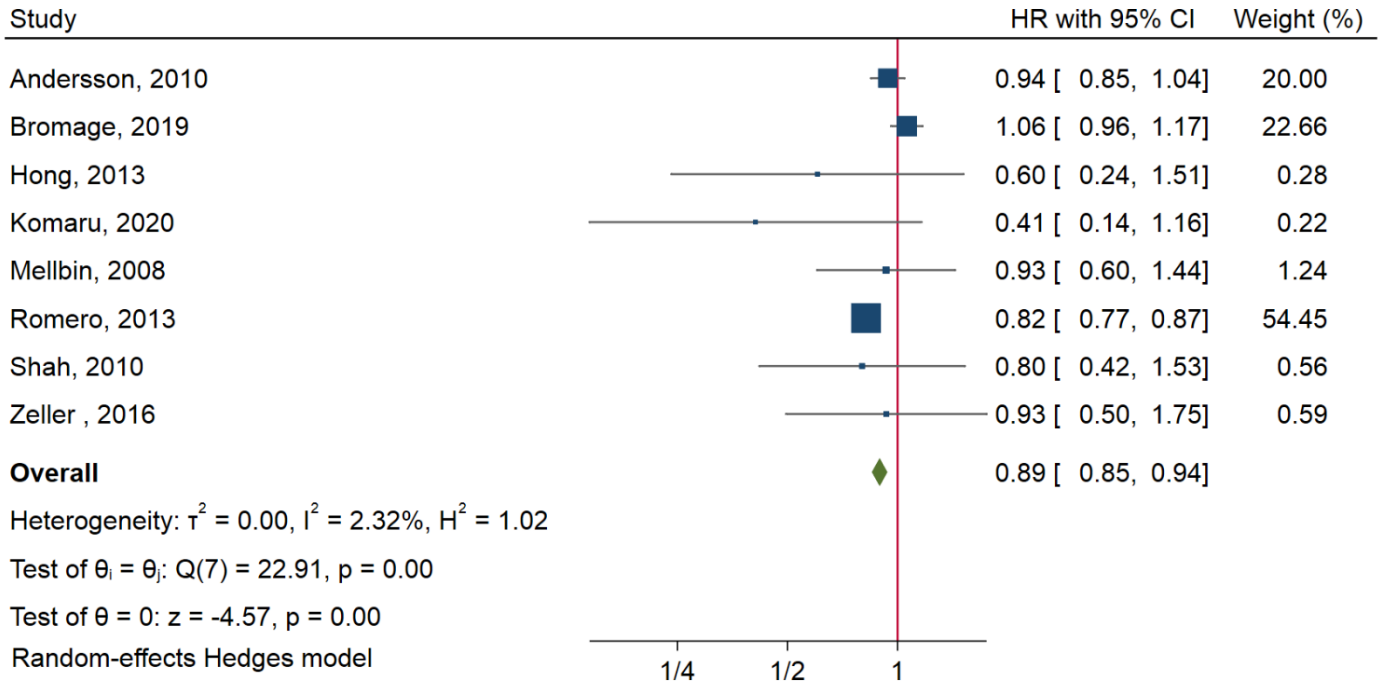


Fig 6. Subgroup analysis of cardiovascular mortality among patients with metformin vs control.

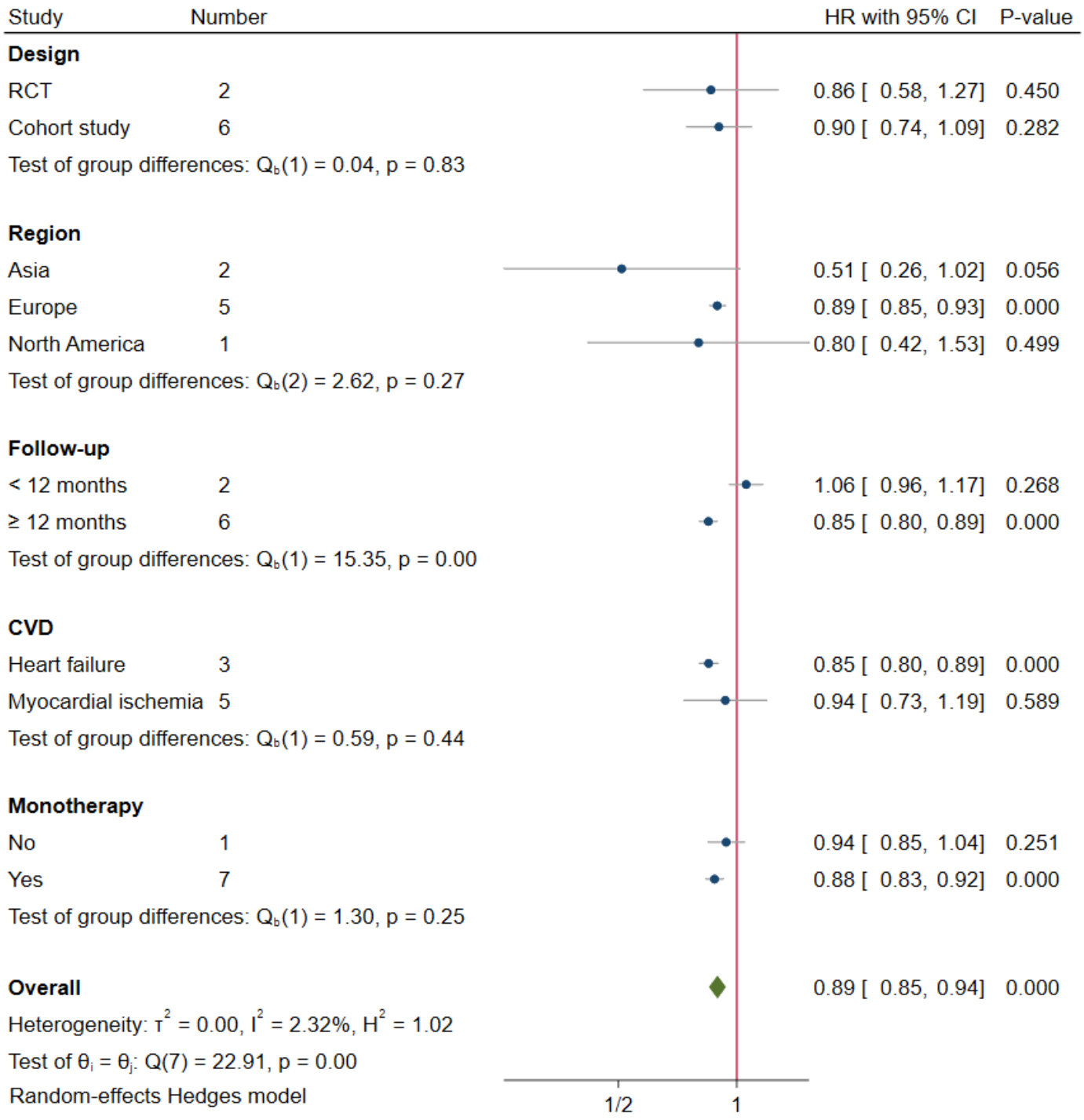


Fig 7. Choropleth map of cardiovascular mortality among patients with metformin vs control.