Sex disparities in cardiovascular outcome trials of diabetes populations: a systematic review and meta-analysis

Running title: Sex disparities in cardiovascular outcome trials

Kristin K. Clemens MD MSc,[1-4] Mark Woodward PhD,[5-7] Bruce Neal MB ChB PhD ,[6,8]

Bernard Zinman MD [9]

1. Department of Medicine, Division of Endocrinology and Metabolism, Western University, London Ontario Canada

2. Department of Epidemiology and Biostatistics, Western University, London Ontario Canada

3. Centre for Diabetes, Endocrinology and Metabolism, St. Joseph's Health Care London

4. Lawson Health Research Institute, London Ontario Canada

5. The George Institute for Global Health, University of Oxford, UK

6. The George Institute for Global Health, Sydney, Australia

7. Department of Epidemiology and Welch Center for Prevention, Epidemiology, and Clinical Research, Johns Hopkins Bloomberg School of Public Health, Baltimore Maryland USA

8. Imperial College London, London, UK.

9. Lunenfeld-Tanenbaum Research Institute, Mount Sinai Hospital, University of Toronto, Toronto Ontario Canada

Corresponding Author: Dr. Kristin K. Clemens, Centre for Diabetes, Endocrinology and Metabolism, St. Joseph's Health Care London, London Ontario Canada, N6A 4V2,

Phone: 519-646-6316, Fax: 519-646-6212, Email: kristin.clemens@sjhc.london.on.ca

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Abstract

Background: Sex differences have been described in cardiovascular outcomes trials (CVOTs) of diabetes populations.

Purpose: We systematically reviewed for baseline sex differences in CV risk factors and CV protection therapy in diabetes CVOTs published since 2008.

Data Sources: Randomizedplacebo-controlledtrialsexaminingtheeffectofdiabetesmedications on major adverse cardiovascular events in people ≥18 years of age with type 2 diabetes

Study Selection: Included trials reported baseline sex-specific CV risks and use of CV protection therapy

Data Extraction: Two reviewers independently abstracted study data.

Data Synthesis: We included fiveCVOTswith46,606 participants. We summarized sex-specific data using mean differences (MDs) and relative risks (RRs) and pooled estimates using randomeffectsmeta-analysis.Therewerefewerwomenthanmeninincludedtrials (28.5–35.8% women). Women more often had stroke (RR 1.28; 95% CI 1.09, 1.50), heartfailure(RR1.30;95%CI1.21,1.40),andchronickidneydisease(RR1.33;95%CI 1.17;1.51).Theylessoftenusedstatins(RR0.90;95%CI0.86,0.93),aspirin(RR0.82; 95% CI 0.71, 0.95), and b-blockers (RR 0.93; 95% CI 0.88, 0.97) and had a higher systolic blood pressure (MD 1.66 mmHg; 95% CI 0.90, 2.41), LDL cholesterol (MD 0.34 mmol/L; 95% CI 0.29,

0.39), and hemoglobin A1c (MD 0.11%; 95% CI 0.09, 0.14 [1.2 mmol/mol; 1.0, 1.5]) than men.to 2.41), low-density lipoprotein cholesterol (MD 0.34 mmol/L, 0.29 to 0.39) and hemoglobin A1c (MD 0.11%, 0.09 to 0.14 or 1.2 mmol/mol, 1.0 to 1.5) than men.

Limitations: We could not carry out meaningful subgroup analyses due to a small number of studies. Our study findings may not be generalizable to low CV risk groups, nor to high-risk CV patients in routine care.

Conclusions: There were baseline sex disparities in diabetes CVOTs. We suggest ongoing efforts to recruit women into clinical trials, and the promotion of consistent high quality CV risk management across the sexes.

Background

There are important sex differences in the risk, pathophysiology and complications of diabetes including its vascular consequences.(1–4) In women, type 1 and type 2 diabetes promote a greater excess relative risk of cardiovascular disease (CVD), stroke, heart failure, and mortality than in men.(5–8)

While sex differences in diabetes might be due to biological factors, body composition, fat distribution, or sex hormones (2), variances might also be related to disparities in cardiovascular (CV) risk factor management (e.g. control of blood pressure and cholesterol). (1,4,9) Disparities in CV risk factor management have been described across diabetes populations in routine care. (10–15)

Sex differences in cardiovascular (CV) risk factors and outcomes have also been observed in the clinical trial setting including recent diabetes cardiovascular outcomes trials (CVOTs), (16–18) In TECOS (Trial Evaluating Cardiovascular Outcomes With Sitagliptin) and the EMPA-REG OUTCOME (BI10773[Empagliflozin]CardiovascularOutcomeEventTrialinType2 Diabetes Mellitus Patients) , for example, women had suboptimal risk factor profiles compared with men. (16,17) In TECOS, women were at lower risk of major adverse cardiovascular events (MACE).(19) Where clinical trial participants are typically more adherent, educated, and affluent than those in routine care, (20–22) a systematic understanding of disparities in CV risk factor management in clinical trial participants is of interest.

In this systematic review and meta-analysis, we evaluated for baseline differences in CV risk factors and use of CV protection therapy in women and men who participated in major diabetes CVOTs. We hypothesized that even in clinical trial participants, women would have suboptimal risk factor management and use CV protection therapy less often than men.

Methods

We followed a pre-specified protocol registered at PROSPERO (CRD42019137121), as well as the guidelines for reporting systematic reviews and meta-analyses (Supplementary Table 1).(23)

Data sources and searches

We included all randomized placebo-controlled trials that evaluated the effect of diabetes medications (oral or injectable) on 3 or 4-point MACE (i.e. CV death, non-fatal myocardial infarction, hospitalization for heart failure, non-fatal stroke, hospitalization for unstable angina) in those ≥18 years with type 2 diabetes. To be included, trials had to report sex-specific baseline characteristics and risk factors (described below), and had to be reported in the English language. We excluded observational studies, case series, case reports, cross-over studies, trials with fewer than 100 participants and review articles.

To reduce publication bias, we sought out unpublished sex-specific baseline data by contacting the corresponding authors of known diabetes CVOTs completed by April 2019(SupplementaryTable2). Corresponding authors were informed of our study objectives and asked to contribute data. If authors did not respond to our initial correspondence within

one month, we sent follow-up correspondence 1-2 months later. For authors who expressed interest in providing data, we sent one additional reminder to facilitate data acquisition.

Study selection

Our literature search strategy was created by a Health Sciences Librarian with expertise in systematic reviews ((B.Dishan, St. Joseph's Health Care London). The search strategy used MeSH terms and keywords informed by our study aim, population of interest, and the CVOTs known to be completed up to April 2019 (Supplementary Table 2). We validated our final search strategy through the retrieval of a key set of previously identified relevant articles.

We searched electronic databases including MEDLINE, EMBASE, CIHAHL, Cochrane Library, Scopus, BIOSIS, Web of Science, and Clinical Trials.Net for relevant CVOTs published since 2008 (when the US Food and Drug Administration provided new guidance to pharmaceutical agencies about the development of diabetes medications). (24)

Data extraction and quality assessment

Using standard forms, one reviewer (K.K.C) screened the abstracts and/or full text articles of all identified citations against selection criteria. Citations were marked as include, exclude or uncertain. If citations were marked uncertain, full text articles were reviewed in detail. We used the Cochrane Collaboration tool to assess risk of bias in included studies.(25)

Data synthesis and analysis

Using a structured data abstraction form, two reviewers (K.K.C, Elsie[St.Joseph's Health Care London]) independently abstracted authors, years of publication, sample size, diabetes medications, and sex-specific baseline characteristics (age, % using statin, renin-angiotensin [RAAS] blocking medication, beta blocker, aspirin, % with a history of myocardial infarction, stroke, heart failure, chronic kidney disease [estimated glomerular filtration rate <60 ml/min/1.73m^2], and peripheral arterial disease [PAD]; mean [SD] low-density lipoprotein cholesterol [LDL-C], systolic blood pressure and hemoglobin A1c). Abstractors resolved any disagreements by discussion. If there were unresolved discrepancies, we engaged a third reviewer (B.Z).

Our primary interest was to examine for sex differences in baseline CV risk factors and use of guideline-recommended CV protection therapy. We pooled sex-specific baseline data across included trials using random effects meta-analyses with inverse variance weighting. Continuous variables were summarized using mean differences and dichotomous variables were summarized using relative risks (RRs) and 95% confidence intervals (CIs). We used I^2 and Cochran's Q test to explore heterogeneity. All analyses were performed using Stata version 13.1 (Stata Corporation, College Station, TX, USA).

Results

We identified 1192 relevant citations between Jan 1, 2008 and April 10, 2019 (Supplementary Figure 1). After eliminating duplicates as well as citations based upon their title or abstract, we reviewed 25 full text articles in detail.

Two published trials reported baseline characteristics by sex (EMPA-REG OUTCOME, TECOS). (16,17) The TECOS trial published sex specific data in two related manuscripts.(16,19) In this review, we cite the most comprehensive report.

We contacted the corresponding authors of 17 additional diabetes CVOTs to request unpublished sex-specific baseline data. We received unpublished data from three additional trials (EXAMINE, CANVAS Program, LEADER).(18,26–27)

Characteristics of included trials

Included trials had between 5380 and 14 724 participants, all of whom had established CVD or risk factors for CVD (Table 1). The inclusion criteria of the trials in our study did not vary by sex. In included trials, the diabetes medications under investigation were empagliflozin, canagliflozin, liraglutide, alogliptin and sitagliptin. Across included trials, there were consistently fewer female participants (28.5-35.8% were women). Risk of bias was low in all trials.

Sex differences in baseline characteristics

At baseline, women were older (MD 1.03 years, 95% CI 0.18 to 1.89) (Figure 1). They less often had a history of myocardial infarction than men (RR 0.71 95% CI 0.59 to 0.86), but

more often had stroke (RR 1.28, 1.09 to 1.50),heart failure (RR 1.30, 1.21 to 1.40), PAD ((1.12; 0.97, 1.30), (Figure 1).

Despite their baseline CV risks, women in included trials less often used beta-blockers (RR 0.93, 0.88 to 0.97) and statins (RR 0.90, 0.86 to 0.93) than men, with similar qualitative differences in all trials (I^2 90% and 93%, respectively) (Figure 2). There was no sex difference in the baseline use of RAAS blockers (RR 1.00, 0.99 to 1.05) or aspirin (RR 1.00, 0.99 to 1.02). Women also had higher systolic blood pressure (MD 1.66 mmHg, 0.90 to 2.41), higher LDL-C (MD 0.34 mmol/L, 0.29 to 0.39), and higher hemoglobin A1c than men (MD 0.11%, 0.09 to 0.14 or 1.2 mmol/mol, 1.0 to 1.5) (Figure 3). Although there was evidence of heterogeneity between CVOTs (I^2 51-96%), all within-trial differences were in the same direction.

Discussion

In this systematic review and meta-analysis of diabetes CVOTs, we identified several interesting findings. Only two CVOTs published baseline characteristics by sex, a finding that has also been described in systematic reviews of CV prevention and stroke. (28,29) In the reported diabetes CVOTs the participation of women was also low, as we have described previously.(30) We also found that women in these CVOTs more often had a baseline history of CV risk factors including stroke, CKD, PAD, and heart failure than men. Despite their comorbidities and guideline recommendations that statins be considered in high-risk patients with type 2 diabetes, (31-33) and that beta-blockers be prescribed to patients with coronary artery disease and heart failure, (34-35) fewer women were using statins and beta-

blockers than men across these trials. Women also had higher LDL-C, systolic blood pressure and hemoglobin A1c than men.

There may be a number of reasons for the sex disparities observed in the reported CVOTs; differences might be related to patient, provider, or healthcare system factors. (4,9,12–15,36) With respect to the lower number of women reported CVOTs, it is possible that some trials favored recruitment of men due to their higher absolute risk of CVD. Women might have also faced barriers to trial participation due to family, work, or social reasons (28,37). A lower number of female participants have also been described in previous systematic reviews of CV prevention, (28) stroke, (29) and heart failure. (38) Encouragingly the recently published REWIND trial of dulaglutide recruited the largest proportion of women in diabetes CVOTs to date (46% women).(39) Although unclear if related to the recruitment of those with newly diagnosed diabetes or those with subclinical cardiovascular disease (e.g. carotid artery disease, left ventricular dysfunction), trialists might continue to make efforts to screen and enroll more women in clinical trials.

The baseline sex differences we observed in CV risk factors including heart failure, CKD, PAD and stroke have been described in other settings. Heart failure with preserved ejection fracture for example, has been noted to be more common in women, possibly related to differences in body composition, hormone or reproductive factors, endothelial inflammation and microvascular function, (40) or the presence of diabetes and hypertension (hypertension for example is a more potent risk factor for heart failure in women than in men).(41) A higher prevalence of CKD in women has also been described, which might in part be due to

the longer-life expectancy of women, or overdiagnosis with estimating equations.(42) Stroke may be more common

in women due to suboptimal CV risk factor management, the presence of diabetes (excess risk of stroke is higher in women than men), or growing rates of obesity and the metabolic syndrome in women (5,43).

Despite their comorbidities, the presence of gender-based clinical practice guidelines on CV protection in women,(44) we observed disparities in the baseline use of statins and beta-blockers in women in included CVOTs. It is possible that their providers might not recognize that women with diabetes can also be at high risk of CVD, and as such, they received suboptimal CV risk factor management. Women and men might have different health beliefs that could affect adherence to cardioprotective medications. They may additionally experience different drug side effects that could result in differential discontinuation of CV protection medications.(36,45) Further, women might face barriers to attending clinic appointments to receive CV protection due to social reasons (i.e. children and family). Although we do recognize that fewer women had baseline myocardial infarction than men (indication for both statins and beta-blockers), (34) we do not feel that this difference is enough to explain variance in the use of beta-blockers and statins between the sexes. All trial participants had established type 2 diabetes and CVD or risk factors for CVD (indication for statin). (31) Women also had heart failure more often than men (indication for beta-blockers),(35) along with, stroke and CKD (indications for asprin and statin).(32) Sex differences in CV protection therapy has also been described previously,

including in contemporary routine care settings, in regions across the world. (10,11,13, 46-47) Of note, in theses trials , we did not observe baseline differences in the use of RAAS blockade, a therapy indicated for control of blood pressure and organ protection in diabetes (48). As sex disparities in the use of RAAS blockade have been described in patients with diabetes in routine care previously (11), this finding might be suggestive of recent change.

There are several strengths to our study. We examined a large number of individuals who participated in five diabetes CVOTs in recent times. We followed a pre-specified protocol, as well as recommended guidelines for the conduct and reporting of systematic reviews and meta-analyses. Weaknesses included our inability to carry out meaningful subgroup analyses (i.e. examination of disparities by age) due to the relatively small sample size. Further, we could not determine if the increased prevalence of CV risks including heart failure in women was due to heart failure with preserved ejection fraction or heart failure with reduced ejection fraction, as we used aggregate data from clinical trials and did not have access to echocardiogram result. Over the course of CVOTs, it is possible that investigators may have optimized cardioprotective medications or initiated these therapies due to incident MACE. We could not capture these changes in our study. Although we attempted to reduce publication bias by requesting unpublished data from eligible diabetes CVOTs, it is possible that by sharing our study objectives with investigators, we may have introduced bias (investigators may have been dissuaded from participating if they had a study of sex differences planned or if the topic was not of interest). Our study is also not fully generalizable to low risk groups, nor to high-risk CV patients in real-life practices.

Our results however, might be helpful to diabetes investigators, patients and providers. With few published diabetes CVOTs which report sex-specific baseline data, we suggest that trialists both examine and publish sex-specific characteristics and outcomes. Where diabetes CVOTs have found that drugs including SGLT2 inhibitors meaningfully reduce the risk of heart and kidney failure (27,49–51), it is important to include more women with these comorbidities in future trials, and perform sex-based analyses of key outcomes to better translate trial results into effective clinical care strategies across the sexes.(40) We also suggest providers be increasingly attentive to CV risks in women. Further, it is

important to continue to promote efforts to adopt guideline-based CV care for both women and men, educate women on modifiable risk factors for the development of CVD, and promote equitable access to healthcare across the sexes.

Conclusions

Our study highlights that even in clinical trial participants, there remains a female disadvantage in diabetes. Study investigators should make special efforts to enroll females in clinical trials, and report sex-specific characteristics and outcomes in their studies.(9,28) We suggest ongoing efforts to promote equitable care across the sexes.

Acknowledgments

Author contributions

K.C contributed to the conception and design of the study, the acquisition of data, the interpretation of the results and she drafted the manuscript. M.W contributed to the design of

the study, the analysis, result interpretation, and he revised the manuscript critically for its content. B.N contributed to the design of the study, the interpretation of results, and he reviewed the manuscript for its content. B.Z conceptualized the study, helped to acquire data, interpreted the results, and revised the manuscript. K.C is the guarantor for this work and takes responsibility for the contents of this article. All authors gave final approval to the version to be published.

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Conflict of interest

Unrelated to this work, K.C received a Diabetes Canada Junior Investigator Award in 2017, sponsored by Astra Zeneca. She has also attended conferences sponsored by Merck Inc. M.W is a consultant to Kirin and Amgen. B.Z. has received fees for participation in Advisory boards for Astra Zeneca, Boehringer Ingelheim, Eli Lilly, Novo Nordisk, Merck, Janssen and Sanofi. B.N has received fees for participation in Advisory boards for AstraZeneca, Janssen and Merck and research support from Janssen, all of which was paid to his Institution.

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providing and summarizing unpublished baseline data. We also thank Brad Dishan (St. Joseph's Hospital) for creating our detailed search strategy, Sharlene Elsie (Western University) and Alexandra Ouedraogo (ICES Western) for administrative support.

Table 1. Characteristics of included diabetes Cardiovascular Outcome Trials

Source	n	Trial entry criterion	Diabetes medication	% women
Neal et al(28)	10 142	≥30 years with established CVD or ≥50 years with risk factors for CVD	Canagliflozin	35.8%
Zinman et al(17)	7020	≥18 years with established CVD	Empagliflozin	28.5%
Bethel et al(16)	14 724	≥50 years with established CVD	Sitagliptin	29.3%
White et al(26)	5380	ACS 15-90 days prior to randomization	Alogliptin	32.1%
Marso et al(27)	9340	≥50 years with established CVD or ≥60 years with risk factors for CVD	Liraglutide	35.7%

Abbreviations: ACS, acute coronary syndrome; CVD, cardiovascular disease

Figure 1. Forest plot of baseline sex differences in heart failure, stroke, myocardial infarction peripheral arterial disease and chronic kidney disease. The solid line represents the line of no effect, and the dotted line illustrates the pooled relative risk.

Figure 2. Forest plot of baseline sex differences in statins, RAAS blockade, beta blockers, aspirin. The solid line represents the line of no effect, and the dotted line illustrates the pooled relative risk. Note that LEADER and TECOS reported aspirins/antiplatelets.

Figure 3. Forest plot of baseline sex differences in systolic blood pressure, LDL-C, hemoglobin A1c. The solid line represents the line of no effect, and the dotted line illustrates the pooled mean difference. Note that data on systolic blood pressure were not available from EXAMINE.

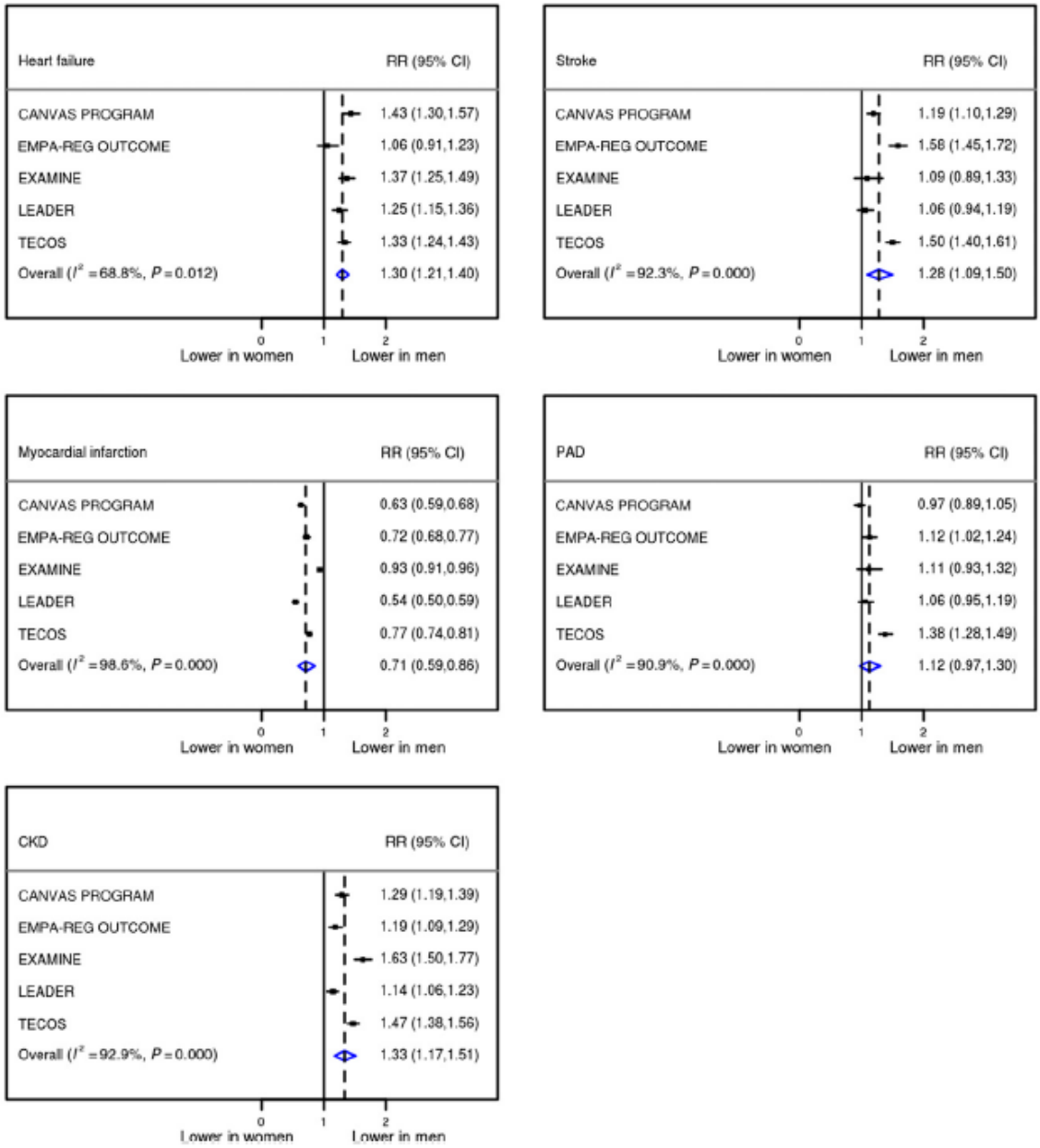

Figure 1—Forest plot of baseline sex differences in heart failure, stroke, myocardial infarction, PAD, and CKD. The solid line represents the line of no difference, and the dotted line highlights the pooled relative risk.

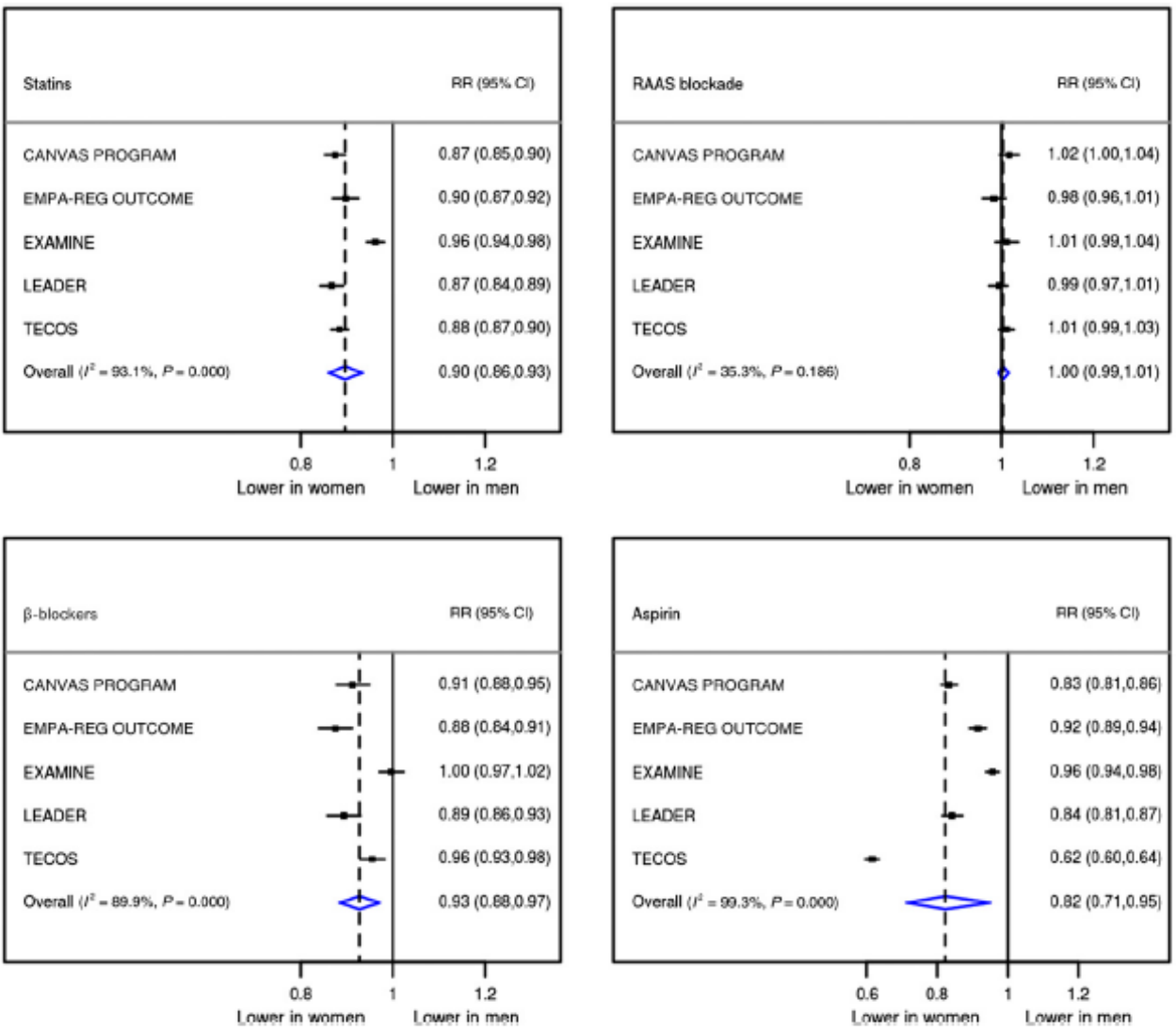

Figure 2—Forest plot of baseline sex differences in statins, RAAS blockade, β-blockers, and aspirin. The solid line represents the line of no difference, and the dotted line highlights the pooled relative risk. Note that LEADER and TECOS reported use of aspirins/antiplatelets.

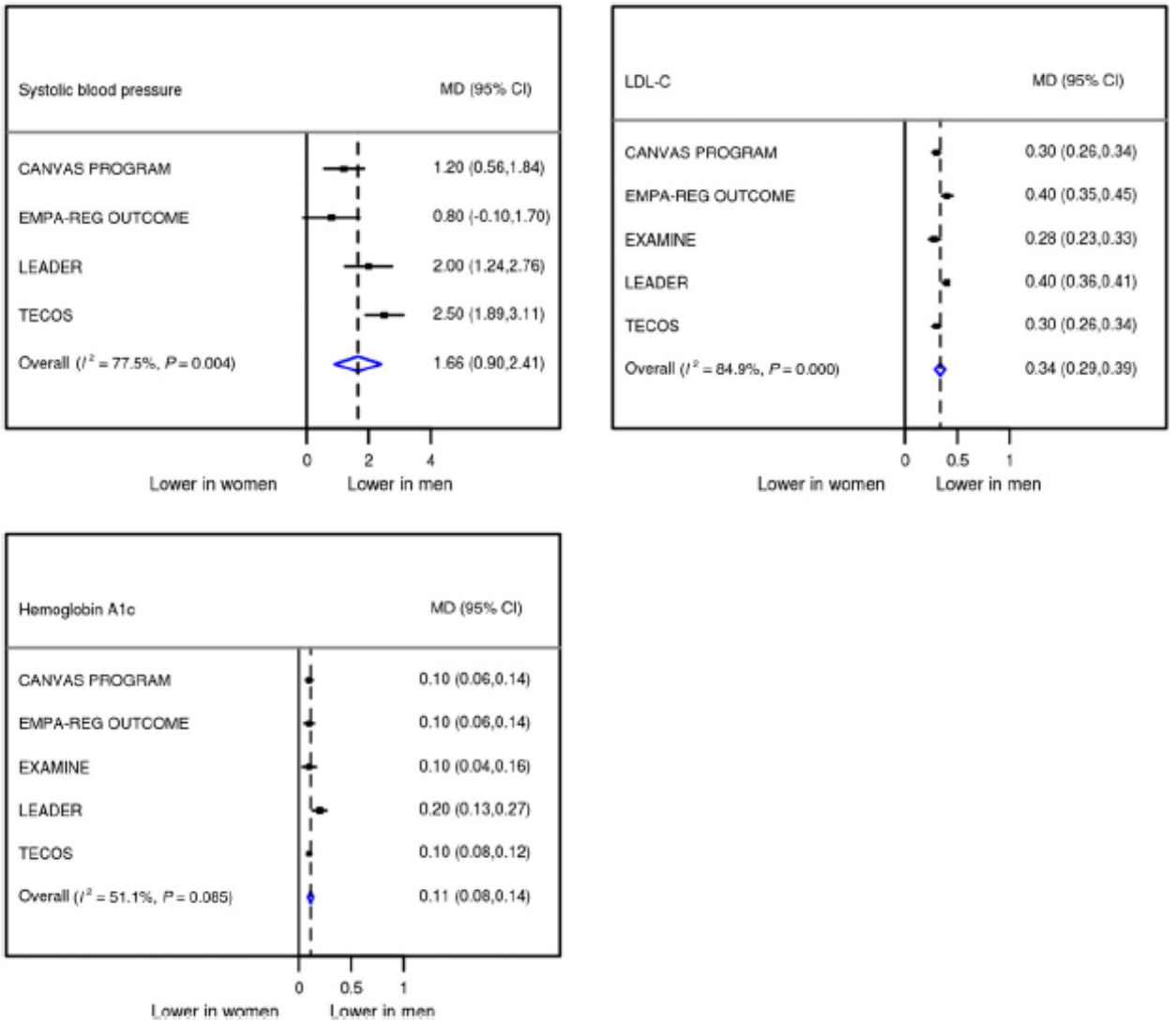

Figure 3—Forest plot of baseline sex differences in systolic blood pressure, LDL-C, and hemoglobin A_{1c}. The solid line represents the line of no difference, and the dotted line illustrates the pooled mean difference. Note that data on systolic blood pressure was not available from EXAMINE.

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