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Metformin Continuation Versus Holding Pre- and Post-Coronary Angiography with Normal Renal Function: A Systematic Review and Meta-Analysis

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ABSTRACT

BACKGROUND: It is common practice to withhold metformin prior to cardiac catheterization due to fear of developing lactic acidosis in the setting of contrast-associated acute kidney injury (AKI). The evidence behind this recommendation is currently weak.

METHODS: We collected 851 articles from PubMed and Embase, of which 3 met our inclusion criteria. Inclusion criteria were age > 18 years, baseline use of long-term metformin with continued or interrupted metformin use in patients during diagnostic or interventional cardiac catheterization. The outcomes studied were differences between post-catheterization and pre-catheterization serum creatinine (SCr) and glomerular filtration rate (GFR). We excluded studies dealing with patients not on long-standing metformin and those in which contrast exposure was through contrast enhanced computerized tomography. We used Hedges's g with inverse variance method to pool standard mean difference with a random effects model using meta-cont module in CRAN-R software with 95% confidence interval (CI) for statistical significance. Higgins I-squared (I^2) statistic was used to evaluate heterogeneity.

RESULTS: Post-catheterization serum creatinine (Hedges's g = -0.12 mg/dL; CI = -0.83 to +0.6, p = 0.75, I2 = 95%), post-catheterization GFR (Hedges's g = +0.18 mL/min; CI = -0.76 to +1.11, p = 0.71, I2 = 97%) and post-catheterization lactate levels (Hedges's g = +0.03 mg/dL; CI = -0.66 to +0.72, p = 0.75, I2 = 95%) failed to reach statistical significance.

CONCLUSIONS: There is no statistically significant difference in SCr or GFR between patients who held metformin prior to cardiac catheterization and those who continued taking the medication.

KEYWORDS: Metformin, coronary angiography, creatinine, GFR

Disclosure Statement: The authors have no conflicts of interest to declare.

INTRODUCTION

The recommended standard of care for coronary angiography performed on patients with diabetes mellitus continues to recommend temporary discontinuation of metformin therapy on the day of the procedure and 48 hours afterward, but evidence behind this recommendation is dubious.[1,2] Contrast-induced nephropathy (CIN) is a complication which is feared after the use of iodine contrast medium, but nephrotoxic risk of intravenous contrast may be much lower than previously accepted.[3] The increased mortality associated with metformin-associated lactic acidosis (MALA) further adds to that fear.[4] The Society of Hospital Medicine has recommended against holding metformin during hospitalization for example, but cardiac catheterization continues to be an exception to this recommendation.[5] Although a synergetic impact of acute kidney injury (AKI) and possible MALA from two combined nephrotoxic agents could be understandably assumed, evidence for its occurrence is sparse as multiple studies have failed to provide convincing evidence that holding metformin prior to cardiac catheterization reduces risk of AKI or MALA.

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Our metanalysis aims to assess changes in post-catheterization creatinine, GFR, and lactate levels in patients with diabetes who continue metformin versus those who held metformin prior to cardiac catheterization.

METHODS

Our search strategy and meta-analysis have been reported in line with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) and AMSTAR-2 (Assessing the methodological quality of systematic reviews-2) Guidelines.[6,7] The checklists of these guidelines are shown in Supplemental S1 and Supplemental S2, respectively. The inclusion criteria of our meta-analysis consist of 1) Patients on chronic metformin therapy. 2) Patients undergoing diagnostic or interventional cardiac catheterization. The exclusion criteria were 1) Patients presenting with cardiogenic shock, cardiac arrest, chronic liver disease, severe chronic kidney disease (glomerular filtration rate – GFR < 30 mL/min/1.73m2 or requiring coronary artery bypass grafting. 2) Patients with known contrast allergy. We excluded studies that are case reports, clinical spotlights, and review articles. Studies comparing patients taking chronic metformin against patients not taking chronic metformin were also excluded. Patients were divided into an experimental group – patients with continuous metformin use, and a control group – patients in whom metformin was held at admission (for urgent cardiac catheterizations) or 24-48 hours before elective cardiac catheterization and resumed 48 hours after the procedure after checking renal function.

A literature search was conducted on MEDLINE (EMBASE and PubMed) for trials or observational studies with the above-mentioned inclusion criteria using a systematic search strategy by PRISMA from inception till January 2023. Search terms employed using medical subject heading (MeSH) terms and keywords using Boolean operators "OR" and "AND" for terms including: "coronary angiography" OR "Cardiac Catheterization" OR "percutaneous coronary intervention" OR "Coronary Balloon Angioplasty" AND "metformin."

Study Selection

We selected randomized clinical trials (RCTs), pilot trials, and retrospective and prospective studies that meet our inclusion guidelines. Two authors (MH and SF) independently screened the articles; articles that met screening were downloaded into the full text to undergo a second screening phase of evaluating the outcome of interest data. We also did backward snowballing to see the references of articles with outcomes of interest to find additional studies on our meta-analysis. The data screening was done under the supervision of senior authors (YS).

Data Collection and Statistical Analysis

The baseline characteristics and outcomes data were exported to Microsoft Excel and were arranged in mean and standard deviation format for the continuous outcome data. Baseline data elements collected were the total number of patients, sex, body mass index, presence of cardiac risk factors (hypertension, hyperlipidemia, smoking, prior myocardial infarction, prior stroke), duration of diabetes, metformin dose, other relevant cardiac and diabetic medications, mean cardiac ejection fraction (EF), mean hemoglobin A1c (HbA1c), Serum creatinine before cardiac catheterization, GFR before cardiac catheterization and serum lactate before cardiac catheterization. The outcomes studied were: 1) post-catheterization creatinine, 2) post-catheterization GFR, and 3) post-catheterization lactate levels.

Statistical analysis was performed using the CRAN-R software. A meta-cont module was used along with the inverse-variance random-effects model to calculate the pooled bias-corrected Standard Mean Difference using Hedges's g with a probability value of $p < 0.05$, considered statistically significant. The "test for overall effect" was reported as a z-value corroborating the 95% confidence interval's inference. Higgins I-squared (I2) was determined as a measure of statistical heterogeneity where values of ≤ 50% corresponded to low to moderate heterogeneity, while values ≥75% indicated high heterogeneity.8 The publication bias was depicted graphically and numerically as a funnel plot and Begg's test, respectively.[9] The quality assessment of the included articles was performed using the Cochrane Risk of Bias (ROB) for RCTs and Newcastle-Ottawa Scale (NOS) for observational studies.[10,11]

RESULTS

Our systematic search resulted in 851 articles. Following removing duplicates (n = 31), 820 records were screened in the first phase. Among them, 802 articles were removed. In the second phase, 18 articles were screened with a full-text review. Of these, four studies were included in the final analysis, which reported on our desired outcome (Figure 1; Supplemental S3).

A total of 1,118 patients were studied, with 538 patients in the metformin-continued group and 580 patients in the metformin-held group. The mean age of patients in the metformin-continued group was 63.72 ± 5.67 years, while the mean age of patients in

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Table 1. Baseline characteristics of patients with Metformin Continued and Metformin Held

Study Population Demographics and Comorbidities	Study	Yu et al. 2020[8]	Namazi et al. 2018[9]	Oktay et al. 2017[10]
	Type of Study	Retrospective Cohort Observational	RCT	Prospective Cohort Observational
Number of Patients (N)	Metformin Continued/ Metformin Held	119/165	83/79	134/134
Age (Mean +/- SD)	Metfomin Continued/ Metfomin Held		61.5/60.1	59.4 +/- 7.7/61.4 +/- 6.5
Male (%)	Metfomin Continued/ Metfomin Held	78.2/71.5	48.1/49.4	70.1/51.5
Female (%)	Metfomin Continued/ Metfomin Held	21.8/27.9	51.9/50.6	29.9/48.5
BMI (Mean +/- SD)	Metfomin Continued/ Metfomin Held			30.8 +/- 3.5/29.9 +/- 5
Hypertension (%)	Metfomin Continued/ Metfomin Held	62.2/69.1		85/83
Hyperlipidemia (%)	Metfomin Continued/ Metfomin Held	44.5/37		64/61
Smoking (%)	Metfomin Continued/ Metfomin Held	67.2/60		28/29
Prior MI (%)	Metfomin Continued/ Metfomin Held	13.4/7.3		10/19
Prior Stroke (%)	Metfomin Continued/ Metfomin Held	6.7/8.5		
Diabetes duration (years) (Mean +/- SD)	Metfomin Continued/ Metfomin Held			7.75 +/- 1.42/10 +/- 1.74
Contrast Media Dosage (mL) (Mean +/- SD)	Metfomin Continued/ Metfomin Held	140 +/- 23.13/152.5 +/- 25.98	220/182	130 +/- 51.986/152.5 +/- 83.74
Metformin Dosage (mg) (Mean +/- SD)	Metfomin Continued/ Metfomin Held		1090/1105	862.5 +/- 303.13/1212.5 +/- 332.003
Acetylsalisylic acid (%)	Metfomin Continued/ Metfomin Held			74/95
Clopidogrel (%)	Metfomin Continued/ Metfomin Held			13/7
ACE/ARB (%)	Metfomin Continued/ Metfomin Held	42.9/41.2		76/83
Beta Blockers (%)	Metfomin Continued/ Metfomin Held	79.8/60		91/85
CCB (%)	Metfomin Continued/ Metfomin Held	5/3		30/27
Statins (%)	Metfomin Continued/ Metfomin Held			62/54
Diuretics (%)	Metfomin Continued/ Metfomin Held			7/13
Insulin (%)	Metfomin Continued/ Metfomin Held			15/38
SGLT2 Inhibitors (%)	Metfomin Continued/ Metfomin Held			

Table 1. Continued

Study Population Demographics and Comorbidities	Study	Yu et al. 2020[8]	Namazi et al. 2018[9]	Oktay et al. 2017[10]
DPP4 (%)	Metfomin Continued/ Metfomin Held			
GLP1 (%)	Metfomin Continued/ Metfomin Held			
Sulfonylurea (%)	Metfomin Continued/ Metfomin Held			
EF % (Mean +/- SD)	Metfomin Continued/ Metfomin Held		50/50	54 +/- 8/53 +/- 7
HbA1c % (Mean +/- SD)	Metfomin Continued/ Metfomin Held	7.95 +/- 3.06/7.82 +/- 0.58		8.15 +/- 2.16/8.25 +/- 2.14
Cr before angiography (mg/dL) (Mean +/- SD)	Metfomin Continued/ Metfomin Held	0.86 +/- 0.21/0.83 +/- 0.21	1.03 +/- 0.07/1.08 +/- 0.04	0.84 +/- 0.18/0.84 +/- 0.13
GFR before angiography (mL/min) (Mean +/- SD)	Metfomin Continued/ Metfomin Held	88.75 +/- 8.94/93.25 +/- 11.8	79 +/- 3.4/76 +/- 2.1	86 +/- 18/81 +/- 9
Lactate before angiography (mg/dL) (Mean +/- SD)	Metfomin Continued/ Metfomin Held		1.42 +/- 0.12/1.37 +/- 0.1	

the metformin-held group was 64 ± 4.84 years. The baseline characteristics of the patients in the included studies are shown in detail in Table 1.[1,12–14] Comorbid conditions and medication use was evenly distributed in each study among each group.

Outcomes

None of the outcomes studied showed any statistical significance. Post-catheterization serum creatinine (Hedges's g = -0.12 mg/dL; CI = -0.83 to +0.6, p = 0.75, I2 = 95%), post-catheterization GFR (Hedges's g = +0.18 mL/min; CI = -0.76 to +1.11, p = 0.71, I2 = 97%) and post-catheterization lactate levels (Hedges's g = +0.03 mg/dL; CI = -0.66 to +0.72, p = 0.75, I2 = 95%) failed to reach statistical significance. The forest plots of these outcomes are shown in Figure 2.

Publication Bias, Quality Assessment and Heterogeneity

To ascertain the publication bias, we plotted funnel plots and then used the Begg's method to assess for funnel plot asymmetry[4]. The plot's vertical axis uses standard error to estimate the sample size of the study, thereby plotting larger studies at the top and smaller studies at the bottom. The horizontal spread depicts the power and effect sizes of the included studies. Since our funnel plot was not symmetric on visual assessment, which indicates possible publication bias, therefore we did numerical assessment of the funnel plot scatter using Begg's test. Begg's regression model did not show any publication bias or small study effects (Supplemental S4).

We used Cochrane Risk of Bias tool (RoB tool 2.0) for RCTs and Newcastle-Ottawa Scale (NOS) scoring for observational studies. RoB assessment is shown in Supplemental S5 and NOS scores are presented in Supplemental S6.

There was considerable heterogeneity among the outcomes of the included studies. This was self-explicable. First, as per the Cochrane handbook of the systematic review and meta-analysis, if number of included studies is less than ten, it is not possible to differentiate between true heterogeneity and findings merely by chance.[15] Second, the high percentage of variability could be explained by the sampling error.

DISCUSSION

There was no demonstrable difference in this meta-analysis for post-catheterization creatinine, GFR, and lactate levels between the metformin-continued group and the metformin-held groups. Results of this study lend further evidence that holding metformin prior to cardiac catheterization is unnecessary in patients without severe renal impairment (eGFR >30 ml/min / 1.73 m2). Furthermore, the guidelines that recommend holding metformin from the day of surgery to 48 hours afterward as standard practice acknowledge

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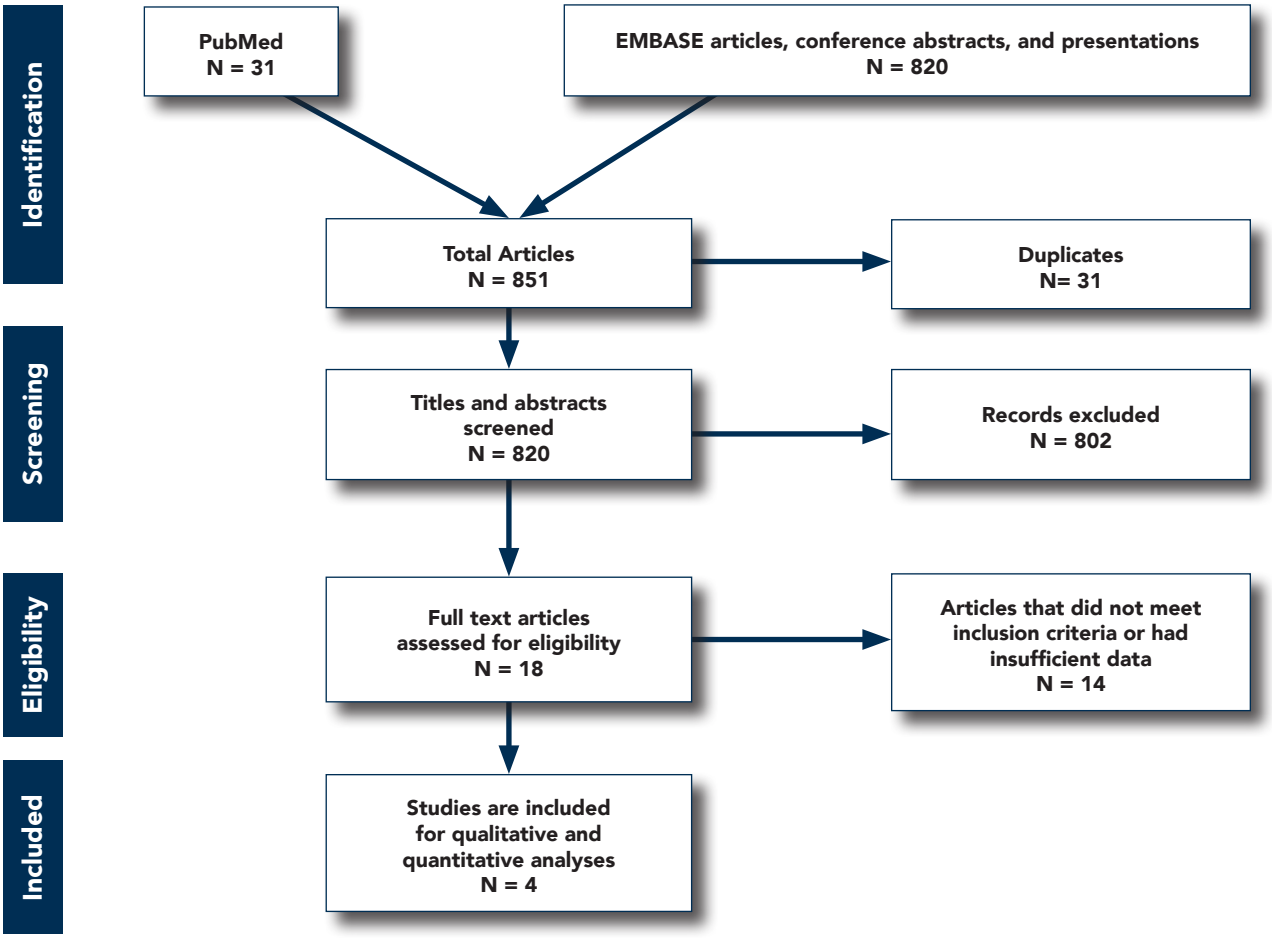
FIGURE 1. Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) Flow of the search strategy for systematic review and meta-analysis.



that the evidence behind these recommendations are weak.[16,17] It is worth noting that although no level of evidence is provided in the guidelines, emphasis with holding metformin is mostly placed on patients with severe renal dysfunction.

To start, the notion that metformin causes lactic acidosis has been grossly overstated.[18,19] A Cochrane meta-analysis published in 2010 which included patients with renal impairment concluded that metformin is not associated with lactic acidosis compared to other antihyperglycemic treatments.[20] A more recent case control study also failed to show an increased risk of lactic acidosis with metformin use, but neither aforementioned study evaluated the continued use of metformin in the setting of contrast use.[18]

Initiation of metformin shortly after cardiac catheterization in patients with normal kidney function and without existing diagnosis of diabetes (i.e. for patients without known diabetes or metformin use prior to the procedure or renal dysfunction) has been shown to have no adverse effect on renal function.21 We examined studies in this metanalysis for patients with both elective and emergent cardiac catheterization but found no evidence to support holding metformin.[1,12–14]

A case can even be made that discontinuing metformin can cause harm given poor glycemic control after holding medication. A secondary outcome observed by Yu el al.was that patients who had their metformin held group had higher blood glucose than the metformin continuation group.

Limitations

Details regarding patients with severe (eGFR < 30 ml/min) and moderate (eGFR 30-40 ml/min) renal impairment was not available because metformin is not recommended for use in this patient population. Finally, the increase heterogeneity and since the number of included studies is less than ten, it is not possible to differentiate between true heterogeneity and findings merely by chance.

FIGURE 2. Outcomes of patients after coronary angiography in Metformin Continued and Metformin Held

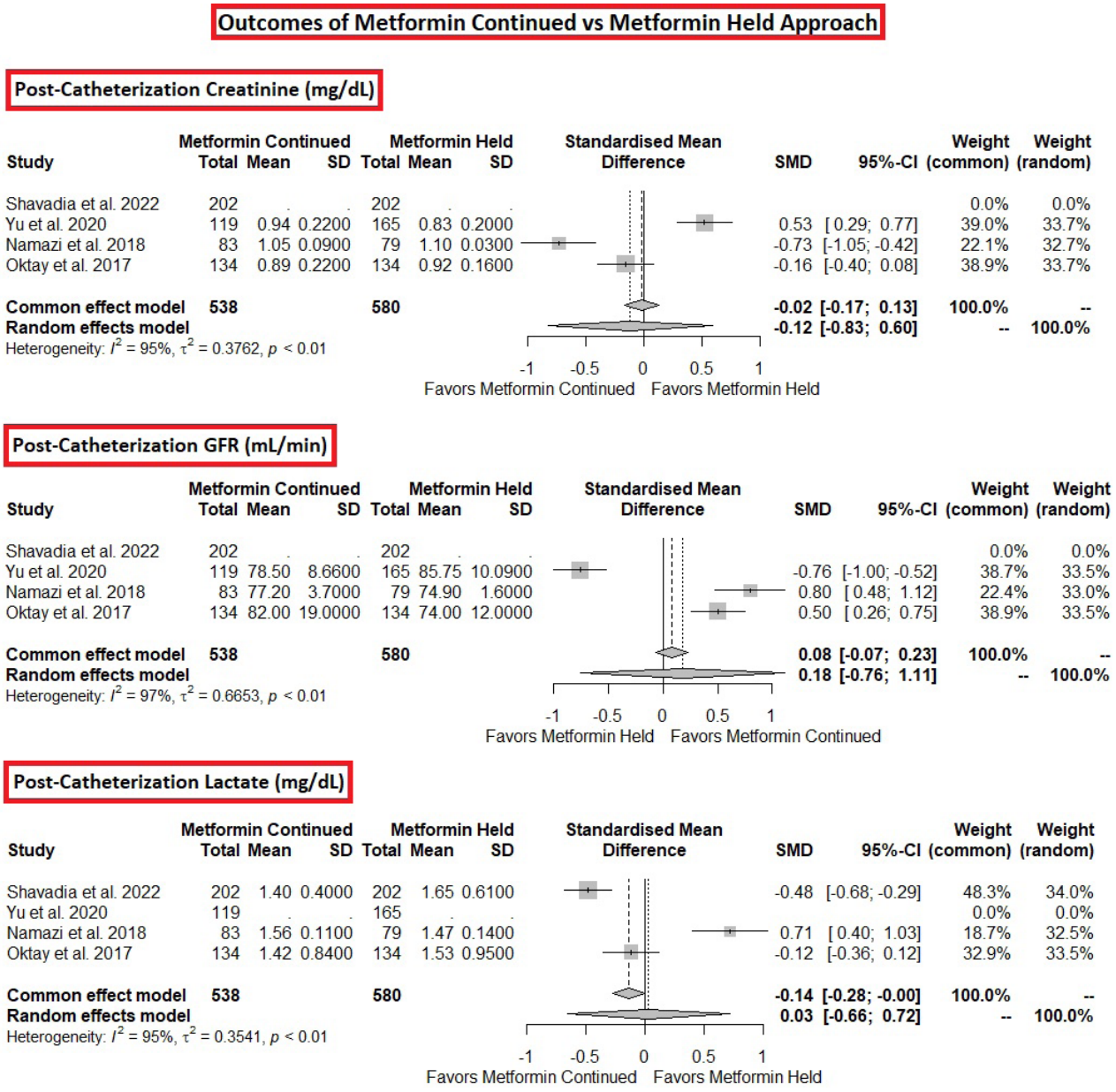


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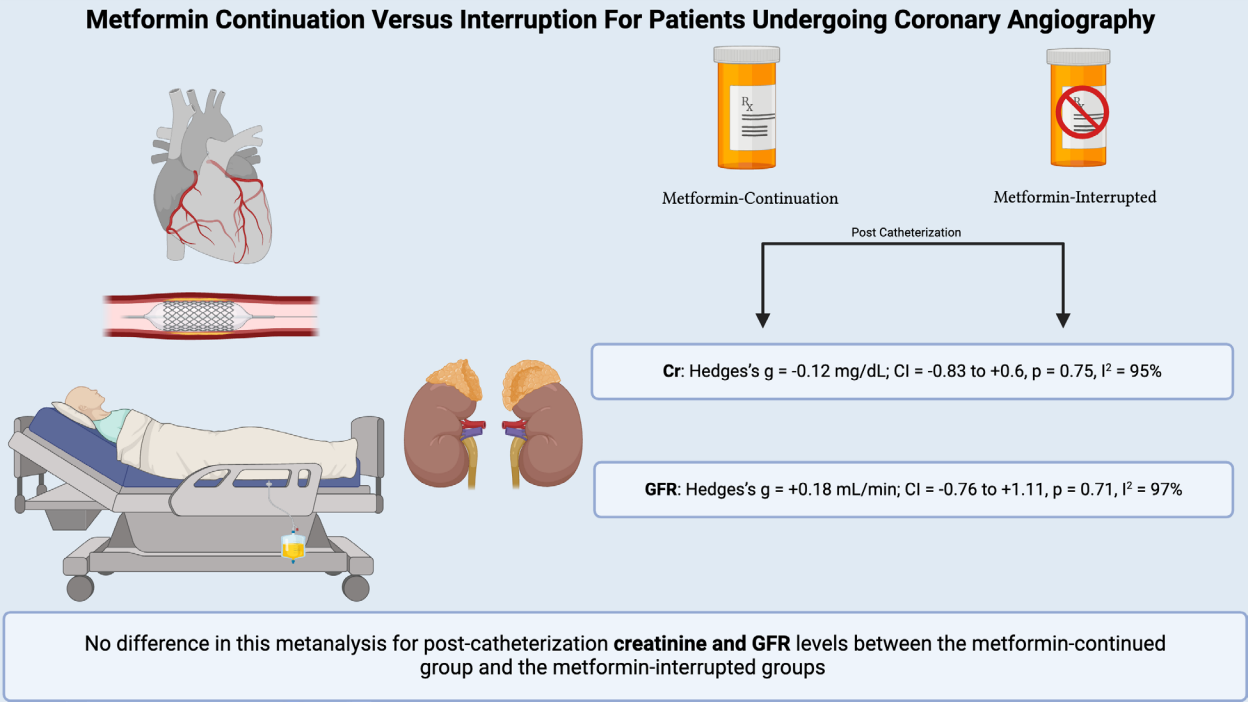
FIGURE 3. Graphical abstract of Comparison outcomes of Metformin Continued against Metformin Held during periprocedural period of diagnostic or interventional coronary angiography.



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SUPPLEMENTAL S1: Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	4
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	4
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	5-6
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	5-6
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	6
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	6
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	6
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	6 – 7
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	6 – 7
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	6-7
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	7
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	7
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	7
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	7
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	7
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	6-7
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	-
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	7
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	7

SUPPLEMENTAL S2: AMSTAR-2 (Assessing the methodological quality of systematic reviews-2) Guidelines checklist

Section and Topic	Item #	Checklist item	Location where item is reported
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	7
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	-
Study characteristics	17	Cite each included study and present its characteristics.	8
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	7
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	-
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	8
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	8
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	8
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	8
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	8
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	8
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	8
	23b	Discuss any limitations of the evidence included in the review.	10
	23c	Discuss any limitations of the review processes used.	-
	23d	Discuss implications of the results for practice, policy, and future research.	8-9
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	-
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	-
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	-
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	-
Competing interests	26	Declare any competing interests of review authors.	-
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	-

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

SUPPLEMENTAL S3: Research Question, PICO, MeSH, Keywords, and Search Strategy

1. Did the research questions and inclusion criteria for the review include the components of PICO?

For Yes:	Optional (recommended)	
☑ Population	☐ Timeframe for follow-up	☑ Yes
☑ Intervention		☐ No
☑ Comparator group		
☑ Outcome		

2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?

For Partial Yes: The authors state that they had a written protocol or guide that included ALL the following:	For Yes: As for partial yes, plus the protocol should be registered and should also have specified:	
		☐ Yes
☑ review question(s)	☐ a meta-analysis/synthesis plan, if appropriate, *and*	☑ Partial Yes
☑ a search strategy	☐ a plan for investigating causes of heterogeneity	☐ No
☑ inclusion/exclusion criteria	☐ justification for any deviations from the protocol	
☑ a risk of bias assessment		

3. Did the review authors explain their selection of the study designs for inclusion in the review?

For Yes, the review should satisfy ONE of the following:	
☐ *Explanation for* including only RCTs	☑ Yes
☐ OR *Explanation for* including only NRSI	☐ No
☑ OR *Explanation for* including both RCTs and NRSI	

4. Did the review authors use a comprehensive literature search strategy?

For Partial Yes (all the following):	For Yes, should also have (all the following):	
☑ searched at least 2 databases (relevant to research question)	☐ searched the reference lists / bibliographies of included studies	☐ Yes
☑ provided key word and/or search strategy	☐ searched trial/study registries	☑ Partial Yes
☑ justified publication restrictions (e.g. language)	☐ included/consulted content experts in the field	☐ No
	☐ where relevant, searched for grey literature	
	☐ conducted search within 24 months of completion of the review	

5. Did the review authors perform study selection in duplicate?

For Yes, either ONE of the following:	
☑ at least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include	☑ Yes
☐ OR two reviewers selected a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder selected by one reviewer.	☐ No

SUPPLEMENTAL S3: Continued

6. Did the review authors perform data extraction in duplicate?

For Yes, either ONE of the following:	
☑ at least two reviewers achieved consensus on which data to extract from included studies	☑ Yes ☐ No
☐ OR two reviewers extracted data from a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder extracted by one reviewer.	

7. Did the review authors provide a list of excluded studies and justify the exclusions?

For Partial Yes:	For Yes, must also have:	
☑ provided a list of all potentially relevant studies that were read in full-text form but excluded from the review	☐ Justified the exclusion from the review of each potentially relevant study	☐ Yes ☑ Partial Yes ☐ No

8. Did the review authors describe the included studies in adequate detail?

For Partial Yes (ALL the following):	For Yes, should also have ALL the following:	
☑ described populations ☑ described interventions ☑ described comparators ☑ described outcomes ☑ described research designs	☐ described population in detail ☐ described intervention in detail (including doses where relevant) ☐ described comparator in detail (including doses where relevant) ☐ described study's setting ☐ timeframe for follow-up	☐ Yes ☑ Partial Yes ☐ No

9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?

RCTs		
For Partial Yes, must have assessed RoB from	For Yes, must also have assessed RoB from:	
☐ unconcealed allocation, *and* ☐ lack of blinding of patients and assessors when assessing outcomes (unnecessary for objective outcomes such as all-cause mortality)	☑ allocation sequence that was not truly random, *and* ☑ selection of the reported result from among multiple measurements or analyses of a specified outcome	☑ Yes ☐ Partial Yes ☐ No ☐ Includes only NRSI
NRSI		
For Partial Yes, must have assessed RoB:	For Yes, must also have assessed RoB:	
☐ from confounding, *and* ☐ from selection bias	☑ methods used to ascertain exposures and outcomes, *and* ☑ selection of the reported result from among multiple measurements or analyses of a specified outcome	☑ Yes ☐ Partial Yes ☐ No ☐ Includes only RCTs

10. Did the review authors report on the sources of funding for the studies included in the review?

For Yes	
☑ Must have reported on the sources of funding for individual studies included in the review. Note: Reporting that the reviewers looked for this information but it was not reported by study authors also qualifies	☑ Yes ☐ No

SUPPLEMENTAL S3: Continued

11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?

RCTs For Yes: ☑ The authors justified combining the data in a meta-analysis ☑ AND they used an appropriate weighted technique to combine study results and adjusted for heterogeneity if present. ☑ AND investigated the causes of any heterogeneity	☑ Yes ☐ No ☐ No meta-analysis conducted
For NRSI For Yes: ☑ The authors justified combining the data in a meta-analysis ☑ AND they used an appropriate weighted technique to combine study results, adjusting for heterogeneity if present ☑ AND they statistically combined effect estimates from NRSI that were adjusted for confounding, rather than combining raw data, or justified combining raw data when adjusted effect estimates were not available ☐ AND they reported separate summary estimates for RCTs and NRSI separately when both were included in the review	☐ Yes ☐ No ☐ No meta-analysis conducted

12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?

For Yes: ☑ included only low risk of bias RCTs ☐ OR, if the pooled estimate was based on RCTs and/or NRSI at variable RoB, the authors performed analyses to investigate possible impact of RoB on summary estimates of effect.	☑ Yes ☐ No ☐ No meta-analysis conducted

13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?

For Yes: ☑ included only low risk of bias RCTs ☐ OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results	☑ Yes ☐ No

14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?

For Yes: ☐ There was no significant heterogeneity in the results ☑ OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review	☑ Yes ☐ No

15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?

For Yes: ☑ performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias	☑ Yes ☐ No ☐ No meta-analysis conducted

https://scholarcommons.towerhealth.org/t-med/vol3/iss1/1
DOI: https://doi.org/10.54299/tmed/blxr6776

SUPPLEMENTAL S3: Continued

16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?

For Yes:		
☑	The authors reported no competing interests OR	☑ Yes
☐	The authors described their funding sources and how they managed potential conflicts of interest	☐ No

To cite this tool: Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, Moher D, Tugwell P, Welch V, Kristjansson E, Henry DA. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017 Sep 21:358:i4008.

Research Question:
Comparison outcomes of Metformin Continued against Metformin Held during periprocedural period of diagnostic or interventional coronary angiography.
PICO:
Population: Coronary Angiography
Intervention: Metformin Continued
Comparison: Metformin Held 24-48 hours before coronary angiography
Outcome: Outcomes studied include change in post and pre-catheterization creatinine and change in post and pre-catheterization Glomerular Filtration Rate.

Study type: Hedges' g to compare continuous outcomes meta-analyses.
MeSH Terms & Keywords:
Coronary Angiography
Cardiac Catheterization
Percutaneous Coronary Interventions
Transluminal Coronary Balloon Dilation
Percutaneous Transluminal Coronary Angioplasty
Metformin
Humans

Population	Intervention	Comparison	Outcomes	Study Type
"Coronary Angiography"[Mesh] OR "Cardiac Catheterization"[Mesh] OR "Percutaneous Coronary Intervention"[Mesh] OR "Angioplasty, Balloon, Coronary"[Mesh] "Metformin"[Mesh]				
Coronary Angiographies OR Cardiac Catheterizations Heart Catheterization Heart Catheterizations OR Percutaneous Coronary Interventions Percutaneous Coronary Revascularization Percutaneous Coronary Revascularizations OR Transluminal Coronary Balloon Dilation Balloon Dilation, Coronary Artery Coronary Balloon Angioplasties Coronary Angioplasty, Transluminal Balloon Percutaneous Transluminal Coronary Angioplasty	Dimethylbiguanidine Dimethylguanylguanidine Glucophage Metformin Hydrochloride Metformin HCl			

Pubmed: 31
((((("Coronary Angiography"[MeSH Terms] OR ("Coronary Angiography"[MeSH Terms] OR ("coronary"[All Fields] AND "angiography"[All Fields]) OR "Coronary Angiography"[All Fields] OR ("coronary"[All Fields] AND "angiographies"[All Fields]) OR "coronary angiographies"[All Fields]) OR ("Cardiac Catheterization"[MeSH Terms] OR ("Cardiac Catheterization"[MeSH Terms] OR ("cardiac"[All Fields] AND "catheterization"[All Fields]) OR "Car-

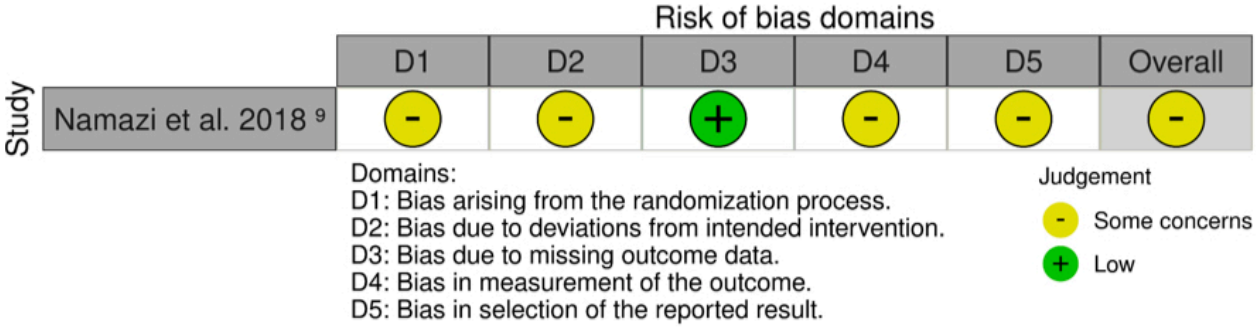
diac Catheterization"[All Fields] OR ("cardiac"[All Fields] AND "catheterizations"[All Fields]) OR "cardiac catheterizations"[All Fields]) OR ("heart catheterisation"[All Fields] OR "Cardiac Catheterization"[MeSH Terms] OR ("cardiac"[All Fields] AND "catheterization"[All Fields]) OR "Cardiac Catheterization"[All Fields] OR ("heart"[All Fields] AND "catheterization"[All Fields]) OR "heart catheterization"[All Fields]) OR ("Cardiac Catheterization"[MeSH Terms] OR ("cardiac"[All Fields] AND "catheterization"[All Fields]) OR "Cardiac Catheterization"[All Fields] OR ("heart"[All Fields] AND "catheterizations"[All Fields]) OR "heart catheterizations"[All Fields])))) OR ((((((("Angioplasty, Balloon, Coronary"[Mesh]) OR (Transluminal Coronary Balloon Dilation)) OR (Balloon Dilation, Coronary Artery)) OR (Coronary Balloon Angioplasties)) OR (Coronary Angioplasty, Transluminal Balloon)) OR (Percutaneous Transluminal Coronary Angioplasty))) OR ((((("Percutaneous Coronary Intervention"[Mesh]) OR (Percutaneous Coronary Interventions)) OR (Percutaneous Coronary Revascularization)) OR (Percutaneous Coronary Revascularizations))) AND ((("Metformin"[MeSH Terms] OR ("Metformin"[MeSH Terms] OR "Metformin"[All Fields] OR "dimethylbiguanidine"[All Fields]) OR ("Metformin"[MeSH Terms] OR "Metformin"[All Fields] OR "dimethylguanylguanidine"[All Fields]) OR ("Metformin"[MeSH Terms] OR "Metformin"[All Fields] OR "glucophage"[All Fields] OR "metformine"[All Fields] OR "metformin s"[All Fields] OR "metformins"[All Fields]) OR ("Metformin"[MeSH Terms] OR "Metformin"[All Fields] OR ("Metformin"[All Fields] AND "hydrochloride"[All Fields]) OR "metformin hydrochloride"[All Fields]) OR ("Metformin"[MeSH Terms] OR "Metformin"[All Fields] OR ("Metformin"[All Fields] AND "hcl"[All Fields]) OR "metformin hcl"[All Fields])))) Filters: Clinical Study, Clinical Trial, Clinical Trial, Phase I, Clinical Trial, Phase II, Clinical Trial, Phase III, Clinical Trial, Phase IV, Comparative Study, Controlled Clinical Trial, Meta-Analysis, Multicenter Study, Observational Study, Pragmatic Clinical Trial, Randomized Controlled Trial, Validation Study

Embase: 819

('coronary angiography'/exp OR 'angiography, coronary' OR 'arteriography, coronary' OR 'coronarography' OR 'coronary angiography' OR 'coronary arteriogram' OR 'coronary arteriography' OR 'coronary arteriograpy' OR 'heart catheterization'/exp OR 'cardiac catheterisation' OR 'cardiac catheterization' OR 'catheterisation, heart' OR 'catheterization, heart' OR 'heart catherization' OR 'heart catheterisation' OR 'heart catheterization' OR 'percutaneous coronary intervention'/exp OR 'percutaneous coronary intervention' OR 'transluminal coronary angioplasty'/exp OR 'angioplasty, balloon, coronary' OR 'angioplasty, transluminal coronary' OR 'angioplasty, transluminal, percutaneous coronary' OR 'coronary angioplasty' OR 'coronary angioplasty, transluminal' OR 'coronary artery dilatation, transluminal' OR 'coronary balloon angioplasty' OR 'p.t.c.a.' OR 'percutaneous coronary transluminal angioplasty' OR 'percutaneous transluminal coronary angioplasty' OR 'ptca' OR 'transluminal coronary angioplasty') AND ('metformin'/exp OR '1, 1 dimethylbiguanide' OR 'anj 900' OR 'anj900' OR 'apophage' OR 'aron' OR 'benofomin' OR 'dabex' OR 'denkaform' OR 'deson' OR 'dextin' OR 'diabetase' OR 'diabetase s' OR 'diabetformin' OR 'diabetmin' OR 'diabetmin retard' OR 'diabetosan' OR 'diabex' OR 'diafat' OR 'diaformin' OR 'diaformina' OR 'diaformina lp' OR 'diametin' OR 'diamin' OR 'dianben' OR 'diformin' OR 'diformin retard' OR 'dimefor' OR 'dimethylbiguanide' OR 'dimethyldiguanide' OR 'dmgg' OR 'dybis' OR 'efb 0027' OR 'efb0027' OR 'eraphage' OR 'espa-formin' OR 'euform retard' OR 'fluamine' OR 'flumamine' OR 'fornidd' OR 'fortamet' OR 'glafornil' OR 'glibudon' OR 'glifage' OR 'gliguanid' OR 'glucaminol' OR 'glucofage' OR 'glucofago' OR 'glucoform' OR 'glucoformin' OR 'glucohexal' OR 'glucoless' OR 'glucomet' OR 'glucomin' OR 'glucomine' OR 'gluconil' OR 'glucophage' OR 'glucophage forte' OR 'glucophage retard' OR 'glucophage sr' OR 'glucophage xr' OR 'glucophage xr extended release' OR 'glucophage-mite' OR 'glucostop' OR 'glucotika' OR 'gludepatic' OR 'glufor' OR 'gluformin' OR 'glukophage' OR 'glumeformin' OR 'glumet' OR 'glumetza' OR 'glupa' OR 'glustress' OR 'glyciphage' OR 'glycomet' OR 'glycon' OR 'glycoran' OR 'glyformin' OR 'glymet' OR 'haurymellin' OR 'hipoglucin' OR 'i-max' OR 'islotin' OR 'jesacrin' OR 'juformin' OR 'la 6023' OR 'la6023' OR 'lyomet (drug)' OR 'maformin' OR 'meglucon' OR 'meguan' OR 'melbin' OR 'melformin' OR 'mellittin' OR 'merckformin' OR 'mescorit' OR 'metaformin' OR 'metfogamma' OR 'metfoliquid geriasan' OR 'metforal' OR 'metformax' OR 'metformin' OR 'metformin hydrochloride' OR 'metformina' OR 'metformine' OR 'metformine hcl' OR 'methformin' OR 'metiguanide' OR 'metomin' OR 'metphormin' OR 'miformin' OR 'n` dimethylguanylguanide' OR 'n` dimethylguanylguanidine' OR 'n`, n` dimethyldiguanide' OR 'n, n dimethyl biguanidine' OR 'n, n dimethylbiguanide' OR 'n, n dimethylbiguanide retard' OR 'n, n dimethylbiguanidine' OR 'n, n dimethyldiguanide' OR 'n, n dimethylguanylguanidine' OR

'neoform' OR 'newmet' OR 'nndg' OR 'reglus-500' OR 'riomet' OR 'riomet er' OR 'risidon' OR 'rudimet' OR 'siamformet' OR 'siofor' OR 'thiabet' OR 'vimetrol' OR 'walaphage') AND ('clinical study'/exp OR 'clinical data' OR 'clinical studies as topic' OR 'clinical study' OR 'medical trial' OR 'randomized controlled trial'/exp OR 'controlled trial, randomized' OR 'randomised controlled study' OR 'randomised controlled trial' OR 'randomized controlled study' OR 'randomized controlled trial' OR 'trial, randomized controlled' OR 'observational study'/exp OR 'non experimental studies' OR 'non experimental study' OR 'nonexperimental studies' OR 'nonexperimental study' OR 'observation studies' OR 'observation study' OR 'observational studies' OR 'observational studies as topic' OR 'observational study' OR 'observational study as topic' OR 'controlled study'/exp OR 'control group study' OR 'control group trial' OR 'controlled study' OR 'controlled trial' OR 'retrospective study'/exp OR 'ex post facto design' OR 'retrospective design' OR 'retrospective panel studies' OR 'retrospective panel study' OR 'retrospective studies' OR 'retrospective study' OR 'study, retrospective' OR 'prospective study'/exp OR 'prospective method' OR 'prospective studies' OR 'prospective study' OR 'study, prospective' OR 'validation study'/exp OR 'validation studies' OR 'validation studies as topic' OR 'validation study' OR 'comparative study'/exp OR 'comparative studies' OR 'comparative study' OR 'comparison' OR 'pragmatic trial'/exp OR 'practical clinical trial' OR 'pragmatic clinical trial' OR 'pragmatic clinical trials' OR 'pragmatic trial' OR 'randomised controlled pragmatic trial' OR 'randomized controlled pragmatic trial' OR 'multicenter study'/exp OR 'multi-center study' OR 'multi-center trial' OR 'multi-centre study' OR 'multi-centre trial' OR 'multicenter study' OR 'multicenter trial' OR 'multicentre study' OR 'multicentre trial' OR 'study, multicenter' OR 'trial, multicenter')

SUPPLEMENTAL S4: Cochrane Risk of Bias (ROB) tool assessment for included randomized controlled trials (RCTs)



SUPPLEMENTAL S5: Newcastle-Ottawa scale (NOS) scoring to assess the quality of non-randomized observational studies

Study	NOS score
Yu et al.[9]	9/9
Oktay et al.[10]	9/9

Author Contributions

NP, MH performed initial screening and data collection, YS and MH: performed data analysis and contributed content to the first draft of the manuscript; MH, SF, and NP: wrote the first draft of the manuscript and composed the tables. SF, and MH: made all the graphics and figures for the manuscript. MK, SR, AS, KH all contribute to writing and editing manuscript. IE, MM, AP, WA made critical and final edits. YS, MCA final critical edits and supervision of this project.