PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Is Cardiovascular Risk Reduction Therapy Effective in South Asian, Chinese, and Other Patients with Diabetes? A Population-Based Cohort Study from Canada
AUTHORS	Ke, Calvin; Morgan, Steve; Smolina, Kate; Gasevic, Danijela; Qian, Hong; Khan, Nadia

VERSION 1 - REVIEW

REVIEWER	Juliana CN Chan Professor of Medicine and Therapeutics Director, Hong Kong Institute of Diabetes and Obesity The Chinese University of Hong Kong Prince of Wales Hospital Shatin HONG KONG
REVIEW RETURNED	14-Nov-2016

GENERAL COMMENTS	In this paper, the authors used well characterized administrative databases to evaluate the effects of BP lowering drugs (ACEi, ARB, diurectics, CCB) on mortality in a cohort of 208,000 subjects (6% South Asian and 10% Chinese) with type 2 diabetes in Ontario State, Canada. These data aim to complement the efficacy data demonstrated with these drugs in RCTs and explore potential inter-ethnic differences in treatment effectiveness in a real world setting. The group has clearly described the methodology used to define exposure (diabetes/drug classes), outcomes (all-cause mortality), ethnicity (using surnames) and covariables including socio-economic classes and co-morbidities. Some of these methods have been published, thus supporting the validity and utility of these databases. They also used dispensing data to estimate the duration of drug exposure as an index of adherence. After 3 years of observation, 6% of patients have died, highlighting the high risk nature of type 2 diabetic patients with hypertension. After adjustment for confounders, ARB, ACEi and diuretics usage were associated with reduced mortality in Caucasians. In Chinese, only ARB and diuretics reduced mortality. None of these drugs reduced death rate in South Asians and no effect was observed with CCB in all ethnic groups. A lower proportion of Chinese patients were prescribed with ACEi compared to ARB in keeping with poor tolerance of ACEi in this population often due to cough. In the entire group, high adherence rate was associated with low mortality rate athough the small number within each group does not allow further analysis stratified by ethnicity and drug class.

	Overall the paper is well written with clear rationale, data analysis and reporting. One noticeable point is the relatively low prescription rate of statin (20%) and RASi (40-50%) in this high risk population and the tendency of a higher prescription rate of these drugs in Caucasians than Chinese and Indian subjects. These observations raised the question whether inter-ethnic differences in the associations of drug usage and mortality may be in part due to intensity of treatment in addition to adherence. As such, it will be interesting to see whether combination therapy for BP lowering are less likely to be prescribed in the non-Caucasian population. In a way, the authors have already adjusted for the usage of other drugs in the models, however, it will be useful to highlight these treatment gaps to inform clinical practice.

REVIEWER	Julius Chacha Mwita University of Botswana, Botswana
REVIEW RETURNED	19-Nov-2016

GENERAL COMMENTS	1. The study was aimed to research on Cardiovascular Risk Reduction Therapy Effectiveness , but the measured outcome was mortality from any cause. [Previous studies have shown that mortality and cardiovascular complications among are less among these minority Canadian population , Shah et al Diabetes Care 2013 Sep; 36(9): 2670-2676] 2.The comparison group for each drug use was not clear. For instance, for patients who were using ARBs, did the the comparison group ('untreated') include patients who were not on ARB regardless of the other antihypertensives? 3.How comparable were the two groups - treated vs untreated ? were there any differences on indications for treatment between treated and untreated groups- in terms of different factors that include indication for treatment.

REVIEWER	Professor Y.K.Seedat University of KwaZulu Natal.
REVIEW RETURNED	23-Jan-2017

GENERAL COMMENTS	The BMJ open paper is interesting, being a” real life study”. The effect on mortality is agreed to depend on blood pressure, and the authors apparently did not adjust for this. Moreover, drugs are not prescribed at random, diuretics are likely to be confounded by age, calcium channel blockers by severity of hypertension and even therapy resistance, and angiotensin converting enzyme inhibitors by kidney dysfunction. It is not clear how the authors handled combination therapy, initially or sequential. Therefore the conclusions on associations between drugs and mortality are likely to be biased.

	There are two articles in non- diabetic patients which could be quoted from the literature. 1. Brewster LM, van Montfrans GA, Oehlers GP, Seedat YK. Systematic review: Antihypertensive drug therapy in patients of African and South Asian ethnicity. Intern Emerg Med. 2016;3 : 355-74. 2. Brewster LM, Seedat YK. Why do hypertensive patients of African ancestry respond better to calcium blockers and diuretics than to ACE inhibitors and B adrenergic blockers. A systematic review. BMC Med 2013; 11:141. A Summary is as follows: Article 2 shows that black patients in the US and South Africa respond better to diuretics and calcium channel compared to beta blockers and ACE inhibitors. The complications of hypertension occurs at a younger age group. Guidelines for hypertension in black patients suggest that diuretics and calcium channel blockers are the drugs of choice. There are no mortality data in blacks in Africa. Article 1. The article suggest that response to antihypertensive drugs are used at a younger age in South Asians similar to blacks. Data on morbidity and mortality are not available in South Asians.

REVIEWER	Dr Nitin Gholap Consultant in Diabetes and Endocrinogy University Hospital Coventry and Warwickshire, NHS Trust Coventry UK
REVIEW RETURNED	23-Feb-2017

GENERAL COMMENTS	In this article, Ke and colleagues report findings of their population-based cohort study conducted using administrative health database. The objective of the study is to compare the benefits ACEi, ARB, CCB and diuretics (used alone or in combination) on all-cause mortality among patients newly diagnosed with diabetes and belonging to South Asian, Chinese or other (predominantly Caucasians) groups. The landmark randomised controlled trials in this area (e.g HOPE, ONTARGET) have mainly involved Western population and have shown benefits of therapies such as ACEi and ARBs on primary outcomes of cardiovascular events or deaths. While adults from South and Chinese populations comprise 62% of global diabetes population, there is a paucity of such trials involving these populations. Their stated rationale behind conducting the study is to fill this gap in the knowledge relevant to the South Asian and Chinese groups. They found that ACEi reduced mortality in other patients but not in South Asian or Chinese. ARB and diuretics reduced mortality in other and Chinese patients but not in South Asian patients. CCB did not reduce mortality in any ethnic groups. Importantly none of these four classes of drugs reduced mortality in South Asian individuals. While their rationale behind undertaking this study is very valid this observational study has several deficiencies as described below.

	Therefore, one needs to be cautious about any message implying that the time-tested therapies of ACEi or ARBs are less beneficial in South Asian or Chinese populations. These populations suffer from the excess risk of diabetes and CHD and furthermore face challenges of inequalities in care due to various reasons. Furthermore, the excess cardiovascular risk is evident at a younger age and lower level of risk factors such as body mass index and blood pressure. Indeed, this has led to the calls for lower treatment targets for the South Asian patients. The observed lack of mortality benefits from these therapies in the two ethnic groups in this study, likely due to methodological and other reasons can be easily be misinterpreted as a true lack of the benefits. This can potentially lead to a waning of enthusiasm in use of the therapies in these high-risk ethnic populations. Specific comments: 1. The lack of mortality benefits in the South Asian and Chinese patients in the study could be due to their lower baseline cardiovascular risk, as seen from Table 1. The landmark trials such as the HOPE and the ONTARGET, confirming the benefits of ACEi and ARBS respectively involved high-risk diabetes patients. For example, in the HOPE trial, about 58% had hypertension and 58% had previous coronary artery disease. When such high-risk patients with diabetes were treated with Ramipril in the HOPE trial they benefited from lowering of cardiovascular events or death. In comparison with the HOPE study cohort, South Asians enrolled in this study had a lower burden of risk factors at baseline (Table 1). For example, 42% had hypertension and about 2.2% had a myocardial infarction (Table 1). Furthermore, compared with the South Asian or Chinese patients, patients from the other group had a higher prevalence of hypertension (Table 1), congestive cardiac failure, peripheral vascular disease, cerebrovascular disease and renal disease. If these differences between South Asian and other group are statistically significant, it can partially explain the difference in mortality benefits between the two ethnic groups reported in the study. Authors have stated in the methods that they have used Chi-square tests and ANOVA for comparing baseline differences among the ethnic groups. However, there is no mention of the results of these tests in Table 1. While Cox regression models were used to make statistical adjustments, it may not have fully adjusted for these differences. There could be residual confounding due to unmeasured variable related to duration, severity and treatment of these cardiovascular comorbidities, especially if these disorders are occurring at a younger age in South Asian and Chinese patients. In the UKPDS study, compared with White Caucasians, Asian Indian ethnicity was not associated with an increased risk of major vascular complications or death despite the greater burden of diabetes-related end points. (Davis et al. Diabet. Med. 2014;31:200–207). These above-mentioned issues potentially weaken the study findings and its interpretations. These therapies are likely to equally beneficial in those with high-risk diabetes across the ethnic groups. However the study does not fully address this due low-risk cohort. 2. Reporting of cause-specific mortality and other cardiovascular events would have been more useful. I guess, due to the limitation of the dataset such information wasn't available. Drugs such as ACEi and ARB have a major role in reducing cardiovascular mortality and as such cardiovascular mortality was one of the components of the

	composite primary outcome in the HOPE, ONTARGET, LIFE, and similar other trials (the other important components of the primary outcome being cardiovascular events e.g. myocardial infarction, stroke). All-cause mortality was a secondary outcome in these trials. This needs to be highlighted in the introduction and the discussion section where you have compared your findings with these trials. 3. The actual number of deaths in each ethnic group needs to be stated. You have mentioned low event numbers as a limitation. Please state any loss to follow-up. 4. Within each ethnic group, you have excluded those who died within 1 month of initiation of medication (ACEi, ARB, CCB, DIU). On the contrary, I presume, you have included all the deaths in the comparator group i.e those who were not commenced on these medications. Would this not cause a selection bias in favour of the former group. 5. Although this is a retrospective observational study, it would be useful if the authors give some idea about the statistical power of this study. 6. How you identified the newly detected diabetes is slightly confusing and needs further clarification. Similarly, please clarify method on collecting information on comorbidities (ICD codes, etc). 7. The limitations of the study needs discussing in detail.

REVIEWER	Mohammad Ali Mansournia Department of Epidemiology and Biostatistics, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran
REVIEW RETURNED	06-Mar-2017

GENERAL COMMENTS	The paper estimates the effects of several drugs on mortality in diabetic patients using inverse-probability-of-treatment weighting. I have several concerns for the authors to consider. 1) The authors should explain why they used IPTW rather than conventional regression modeling for confounding adjustment. The key point is confounding by indication e.g., see P. 668, second column, first paragraph of the following paper: Gharibzadeh S, Mohammad K, Rahimiforoushani A, Amouzegar A, Mansournia MA. Standardization as a Tool for Causal Inference in Medical Research. Arch Iran Med. 2016;19(9):666-70. 2) The mean and SD of the stabilized weights should be reported and their appropriateness should be discussed. 3) The IPTW has not been explained in detail in the Methods section. I suggest that the authors at least cite the following two references on IPTW so that the reader can refer to them for further explanations: Mansournia MA, Altman DG. Inverse probability weighting. BMJ. 2016 Jan 15;352:i189. Mansournia MA, Danaei G, Forouzanfar MH, Mahmoudi M, Jamali

	M, Mansournia N, Mohammad K. Effect of physical activity on functional performance and knee pain in patients with osteoarthritis : analysis with marginal structural models. Epidemiology. 2012;23(4):631-40. 4) Figure 1 presents cumulative hazard curves, though the legend and the Methods refer to adjusted (weighted) survival curves. The authors should either revise their explanations or present weighted survival curves as discussed in the following references: Cole SR, Hernán MA.Adjusted survival curves with inverse probability weights.Comput Methods Programs Biomed. 2004;75(1):45-9. Hernán MA, Robins JM. Causal Inference. London: Chapman & Hall/CRC. In press, chapter 17. Available at: http://www.hsph.harvard.edu/faculty/miguel-hernan/causal-inference-book/ 5) The number of censored subjects by loss-to-follow-up should be mentioned and IPCW (inverse-probability-of-censoring weighting) should be implemented if the percentage of censoring by loss-to-follow-up is not ignorable; see Mansournia et al Epidemiology paper cited above. 6) The proportional hazard assumption should be checked and time-specific hazard ratios should be reported in the case of substantial non-proportionality. Moreover, hazard ratio suffers from a built-in selection bias. The authors should at least mention these issues as a limitation in the Discussion citing the following reference: Hernán MA. The hazards of hazard ratios. Epidemiology. 2010;21:13–15. 7) P. 12, L. 51: "Relative risk" is different from "hazard ratio". 8) P. 9, L. 15: "age" was mentioned twice.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Juliana CN Chan
Institution and Country: Professor of Medicine and Therapeutics, Director, Hong Kong Institute of Diabetes and Obesity
The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, HONG KONG
Please state any competing interests : Nil

Please leave your comments for the authors below

In this paper, the authors used well characterized administrative databases to evaluate the effects of BP lowering drugs (ACEi, ARB, diurectics, CCB) on mortality in a cohort of 208,000 subjects (6% South Asian and 10% Chinese) with type 2 diabetes in Ontario State, Canada. These data aim to complement the efficacy data demonstrated with these drugs in RCTs and explore potential inter-ethnic differences in treatment effectiveness in a real world setting.

The group has clearly described the methodology used to define exposure (diabetes/drug classes), outcomes (all-cause mortality), ethnicity (using surnames) and covariables including socio-economic classes and co-morbidities. Some of these methods have been published, thus supporting the validity

and utility of these databases. They also used dispensing data to estimate the duration of drug exposure as an index of adherence.

After 3 years of observation, 6% of patients have died, highlighting the high risk nature of type 2 diabetic patients with hypertension. After adjustment for confounders, ARB, ACEi and diuretics usage were associated with reduced mortality in Caucasians. In Chinese, only ARB and diuretics reduced mortality. None of these drugs reduced death rate in South Asians and no effect was observed with CCB in all ethnic groups.

A lower proportion of Chinese patients were prescribed with ACEi compared to ARB in keeping with poor tolerance of ACEi in this population often due to cough. In the entire group, high adherence rate was associated with low mortality rate athough the small number within each group does not allow further analysis stratified by ethnicity and drug class.

Overall the paper is well written with clear rationale, data analysis and reporting. One noticeable point is the relatively low prescription rate of statin (20%) and RASi (40-50%) in this high risk population and the tendency of a higher prescription rate of these drugs in Caucasians than Chinese and Indian subjects. These observations raised the question whether inter-ethnic differences in the associations of drug usage and mortality may be in part due to intensity of treatment in addition to adherence. As such, it will be interesting to see whether combination therapy for BP lowering are less likely to be prescribed in the non-Caucasian population. In a way, the authors have already adjusted for the usage of other drugs in the models, however, it will be useful to highlight these treatment gaps to inform clinical practice.
Thank you for your comments and insight. As suggested, we have highlighted in our discussion the gaps in prescription filling of cardiovascular risk reduction therapies, particularly among Chinese and South Asian patients, who had the lowest use of RAS blockade (page 13, paragraph 3; page 15, paragraph 1).

Reviewer: 2
Reviewer Name: Julius Chacha Mwita
Institution and Country: University of Botswana, Botswana
Please state any competing interests: None declared

Please leave your comments for the authors below

1. The study was aimed to research on Cardiovascular Risk Reduction Therapy Effectiveness , but the measured outcome was mortality from any cause.
[Previous studies have shown that mortality and cardiovascular complications among are less among these minority Canadian population , Shah et al Diabetes Care 2013 Sep; 36(9): 2670-2676]

2.The comparison group for each drug use was not clear. For instance, for patients who were using ARBs, did the the comparison group ('untreated') include patients who were not on ARB regardless of the other antihypertensives?
What you have mentioned is correct. That is, the comparison group included patients who were not the antihypertensive of interest, regardless of other antihypertensives. We adjusted for use of other antihypertensive agents. We have clarified this point on page 9, paragraph 1.
3.How comparable were the two groups - treated vs untreated ?
were there any differences on indications for treatment between treated and untreated groups- in terms of different factors that include indication for treatment.
The administrative databases utilized for this study did not capture specific indication for treatment. All the measured differences between the treated and untreated groups are addressed in the study design, which uses inverse probability of treatment weighted Cox proportional hazards models to

minimize bias due to confounding by indication. However, the specific indication for treatment is not a measured confounder. Thus, there may be some residual confounding for this unmeasured variable. We have now added this to the limitations paragraph within discussion (page 16, paragraph 2).

Reviewer: 3
Reviewer Name: Professor Y.K.Seedat
Institution and Country: University of KwaZulu Natal
Please state any competing interests: None declared

Please leave your comments for the authors below

The BMJ open paper is interesting, being a" real life study". The effect on mortality is agreed to depend on blood pressure, and the authors apparently did not adjust for this. Moreover, drugs are not prescribed at random, diuretics are likely to be confounded by age, calcium channel blockers by severity of hypertension and even therapy resistance, and angiotensin converting enzyme inhibitors by kidney dysfunction. It is not clear how the authors handled combination therapy, initially or sequential. Therefore the conclusions on associations between drugs and mortality are likely to be biased.

There are two articles in non- diabetic patients which could be quoted from the literature.

1. Brewster LM, van Montfrans GA, Oehlers GP, Seedat YK. Systematic review: Antihypertensive drug therapy in patients of African and South Asian ethnicity. Intern Emerg Med. 2016;3 : 355-74.
2. Brewster LM, Seedat YK. Why do hypertensive patients of African ancestry respond better to calcium blockers and diuretics than to ACE inhibitors and B adrenergic blockers. A systematic review.

BMC Med 2013; 11:141.
A Summary is as follows:

Article 2 shows that black patients in the US and South Africa respond better to diuretics and calcium channel compared to beta blockers and ACE inhibitors. The complications of hypertension occurs at a younger age group. Guidelines for hypertension in black patients suggest that diuretics and calcium channel blockers are the drugs of choice. There are no mortality data in blacks in Africa.
Article 1. The article suggest that response to antihypertensive drugs are used at a younger age in South
Asians similar to blacks. Data on morbidity and mortality are not available in South Asians.
Thank you for these relevant references. We have included these in the manuscript (page 4, paragraph 2, reference 8; page 5, paragraph 2, reference 19).

Reviewer: 4
Reviewer Name: Dr Nitin Gholap
Institution and Country: Consultant in Diabetes and Endocrinogy, University Hospital Coventry and Warwickshire, NHS Trust, Coventry, UK
Please state any competing interests: None

Please leave your comments for the authors below

In this article, Ke and colleagues report findings of their population-based cohort study conducted using administrative health database. The objective of the study is to compare the benefits ACEi, ARB, CCB and diuretics (used alone or in combination) on all-cause mortality among patients newly diagnosed with diabetes and belonging to South Asian, Chinese or other (predominantly Caucasians) groups. The landmark randomised controlled trials in this area (e.g HOPE, ONTARGET) have mainly

involved Western population and have shown benefits of therapies such as ACEi and ARBs on primary outcomes of cardiovascular events or deaths. While adults from South and Chinese populations comprise 62% of global diabetes population, there is a paucity of such trials involving these populations. Their stated rationale behind conducting the study is to fill this gap in the knowledge relevant to the South Asian and Chinese groups. They found that ACEi reduced mortality in other patients but not in South Asian or Chinese. ARB and diuretics reduced mortality in other and Chinese patients but not in South Asian patients. CCB did not reduce mortality in any ethnic groups. Importantly none of these four classes of drugs reduced mortality in South Asian individuals.

While their rationale behind undertaking this study is very valid this observational study has several deficiencies as described below. Therefore, one needs to be cautious about any message implying that the time-tested therapies of ACEi or ARBs are less beneficial in South Asian or Chinese populations. These populations suffer from the excess risk of diabetes and CHD and furthermore face challenges of inequalities in care due to various reasons. Furthermore, the excess cardiovascular risk is evident at a younger age and lower level of risk factors such as body mass index and blood pressure. Indeed, this has led to the calls for lower treatment targets for the South Asian patients. The observed lack of mortality benefits from these therapies in the two ethnic groups in this study, likely due to methodological and other reasons can be easily be misinterpreted as a true lack of the benefits. This can potentially lead to a waning of enthusiasm in use of the therapies in these high-risk ethnic populations.

Specific comments:

1. The lack of mortality benefits in the South Asian and Chinese patients in the study could be due to their lower baseline cardiovascular risk, as seen from Table 1. The landmark trials such as the HOPE and the ONTARGET, confirming the benefits of ACEi and ARBS respectively involved high-risk diabetes patients. For example, in the HOPE trial, about 58% had hypertension and 58% had previous coronary artery disease. When such high-risk patients with diabetes were treated with Ramipril in the HOPE trial they benefited from lowering of cardiovascular events or death. In comparison with the HOPE study cohort, South Asians enrolled in this study had a lower burden of risk factors at baseline (Table 1). For example, 42% had hypertension and about 2.2% had a myocardial infarction (Table 1). Furthermore, compared with the South Asian or Chinese patients, patients from the other group had a higher prevalence of hypertension (Table 1), congestive cardiac failure, peripheral vascular disease, cerebrovascular disease and renal disease. If these differences between South Asian and other group are statistically significant, it can partially explain the difference in mortality benefits between the two ethnic groups reported in the study. Authors have stated in the methods that they have used Chi-square tests and ANOVA for comparing baseline differences among the ethnic groups. However, there is no mention of the results of these tests in Table 1. While Cox regression models were used to make statistical adjustments, it may not have fully adjusted for these differences. There could be residual confounding due to unmeasured variable related to duration, severity and treatment of these cardiovascular comorbidities, especially if these disorders are occurring at a younger age in South Asian and Chinese patients. In the UKPDS study, compared with White Caucasians, Asian Indian ethnicity was not associated with an increased risk of major vascular complications or death despite the greater burden of diabetes-related end points. (Davis et al. Diabet. Med. 2014;31:200–207). These above-mentioned issues potentially weaken the study findings and its interpretations. These therapies are likely to equally beneficial in those with high-risk diabetes across the ethnic groups. However the study does not fully address this due low-risk cohort.
Thank you for the insightful comments. We agree with cautious interpretation of our study findings. Comparison of the baseline characteristics by chi-square tests and ANOVA yielded highly significant results for all the variables ($p<0.0001$). We have clarified this result by describing them explicitly in the Table 1 caption (page 23). However, in a nonrandomized observational study of this size, these significant differences are to be expected. Instead, we used the inverse probability of treatment

weighting (IPTW) method described above to minimize confounding by indication and difference in comorbid conditions. We acknowledge that this method can only control for confounding due to measured confounders. The problem of residual confounding is an important limitation of this technique that is relevant to our analysis. We have augmented the limitations section to discuss this issue in detail: “there could have been residual confounding due to unmeasured variables including hypertension severity and duration, age of hypertension onset, treatment indication, treatment of previous cardiovascular comorbidities, blood pressure levels, and hemoglobin A1C” (page 16, paragraph 2). As well, we have already noted previously on page 11, paragraph 1 that the ethnic populations have lower prevalence of comorbidities compared to the other population. We have now additionally included the point that our patient population is of lower risk than that observed in clinical trials (page 16, paragraph 2).
We agree that it is entirely possible that ACEi and other cardiovascular risk reduction agents may exhibit a benefit among higher risk South Asians, but more research would be required to confirm this definitively. We have updated the discussion to this effect: “we recognize that our cohort had lower prevalence of comorbid conditions compared to the more high-risk populations included in clinical trials. Thus, it is possible that a mortality benefit for ACEi and other cardiovascular risk reduction therapies may indeed exist among the subset of high-risk South Asian (and Chinese) patients that was not captured in this study. Additional studies with a larger sample size (given the relative lack of power in the South Asian cohort) or with a higher-risk cohort would be required to evaluate this possibility” (page 16, paragraph 2). We have also mentioned this prominently in the conclusion: “Although it is likely that these drugs are effective in high-risk diabetes patients across all ethnicities including South Asians, we were unable to demonstrate this with our usual-risk population. Given that this study was not a randomized controlled trial examining antihypertensive efficacy in these populations, these findings should be interpreted with caution. More research is required to evaluate the effectiveness of antihypertensive agents in South Asians, and to confirm the benefit of ACEi in Chinese patients. Inclusion of these groups in future clinical trials is essential to examine for differential response by ethnicity” (page 17, paragraph 2).

2. Reporting of cause-specific mortality and other cardiovascular events would have been more useful. I guess, due to the limitation of the dataset such information wasn’t available. Drugs such as ACEi and ARB have a major role in reducing cardiovascular mortality and as such cardiovascular mortality was one of the components of the composite primary outcome in the HOPE, ONTARGET, LIFE, and similar other trials (the other important components of the primary outcome being cardiovascular events e.g. myocardial infarction, stroke). All-cause mortality was a secondary outcome in these trials. This needs to be highlighted in the introduction and the discussion section where you have compared your findings with these trials.

Thank you for this comment. We unfortunately did not have cause of death data. We have highlighted in the introduction that all-cause mortality was a secondary outcome in these trials (page 4, paragraph 3) and that we are focusing on all-cause mortality (page 5, paragraph 2). We have also updated the discussion to make this point clear: “It is difficult to directly compare our findings with those of previous major clinical trials due to differences in study methodology, inability to directly compare the magnitude of hazards ratios and relative risks, and due to the specification of all-cause mortality as a non-primary outcome in most of these trials” (page 13, paragraph 2).
3. The actual number of deaths in each ethnic group needs to be stated. You have mentioned low event numbers as a limitation. Please state any loss to follow-up.
We have added the event rates and number of events on page 15, paragraph 1 where this limitation is stated: “A major reason for the lack of findings could have been a lack of power (Supplemental Table S2) given low event rates (355 events, 2.6% event rate in South Asians; 679 events, 3.0% in Chinese) and low treatment rates in this cohort.” Due to the universal healthcare system in Canada, there was virtually no loss to follow-up. This point has been added to the discussion (page 16, paragraph 2).

4. Within each ethnic group, you have excluded those who died within 1 month of initiation of medication (ACEi, ARB, CCB, DIU). On the contrary, I presume, you have included all the deaths in the comparator group i.e those who were not commenced on these medications. Would this not cause a selection bias in favour of the former group.
In our analysis, patients were excluded if they died within 1 month of the index date, i.e. diabetes diagnosis (not within 1 month of medication initiation). We apologize for the oversight in the wording of the previous manuscript version; this has been corrected. The manuscript now reads, “Patients who died within 1 month of the index date were excluded from the analysis” (page 7, paragraph 2). This manoeuvre was included because patients who were diagnosed with diabetes less than a month before death were likely more sick, representing outliers who did not have sufficient opportunity for long-term cardiovascular risk reduction. This exclusion would apply equally to the treatment and comparator groups so there is no selection bias per se.

5. Although this is a retrospective observational study, it would be useful if the authors give some idea about the statistical power of this study.
To provide an idea about the statistical power of this study, we have included a power calculation done using Fisher’s exact method (two-sided $\alpha=0.05$) specifying the actual sample sizes, the treatment and event rates observed, and the risk reduction observed in major clinical trials cited in the manuscript. The same expected risk reduction was used for CCB and diuretics because the ALLHAT study utilized an active comparator instead of a placebo control, showing no significant difference between effectiveness of amlodipine and chlorthalidone in reducing all-cause mortality.

Expected Risk Reduction	Power			
	South Asian	Chinese	Other	
ACEi	24%	66.9%	70.6%	>99.9%
ARB	39%	74.3%	98.6%	>99.9%
CCB	20%	23.0%	45.4%	>99.9%
Diuretic	20%	30.9%	55.5%	>99.9%

The analysis substantiates our claim that the lack of effect observed could have been related to insufficient power. Power was less than 80% in drugs for all ethnic groups except for ARB in Chinese, which did demonstrate an effect.
We have updated our manuscript to highlight this issue (page 15, paragraph 1; page 16, paragraph 2), and included these results in an additional table (Supplemental Table S2) within the appendix.
References:
1. Heart Outcomes Prevention Evaluation (HOPE) Study Investigators. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. The Lancet. 2000 Jan 22;355(9200):253–9.
2. ONTARGET Investigators, Yusuf S, Teo KK, Pogue J, Dyal L, Copland I, et al. Telmisartan, ramipril, or both in patients at high risk for vascular events. N Engl J Med. 2008 Apr 10;358(15):1547–59.
3. Whelton PK, Barzilay J, Cushman WC, Davis BR, Iiamathi E, Kostis JB, et al. Clinical outcomes in antihypertensive treatment of type 2 diabetes, impaired fasting glucose concentration, and normoglycemia: Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). Arch Intern Med. 2005 Jun 27;165(12):1401–9.
4. Kostis JB, Wilson AC, Freudenberger RS, Cosgrove NM, Pressel SL, Davis BR. Long-term effect of diuretic-based therapy on fatal outcomes in subjects with isolated systolic hypertension with and without diabetes. The American Journal of Cardiology. 2005 Jan 1;95(1):29–35.

6. How you identified the newly detected diabetes is slightly confusing and needs further clarification. Similarly, please clarify method on collecting information on comorbidities (ICD codes, etc).
We have clarified the methodology of detecting diabetes and identifying comorbidities as follows:

“British Columbia has a total population of 4.6 million people, including approximately 210 400 South Asian and 373 800 Chinese people (21,22). Because the public health insurance program covers virtually all health encounters, data from physician billing claims can be used to identify diagnoses. We extracted International Classification of Diseases (ICD-9 and ICD-10) codes from physician claims including both inpatient and outpatient encounters. Outpatient billing data includes a single diagnosis for each encounter. Inpatient data includes both primary and secondary discharge diagnosis codes from hospital discharge abstracts (up to 25 codes for each encounter). Data on medication use were extracted from PharmaNet, a provincial electronic database that contains a record of all dispensed prescriptions from community pharmacies. The accuracy of this database against prescriptions is estimated to be greater than 99% (23). Data on time of death were obtained from the vital statistics database and reporting of all deaths in the province is mandatory.” (page 6, paragraph 3)
“The study population was restricted to people with a new diagnosis of diabetes during the study period. A new diagnosis of diabetes was defined as an ICD-9 or ICD-10 code for diabetes for at least one hospital discharge abstract or two physician claims within 2 years (ICD-9-CM: 250.x; ICD-10: E109, E119, E139, E149, E101, E111, E131, E141, E105, E115, E135, and E145). To ensure that these cases were truly new diagnoses, we set a washout period of 3 years (i.e., no physician claims for diabetes in the preceding 3 years). This algorithm is entirely based on administrative billing data, and was previously validated against physician diagnosis of diabetes in adults aged ≥35 years with sensitivity 92% and specificity 97% in identifying diagnoses of diabetes in British Columbia (24–26). Index date was defined as the earliest contact with the healthcare system with the diabetes diagnosis. Patients who died within 1 month of diabetes diagnosis were excluded from the analysis.” (page 7, paragraph 2)
“We also included comorbidities from the Charlson comorbid conditions list (31). These conditions were extracted from all inpatient and outpatient claims dating from up to 1 year prior to the index date.” (page 8, paragraph 2)

7. The limitations of the study needs discussing in detail.

We have revised and substantially expanded the discussion of limitations in detail, incorporating suggestions from all reviewers:
“Our large population-based observational study allowed for measurement of real-world effects on mortality, minimizing outcome misclassification and with virtually no loss to follow-up in the context of Canada’s universal healthcare system. Although observational studies of this nature have been shown to generally correlate with randomized control trials (45), we recognize that our cohort had lower prevalence of comorbid conditions compared to the more high-risk populations included in clinical trials. Thus, it is possible that a mortality benefit for ACEi and other cardiovascular risk reduction therapies may indeed exist among the subset of high-risk South Asian (and Chinese) patients that was not captured in this study. Additional studies with a larger sample size (given the relative lack of power in the South Asian cohort) or with a higher-risk cohort would be required to evaluate this possibility. Moreover, the IPTW can be used to estimate exposure effects adjusted for measured confounders only. However, there could have been residual confounding due to unmeasured variables including hypertension severity and duration, age of hypertension onset, treatment indication, treatment of previous cardiovascular comorbidities, blood pressure levels, and hemoglobin A1C. Finally, there is a built-in selection bias that has been described with use of hazard ratios (46). Given the limitations we have described, further investigations using different methodologies are required to confirm the present findings.” (page 16, paragraph 2)

Reviewer: 5
Reviewer Name: Mohammad Ali Mansournia
Institution and Country: Department of Epidemiology and Biostatistics, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran
Please state any competing interests: None declared

Please leave your comments for the authors below

The paper estimates the effects of several drugs on mortality in diabetic patients using inverse-probability-of-treatment weighting. I have several concerns for the authors to consider.

1) The authors should explain why they used IPTW rather than conventional regression modeling for confounding adjustment. The key point is confounding by indication e.g., see P. 668, second column, first paragraph of the following paper:
Gharibzadeh S, Mohammad K, Rahimiforoushani A, Amouzegar A, Mansournia MA. Standardization as a Tool for Causal Inference in Medical Research. Arch Iran Med. 2016;19(9):666-70.
Thank you for pointing this out. We have updated the methods section to reflect this point with the inclusion of this reference (number 35): “We constructed inverse probability of treatment weighted (IPTW) Cox proportional hazards models for the treatment effect on mortality (33,34). This method is aimed at minimizing effects of confounding by indication (35)” (page 9, paragraph 2).
2) The mean and SD of the stabilized weights should be reported and their appropriateness should be discussed.
We have added this point to our methodology section (page 9, paragraph 2) and reported the values in a supplemental table (S1, page 26). We have described the appropriateness of the characteristics as follows: “Consistent with the positivity assumption, the means of the stabilized weights were close to one with low standard deviations (Supplemental Table S1).” (page 11, paragraph 3)

3) The IPTW has not been explained in detail in the Methods section. I suggest that the authors at least cite the following two references on IPTW so that the reader can refer to them for further explanations:

Mansournia MA, Altman DG. Inverse probability weighting. BMJ. 2016 Jan 15;352:i189.

Mansournia MA, Danaei G, Forouzanfar MH, Mahmoudi M, Jamali M, Mansournia N, Mohammad K. Effect of physical activity on functional performance and knee pain in patients with osteoarthritis : analysis with marginal structural models. Epidemiology. 2012;23(4):631-40.
Thank you for these references. We have added these (reference number 34 and 35) to our Methods section (page 9, paragraph 2).

4) Figure 1 presents cumulative hazard curves, though the legend and the Methods refer to adjusted (weighted) survival curves. The authors should either revise their explanations or present weighted survival curves as discussed in the following references:
Cole SR, Hernán MA.Adjusted survival curves with inverse probability weights.Comput Methods Programs Biomed. 2004;75(1):45-9.

Hernán MA, Robins JM. Causal Inference. London: Chapman & Hall/CRC. In press, chapter 17. Available at: http://www.hsph.harvard.edu/faculty/miguel-hernan/causal-inference-book/
Thank you for pointing this out. The figures were originally created based on the first reference that you have provided. However, we did not present the adjusted survival curves as you pointed out. The figures presented represent (1 – survival), or the cumulative incidence of death. We have corrected the explanation to label these as figures showing the cumulative incidence death for the weighted sample (page 9, paragraph 2; page 25 figure caption).
5) The number of censored subjects by loss-to-follow-up should be mentioned and IPCW (inverse-probability-of-censoring weighting) should be implemented if the percentage of censoring by loss-to-follow-up is not ignorable; see Mansournia et al Epidemiology paper cited above.
There was virtually no loss to follow-up in this study due to the nature of the universal healthcare system in Canada. This point has been added to the discussion (page 16, paragraph 2).

6) The proportional hazard assumption should be checked and time-specific hazard ratios should be reported in the case of substantial non-proportionality. Moreover, hazard ratio suffers from a built-in selection bias. The authors should at least mention these issues as a limitation in the Discussion citing the following reference:
Hernán MA. The hazards of hazard ratios. Epidemiology. 2010;21:13–15.
The proportional hazard assumption was verified. We have added this to the manuscript (page 9, paragraph 2). We have mentioned the selection bias from hazard ratios as a limitation and included the reference provided (page 16, paragraph 2).

7) P. 12, L. 51: "Relative risk" is different from "hazard ratio".
Thank you for pointing this out. We have clarified the discussion as follows, “It is difficult to directly compare our findings with those of previous major clinical trials due to differences in study methodology, inability to directly compare the magnitude of hazards ratios and relative risks, and due to the specification of all-cause mortality as a non-primary outcome in most of these trials.” (page 13, paragraph 2).

8) P. 9, L. 15: "age" was mentioned twice.
We have corrected this error.

VERSION 2 – REVIEW

REVIEWER	Dr Julius Mwita Department of Internal Medicine, Faculty of Medicine University of Botswana, Botswana
REVIEW RETURNED	09-Apr-2017

GENERAL COMMENTS	The authors have incorporated the comments, and acknowledged methodological deficiencies

REVIEWER	Professor YK Seedat Nelson Mandela School of Medicine, University of KwaZulu Natal , Durban, South Africa.
REVIEW RETURNED	13-Apr-2017

GENERAL COMMENTS	The main concern with this study remains the methodology. In particular the conclusion that ACE inhibitors are not effective in South Asian (SA) patients in reducing mortality is not valid. The authors should be clearer on the sample size calculation needed to assess this association in subgroups, and provide these data in the method section, and not in a supplement, such that it becomes clear to the reader that the study is underpowered for this subgroup analysis. Also, the mortality data (n) in each subgroup should be briefly mentioned in the text. No conclusion should be drawn on ACE inhibitors and mortality in SA, and this “result” should be removed from the abstract, stating the study did not have sufficient power to study this. Also, the limitation that ACE inhibitors are mostly used for kidney conditions (mortality in SA patients is in general nit due to kidney disease) and the lower age of SA patients should be more explicitly discussed. The authors should discuss their findings in comparison to the HOPE-3 study results, which was partly

	conducted in Canada. The authors now address the lack of blood pressure as a limitation. However, although the authors mention potential bias by clinical indication in general and for CCB, they did not follow the reviewer's request to analyze and/or discuss the potential confounding of the use of diuretics by age (and the greater effect on mortality in older than in younger patients), of calcium channel blockers by therapy resistance (and potentially: African ethnicity), or angiotensin converting enzyme inhibitors by kidney dysfunction as stated above. Furthermore, it remains unclear how the authors handled combination therapy, initially or sequential. Therefore the conclusions on associations between drugs and mortality are likely to be biased. The authors should not use "effect" in their paper to describe the association between drug use and outcomes in their cross sectional population data. Please replace throughout the manuscript, as this implies causality which was not studied. The absence of information regarding African ancestry (AA) and European (EA) patients affects the validity of the results "based on ethnicity". Can the authors perhaps estimate how many AA/EA are included? At least discuss the lack of this information in the limitation section.

REVIEWER	Nitin Gholap Department of Diabetes, Endocrinology, Metabolism. University Hospitals Coventry and Warwickshire, NHS Trust Coventry UK
REVIEW RETURNED	16-Apr-2017

GENERAL COMMENTS	My comments have been adressed adequately.

REVIEWER	Mohammad Ali Mansournia Department of Epidemiology and Biostatistics, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran
REVIEW RETURNED	06-Apr-2017

GENERAL COMMENTS	The authors' revisions are quite responsive to my comments and suggestions and so I recommend publication.

VERSION 2 – AUTHOR RESPONSE

Thank you for the opportunity to revise and re-submit this manuscript based on reviewer feedback. We have carefully considered the reviewers' responses and detailed them below. We believe that these suggestions have again strengthened and improved the manuscript.
The main concern with this study remains the methodology.
In particular the conclusion that ACE inhibitors are not effective in South Asian (SA) patients in reducing mortality is not valid. The authors should be clearer on the sample size calculation needed to assess this association in subgroups, and provide these data in the method section, and not in a

supplement, such that it becomes clear to the reader that the study is underpowered for this subgroup analysis. Also, the mortality data (n) in each subgroup should be briefly mentioned in the text. No conclusion should be drawn on ACE inhibitors and mortality in SA, and this “result” should be removed from the abstract, stating the study did not have sufficient power to study this. Also, the limitation that ACE inhibitors are mostly used for kidney conditions (mortality in SA patients is in general nit due to kidney disease) and the lower age of SA patients should be more explicitly discussed. The authors should discuss their findings in comparison to the HOPE-3 study results, which was partly conducted in Canada.

Response: Thank you for your insightful comments. We agree that the study was under-powered to properly evaluate the effectiveness of ACEi among South Asian patients. We have updated the methods section (page 10, paragraph 1) to include a clear description of the sample size calculation: “Statistical power for each drug by ethnicity was calculated using the log-rank test, specifying actual sample sizes, allocation ratio, treatment and event rates observed, and hazard ratio as derived from the risk reduction observed in major clinical trials (Supplemental Table S2). Estimated power was >99.9% for the other group (all classes) and for ARB in Chinese, >80% for ARB in South Asians and ACEi in Chinese patients, and <80% for the remaining categories.”

We have also highlighted the exact number of deaths for each ethnicity in the results section as requested (page 12, paragraph 1), and this again is mentioned in the discussion section (page 15, paragraph 2) when we discuss power in the context of event rates for South Asian and Chinese patients.

We have updated the abstract as requested. The results section in question now reads, “ACEi reduced mortality in other patients (HR=0.88, 0.84-0.91), but power was insufficient to evaluate for benefit of ACEi in Chinese and South Asian patients.” Our discussion has already been revised to state the findings very carefully and cautiously, without any implication that these agents are ineffective in South Asians (page 17, paragraph 2): “Although it is likely that these drugs are effective in high-risk diabetes patients across all ethnicities including South Asians, we were unable to demonstrate this with our unselected, lower-risk population.”

Although ACEi and ARB are definitely indicated in diabetic kidney disease, their use is recommended as first-line agents for blood pressure control and cardiovascular risk reduction, and their use for “vascular protection” has even been expanded by the Canadian Diabetes Association to include all diabetes patients over age 55 years regardless of end-organ damage or hypertension (1). These recommendations were made based on the findings of the HOPE study (2) and others (3) with the hypothesis that there may be benefit to ACEi beyond blood pressure lowering effects. Therefore, we expect that the use of ACEi would still reduce mortality (from cardiovascular causes) among South Asians with diabetes, regardless of whether chronic kidney disease causes mortality in this population. However, we agree that the younger age of the South Asian population may have partially contributed to the lack of significant effects detected given the low event rates overall. We have clarified these points in the manuscript on page 15, paragraph 2 and on page 16, paragraph 2: “Additional studies with a larger sample size (given the relative lack of power in the South Asian cohort) or with a higher-risk cohort would be required to evaluate this possibility, especially considering the Canadian recommendation that ACEi or ARB be used for all diabetes patients over age 55 years—even in the absence of end-organ damage or hypertension”.

The blood pressure arm of the HOPE-3 trial was a randomized control trial aimed to assess the effect of treatment with hydrochlorothiazide and candesartan among participants at intermediate risk of cardiovascular disease. Although the trial did not detect a significant difference in major cardiovascular events, only 5.8% of the enrolled patients had diabetes. Thus, we believe that the negative findings of this trial are not entirely applicable given that the population of interest is diabetes patients. However, the international and multi-ethnic nature of the HOPE-3 trial is in a general sense helpful in assessing the utility of agents for cardiovascular risk reduction among Asian populations. We have noted that there is a need for additional similar studies to specifically assess combination therapies among South Asian and Chinese diabetes populations (page 17, paragraph 1).

1. Canadian Diabetes Association Clinical Practice Guidelines Expert Committee. Canadian Diabetes

Association 2013 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada. Can J Diabetes. 2013 Apr;37(Suppl 1):S1–212.
2. Heart Outcomes Prevention Evaluation (HOPE) Study Investigators. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. The Lancet. 2000 Jan 22;355(9200):253–9.
3. McAlister FA. Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers are beneficial in normotensive atherosclerotic patients: a collaborative meta-analysis of randomized trials. Eur Heart J. 2012 Feb 1;33(4):505–14.
The authors now address the lack of blood pressure as a limitation.
However, although the authors mention potential bias by clinical indication in general and for CCB, they did not follow the reviewer's request to analyze and/or discuss the potential confounding of the use of diuretics by age (and the greater effect on mortality in older than in younger patients), of calcium channel blockers by therapy resistance (and potentially: African ethnicity), or angiotensin converting enzyme inhibitors by kidney dysfunction as stated above.
Response: It is possible that diuretics could have had a stronger effect on reducing mortality among older patients, and this may have reduced the likelihood of observing an effect especially given the younger age distribution of the South Asian cohort. We have now added this point to discussion (page 15, paragraph 2): "the South Asian cohort had the youngest age distribution, and this could have led to relatively fewer mortality events and weaker associations particularly with diuretics, which may be more effective in older patients".
Although it is possible that some patients were more resistant to calcium channel blockers, the percentage of patients with African ethnicity was <1% in the other group. This is now clarified on page 8, paragraph 1.
We have addressed the issue of ACEi and kidney dysfunction in the previous response above.
Furthermore, it remains unclear how the authors handled combination therapy, initially or sequential. Therefore the conclusions on associations between drugs and mortality are likely to be biased.
Response: We adjusted for the use of other antihypertensive medications at baseline. As pointed out, it is possible that patients who were initially classified as being on one antihypertensive class could have been switched at a later time to a different agent, or escalated to a combination therapy.
We attempted to address differential drug exposure (including cessation or switching of medications) by performing a sensitivity analysis accounting for medication adherence. This analysis accounts for number of prescriptions per year for each medication of interest, and assesses whether increased putative medication exposure is associated with increased mortality benefit. We have updated the methods section with additional clarification to improve readers' understanding of this sensitivity analysis (page 10, paragraph 2). We did not observe any significant associations in either South Asian or Chinese patients, and in the manuscript we had attributed this result to be most likely related to power issues. We recognize that another possibility for the lack of association could have been switching between medication classes, such that the subsequent medication could have attenuated the negative effect of being unexposed to the initial medication of interest. We have now included this as part of the discussion (page 16, paragraph 1).
Due to the sample size issues in the ethnic cohorts, we could not assess for effectiveness of different combinations of risk reduction therapies. It is possible that the subsets of patients on combination therapies may have had additional mortality benefits conferred by subsequently added medications. This effect would not have specifically explained the lack of associations observed among the Asian cohorts. Nevertheless, we acknowledge this as a limitation of our study and call for the need for more studies such as HOPE-3 in assessing the benefits of combination therapies in international populations (page 16, paragraph 2).
The authors should not use "effect" in their paper to describe the association between drug use and outcomes in their cross sectional population data. Please replace throughout the manuscript, as this implies causality which was not studied.
Response: We agree that the associations observed do not necessarily represent cause and effect unless bias and confounding are appropriately controlled for. In recognition of the limitations of this

study, we have accordingly replaced the term “effect” with “association” through the results and discussion.
However, we would like to note that the data in our study were not cross-sectional, but based on a retrospective cohort that was followed longitudinally using a survival analysis from 2006 to 2013. Indeed, it would not be otherwise possible to study real-world effectiveness outside of the artificial conditions of a randomized control trial. We therefore feel that it is still appropriate to mention that we are attempting to assess for the effectiveness of these medications on mortality, although we still present the results as associations for the reasons stated above.
The absence of information regarding African ancestry (AA) and European (EA) patients affects the validity of the results “based on ethnicity”. Can the authors perhaps estimate how many AA/EA are included? At least discuss the lack of this information in the limitation section.
Response: The “other” category consists of >90% of European ancestry. In this group, there are very few (<1%) of African descent. This has been clarified on page 8, paragraph 1.

VERSION 3 – REVIEW

REVIEWER	Professor YK Seedat Nelson Mandela School of Medicine, University of KwaZulu Natal,Durban, South Africa.
REVIEW RETURNED	30-May-2017

GENERAL COMMENTS	The article has defects in the methodology. This is now stated by the authors. The defects may be stated by future researchers. It is a retrospective study and as such has its defects.