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Cardiovascular Risk Reduction Therapy Effectiveness in South Asian, Chinese, and Other Patients with Diabetes

Running Title: Cardiovascular Risk Reduction in Diabetes

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Abstract

Objectives: Guidelines recommend angiotensin converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB), calcium channel blockers (CCB) and diuretics in all patients with diabetes mellitus. However, the effectiveness of these agents in South Asian and Chinese populations is unknown. We sought to determine whether ACEi, ARB, CCB, and diuretics are associated with reduced mortality in South Asian, Chinese, and other patients with diabetes.

Design: Population-based cohort study using administrative health databases

Setting: Province of British Columbia, Canada (2004-2013)

Participants: Patients aged ≥35 years with incident diabetes

Primary and secondary outcome measures: Primary outcome was hazard ratio (HR) of mortality on each medication class compared to untreated patients within each ethnicity. Treatment effect was assessed using inverse probability of treatment weighted Cox proportional hazards models. Mortality adjusted for medication adherence was also evaluated.

Results: 208,870 patients (13,755 South Asian, 22,871 Chinese, 172,244 other Canadian) were included. ACEi reduced mortality in other patients (HR=0.88, 0.84-0.9) with no significant benefit in Chinese patients. ARB and diuretics reduced mortality in Chinese (ARB HR=0.64, 0.50-0.82; diuretics HR=0.78, 0.62-0.96) and other patients (ARB HR=0.69, 0.64-0.74; diuretics HR=0.66, 0.63-0.69) compared with untreated patients. No mortality benefit was observed among South Asians for any drug class or for CCB among all ethnicities. Higher medication adherence was associated with lower mortality for other patients only (HR=0.80, 0.74-0.85).

Conclusions: Effectiveness of cardiovascular risk reduction therapy on mortality varies considerably by ethnicity. Further study is needed to evaluate the lack of mortality benefit of

antihypertensive agents in South Asians. Inclusion of these ethnic groups in future clinical trials is essential to examine for differential responses.

Strengths and limitations of this study:

- This study addresses a substantial gap in the literature regarding long-term effectiveness of commonly used antihypertensive drug classes among diabetes patients of South Asian and Chinese descent
- The analysis is conducted on a large, population-based data set including significant numbers of people of different ethnicities in Canada, allowing for measurement of real-world effects on mortality
- Limitations include possible residual confounding due to unmeasured variables

Introduction

Pharmacologic treatment of hypertension in patients with type 2 diabetes mellitus (diabetes) is associated with significantly reduced mortality (1). International guidelines recommend routinely using antihypertensive medications to control blood pressure in all diabetes patients, including those of Asian ethnicity (2–5). However, most trials of cardiovascular risk reduction therapy in patients with diabetes occurred in western populations.

Response to these therapies can be affected by ethnicity. ACE inhibitors (ACEi) were found to be less effective in reducing mortality and cardiovascular events among Black patients with hypertension and diabetes compared with other antihypertensive agents (6,7). Several studies also reported higher risk of ACEi-induced cough in Chinese patients suggesting that there may be some underlying differences in response to these medications (8). Others reported that South Asians may have increased sympathetic activity, possibly causing differing responses to antihypertensive classes (9). An analysis in South Asian and Chinese patients with newly diagnosed diabetes found significant mortality reductions associated with statin use (10). However, similar analyses are currently lacking for antihypertensive agents.

The benefit of ACEi in reducing cardiovascular risk in diabetes was established in multiple large randomized-control trials of western patients, with 24% total mortality reduction seen in the HOPE study (11–13). These benefits were similar to angiotensin receptor blockers (ARB) based on the ONTARGET study subset of diabetes patients (14). However, the PRoFESS trial included 18% of patients of Chinese ethnicity and 8.4% of South Asian ethnicity, found no benefit of telmisartan in reducing major cardiovascular events (15). Additionally, major randomized trials

examining thiazide and thiazide-like diuretics ((SHEP (16), ALLHAT (7)), CCB (ALLHAT (7)) and CCB-based combinations (ACCOMPLISH (17)) were conducted in predominantly western populations.

The burden of diabetes in South Asian and Chinese populations is tremendous, with these ethnic groups representing 62% of all adults with diabetes globally (18). In this context, the paucity of large studies specifically comparing long-term effectiveness of major antihypertensive drug classes in these ethnicities is concerning. With the existing, widespread use of these medications, such studies are unlikely to be conducted in the near future. In an effort to fill the information gap, we conducted a population-based cohort study to determine whether ACEi, ARB, dihydropyridine CCB, and diuretics are effective in reducing mortality in a population cohort of South Asian (originating from Pakistan, India, or Bangladesh), Chinese (originating from China, Taiwan, or Hong Kong), and other patients with newly diagnosed diabetes.

Research Design and Methods

Study Overview

We conducted an analysis using population-based administrative data of adults aged ≥35 years living in British Columbia, Canada with newly diagnosed diabetes between April 1, 2004 and March 31, 2013.

Data Sources

We used administrative data from British Columbia, Canada. We obtained de-identified linked health datasets through Population Data BC with approval of relevant data stewards and the University of British Columbia's Behavioural Research Ethics Board (19). All inferences, opinions, and conclusions drawn in this report are those of the authors, and do not reflect the opinions or policies of Population Data BC.

The databases covered all British Columbians except those whose prescription drug coverage fell under federal jurisdiction (i.e., military, veterans, inmates of federal penitentiaries, and status Indians living on reserves, approximately 4.0% of the total population). All residents included in our dataset are covered under British Columbia's universal, public health insurance program for medical and hospital care; and all are eligible for coverage under British Columbia's universal, public drug benefit plan, under which deductibles are set in relation to household income.

British Columbia has a total population of 4.6 million people, including approximately 210 400 South Asian and 373 800 Chinese people (20, 21). We extracted International Classification of Diseases (ICD-9 and ICD-10) codes from physician claims including both inpatient and outpatient encounters. Inpatient data included both primary and secondary discharge diagnosis codes from hospital discharge abstracts. 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% (22). Data on time of death were obtained from the vital statistics database and reporting of all deaths in the province is mandatory.

Study Population

The study population was restricted to people with a new diagnosis of diabetes during the study period. A 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). This algorithm was 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 (23–25). A washout period of minimum 3 years was used to identify newly diagnosed diabetes. Index date was defined as the earliest contact with the healthcare system with the diabetes diagnosis. Patients who died within 1 month of medication initiation were excluded from the analysis.

Categorizing Ethnic Group

Because ethnicity is not routinely recorded in Canadian administrative health data, we used an algorithm developed to identify surnames of South Asian and Chinese origin that has been validated for use in administrative data research by Shah et al. (26). Canadian census data show that 93% of South Asians and 90% of Chinese marry people of the same ethnic background, minimizing the chance of misidentification due to mixed marriages (27). We labelled the remaining population as "other." In the province of British Columbia, the vast majority of this group consists of Caucasian individuals (93%) (28).

Sociodemographics and Comorbid Conditions

We estimated socioeconomic status (SES) using income quintile. We estimated household income based on a combination of household-specific and area-based income data (29). We also included comorbidities from the Charlson comorbid conditions list (30).

Cardiovascular Risk Reduction Medications

Within each ethnicity, we classified study patients as either treated or untreated with each antihypertensive medication class: ARB, ACEi, dihydropyridine CCB, and thiazide or thiazide-type diuretics. We considered patients as treated with a medication if they received at least one prescription within 1 year after index diagnosis, a time period used in other similar studies (10).

Outcome Measures

Patients were followed for up to 4 years for the primary outcome measure, time to death from any cause. Risk was determined for South Asian, Chinese, and other patients treated on each medication as compared to untreated patients within each ethnicity as a baseline.

Statistical Analysis

Comparisons of baseline characteristics for each ethnic group were made using the Chi square test for categorical variables and analysis of variance for continuous variables. We constructed inverse probability of treatment weighted (IPTW) Cox proportional hazards models for the treatment effect on mortality to minimize effects of confounding by indication. The weight was based on a propensity score of having treatment, estimated from a multivariable logistic regression model with receiving treatment as a binary outcome variable and age, gender, age, SES, Charlson comorbidities, and baseline use of other medications as independent variables. In particular, the weight for each subject was computed by taking the inverse probability of receiving treatment that the subject received and stabilized by multiplying marginal probability of the actual treatment received (31). Adjusted survival curves were also created for the weighted sample. Use of other medications (insulin, use of other antihypertensive agents and statins) at baseline was defined as a prescription recorded within 1 month before or after diagnosis. The data were censored at the end of the 4-year observation period or at death, whichever came first.

In a sensitivity analysis to account for effects of differential drug exposure, we evaluated the association of level of medication adherence with mortality among patients who were treated with at least one of the four study medication classes. We constructed the weighted Cox proportional hazards models to compare among the medication adherence levels. In particular, the adherence of each medication was measured over 1 year since the first prescription using proportion of days covered (PDC), which has a high predictive validity for hospitalization episodes (32). The PDC is defined as [(number of days supply of medication in the index period)/(number of days in the study period)] × 100. The mean PDC across the four classes was

calculated and classified into three levels with PDC ≥ 0.80 classified as high adherence, 0.50 ≤ PDC < 0.80 as moderate adherence, and PDC < 0.50 as low adherence.

All *p* values presented are 2-tailed, and a value of less than 0.05 was considered significant. Analyses were performed with SAS version 9.2 (SAS Institute Inc.).

Results

Baseline Characteristics and Prescribing

There were 208 870 patients (13 755 South Asian, 22 871 Chinese, 172 244 other) included in the analysis (Table 1). Most patients were elderly with South Asian patients being younger than the other groups at time of diagnosis. South Asian and Chinese patients were more likely than other patients to be in the 2 lowest socioeconomic quintiles. Hypertension was present in almost half of patients across all ethnicities (42% South Asian, 44% Chinese, 48% other). The prevalence of comorbid conditions was low in this cohort with South Asian and Chinese patients having generally a lower prevalence of conditions compared with others, including myocardial infarction, congestive heart failure, peripheral vascular disease, and cerebrovascular disease.

Other patients were the most likely to be prescribed antihypertensive agents at baseline, with the most frequently prescribed classes being ACEi (23%) and diuretics (18%). South Asians were also likely to be prescribed with ACEi (16%) and diuretics (11%). Chinese patients had a more equal distribution among ACEi, ARB, CCB, and diuretic prescriptions (9.1-12%). By the end of

one year since initial diabetes diagnosis, almost two-thirds of other patients were prescribed at least one antihypertensive agent, with a lower proportion in South Asian and Chinese patients. The most frequently prescribed class of antihypertensive agent by this time was ACEi (26% South Asians, 18% Chinese, 34% other), followed by diuretics (19% South Asians, 19% Chinese, 27% other).

Mortality

Overall, 6.5% of patients died during the follow up period (median 3 years; Figure 1). Among other patients, ACEi (HR=0.88, 0.84-0.91; Table 2), ARB (HR=0.69, 0.64-0.74) and diuretics (HR=0.66, 0.63-0.69) were associated with substantial reductions in all-cause mortality, with minimal effect observed with CCB (HR=1.00, 0.94-1.05).

Similarly, among Chinese patients, ARB (HR=0.64, 0.50-0.82) and diuretics (HR=0.78, 0.62-0.96) were associated with significant mortality reduction. There was a non-significant trend towards benefit with ACEi (HR=0.84, 0.69-1.03), but there was no significant effect observed with CCB.

In South Asian patients, no statistically significant mortality benefits were observed with ACEi (HR=0.91, 0.71-1.17), ARB (HR=0.88, 0.63-1.25), CCB (HR=1.25, 0.93-1.68), or diuretics (HR=0.83, 0.61-1.12).

In our sensitivity analysis that included level of drug exposure in all drug classes, a moderate to high adherence to the 4 antihypertensive classes was associated with lower mortality among other patients compared to low adherence (Table 3). However, high or moderate adherence was not associated with reduced mortality compared with low adherence of antihypertensive medications among Chinese and South Asian patients. There was insufficient power to analyze the effects of high versus low adherence, or adherence within single medication classes.

Conclusions

Overall, we observed substantial ethnic differences in effectiveness of cardiovascular risk reduction therapies on mortality in patients with diabetes. Mortality reduction associated with treatment with ARB, diuretics and a trend towards mortality benefit with ACEi were observed Chinese patients. However, no significant associations with mortality and cardiovascular risk reduction therapy were seen in South Asians for any drug class.

The findings in the other population in the current analysis are generally consistent with results from major clinical trials in patients with diabetes (13,14, 33). For ACEi, the benefit we observed (HR=0.88, 0.84-0.91) is smaller than that reported in the HOPE study (total mortality relative risk 0.76, 0.63-0.92) that compared ramipril to placebo in patients with diabetes and an additional cardiovascular risk factor (13). The mortality reduction for ARB (HR=0.69, 0.64-0.74) is similar to that seen in the LIFE study (relative risk 0.61, 0.45-0.84), comparing losartan to atenolol (33).

Among Chinese patients, we observed generally similar mortality reductions associated with ACEi (HR=0.84, 0.69-1.03) and ARB (HR=0.64, 0.50-0.82) use. The magnitude of mortality reduction is similar to the trials mentioned above, although the benefit of ACEi did not reach statistical significance. Notably, adherence to ACEi among Chinese patients (52%) compared to ARB (72%) is reported to be lower than other patients, and this difference may have attenuated the effect with ACEi (22). Nevertheless, our results provide new evidence on the effectiveness of these agents in a real world population extending the findings of the ONTARGET (14) study, that included 14% of patients of Asian ethnicity.

Diuretics were associated with effectiveness in Chinese. The effects observed (Chinese HR=0.77, 0.62-0.96) are largely consistent with those reported in the placebo-controlled SHEP trial (7) diabetes subgroup (hazard ratio 0.80, 0.68-0.95). The present findings are the first to our knowledge to evaluate thiazide and thiazide like diuretics to Chinese patients with diabetes.

We did not observe substantial benefits of CCB in any ethnic category. This result was unexpected given the findings of the ALLHAT study, that showed that CCB were equivalent to ACEi and diuretics as first-line antihypertensive agents in diabetes (7). These findings may reflect the trend that CCB are decreasingly likely to be used as initial antihypertensive therapy compared to ACEi and diuretics in Canada (34). This trend is in accordance with guidelines promoting CCB as an add-on agent given the ACCOMPLISH trial findings (17). Patients in the CCB group may have had more severe hypertension requiring more than one agent, thereby causing confounding by indication. Moreover, the comparison group in our study likely included patients treated with other agents such as ACEi, ARB, and diuretics, leading to an attenuation of

observed effect. It is also possible that the real-world effect size varies from that observed in randomized control trials (RCTs) due to rigid selection criteria and selection bias. Further research is required to clarify the benefit of CCB, especially in South Asian and Chinese populations.

None of the drug classes were associated with any statistically significant mortality benefits among South Asians. It is conceivable that the effect may have been attenuated by additional factors such as cultural dietary practices (e.g. salt intake (35)) and pharmacogenetic influences. For instance, ACE gene insertion/deletion polymorphisms affect serum levels of ACEi, although a long-term effect on cardiovascular outcomes has yet to be demonstrated (36). Pharmacogenetic differences may also lead to heterogeneous responses to antihypertensive agents within the same class (37). This concerning result may also be due to insufficient power given the relatively low event rate in this younger incident cohort. With these considerations in mind, further research is required to confirm the effectiveness and magnitude of mortality benefit of cardiovascular risk reduction therapy in South Asians.

The lack of significant associations among South Asians may also relate to poor medication adherence and reduced drug exposure. Although we performed a sensitivity analysis using drug adherence to evaluate whether drug discontinuation, switching between classes, or decreased adherence may have affected our results, only in other patients was a significant mortality reduction seen in those with moderate or high adherence. No significant associations were observed for South Asian and Chinese patients. The lack of adherence effects may be related to inadequate power to detect smaller treatment related effect size in these groups. South Asian and

Chinese patients may also import antihypertensive medications from out of country, limiting our ability to detect treatment differences (38). In the context of these limitations, more studies are required to evaluate the interaction between medication adherence and antihypertensive therapies in South Asian and Chinese patients.

Our large population-based observational study allowed for measurement of real-world effects on mortality, minimizing outcome misclassification and controlling for confounding using propensity matching. Observational studies of this nature have been shown to generally correlate with randomized control trials (39). However, there could have been residual confounding due to unmeasured variables including blood pressure levels and hemoglobin A1C. Accordingly, further investigations using different methodologies are required to confirm the present findings.

Given the tremendous and increasing burden of diabetes in South Asian and Chinese patients globally, there is an alarming paucity of large studies evaluating the effectiveness of routinely used cardiovascular risk reduction therapies in these groups. ACEi, ARB, and diuretics are likely effective among Chinese and other patients. More research is required to evaluate the effectiveness of antihypertensive agents in South Asians, to confirm the benefit of ACEi in Chinese patients, and to examine CCB effectiveness in all patients. Inclusion of these groups in future clinical trials is essential to examine for differential response by ethnicity.

Author Contributions

NAK, CK made substantial contributions to conception and design, SM and KS made substantial contributions towards acquisition of data, all authors made substantial contribution to analysis of data, all authors made substantial contribution towards interpretation of data, CK wrote the first draft and all authors participated in revising it critically for important intellectual content; and all authors give final approval of the version submitted.

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Drs. Nadia Khan and Calvin Ke take full responsibility for the work as a whole, including the study design, access to data, and the decision to submit and publish the manuscript.

Data Sharing Statement: all datasets are available through Population Data BC, subject to approval by relevant data stewards at the BC Ministry of Health.

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Table 1 Baseline characteristics among diabetes patients aged 35 years and older*

Characteristics	South Asian (*n*=13 755)	Chinese (*n*=22 871)	Other (*n*=172 244)
Age, mean age (years) ±SD or %			
All patients	56.4 ±12.6	59.2 ±12.7	61.5 ±12.8
35-49 years	33.2	24.7	18.8
50-64 years	39.8	43.1	42.0
65-79 years	23.2	25.3	29.5
≥80 years	3.87	6.8	9.7
Women (%)	45.0	48.4	45.1
Income Quintile (%)			
1st quintile (low)	25.6	27.4	21.2
2nd quintile	32.2	23.4	20.7
3rd quintile	20.4	20.2	20.0
4th quintile	12.3	14.4	19.3
5th quintile (high)	8.8	13.4	17.5
Unknown	0.7	1.0	1.2
Hypertension	42.0	44.0	47.9
Myocardial infarction	2.2	1.0	2.6
Congestive heart failure	3.0	2.1	5.3
Peripheral vascular disease	0.6	1.3	2.0
Cancer	2.8	3.8	6.3
Cerebrovascular disease	1.8	2.0	3.2
Chronic pulmonary disease	11.2	6.4	11.4
Renal disease	2.2	2.3	3.1
Medications prescribed at baseline *n* (%)			
ACEi	15.7	11.0	22.8
ARB	7.2	10.0	8.7
CCB	8.1	9.1	8.5
Diuretic	11.3	12.4	18.3
β-blocker	9.5	8.4	13.3
Metformin	21.3	15.4	23.8
Sulfonylurea	3.8	2.6	3.5
Insulin	0.6	0.7	1.7
Statin	24.2	20.8	26.9
Medications prescribed after 1 year of diabetes diagnosis *n* (%)			
ACEi	26.1	17.8	33.5
ARB	12.6	16.3	13.7
CCB	12.6	13.9	12.8
Diuretic	18.7	18.6	27.0
Any ACEi, ARB, CCB, diuretic**	55.2	47.7	64.9

*All p-values comparing the 3 ethnic groups were less than 0.001

**Abbreviations: SD = standard deviation, ACEi = angiotensin converting enzyme inhibitor, ARB = angiotensin receptor blocker, CCB = dihydropyridine calcium channel blocker

Table 2 Association between antihypertensive medications and all-cause mortality according to ethnicity

Drug	Adjusted HR* (95% CI)					
	South Asian (*n*=13 755)	p-value	Chinese (*n*=22 871)	p-value	Other (*n*=172 244)	p-value
ACEi	0.91 (0.71-1.17)	0.47	0.84 (0.69-1.03)	0.09	0.88 (0.84-0.91)	<0.0001
ARB	0.88 (0.63-1.25)	0.48	0.64 (0.50-0.82)	0.0004	0.69 (0.64-0.74)	<0.0001
CCB	1.25 (0.93-1.68)	0.14	0.94 (0.77-1.15)	0.56	1.00 (0.94-1.05)	0.89
Diuretic	0.83 (0.61-1.12)	0.22	0.77 (0.62-0.96)	0.02	0.66 (0.63-0.69)	<0.0001

* Cox proportional hazards models were weighted using a propensity score model by the IPTW method adjusted for age, sex, SES, Charlson comorbidities, and use of other medications (insulin, ACEi, ARB, beta-blockers, CCB, diuretics, and statins) at baseline, defined as a prescription within 1 month before or after diagnosis.
Abbreviations: HR = hazard ratio, ACEi = angiotensin converting enzyme inhibitor, ARB = angiotensin receptor blocker, CCB = dihydropyridine calcium channel blocker

Table 3 Association between medication adherence and all-cause mortality according to ethnicity

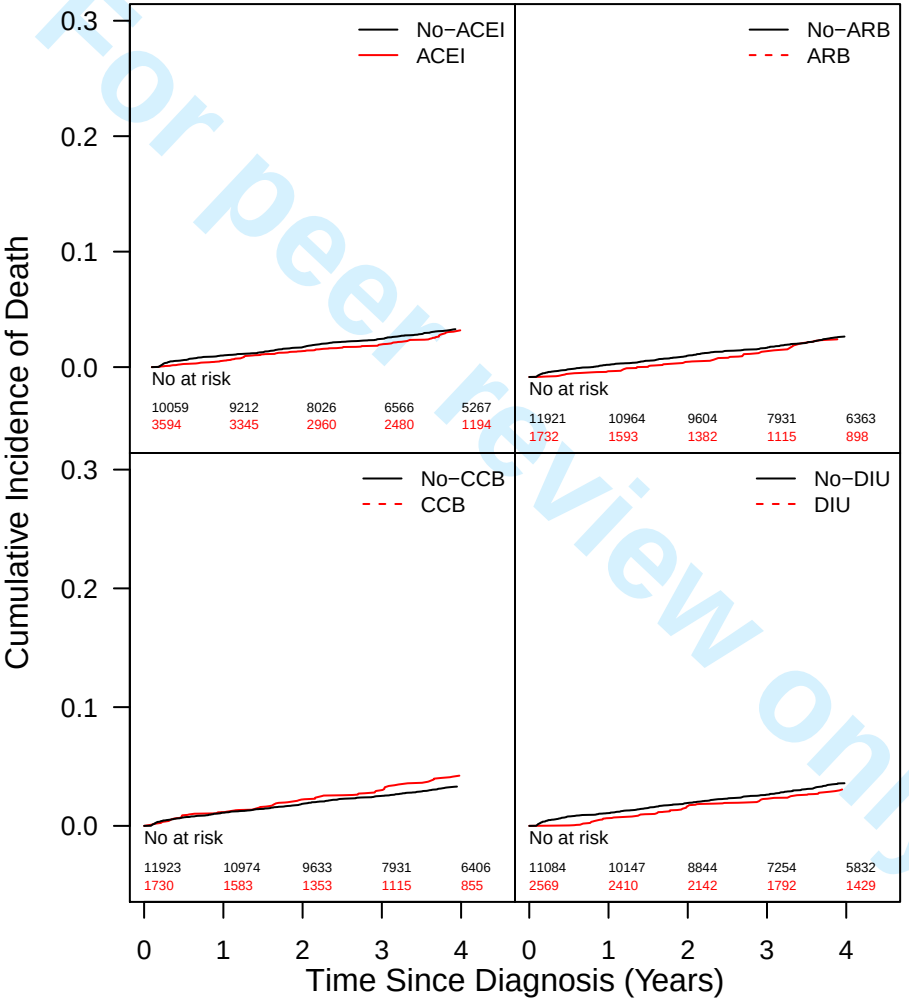
Adjusted HR* (95% CI)						
Drug	South Asian (*n*=13 755)	p-value	Chinese (*n*=22 871)	p-value	Other (*n*=172 244)	p-value
Any ACEi, ARB, CCB, diuretic†	0.94 (0.68-1.31)	0.73	1.12 (0.82-1.54)	0.46	0.80 (0.74-0.85)	<0.0001

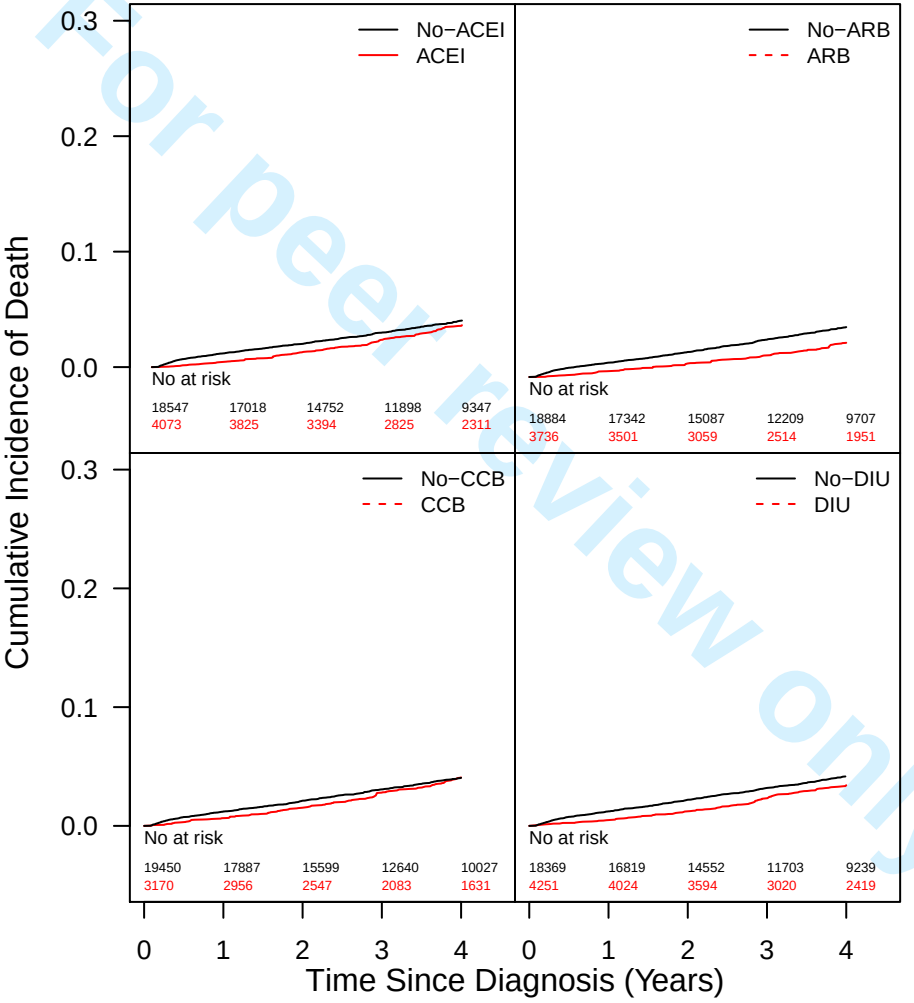
* Cox proportional hazards models were weighted using a propensity score model by the IPTW method adjusted for age, sex, SES, Charlson comorbidities, and use of other medications (insulin, ACEi, ARB, beta-blockers, CCB, diuretics, and statins) at baseline, defined as a prescription within 1 month before or after diagnosis.
† Hazard ratios for patients prescribed any antihypertensive (ACEi, ARB, CCB, diuretic) with moderate or high adherence compared to low adherence
Abbreviations: HR = hazard ratio, ACEi = angiotensin converting enzyme inhibitor, ARB = angiotensin receptor blocker, CCB = dihydropyridine calcium channel blocker

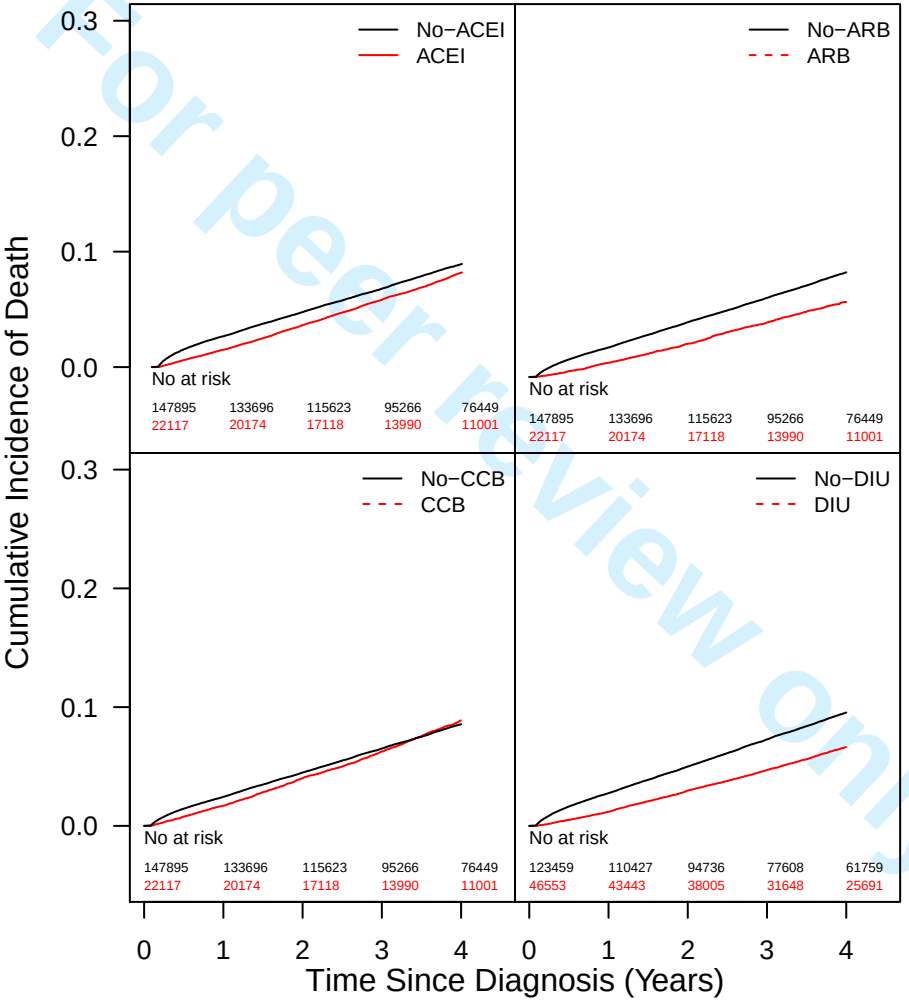
Figure 1 Adjusted* Kaplan-Meier survival curves for patients treated with ACEi, ARB, CCB, and diuretics ("DIU") according to ethnicity: (A) South Asian; (B) Chinese; (C) Other

(see Figure 1A, 1B, 1C files attached separately)

* Cox proportional hazards models were weighted using a propensity score model by the IPTW method adjusted for age, sex, SES, Charlson comorbidities, and use of other medications (insulin, ACEi, ARB, beta-blockers, CCB, diuretics, and statins) at baseline, defined as a prescription within 1 month before or after diagnosis.
Abbreviations: ACEi = angiotensin converting enzyme inhibitor, ARB = angiotensin receptor blocker, CCB = dihydropyridine calcium channel blocker







STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract **[title page 1 and abstract page 2]**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **[abstract page 2]**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **[introduction page 4]**
Objectives	3	State specific objectives, including any prespecified hypotheses **[introduction page 5]**
Methods		
Study design	4	Present key elements of study design early in the paper **[methods page 5]**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **[methods pages 5-7]**
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up **[methods pages 5-8]** *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed **[methods page 9]** *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **[methods pages 7-9]**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **[methods pages 8-9]**
Bias	9	Describe any efforts to address potential sources of bias **[methods page 9]**
Study size	10	Explain how the study size was arrived at **[methods page 6]**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **[methods page 9]**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding **[methods pages 9-10]**
		(*b*) Describe any methods used to examine subgroups and interactions **N/A**
		(*c*) Explain how missing data were addressed **N/A**
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed **N/A** *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses **[methods page 9]**

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed **[results page 10]**
		(b) Give reasons for non-participation at each stage **N/A**
		(c) Consider use of a flow diagram **N/A**
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **[page 21 Table 1]**
		(b) Indicate number of participants with missing data for each variable of interest **[page 21 Table 1]**
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount) **[results page 11]**
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time **[results page 11]**
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included **[page 22 Table 2]**
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **[page 22 Table 3]**
Discussion		
Key results	18	Summarise key results with reference to study objectives **[Discussion page 12]**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **[Discussion page 15]**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **[Discussion pages 12-15]**
Generalisability	21	Discuss the generalisability (external validity) of the study results **[Discussion page 15]**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **[page 16]**

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Is Cardiovascular Risk Reduction Therapy Effective in South Asian, Chinese, and Other Patients with Diabetes? A Population-Based Cohort Study from Canada

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Is Cardiovascular Risk Reduction Therapy Effective in South Asian, Chinese, and Other Patients with Diabetes? A Population-Based Cohort Study from Canada

Running Title: Cardiovascular Risk Reduction in Diabetes

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Abstract

Objectives: Guidelines recommend angiotensin converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB), calcium channel blockers (CCB) and diuretics in all patients with diabetes mellitus. However, the effectiveness of these agents in South Asian and Chinese populations is unknown. We sought to determine whether ACEi, ARB, CCB, and diuretics are associated with reduced mortality in South Asian, Chinese, and other patients with diabetes.

Design: Population-based cohort study using administrative health databases

Setting: Province of British Columbia, Canada (2006-2013)

Participants: Patients aged ≥35 years with incident diabetes

Primary and secondary outcome measures: Primary outcome was all-cause mortality for each medication class compared to untreated patients within each ethnicity. Treatment effect was assessed using inverse probability of treatment weighted Cox proportional hazards models. Medication adherence effect on mortality was also evaluated.

Results: 208,870 patients (13,755 South Asian, 22,871 Chinese, 172,244 other Canadian) were included. ACEi reduced mortality in other patients (HR=0.88, 0.84-0.91) with no significant benefit in Chinese and South Asian patients. ARB and diuretics reduced mortality in Chinese (ARB HR=0.64, 0.50-0.82; diuretics HR=0.77, 0.62-0.96) and other patients (ARB HR=0.69, 0.64-0.74; diuretics HR=0.66, 0.63-0.69) compared with untreated patients. No mortality benefit was observed among South Asians for any drug class or for CCB among all ethnicities. Higher medication adherence was associated with lower mortality for other patients only (HR=0.79, 0.72-0.86).

Conclusions: Effectiveness of cardiovascular risk reduction therapy on mortality varies considerably by ethnicity. Further study is needed to evaluate the lack of mortality benefit of antihypertensive agents in South Asians. Inclusion of these ethnic groups in future clinical trials is essential to examine for differential responses.

Strengths and limitations of this study:

- This study addresses a substantial gap in the literature regarding long-term effectiveness of commonly used antihypertensive drug classes among diabetes patients of South Asian and Chinese descent
- The analysis is conducted on a large, population-based data set including significant numbers of people of different ethnicities in Canada, allowing for measurement of real-world effects on mortality
- Limitations include possible residual confounding due to unmeasured variables

Introduction

Pharmacologic treatment of hypertension in patients with type 2 diabetes mellitus (diabetes) is associated with significantly reduced mortality (1). International guidelines recommend routinely using antihypertensive medications to control blood pressure in all diabetes patients, including those of Asian ethnicity (2–5). However, most trials of cardiovascular risk reduction therapy in patients with diabetes occurred in western populations.

Response to these therapies can be affected by ethnicity. ACE inhibitors (ACEi) were found to be less effective in reducing mortality and cardiovascular events among Black patients with hypertension and diabetes compared with other antihypertensive agents (6–8). Several studies also reported higher risk of ACEi-induced cough in Chinese patients suggesting that there may be some underlying differences in response to these medications (9). Others reported that South Asians may have increased sympathetic activity, possibly causing differing responses to antihypertensive classes (10). An analysis in South Asian and Chinese patients with newly diagnosed diabetes found significant mortality reductions associated with statin use (10). However, similar analyses are currently lacking for antihypertensive agents.

The benefit of ACEi in reducing cardiovascular risk in diabetes was established in multiple large randomized-control trials of western patients, with 24% reduction in the secondary outcome of total mortality seen in the HOPE study (11–13). These benefits were similar to angiotensin receptor blockers (ARB) based on the ONTARGET study subset of diabetes patients (14). However, the PRoFESS trial included 18% of patients of Chinese ethnicity and 8.4% of South Asian ethnicity, found no benefit of telmisartan in reducing major cardiovascular events (15).

Additionally, major randomized trials examining thiazide and thiazide-like diuretics ((SHEP (16), ALLHAT (7)), CCB (ALLHAT (7)) and CCB-based combinations (ACCOMPLISH (17)) were conducted in predominantly western populations.

The burden of diabetes in South Asian and Chinese populations is tremendous, with these ethnic groups representing 62% of all adults with diabetes globally (18). In this context, the paucity of large studies specifically comparing long-term effectiveness of major antihypertensive drug classes in these ethnicities is concerning (19). With the existing, widespread use of these medications, such studies are unlikely to be conducted in the near future. In an effort to fill the information gap, we conducted a population-based cohort study to determine whether ACEi, ARB, dihydropyridine CCB, and diuretics are effective in reducing all-cause mortality in a population cohort of South Asian (originating from Pakistan, India, or Bangladesh), Chinese (originating from China, Taiwan, or Hong Kong), and other patients with newly diagnosed diabetes.

Research Design and Methods

Study Overview

We conducted an analysis using population-based administrative data of adults aged ≥35 years living in British Columbia, Canada with newly diagnosed diabetes between April 1, 2006 and March 31, 2013.

Data Sources

We used administrative data from British Columbia, Canada. We obtained de-identified linked health datasets through Population Data BC with approval of relevant data stewards and the University of British Columbia's Behavioural Research Ethics Board (20). All inferences, opinions, and conclusions drawn in this report are those of the authors, and do not reflect the opinions or policies of Population Data BC.

The databases covered all British Columbians except those whose prescription drug coverage fell under federal jurisdiction (i.e., military, veterans, inmates of federal penitentiaries, and status Indians living on reserves, approximately 4.0% of the total population). All residents included in our dataset are covered under British Columbia's universal, public health insurance program for medical and hospital care; and all are eligible for coverage under British Columbia's universal, public drug benefit plan, under which deductibles are set in relation to household income.

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 include a single diagnosis for each encounter. Inpatient data include both primary (most responsible diagnosis) and secondary (comorbid conditions) 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.

Study Population

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.

Categorizing Ethnic Group

Because ethnicity is not routinely recorded in Canadian administrative health data, we used an algorithm developed to identify surnames of South Asian and Chinese origin that has been

validated for use in administrative data research by Shah et al. (27). Canadian census data show that 93% of South Asians and 90% of Chinese marry people of the same ethnic background, minimizing the chance of misidentification due to mixed marriages (28). We labelled the remaining population as "other." In the province of British Columbia, the vast majority of this group consists of Caucasian individuals (93%) (29).

Sociodemographics and Comorbid Conditions

We estimated socioeconomic status (SES) using income quintile. We estimated household income based on a combination of household-specific and area-based income data (30). 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.

Cardiovascular Risk Reduction Medications

Within each ethnicity, we classified study patients as either treated or untreated with each antihypertensive medication class: ARB, ACEi, dihydropyridine CCB, and thiazide or thiazide-type diuretics. We considered patients as treated with a medication if they received at least one prescription within 1 year after index diagnosis, a time period used in other similar studies (32).

Outcome Measures

Patients were followed for up to 4 years for the primary outcome measure, time to death from any cause. Risk was determined for South Asian, Chinese, and other patients treated on each medication as compared to untreated patients (regardless of other antihypertensive use) within each ethnicity as a baseline.

Statistical Analysis

Baseline characteristics for each ethnic group were summarized and compared among the groups using the Chi square test for categorical variables and analysis of variance for continuous variables. 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). The weight was based on a propensity score of having treatment, estimated from a multivariable logistic regression model with receiving treatment as a binary outcome variable and age, gender, SES, Charlson comorbidities, and baseline use of other medications as independent variables. In particular, the weight for each subject was computed by taking the inverse probability of receiving treatment that the subject received and stabilized by multiplying marginal probability of the actual treatment received (36). Means and standard deviations of the weights were assessed to verify the positivity assumption. The proportional hazards assumption was verified using Schoenfeld residuals. Cumulative incidence of death was also visualized for the weighted sample. Use of other medications (insulin, use of other antihypertensive agents and statins) at baseline was defined as a prescription recorded within 1 month before or after diagnosis. The data were censored at the end of the 4-year observation period or at death, whichever came first.

In a sensitivity analysis to account for effects of differential drug exposure, we evaluated the association of level of medication adherence with mortality among patients who were treated with at least one of the four study medication classes. We constructed the IPTW Cox proportional hazards models to compare among the medication adherence levels. In particular, the adherence of each medication was measured over 1 year since the first prescription using proportion of days covered (PDC), which has a high predictive validity for hospitalization episodes (37). The PDC is defined as [(number of days supply of medication in the index period)/(number of days in the study period)] × 100. The mean PDC across the four classes was calculated and classified into three levels with PDC ≥ 0.80 classified as high adherence, 0.50 ≤ PDC < 0.80 as moderate adherence, and PDC < 0.50 as low adherence.

All *p* values presented are 2-tailed, and a value of less than 0.05 was considered significant. Analyses were performed with SAS version 9.4 (SAS Institute Inc.).

Results

Baseline Characteristics and Prescribing

There were 208 870 patients (13 755 South Asian, 22 871 Chinese, 172 244 other) included in the analysis (Table 1). Most patients were elderly with South Asian patients being younger than the other groups at time of diagnosis. South Asian and Chinese patients were more likely than other patients to be in the 2 lowest socioeconomic quintiles. Hypertension was present in almost

half of patients across all ethnicities (42% South Asian, 44% Chinese, 48% other). The prevalence of comorbid conditions was low in this cohort with South Asian and Chinese patients having generally a lower prevalence of conditions compared with others, including myocardial infarction, congestive heart failure, peripheral vascular disease, and cerebrovascular disease.

Other patients were the most likely to be prescribed antihypertensive agents at baseline, with the most frequently prescribed classes being ACEi (23%) and diuretics (18%). South Asians were also likely to be prescribed with ACEi (16%) and diuretics (11%). Chinese patients had a more equal distribution among ACEi, ARB, CCB, and diuretic prescriptions (9.1-12%). By the end of one year since initial diabetes diagnosis, almost two-thirds of other patients were prescribed at least one antihypertensive agent, with a lower proportion in South Asian and Chinese patients. The most frequently prescribed class of antihypertensive agent by this time was ACEi (26% South Asians, 18% Chinese, 34% other), followed by diuretics (19% South Asians, 19% Chinese, 27% other).

Mortality

Overall, 6.5% of patients died during the follow up period (median 3 years; Figure 1). Among other patients, ACEi (HR=0.88, 0.84-0.91; Table 2), ARB (HR=0.69, 0.64-0.74) and diuretics (HR=0.66, 0.63-0.69) were associated with substantial reductions in all-cause mortality, with minimal effect observed with CCB (HR=1.00, 0.94-1.05). Consistent with the positivity assumption, the means of the stabilized weights were close to one with low standard deviations (Supplemental Table S1).

Similarly, among Chinese patients, ARB (HR=0.64, 0.50-0.82) and diuretics (HR=0.77, 0.62-0.96) were associated with significant mortality reduction. There was a non-significant trend towards benefit with ACEi (HR=0.84, 0.69-1.03), but there was no significant effect observed with CCB.

In South Asian patients, no statistically significant mortality benefits were observed with ACEi (HR=0.91, 0.71-1.17), ARB (HR=0.88, 0.63-1.25), CCB (HR=1.25, 0.93-1.68), or diuretics (HR=0.83, 0.61-1.12).

In our sensitivity analysis that included level of drug exposure in all drug classes, a moderate to high adherence to the 4 antihypertensive classes was associated with lower mortality among other patients compared to low adherence (Table 3). However, high or moderate adherence was not associated with reduced mortality compared with low adherence of antihypertensive medications among Chinese and South Asian patients. There was insufficient power to analyze the effects of high versus low adherence, or adherence within single medication classes.

Discussion

Overall, we observed substantial ethnic differences in effectiveness of cardiovascular risk reduction therapies on mortality in patients with diabetes. Mortality reduction associated with treatment with ARB, diuretics and a trend towards mortality benefit with ACEi were observed

Chinese patients. However, no significant associations with mortality and cardiovascular risk reduction therapy were seen in South Asians for any drug class.

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. Nevertheless, the effects we observed in the other population are generally consistent in direction with results from major clinical trials in patients with diabetes (13,14, 33). For ACEi, the benefit we observed (HR=0.88, 0.84-0.91) is consistent with findings reported in the HOPE study (total mortality relative risk 0.76, 0.63-0.92) that compared ramipril to placebo in patients with diabetes and an additional cardiovascular risk factor (13). The mortality reduction for ARB (HR=0.69, 0.64-0.74) is similar to that seen in the LIFE study (relative risk 0.61, 0.45-0.84), comparing losartan to atenolol (38).

Among Chinese patients, we observed generally similar mortality reductions associated with ACEi (HR=0.84, 0.69-1.03) and ARB (HR=0.64, 0.50-0.82) use, although the benefit of ACEi did not reach statistical significance. Notably, adherence to ACEi among Chinese patients (52%) compared to ARB (72%) is reported to be lower than other patients, and this difference may have attenuated the effect with ACEi (23). Nevertheless, our results provide new evidence on the effectiveness of these agents in a real world population extending the findings of the ONTARGET (14) study, that included 14% of patients of Asian ethnicity. Given these findings, it is particularly important to emphasize the increased use of these medications, particularly

given the gaps in prescription filling observed among Chinese and South Asian patients, who had lower than expected rates of renin-angiotensin system antagonist prescription.

Diuretics were associated with effectiveness in Chinese. The effects observed (Chinese HR=0.77, 0.62-0.96) are largely consistent with those reported in the placebo-controlled SHEP trial (16) diabetes subgroup (HR 0.80, 0.68-0.95). The present findings are the first to our knowledge to evaluate thiazide and thiazide like diuretics to Chinese patients with diabetes.

We did not observe substantial benefits of CCB in any ethnic category. This result was unexpected given the findings of the ALLHAT study, that showed that CCB were equivalent to ACEi and diuretics as first-line antihypertensive agents in diabetes (7). These findings may reflect the trend that CCB are decreasingly likely to be used as initial antihypertensive therapy compared to ACEi and diuretics in Canada (39). This trend is in accordance with guidelines promoting CCB as an add-on agent given the ACCOMPLISH trial findings (17). Patients in the CCB group may have had more severe hypertension requiring more than one agent, thereby causing confounding by indication. Moreover, the comparison group in our study likely included patients treated with other agents such as ACEi, ARB, and diuretics, leading to an attenuation of observed effect. It is also possible that the real-world effect size varies from that observed in randomized control trials (RCTs) due to rigid selection criteria and selection bias. Further research is required to clarify the benefit of CCB, especially in South Asian and Chinese populations.

None of the drug classes were associated with any statistically significant mortality benefits among South Asians. 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 prescription filling rates in this cohort. The lower rate of mortality events is consistent with evidence in our population demonstrating a lower rate of mortality following myocardial infarction, uniquely among South Asians (40). It is conceivable that the effect may also have been attenuated by additional factors such as cultural dietary practices (e.g. salt intake (41)) and pharmacogenetic influences. For instance, ACE gene insertion/deletion polymorphisms affect serum levels of ACEi, although a long-term effect on cardiovascular outcomes has yet to be demonstrated (42). Pharmacogenetic differences may also lead to heterogeneous responses to antihypertensive agents within the same class (43). With these considerations in mind, further research is required to confirm the effectiveness and magnitude of mortality benefit of cardiovascular risk reduction therapy in South Asians.

The lack of significant associations among South Asians may also relate to poor medication adherence and reduced drug exposure. Although we performed a sensitivity analysis using drug adherence to evaluate whether drug discontinuation, switching between classes, or decreased adherence may have affected our results, only in other patients was a significant mortality reduction seen in those with moderate or high adherence. No significant associations were observed for South Asian and Chinese patients. The lack of adherence effects may be related to inadequate power to detect smaller treatment related effect size in these groups. South Asian and Chinese patients may also import antihypertensive medications from out of country, limiting our ability to detect treatment differences (44). In the context of these limitations, more studies are

required to evaluate the interaction between medication adherence and antihypertensive therapies in South Asian and Chinese patients.

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.

Given the tremendous and increasing burden of diabetes in South Asian and Chinese patients globally, there is an alarming paucity of large studies evaluating the effectiveness of routinely

used cardiovascular risk reduction therapies in these groups. ACEi, ARB, and diuretics are likely effective among Chinese and other patients. 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.

Author Contributions

NAK, CK made substantial contributions to conception and design, SM and KS made substantial contributions towards acquisition of data, all authors made substantial contribution to analysis of data, all authors made substantial contribution towards interpretation of data, CK wrote the first draft and all authors participated in revising it critically for important intellectual content; and all authors give final approval of the version submitted.

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Conflict of Interest: There are no potential conflicts of interest involving the work under consideration for publication (during the time involving the work, from initial conception and planning to present), no relevant financial activities outside the submitted work (over the 3 years prior to submission), and no other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing what is written in the submitted work (based on all relationships that were present during the 3 years prior to submission) for any of the co-authors.

Drs. Nadia Khan and Calvin Ke take full responsibility for the work as a whole, including the study design, access to data, and the decision to submit and publish the manuscript.

Data Sharing Statement: all datasets are available through Population Data BC, subject to approval by relevant data stewards at the BC Ministry of Health.

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Table 1 Baseline characteristics among diabetes patients aged 35 years and older*. Chi-square tests and analyses of variance showed statistically significant differences among the three groups (p<0.0001) for all baseline characteristics.

Characteristics	South Asian (*n*=13 755)	Chinese (*n*=22 871)	Other (*n*=172 244)
Age, mean age (years) ±SD or %			
All patients	56.4 ±12.6	59.2 ±12.7	61.5 ±12.8
35-49 years	33.2	24.7	18.8
50-64 years	39.8	43.1	42.0
65-79 years	23.2	25.3	29.5
≥80 years	3.87	6.8	9.7
Women (%)	45.0	48.4	45.1
Income Quintile (%)			
1st quintile (low)	25.6	27.4	21.2
2nd quintile	32.2	23.4	20.7
3rd quintile	20.4	20.2	20.0
4th quintile	12.3	14.4	19.3
5th quintile (high)	8.8	13.4	17.5
Unknown	0.7	1.0	1.2
Comorbidities (%)			
Hypertension	42.0	44.0	47.9
Myocardial infarction	2.2	1.0	2.6
Congestive heart failure	3.0	2.1	5.3
Peripheral vascular disease	0.6	1.3	2.0
Cancer	2.8	3.8	6.3
Cerebrovascular disease	1.8	2.0	3.2
Chronic pulmonary disease	11.2	6.4	11.4
Renal disease	2.2	2.3	3.1
Medications prescribed at baseline *n* (%)			
ACEi	15.7	11.0	22.8
ARB	7.2	10.0	8.7
CCB	8.1	9.1	8.5
Diuretic	11.3	12.4	18.3
β-blocker	9.5	8.4	13.3
Metformin	21.3	15.4	23.8
Sulfonylurea	3.8	2.6	3.5
Insulin	0.6	0.7	1.7
Statin	24.2	20.8	26.9
Medications prescribed after 1 year of diabetes diagnosis *n* (%)			
ACEi	26.1	17.8	33.5
ARB	12.6	16.3	13.7
CCB	12.6	13.9	12.8
Diuretic	18.7	18.6	27.0

	Any ACEi, ARB, CCB, diuretic**	55.2	47.7	64.9

*All p-values comparing the 3 ethnic groups were less than 0.001
**Abbreviations: SD = standard deviation, ACEi = angiotensin converting enzyme inhibitor, ARB = angiotensin receptor blocker, CCB = dihydropyridine calcium channel blocker

Table 2 Association between antihypertensive medications and all-cause mortality according to ethnicity

Drug	Adjusted HR* (95% CI)					
	South Asian		Chinese		Other	
	HR	p-value	HR	p-value	HR	p-value
ACEi	0.91 (0.71-1.17)	0.47	0.84 (0.69-1.03)	0.09	0.88 (0.84-0.91)	<0.0001
ARB	0.88 (0.63-1.25)	0.48	0.64 (0.50-0.82)	0.0004	0.69 (0.64-0.74)	<0.0001
CCB	1.25 (0.93-1.68)	0.14	0.94 (0.77-1.15)	0.56	1.00 (0.94-1.05)	0.89
Diuretic	0.83 (0.61-1.12)	0.22	0.77 (0.62-0.96)	0.02	0.66 (0.63-0.69)	<0.0001

* Cox proportional hazards models were weighted using a propensity score model by the IPTW method adjusted for age, sex, SES, Charlson comorbidities, and use of other medications (insulin, ACEi, ARB, beta-blockers, CCB, diuretics, and statins) at baseline, defined as a prescription within 1 month before or after diagnosis.
Abbreviations: HR = hazard ratio, ACEi = angiotensin converting enzyme inhibitor, ARB = angiotensin receptor blocker, CCB = dihydropyridine calcium channel blocker

Table 3 Association between medication adherence and all-cause mortality according to ethnicity

Adjusted HR* (95% CI)						
Drug	South Asian (*n*=9404)	p-value	Chinese (*n*=13 173)	p-value	Other (*n*=124 594)	p-value
Any ACEi, ARB, CCB, diuretic†	1.11 (0.71-1.73)	0.65	1.29 (0.83-2.01)	0.25	0.79 (0.72-0.86)	<0.0001

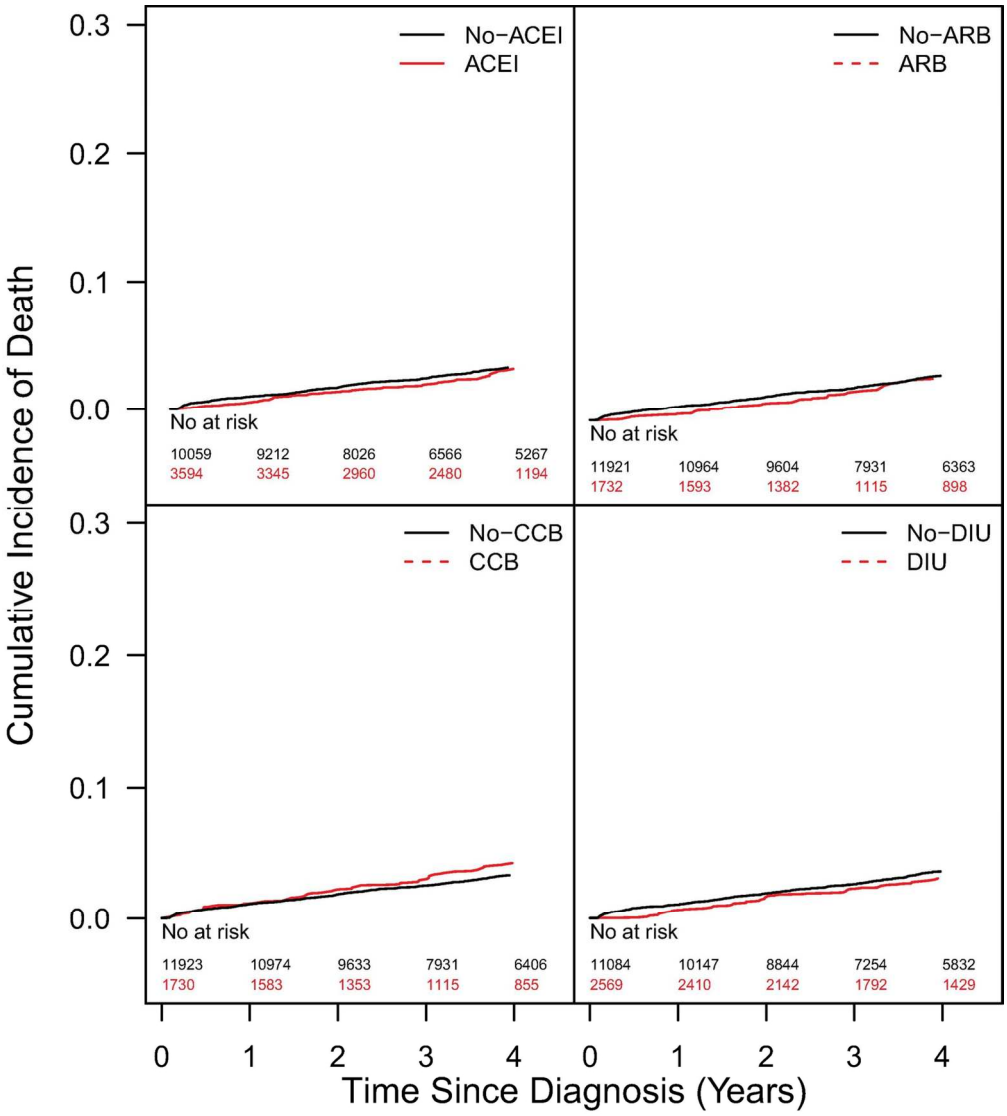
* Cox proportional hazards models were weighted using a propensity score model by the IPTW method adjusted for age, sex, SES, Charlson comorbidities, and use of other medications (insulin, ACEi, ARB, beta-blockers, CCB, diuretics, and statins) at baseline, defined as a prescription within 1 month before or after diagnosis.
† Hazard ratios for patients prescribed any antihypertensive (ACEi, ARB, CCB, diuretic) with moderate or high adherence compared to low adherence

Abbreviations: HR = hazard ratio, ACEi = angiotensin converting enzyme inhibitor, ARB = angiotensin receptor blocker, CCB = dihydropyridine calcium channel blocker

Figure 1 Cumulative incidence of death* for patients treated with ACEi, ARB, CCB, and diuretics ("DIU") according to ethnicity: (A) South Asian; (B) Chinese; (C) Other

(see Figure 1A, 1B, 1C files attached separately)

* Cox proportional hazards models were weighted using a propensity score model by the IPTW method adjusted for age, sex, SES, Charlson comorbidities, and use of other medications (insulin, ACEi, ARB, beta-blockers, CCB, diuretics, and statins) at baseline, defined as a prescription within 1 month before or after diagnosis.
Abbreviations: ACEi = angiotensin converting enzyme inhibitor, ARB = angiotensin receptor blocker, CCB = dihydropyridine calcium channel blocker



Caption : Cumulative incidence of death* for patients treated with ACEi, ARB, CCB, and diuretics ("DIU") according to ethnicity: (A) South Asian; (B) Chinese; (C) Other┼ * Cox proportional hazards models were weighted using a propensity score model by the IPTW method adjusted for age, sex, SES, Charlson comorbidities, and use of other medications (insulin, ACEi, ARB, beta-blockers, CCB, diuretics, and statins) at baseline, defined as a prescription within 1 month before or after diagnosis.┼ Abbreviations: ACEi = angiotensin converting enzyme inhibitor, ARB = angiotensin receptor blocker, CCB = dihydropyridine calcium channel blocker

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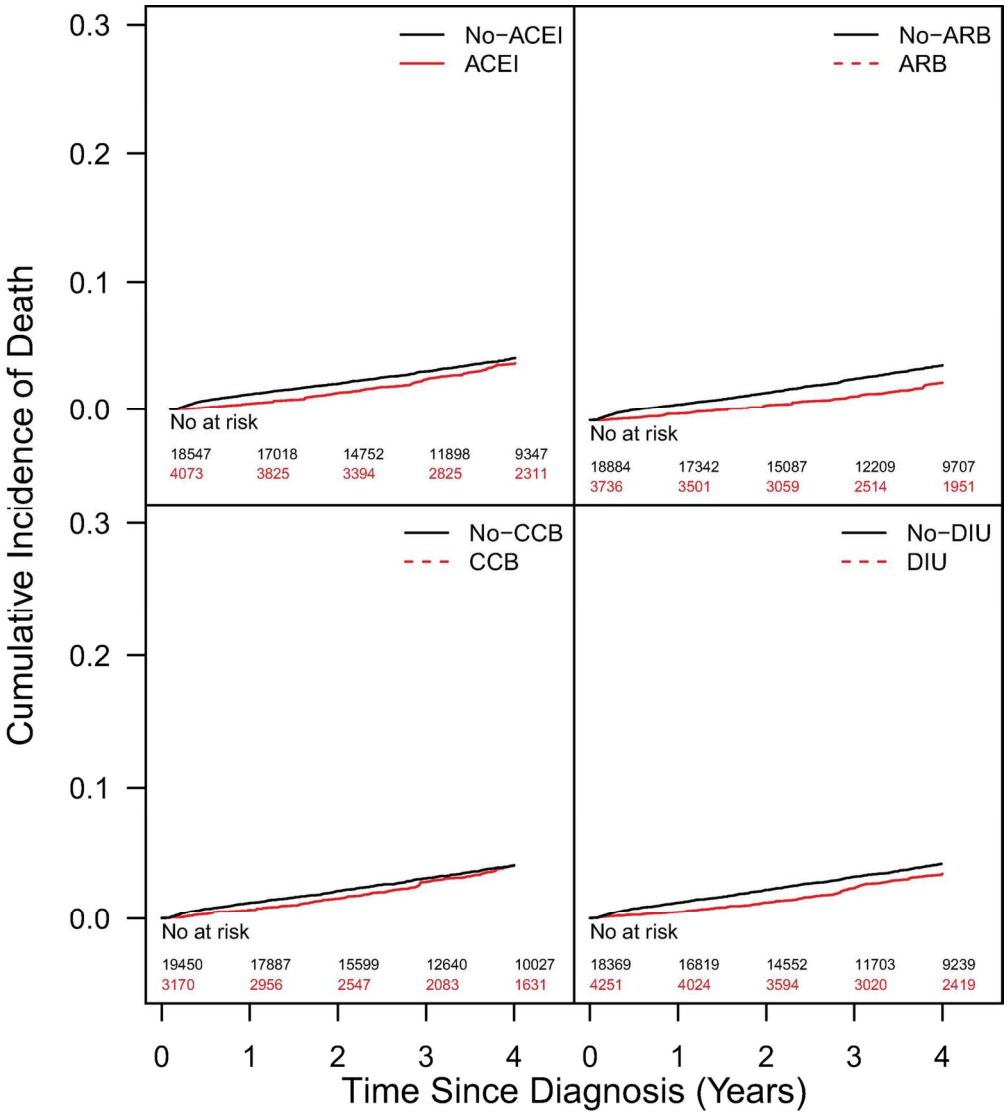

Caption : Cumulative incidence of death* for patients treated with ACEi, ARB, CCB, and diuretics ("DIU") according to ethnicity: (A) South Asian; (B) Chinese; (C) Other┼ * Cox proportional hazards models were weighted using a propensity score model by the IPTW method adjusted for age, sex, SES, Charlson comorbidities, and use of other medications (insulin, ACEi, ARB, beta-blockers, CCB, diuretics, and statins) at baseline, defined as a prescription within 1 month before or after diagnosis.┼ Abbreviations: ACEi = angiotensin converting enzyme inhibitor, ARB = angiotensin receptor blocker, CCB = dihydropyridine calcium channel blocker

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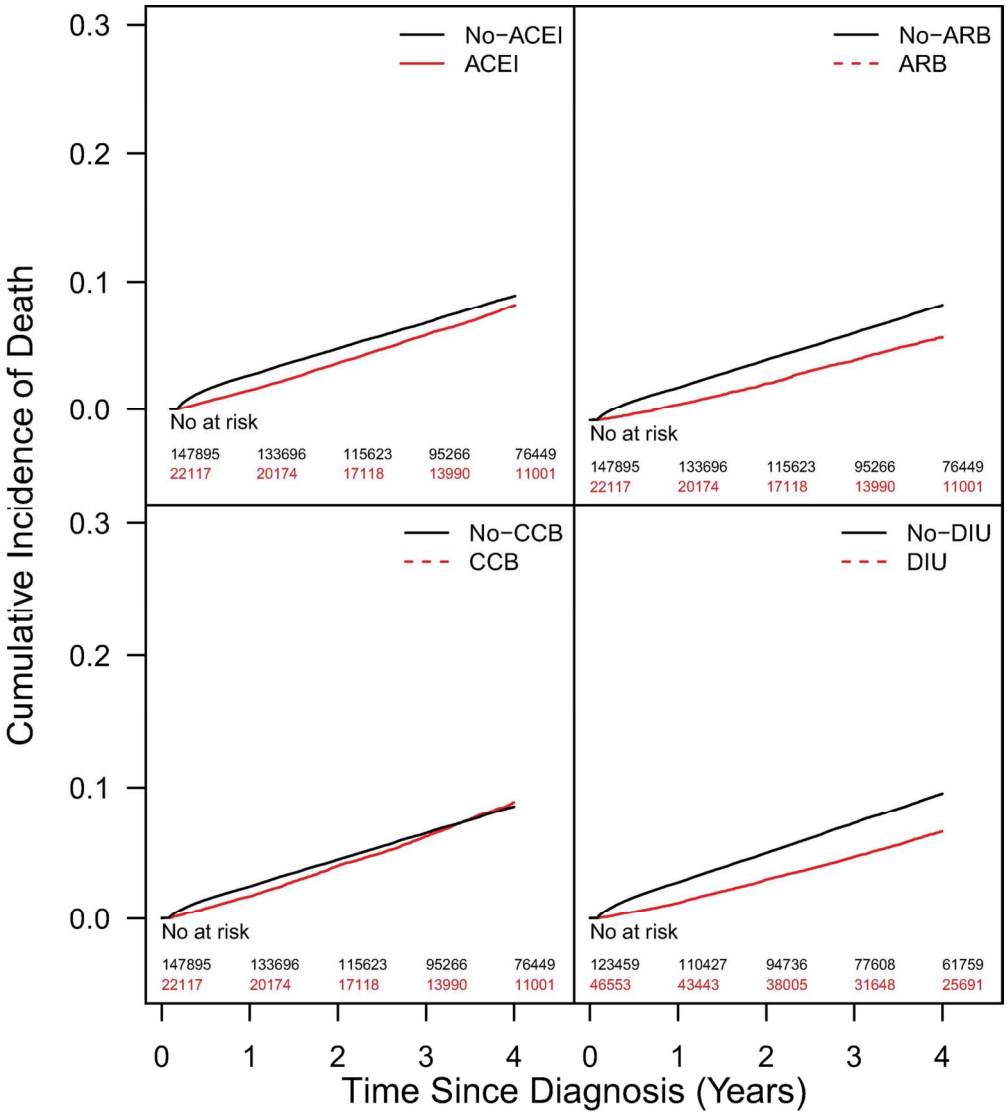

Caption : Cumulative incidence of death* for patients treated with ACEi, ARB, CCB, and diuretics ("DIU") according to ethnicity: (A) South Asian; (B) Chinese; (C) Other┼ * Cox proportional hazards models were weighted using a propensity score model by the IPTW method adjusted for age, sex, SES, Charlson comorbidities, and use of other medications (insulin, ACEi, ARB, beta-blockers, CCB, diuretics, and statins) at baseline, defined as a prescription within 1 month before or after diagnosis.┼ Abbreviations: ACEi = angiotensin converting enzyme inhibitor, ARB = angiotensin receptor blocker, CCB = dihydropyridine calcium channel blocker

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Appendix I. Additional Tables

Supplemental Table S1 Mean and standard deviation of stabilized inverse probability weights

Ethnicity	Estimated Weights	
	Mean	Standard Deviation
South Asian	0.98	0.42
Chinese	0.98	0.33
Other	0.98	0.46

Supplemental Table S2 Statistical power for each drug by ethnicity calculated using Fisher's exact method (two-sided α=0.05), specifying 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%

References:

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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.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract **[title page 1 and abstract page 2]**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **[abstract page 2]**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **[introduction page 4]**
Objectives	3	State specific objectives, including any prespecified hypotheses **[introduction page 5]**
Methods		
Study design	4	Present key elements of study design early in the paper **[methods page 5]**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **[methods pages 5-7]**
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up **[methods pages 5-8]** *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed **[methods page 9]** *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **[methods pages 7-9]**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **[methods pages 8-9]**
Bias	9	Describe any efforts to address potential sources of bias **[methods page 9]**
Study size	10	Explain how the study size was arrived at **[methods page 6]**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **[methods page 9]**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding **[methods pages 9-10]**
		(*b*) Describe any methods used to examine subgroups and interactions **N/A**
		(*c*) Explain how missing data were addressed **N/A**
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed **N/A** *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses **[methods page 9]**

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed **[results page 10]**
		(b) Give reasons for non-participation at each stage **N/A**
		(c) Consider use of a flow diagram **N/A**
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **[page 21 Table 1]**
		(b) Indicate number of participants with missing data for each variable of interest **[page 21 Table 1]**
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount) **[results page 11]**
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time **[results page 11]**
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included **[page 22 Table 2]**
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **[page 22 Table 3]**
Discussion		
Key results	18	Summarise key results with reference to study objectives **[Discussion page 12]**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **[Discussion page 15]**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **[Discussion pages 12-15]**
Generalisability	21	Discuss the generalisability (external validity) of the study results **[Discussion page 15]**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **[page 16]**

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Is Cardiovascular Risk Reduction Therapy Effective in South Asian, Chinese, and Other Patients with Diabetes? A Population-Based Cohort Study from Canada

Running Title: Cardiovascular Risk Reduction in Diabetes

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Abstract

Objectives: Guidelines recommend angiotensin converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB), calcium channel blockers (CCB) and diuretics in all patients with diabetes mellitus. However, the effectiveness of these agents in South Asian and Chinese populations is unknown. We sought to determine whether ACEi, ARB, CCB, and diuretics are associated with reduced mortality in South Asian, Chinese, and other patients with diabetes.

Design: Population-based cohort study using administrative health databases

Setting: Province of British Columbia, Canada (2006-2013)

Participants: Patients aged ≥35 years with incident diabetes

Primary and secondary outcome measures: Primary outcome was all-cause mortality for each medication class compared to untreated patients within each ethnicity. Treatment effect was assessed using inverse probability of treatment weighted Cox proportional hazards models. Medication adherence effect on mortality was also evaluated.

Results: 208,870 patients (13,755 South Asian, 22,871 Chinese, 172,244 other Canadian) were included. ACEi reduced mortality in other patients (HR=0.88, 0.84-0.91), but power was insufficient to evaluate for benefit in Chinese and South Asian patients. ARB and diuretics reduced mortality in Chinese (ARB HR=0.64, 0.50-0.82; diuretics HR=0.77, 0.62-0.96) and other patients (ARB HR=0.69, 0.64-0.74; diuretics HR=0.66, 0.63-0.69) compared with untreated patients. No mortality benefit was observed among South Asians for any drug class or for CCB among all ethnicities. Higher medication adherence was associated with lower mortality for other patients only (HR=0.79, 0.72-0.86).

Conclusions: Effectiveness of cardiovascular risk reduction therapy on mortality varies considerably by ethnicity. Further study is needed to evaluate the mortality benefit of antihypertensive agents in South Asians. Inclusion of these ethnic groups in future clinical trials is essential to examine for differential responses.

Strengths and limitations of this study:

- This study addresses a substantial gap in the literature regarding long-term effectiveness of commonly used antihypertensive drug classes among diabetes patients of South Asian and Chinese descent
- The analysis is conducted on a large, population-based data set including significant numbers of people of different ethnicities in Canada, allowing for measurement of real-world effects on mortality
- Limitations include possible residual confounding due to unmeasured variables

Introduction

Pharmacologic treatment of hypertension in patients with type 2 diabetes mellitus (diabetes) is associated with significantly reduced mortality (1). International guidelines recommend routinely using antihypertensive medications to reduce cardiovascular risk in all diabetes patients, including those of Asian ethnicity (2–5). However, most trials of cardiovascular risk reduction therapy in patients with diabetes occurred in western populations.

Response to these therapies can be affected by ethnicity. ACE inhibitors (ACEi) were found to be less effective in reducing mortality and cardiovascular events among Black patients with hypertension and diabetes compared with other antihypertensive agents (6–8). Several studies also reported higher risk of ACEi-induced cough in Chinese patients suggesting that there may be some underlying differences in response to these medications (9). Others reported that South Asians may have increased sympathetic activity, possibly causing differing responses to antihypertensive classes (10). An analysis in South Asian and Chinese patients with newly diagnosed diabetes found significant mortality reductions associated with statin use (10). However, similar analyses are currently lacking for antihypertensive agents.

The benefit of ACEi in reducing cardiovascular risk in diabetes was established in multiple large randomized-control trials of western patients, with 24% reduction in the secondary outcome of total mortality seen in the HOPE study (11–13). These benefits were similar to angiotensin receptor blockers (ARB) based on the ONTARGET study subset of diabetes patients (14). However, the PRoFESS trial included 18% of patients of Chinese ethnicity and 8.4% of South Asian ethnicity, found no benefit of telmisartan in reducing major cardiovascular events (15).

Additionally, major randomized trials examining thiazide and thiazide-like diuretics ((SHEP (16), ALLHAT (7)), CCB (ALLHAT (7)) and CCB-based combinations (ACCOMPLISH (17)) were conducted in predominantly western populations.

The burden of diabetes in South Asian and Chinese populations is tremendous, with these ethnic groups representing 62% of all adults with diabetes globally (18). In this context, the paucity of large studies specifically comparing long-term effectiveness of major antihypertensive drug classes in these ethnicities is concerning (19). With the existing, widespread use of these medications, such studies are unlikely to be conducted in the near future. In an effort to fill the information gap, we conducted a population-based cohort study to determine whether ACEi, ARB, dihydropyridine CCB, and diuretics are effective in reducing all-cause mortality in a population cohort of South Asian (originating from Pakistan, India, or Bangladesh), Chinese (originating from China, Taiwan, or Hong Kong), and other patients with newly diagnosed diabetes.

Research Design and Methods

Study Overview

We conducted an analysis using population-based administrative data of adults aged ≥35 years living in British Columbia, Canada with newly diagnosed diabetes between April 1, 2006 and March 31, 2013.

Data Sources

We used administrative data from British Columbia, Canada. We obtained de-identified linked health datasets through Population Data BC with approval of relevant data stewards and the University of British Columbia's Behavioural Research Ethics Board (20). All inferences, opinions, and conclusions drawn in this report are those of the authors, and do not reflect the opinions or policies of Population Data BC.

The databases covered all British Columbians except those whose prescription drug coverage fell under federal jurisdiction (i.e., military, veterans, inmates of federal penitentiaries, and status Indians living on reserves, approximately 4.0% of the total population). All residents included in our dataset are covered under British Columbia's universal, public health insurance program for medical and hospital care; and all are eligible for coverage under British Columbia's universal, public drug benefit plan, under which deductibles are set in relation to household income.

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 include a single diagnosis for each encounter. Inpatient data include both primary (most responsible diagnosis) and secondary (comorbid conditions) 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.

Study Population

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.

Categorizing Ethnic Group

Because ethnicity is not routinely recorded in Canadian administrative health data, we used an algorithm developed to identify surnames of South Asian and Chinese origin that has been

validated for use in administrative data research by Shah et al. (27). Canadian census data show that 93% of South Asians and 90% of Chinese marry people of the same ethnic background, minimizing the chance of misidentification due to mixed marriages (28). We labelled the remaining population as "other." In the province of British Columbia, the vast majority of this group consists of individuals of European ancestry (>90%), with very few people of African ancestry (<1%) (29).

Sociodemographics and Comorbid Conditions

We estimated socioeconomic status (SES) using income quintile. We estimated household income based on a combination of household-specific and area-based income data (30). 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.

Cardiovascular Risk Reduction Medications

Within each ethnicity, we classified study patients as either treated or untreated with each antihypertensive medication class: ARB, ACEi, dihydropyridine CCB, and thiazide or thiazide-type diuretics. We considered patients as treated with a medication if they received at least one prescription within 1 year after index diagnosis, a time period used in other similar studies (32).

Outcome Measures

Patients were followed for up to 4 years for the primary outcome measure, time to death from any cause. Risk was determined for South Asian, Chinese, and other patients treated on each medication as compared to untreated patients (regardless of other antihypertensive use) within each ethnicity as a baseline.

Statistical Analysis

Baseline characteristics for each ethnic group were summarized and compared among the groups using the Chi square test for categorical variables and analysis of variance for continuous variables. 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). The weight was based on a propensity score of having treatment, estimated from a multivariable logistic regression model with receiving treatment as a binary outcome variable and age, gender, SES, Charlson comorbidities, and baseline use of other medications as independent variables. In particular, the weight for each subject was computed by taking the inverse probability of receiving treatment that the subject received and stabilized by multiplying marginal probability of the actual treatment received (36). Means and standard deviations of the weights were assessed to verify the positivity assumption. Schoenfeld residuals were explored to examine the proportional hazards assumption. Cumulative incidence of death was also visualized for the weighted sample. Use of other medications (insulin, use of other antihypertensive agents and statins) at baseline was defined as a prescription recorded within 1 month before or after diagnosis. The data were censored at the end of the 4-year observation period or at death, whichever came first.

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 S1). 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.

In a sensitivity analysis to account for effects of differential drug exposure (including treatment cessation or switching between classes), we evaluated the association of level of medication adherence with mortality among patients who were treated with at least one of the four study medication classes. We constructed the IPTW Cox proportional hazards models to compare among the medication adherence levels. In particular, the adherence of each medication was measured over 1 year since the first prescription using proportion of days covered (PDC), which has a high predictive validity for hospitalization episodes (37). The PDC is defined as [(number of days supply of medication in the index period)/(number of days in the study period)] × 100. The mean PDC across the four classes was calculated and classified into three levels with PDC ≥ 0.80 classified as high adherence, 0.50 ≤ PDC < 0.80 as moderate adherence, and PDC < 0.50 as low adherence.

All *p* values presented are 2-tailed, and a value of less than 0.05 was considered significant for all computations. Analyses were performed with SAS version 9.4 (SAS Institute Inc.).

Results

Baseline Characteristics and Prescribing

There were 208 870 patients (13 755 South Asian, 22 871 Chinese, 172 244 other) included in the analysis (Table 1). Most patients were elderly with South Asian patients being younger than the other groups at time of diagnosis. South Asian and Chinese patients were more likely than other patients to be in the 2 lowest socioeconomic quintiles. Hypertension was present in almost half of patients across all ethnicities (42% South Asian, 44% Chinese, 48% other). The prevalence of comorbid conditions was low in this cohort with South Asian and Chinese patients having generally a lower prevalence of conditions compared with others, including myocardial infarction, congestive heart failure, peripheral vascular disease, and cerebrovascular disease.

Other patients were the most likely to be prescribed antihypertensive agents at baseline, with the most frequently prescribed classes being ACEi (23%) and diuretics (18%). South Asians were also likely to be prescribed with ACEi (16%) and diuretics (11%). Chinese patients had a more equal distribution among ACEi, ARB, CCB, and diuretic prescriptions (9.1-12%). By the end of one year since initial diabetes diagnosis, almost two-thirds of other patients were prescribed at least one antihypertensive agent, with a lower proportion in South Asian and Chinese patients. The most frequently prescribed class of antihypertensive agent by this time was ACEi (26% South Asians, 18% Chinese, 34% other), followed by diuretics (19% South Asians, 19% Chinese, 27% other).

Mortality

Overall, 6.5% of patients (*n*=355 for South Asian, *n*=679 for Chinese, *n*=11480 for other) died during the follow up period (median 3 years; Figure 1). Among other patients, ACEi (HR=0.88, 0.84-0.91; Table 2), ARB (HR=0.69, 0.64-0.74) and diuretics (HR=0.66, 0.63-0.69) were associated with substantial reductions in all-cause mortality, with minimal association observed with CCB (HR=1.00, 0.94-1.05). Consistent with the positivity assumption, the means of the stabilized weights were close to one with low standard deviations (Supplemental Table S2).

Similarly, among Chinese patients, ARB (HR=0.64, 0.50-0.82) and diuretics (HR=0.77, 0.62-0.96) were associated with significant mortality reduction. There was a non-significant trend towards benefit with ACEi (HR=0.84, 0.69-1.03), but there was no significant association observed with CCB.

In South Asian patients, no statistically significant mortality benefits were observed with ACEi (HR=0.91, 0.71-1.17), ARB (HR=0.88, 0.63-1.25), CCB (HR=1.25, 0.93-1.68), or diuretics (HR=0.83, 0.61-1.12).

In our sensitivity analysis that included level of drug exposure in all drug classes, a moderate to high adherence to the 4 antihypertensive classes was associated with lower mortality among other patients compared to low adherence (Table 3). However, high or moderate adherence was not associated with reduced mortality compared with low adherence of antihypertensive medications among Chinese and South Asian patients. There was insufficient power to analyze the effects of high versus low adherence, or adherence within single medication classes.

Discussion

Overall, we observed substantial ethnic differences in the association between of cardiovascular risk reduction therapies and mortality in patients with diabetes. Mortality reduction associated with treatment with ARB, diuretics and a trend towards mortality benefit with ACEi were observed Chinese patients. However, no significant associations with mortality and cardiovascular risk reduction therapy were seen in South Asians for any drug class.

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. Nevertheless, the associations we observed in the other population are generally consistent in direction with results from major clinical trials in patients with diabetes (13,14, 33). For ACEi, the benefit we observed (HR=0.88, 0.84-0.91) is consistent with findings reported in the HOPE study (total mortality relative risk 0.76, 0.63-0.92) that compared ramipril to placebo in patients with diabetes and an additional cardiovascular risk factor (13). The mortality reduction for ARB (HR=0.69, 0.64-0.74) is similar to that seen in the LIFE study (relative risk 0.61, 0.45-0.84), comparing losartan to atenolol (38).

Among Chinese patients, we observed generally similar mortality reductions associated with ACEi (HR=0.84, 0.69-1.03) and ARB (HR=0.64, 0.50-0.82) use, although the benefit of ACEi did not reach statistical significance. Notably, adherence to ACEi among Chinese patients (52%) compared to ARB (72%) is reported to be lower than other patients, and this difference may have

attenuated the association with ACEi (23). Nevertheless, our results provide new evidence of these agents in a real world population extending the findings of the ONTARGET (14) study, that included 14% of patients of Asian ethnicity. Given these findings, it is particularly important to emphasize the increased use of these medications, particularly given the gaps in prescription filling observed among Chinese and South Asian patients, who had lower than expected rates of renin-angiotensin system antagonist prescription.

Diuretics were associated with reduced mortality in Chinese. The effects observed (Chinese HR=0.77, 0.62-0.96) are largely consistent with those reported in the placebo-controlled SHEP trial (16) diabetes subgroup (HR 0.80, 0.68-0.95). The present findings are the first to our knowledge to evaluate thiazide and thiazide like diuretics to Chinese patients with diabetes.

We did not observe substantial benefits of CCB in any ethnic category. This result was unexpected given the findings of the ALLHAT study, that showed that CCB were equivalent to ACEi and diuretics as first-line antihypertensive agents in diabetes (7). These findings may reflect the trend that CCB are decreasingly likely to be used as initial antihypertensive therapy compared to ACEi and diuretics in Canada (39). This trend is in accordance with guidelines promoting CCB as an add-on agent given the ACCOMPLISH trial findings (17). Patients in the CCB group may have had more severe hypertension requiring more than one agent, thereby causing confounding by indication. Moreover, the comparison group in our study likely included patients treated with other agents such as ACEi, ARB, and diuretics, leading to an attenuation of observed association. It is also possible that the real-world effect size varies from that observed in randomized control trials (RCTs) due to rigid selection criteria and selection bias. Further

research is required to clarify the benefit of CCB, especially in South Asian and Chinese populations.

None of the drug classes were associated with any statistically significant mortality benefits among South Asians. A major reason for the lack of findings could have been a lack of power (Supplemental Table S1) given low event rates (*n*=355 events, 2.6% event rate in South Asians; *n*=679 events, 3.0% in Chinese) and low prescription filling rates in this cohort. The lower rate of mortality events is consistent with evidence in our population demonstrating a lower rate of mortality following myocardial infarction, uniquely among South Asians (40). Moreover, 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. It is conceivable that the association may also have been attenuated by additional factors such as cultural dietary practices (e.g. salt intake (41)) and pharmacogenetic influences. For instance, ACE gene insertion/deletion polymorphisms affect serum levels of ACEi, although a long-term effect on cardiovascular outcomes has yet to be demonstrated (42). Pharmacogenetic differences may also lead to heterogeneous responses to antihypertensive agents within the same class (43). With these considerations in mind, further research is required to confirm the effectiveness and magnitude of mortality benefit of cardiovascular risk reduction therapy in South Asians.

The lack of significant associations among South Asians may also relate to poor medication adherence and reduced drug exposure. Although we performed a sensitivity analysis using drug adherence to evaluate whether drug discontinuation, switching between classes, or decreased

adherence may have affected our results, only in other patients was a significant mortality reduction seen in those with moderate or high adherence. No significant associations were observed for South Asian and Chinese patients. The lack of adherence effects may be related to inadequate power to detect smaller treatment related effect size in these groups. Another possibility is that some of these patients could have switched from one medication class to another, thus attenuating the negative effects of being unexposed to the initial medication (for example, switching from ACEi to ARB in Chinese patients due to cough). South Asian and Chinese patients may also import antihypertensive medications from out of country, limiting our ability to detect treatment differences (44). In the context of these limitations, more studies are required to evaluate the interaction between medication adherence and antihypertensive therapies in South Asian and Chinese patients.

Our large population-based observational study allowed for measurement of real-world mortality differences, 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, 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 (4). To ensure that the results are generalizable to other real-world populations, more studies in other countries with different practice patterns and population compositions are required to improve external validity. We were also unable to assess for the additional benefits of combination therapies due to sample size considerations, although this likely would not have explained the lack of associations observed in the Asian cohorts. Further studies are required to assess these effects specifically in South Asian and Chinese populations with diabetes (46). 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 (47). Given the limitations we have described, further investigations using different methodologies are required to confirm the present findings.

Given the tremendous and increasing burden of diabetes in South Asian and Chinese patients globally, there is an alarming paucity of large studies evaluating the effectiveness of routinely used cardiovascular risk reduction therapies in these groups. ACEi, ARB, and diuretics are likely effective among Chinese and other patients. 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. 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.

Author Contributions

NAK, CK made substantial contributions to conception and design, SM and KS made substantial contributions towards acquisition of data, all authors made substantial contribution to analysis of data, all authors made substantial contribution towards interpretation of data, CK wrote the first draft and all authors participated in revising it critically for important intellectual content; and all authors give final approval of the version submitted.

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Drs. Nadia Khan and Calvin Ke take full responsibility for the work as a whole, including the study design, access to data, and the decision to submit and publish the manuscript.

Data Sharing Statement: all datasets are available through Population Data BC, subject to approval by relevant data stewards at the BC Ministry of Health.

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Table 1 Baseline characteristics among diabetes patients aged 35 years and older*. Chi-square tests and analyses of variance showed statistically significant differences among the three groups (p<0.0001) for all baseline characteristics.

Characteristics	South Asian (*n*=13 755)	Chinese (*n*=22 871)	Other (*n*=172 244)
Age, mean age (years) ±SD or %			
All patients	56.4 ±12.6	59.2 ±12.7	61.5 ±12.8
35-49 years	33.2	24.7	18.8
50-64 years	39.8	43.1	42.0
65-79 years	23.2	25.3	29.5
≥80 years	3.87	6.8	9.7
Women (%)	45.0	48.4	45.1
Income Quintile (%)			
1st quintile (low)	25.6	27.4	21.2
2nd quintile	32.2	23.4	20.7
3rd quintile	20.4	20.2	20.0
4th quintile	12.3	14.4	19.3
5th quintile (high)	8.8	13.4	17.5
Unknown	0.7	1.0	1.2
Comorbidities (%)			
Hypertension	42.0	44.0	47.9
Myocardial infarction	2.2	1.0	2.6
Congestive heart failure	3.0	2.1	5.3
Peripheral vascular disease	0.6	1.3	2.0
Cancer	2.8	3.8	6.3
Cerebrovascular disease	1.8	2.0	3.2
Chronic pulmonary disease	11.2	6.4	11.4
Renal disease	2.2	2.3	3.1
Medications prescribed at baseline *n* (%)			
ACEi	15.7	11.0	22.8
ARB	7.2	10.0	8.7
CCB	8.1	9.1	8.5
Diuretic	11.3	12.4	18.3
β-blocker	9.5	8.4	13.3
Metformin	21.3	15.4	23.8
Sulfonylurea	3.8	2.6	3.5
Insulin	0.6	0.7	1.7
Statin	24.2	20.8	26.9
Medications prescribed after 1 year of diabetes diagnosis *n* (%)			
ACEi	26.1	17.8	33.5
ARB	12.6	16.3	13.7
CCB	12.6	13.9	12.8
Diuretic	18.7	18.6	27.0

	Any ACEi, ARB, CCB, diuretic**	55.2	47.7	64.9

*All p-values comparing the 3 ethnic groups were less than 0.001
**Abbreviations: SD = standard deviation, ACEi = angiotensin converting enzyme inhibitor, ARB = angiotensin receptor blocker, CCB = dihydropyridine calcium channel blocker

Table 2 Association between antihypertensive medications and all-cause mortality according to ethnicity

Drug	Adjusted HR* (95% CI)					
	South Asian		Chinese		Other	
	HR	p-value	HR	p-value	HR	p-value
ACEi	0.91 (0.71-1.17)	0.47	0.84 (0.69-1.03)	0.09	0.88 (0.84-0.91)	<0.0001
ARB	0.88 (0.63-1.25)	0.48	0.64 (0.50-0.82)	0.0004	0.69 (0.64-0.74)	<0.0001
CCB	1.25 (0.93-1.68)	0.14	0.94 (0.77-1.15)	0.56	1.00 (0.94-1.05)	0.89
Diuretic	0.83 (0.61-1.12)	0.22	0.77 (0.62-0.96)	0.02	0.66 (0.63-0.69)	<0.0001

* Cox proportional hazards models were weighted using a propensity score model by the IPTW method adjusted for age, sex, SES, Charlson comorbidities, and use of other medications (insulin, ACEi, ARB, beta-blockers, CCB, diuretics, and statins) at baseline, defined as a prescription within 1 month before or after diagnosis.
Abbreviations: HR = hazard ratio, ACEi = angiotensin converting enzyme inhibitor, ARB = angiotensin receptor blocker, CCB = dihydropyridine calcium channel blocker

Table 3 Association between medication adherence and all-cause mortality according to ethnicity

Adjusted HR* (95% CI)						
Drug	South Asian (*n*=9404)	p-value	Chinese (*n*=13 173)	p-value	Other (*n*=124 594)	p-value
Any ACEi, ARB, CCB, diuretic†	1.11 (0.71-1.73)	0.65	1.29 (0.83-2.01)	0.25	0.79 (0.72-0.86)	<0.0001

* Cox proportional hazards models were weighted using a propensity score model by the IPTW method adjusted for age, sex, SES, Charlson comorbidities, and use of other medications (insulin, ACEi, ARB, beta-blockers, CCB, diuretics, and statins) at baseline, defined as a prescription within 1 month before or after diagnosis.
† Hazard ratios for patients prescribed any antihypertensive (ACEi, ARB, CCB, diuretic) with moderate or high adherence compared to low adherence

Abbreviations: HR = hazard ratio, ACEi = angiotensin converting enzyme inhibitor, ARB = angiotensin receptor blocker, CCB = dihydropyridine calcium channel blocker

Figure 1 Cumulative incidence of death* for patients treated with ACEi, ARB, CCB, and diuretics ("DIU") according to ethnicity: (A) South Asian; (B) Chinese; (C) Other

(see Figure 1A, 1B, 1C files attached separately)

* Cox proportional hazards models were weighted using a propensity score model by the IPTW method adjusted for age, sex, SES, Charlson comorbidities, and use of other medications (insulin, ACEi, ARB, beta-blockers, CCB, diuretics, and statins) at baseline, defined as a prescription within 1 month before or after diagnosis.
Abbreviations: ACEi = angiotensin converting enzyme inhibitor, ARB = angiotensin receptor blocker, CCB = dihydropyridine calcium channel blocker

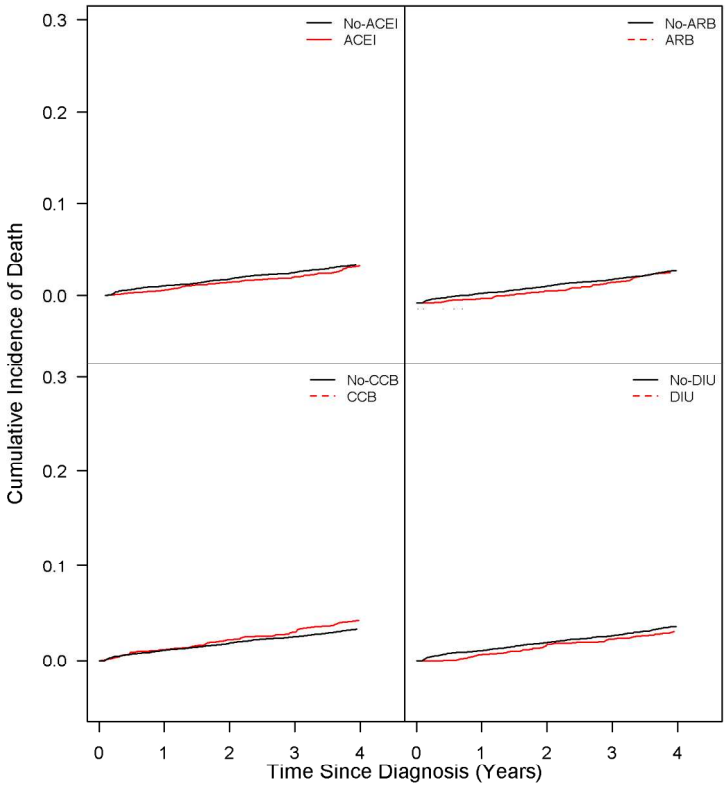

Figure 1A. Cumulative incidence of death* for patients treated with ACEi, ARB, CCB, and diuretics ("DIU") according to ethnicity: (A) South Asian; (B) Chinese; (C) Other

* Cox proportional hazards models were weighted using a propensity score model by the IPTW method adjusted for age, sex, SES, Charlson comorbidities, and use of other medications (insulin, ACEi, ARB, beta-blockers, CCB, diuretics, and statins) at baseline, defined as a prescription within 1 month before or after diagnosis.

Abbreviations: ACEi = angiotensin converting enzyme inhibitor, ARB = angiotensin receptor blocker, CCB = dihydropyridine calcium channel blocker

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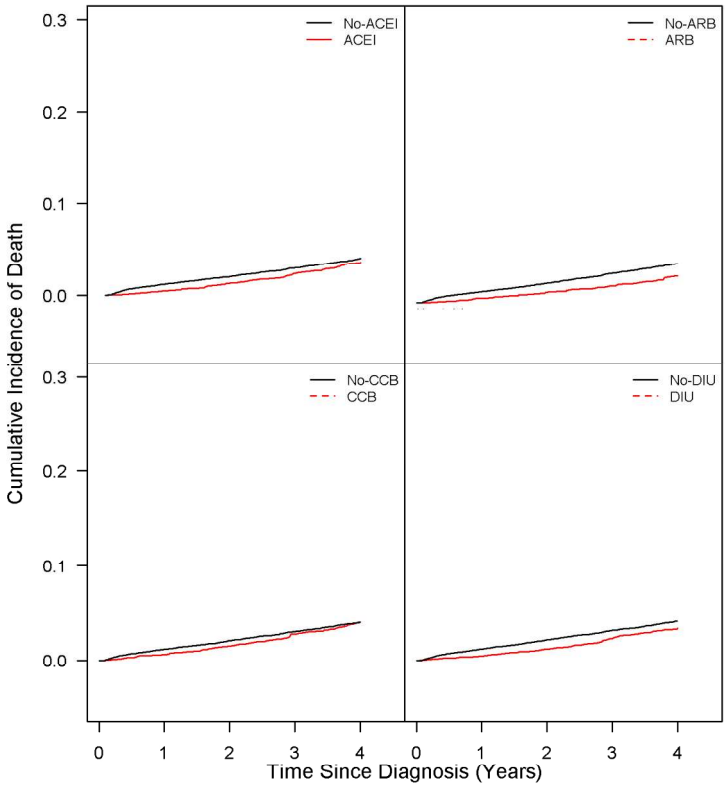

Figure 1B. Cumulative incidence of death* for patients treated with ACEi, ARB, CCB, and diuretics ("DIU") according to ethnicity: (A) South Asian; (B) Chinese; (C) Other

* Cox proportional hazards models were weighted using a propensity score model by the IPTW method adjusted for age, sex, SES, Charlson comorbidities, and use of other medications (insulin, ACEi, ARB, beta-blockers, CCB, diuretics, and statins) at baseline, defined as a prescription within 1 month before or after diagnosis.

Abbreviations: ACEi = angiotensin converting enzyme inhibitor, ARB = angiotensin receptor blocker, CCB = dihydropyridine calcium channel blocker

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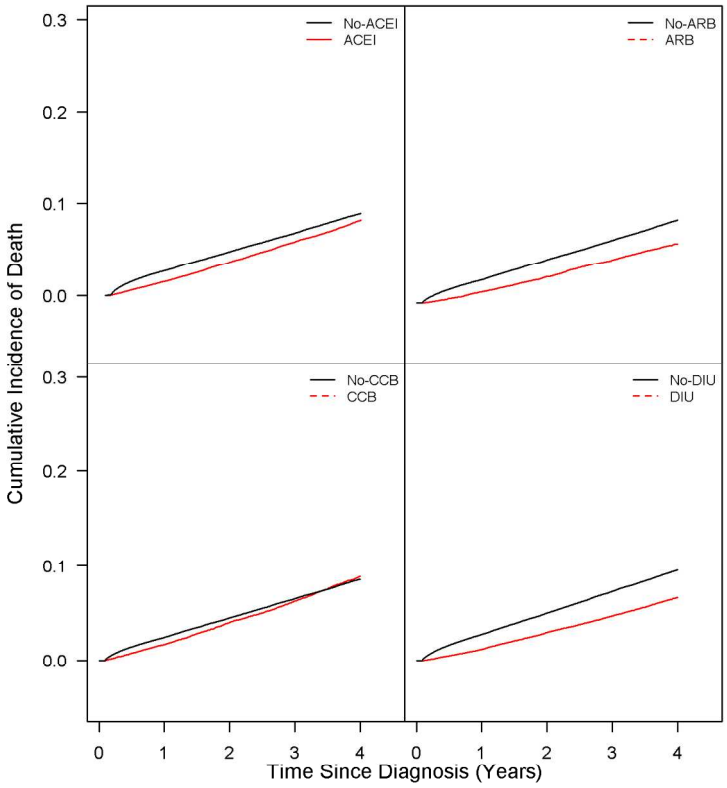

Figure 1C. Cumulative incidence of death* for patients treated with ACEi, ARB, CCB, and diuretics ("DIU") according to ethnicity: (A) South Asian; (B) Chinese; (C) Other

* Cox proportional hazards models were weighted using a propensity score model by the IPTW method adjusted for age, sex, SES, Charlson comorbidities, and use of other medications (insulin, ACEi, ARB, beta-blockers, CCB, diuretics, and statins) at baseline, defined as a prescription within 1 month before or after diagnosis.

Abbreviations: ACEi = angiotensin converting enzyme inhibitor, ARB = angiotensin receptor blocker, CCB = dihydropyridine calcium channel blocker

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Appendix I. Supplemental Tables

Supplemental Table S1 Statistical power for each drug by ethnicity calculated using the log-rank test (two-sided α=0.05), specifying actual sample sizes, treatment and event rates observed, allocation ratio, and hazard ratio as derived from the risk reduction observed in major clinical trials cited below and 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.

	Hazard ratio	Power		
		South Asian	Chinese	Other
ACEi	0.76	0.77	0.87	>0.999
ARB	0.61	0.96	>0.999	>0.999
CCB	0.80	0.40	0.62	>0.999
Diuretic	0.80	0.51	0.72	>0.999

Abbreviations: angiotensin-converting enzyme inhibitor, ACEi; angiotensin receptor blocker, ARB; calcium channel blocker, CCB

Supplemental Table S2 Mean and standard deviation of stabilized inverse probability weights

Ethnicity	Estimated Weights	
	Mean	Standard Deviation
South Asian	0.98	0.42
Chinese	0.98	0.33
Other	0.98	0.46

References

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract **[title page 1 and abstract page 2]**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **[abstract page 2]**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **[introduction page 4]**
Objectives	3	State specific objectives, including any prespecified hypotheses **[introduction page 5]**
Methods		
Study design	4	Present key elements of study design early in the paper **[methods page 5]**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **[methods pages 5-7]**
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up **[methods pages 5-8]** *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed **[methods page 9]** *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **[methods pages 7-9]**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **[methods pages 8-9]**
Bias	9	Describe any efforts to address potential sources of bias **[methods page 9]**
Study size	10	Explain how the study size was arrived at **[methods page 6]**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **[methods page 9]**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding **[methods pages 9-10]**
		(*b*) Describe any methods used to examine subgroups and interactions **N/A**
		(*c*) Explain how missing data were addressed **N/A**
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed **N/A** *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses **[methods page 9]**

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed **[results page 10]**
		(b) Give reasons for non-participation at each stage **N/A**
		(c) Consider use of a flow diagram **N/A**
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **[page 21 Table 1]**
		(b) Indicate number of participants with missing data for each variable of interest **[page 21 Table 1]**
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount) **[results page 11]**
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time **[results page 11]**
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included **[page 22 Table 2]**
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **[page 22 Table 3]**
Discussion		
Key results	18	Summarise key results with reference to study objectives **[Discussion page 12]**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **[Discussion page 15]**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **[Discussion pages 12-15]**
Generalisability	21	Discuss the generalisability (external validity) of the study results **[Discussion page 15]**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **[page 16]**

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.