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Article

The Impact of Cardiac Comorbidity Sequence at Baseline and Mortality Risk in Type 2 Diabetes Mellitus: A Retrospective Population-Based Cohort Study

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Abstract: Introduction: The presence of multiple comorbidities increases the risk of all-cause mortality, but the effects of the comorbidity sequence before the baseline date on mortality remained unexplored. This study investigated the relationship between coronary heart disease (CHD), atrial fibrillation (AF) and heart failure (HF) sequence on all-cause mortality risk in type 2 diabetes mellitus. **Methods**: This study included patients with type 2 diabetes mellitus prescribed antidiabetic/cardiovascular medications in public hospitals of Hong Kong between January 1st, 2009 and December 31st, 2009 with follow-up until death or December 31st, 2019. Cox regression was used to identify comorbidity sequences predicting all-cause mortality in patients with different medication subgroups. **Results**: A total of 249291 patients (age: 66.0±12.4 years, 47.4% male) were included. At baseline, 7564, 10900 and 25589 patients had AF, HF and CHD, respectively. Over follow-up (3524±1218 days), 85870 patients died (mortality rate: 35.7 per 1000 person-years). Sulphonylurea users with CHD developed later, but insulin users with CHD developing earlier, in the disease course had lower mortality risks. Amongst insulin users with two of the three comorbidities, CHD with preceding AF (hazard ratio [HR]: 3.06, 95% CI: [2.60-3.61], p<0.001) or HF (HR: 3.84 [3.47- 4.24], p<0.001) had a higher mortality. In users of lipid-lowering agents with all three comorbidities, those with preceding AF had higher risk of mortality (AF-CHD-HF: HR: 3.22, [2.24-4.61], p<0.001; AF-HF-CHD: HR: 3.71, [2.66-5.16], p<0.001). **Conclusion**: The sequence of comorbidity development affects the risk of all-cause mortality to varying degrees in diabetic patients on different antidiabetic/cardiovascular medications.

Keywords: comorbidity; sequence; all-cause mortality; medication

1. Introduction

The presence of multiple comorbidities is a known risk factor for all-cause mortality across the spectrum of illnesses. [1-3] However, the effects of the sequence of comorbidity development on patient mortality remained unexplored. The difference in comorbidity sequence can reflect varying disease severity, disease phenotype and possibly a different disease prognosis which may need alterations to the management approach. Additionally, the temporal variability of risk factors has been increasingly recognized as a prognostic marker for the progression of chronic diseases. [4,5] For example, long term glycemic and lipid variability have been used to predict cardiovascular, renal and mortality in type 2 diabetes mellitus. [6,7] The sequence of comorbidity development can be viewed as another

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form of long term temporal variability in the course of the chronic disease, and therefore has a prognostic potential.

In type 2 diabetes mellitus, a metabolic syndrome that is becoming increasingly prevalent due to prolonged life expectancy under a sedentary lifestyle, macrovascular and microvascular complications often arise along its disease course. Coronary heart disease (CHD), atrial fibrillation (AF) and heart failure (HF) are three common cardiovascular complications that have an interacting and interdependent relationship in their pathogenesis and progression. The combination of cardiovascular comorbidities also affects patients' treatment responses. [8] However, existing studies only focus on the prognostic value of their co-existence, without considering their sequence of development, which may help delineate different disease phenotypes. [9,10] Our team has previously conducted epidemiological studies using a territory-wide diabetes cohort to explore variability in laboratory markers, but not the effects of comorbidity sequence at baseline, for risk prediction [11-13]. Therefore, the present study aims to elucidate the effect of the sequence of CHD, AF and HF development on all-cause mortality risk amongst patients with type 2 diabetes mellitus who were on different antidiabetic and cardiovascular medications.

2. Methods

2.1. Patient selection and data extraction

This study received ethics approval from the Joint Chinese University of Hong Kong – New Territories East Cluster Clinical Research Ethics Committee. The cohort consists of type 2 diabetes mellitus patients prescribed antidiabetic or cardiovascular medications by the Hong Kong hospital authority between January 1st, 2009 to December 31st, 2009. The patients were followed up from their recruitment date till death or December 31st, 2019, whichever was earlier. Demographic, clinical and biochemical data were identified and extracted from the Clinical Data Analysis and Reporting System (CDARS), a Hong Kong-wide electronic healthcare database that compiles data across all hospitals under the Hong Kong Hospital Authority to form a holistic record of medical data for individual patients. CDARS has been used for epidemiological studies by both our team and other teams in Hong Kong. [14,15]

Prior comorbidities between January 1st, 1999 to December 31st, 2008 were extracted based on the respective *International Classification of Disease, Nineth Edition* (ICD-9) codes in the CDARS documentation (**Supplementary Table 1**). The sequence of occurrence between AF, CHD and HF was identified based on their difference in the number of days before January 1st, 2009. Data on the following classes of antidiabetic agents were extracted: biguanide, sulphonylurea, insulin, thiazolidinedione, meglitinide, dipeptidyl peptidase-4 inhibitor and glucagon-like peptide receptor-1 agonist. The extracted classes of cardiovascular medications include angiotensin-converting enzyme inhibitor (ACEI)/ angiotensin receptor blocker (ARB), beta-blocker, calcium channel blocker (CCB) and lipid lowering agents.

2.2. Study outcome and statistical analysis

The study outcome was all-cause mortality, which was extracted from the Hong Kong Death Registry. For descriptive statistics, the continuous variables were presented as mean (standard deviation) and the categorical variables were stated as total number (percentage). The incidence rate of all-cause mortality was calculated by dividing the total number of deceased patients by the sum of years in follow up. Univariable Cox regression was used to evaluate the predictive value of demographic, clinical and biochemical variables. The results would be reported in the form of hazard ratio (HR) (95% confidence interval [CI]). The predictive value of individual antidiabetic and cardiovascular medication use, adjusted for the sequences and combinations of AF, CHD and HF development, were assessed using multivariable Cox regression. Forest plots summarizing the HRs adjusted under different AF/ CHD/ HF combinations and sequences were stratified based on the medication class examined and the comorbidity involved. Statistical significance is

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defined as $p < 0.05$. The statistical analysis was conducted using R Studio (version: 1.1.456).

3. Results

3.1. Baseline characteristics

A total of 249291 patients (baseline age: 66.0±12.4, 47.4% male) were included. The baseline characteristics of the cohort are summarized in **Table 1**. At baseline, 7564, 10900 and 25589 patients had a history of AF, HF and CHD respectively. 170 patients had a history of AF, HF and CHD. Due to the limited availability of more novel antidiabetic agents at the time of follow-up, there were few patients prescribed thiazolidinedione (n= 3637), meglitinides (n= 22), dipeptidyl peptidase-4 inhibitor (n=310) and glucagon-like peptide receptor-1 agonist (n=17), these antidiabetic agents were not included in the comorbidities-adjusted Cox regression model.

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Table 1. Baseline characteristics of the present cohort.

Parameter	Total Number (%)/ Mean (Standard Deviation)
Demographic	
Age	66.04 (12.44)
Male	118262 (47.44)
All-cause mortality	85870 (34.45)
Medications	
Biguanide	185069 (74.24)
Sulphonylurea	172779 (69.31)
Insulin	29401 (11.79)
Thiazolidinedione	3637 (1.46)
Meglitinide	22 (0.01)
Dipeptidyl peptidase-4 inhibitor	310 (0.12)
Glucagon-like receptor peptide-1 agonist	17 (0.01)
Angiotensin-converting enzyme inhibitor/ angiotensin receptor blocker	120604 (48.38)
Beta-blocker	90908 (36.47)
Calcium channel blocker	107879 (43.27)
Lipid-lowering agents	60152 (24.13)
Comorbidities	
Coronary heart disease (CHD)	25589 (10.26)
Atrial fibrillation (AF)	7564 (3.03)
Heart failure (HF)	10900 (4.37)
CHD-HF	3586 (1.44)
CHD-AF	1677 (0.67)
HF-CHD	1919 (0.77)
HF-AF	967 (0.39)
AF-CHD	771 (0.31)
AF-HF	1809 (0.73)
CHD-HF-AF	170 (0.07)
CHD-AF-HF	480 (0.19)
HF-CHD-AF	192 (0.08)
AF-CHD-HF	126 (0.05)
HF-AF-CHD	134 (0.05)
AF-HF-CHD	164 (0.07)
Renal diabetic complications	3323 (1.33)
Peripheral vascular disease	341 (0.14)
Neurological diabetic complications	1144 (0.46)
Ophthalmological diabetic complications	3490 (1.40)
Ischemic stroke and transient ischemic attack	8733 (3.50)
Intracranial hemorrhage	3134 (1.26)
Osteoporosis	134 (0.05)
Dementia	2725 (1.09)
Hypertension	62571 (25.10)
Chronic obstructive pulmonary disease	793 (0.32)
Cancer	11442 (4.59)

3.2. Univariable Cox regression model

Over follow-up of 3524±1218 days, 85870 patients died, which corresponded to an all-cause mortality rate of 35.7 per 1000 person-years. The findings of the univariable Cox

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regression are summarized in **Table 2**. A history of AF (HR: 3.42, 95% CI: [3.32 - 3.51], $p < 0.001$), HF (HR: 4.61, 95% CI: [4.51 - 4.71], $p < 0.001$) and CHD (HR: 2.17, 95% CI: [2.13 - 2.21], $p < 0.001$) are significant predictors for all-cause mortality. Similarly, the use of antidiabetic and cardiovascular medications are significant univariable Cox predictors as well ($p < 0.001$). Whilst all sequences of AF, HF and CHD were demonstrated to be significant predictors, patients with HF-AF had the highest mortality risk (HR: 5.25, 95% CI: [4.91 - 5.62], $p < 0.001$), which is much higher than its AF-HF counterpart (HR: 4.58, 95% CI: [4.35 - 4.82], $p < 0.001$). Similar mortality risks were reported for patients who have a history of AF, HF and CHD. The sequence of CHD-HF-AF reported the highest mortality risk (HR: 6.42, 95% CI: [5.48 - 7.51], $p < 0.001$).

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Table 2. Univariable Cox regression to identify significant risk factors for all-cause mortality.

Parameter	Hazard Ratio (95% Confidence Interval)	P-value
Demographic		
Age	1.09 (1.09 - 1.09)	< 0.001
Male	1.13 (1.12 - 1.15)	< 0.001
Medications		
Biguanide	0.58 (0.57 - 0.58)	< 0.001
Sulphonylurea	1.28 (1.26 - 1.30)	< 0.001
Insulin	1.94 (1.91 - 1.97)	< 0.001
Thiazolidinedione	0.79 (0.74 - 0.83)	< 0.001
Meglitinide	1.48 (0.80 - 2.75)	< 0.001
Dipeptidyl peptidase-4 inhibitor	0.48 (0.37 - 0.62)	< 0.001
Glucagon-like receptor peptide-1 agonist	0.30 (0.07 - 1.19)	< 0.001
Angiotensin converting enzyme inhibitor/ angiotensin receptor blocker	1.43 (1.41 - 1.45)	< 0.001
Beta blocker	1.32 (1.31 - 1.34)	< 0.001
Calcium channel blocker	1.82 (1.80 - 1.85)	< 0.001
Lipid-lowering agents	1.30 (1.28 - 1.32)	< 0.001
Comorbidities		
Coronary heart disease (CHD)	2.17 (2.13 - 2.21)	< 0.001
Atrial fibrillation (AF)	3.42 (3.32 - 3.51)	< 0.001
Heart failure (HF)	4.61 (4.51 - 4.71)	< 0.001
CHD-HF	4.66 (4.49 - 4.83)	< 0.001
CHD-AF	4.00 (3.79 - 4.22)	< 0.001
HF-CHD	4.61 (4.39 - 4.84)	< 0.001
HF-AF	5.25 (4.91 - 5.62)	< 0.001
AF-CHD	4.05 (3.74 - 4.39)	< 0.001
AF-HF	4.58 (4.35 - 4.82)	< 0.001
CHD-HF-AF	6.42 (5.48 - 7.51)	< 0.001
CHD-AF-HF	5.34 (4.86 - 5.87)	< 0.001
HF-CHD-AF	5.87 (5.06 - 6.82)	< 0.001
AF-CHD-HF	5.24 (4.35 - 6.32)	< 0.001
HF-AF-CHD	5.55 (4.65 - 6.63)	< 0.001
AF-HF-CHD	5.51 (4.69 - 6.48)	< 0.001
Renal diabetic complications	3.54 (3.40 - 3.68)	< 0.001
Peripheral vascular disease	4.25 (3.79 - 4.78)	< 0.001
Neurological diabetic complications	2.95 (2.76 - 3.16)	< 0.001
Ophthalmological diabetic complications	2.62 (2.51 - 2.73)	< 0.001
Ischemic stroke and transient ischemic attack	2.74 (2.67 - 2.82)	< 0.001
Intracranial hemorrhage	2.60 (2.49 - 2.71)	< 0.001
Osteoporosis	2.77 (2.25 - 3.40)	< 0.001
Dementia	5.66 (5.43 - 5.89)	< 0.001
Hypertension	2.47 (2.43 - 2.50)	< 0.001
Chronic obstructive pulmonary disease	4.43 (4.10 - 4.79)	< 0.001
Cancer	2.39 (2.33 - 2.45)	< 0.001

3.3. Comorbidities-adjusted mortality risk of cardiovascular and antidiabetic medications

The comorbidities-adjusted mortality risk of cardiovascular and antidiabetic medications is summarized in **Table 3**. Forest plots of comorbidity sequences amongst patients on cardiovascular medications, stratified by the development of AF, HF and CHD, were illustrated in **Figures 1-4**. Several findings can be noted for patients on antidiabetic

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medications. Although the development of CHD in isolation amongst biguanide users (HR: 0.49, 95% CI: [0.47 - 0.51], $p < 0.001$) had a higher mortality risk than their counterparts who only developed AF (HR: 0.48, 95% CI: [0.45 - 0.50], $p < 0.001$) or HF (HR: 0.37, 95% CI: [0.35 - 0.38], $p < 0.001$), in the presence of multiple comorbidities an earlier presentation of CHD marks for a better prognosis. Sulphonylurea users with CHD developing later in the disease course had a better prognosis. On the contrary, insulin users with CHD developing earlier in the disease course had a lower mortality risk. Amongst insulin users with two of the three comorbidities, CHD patients with preceding AF (HR: 3.06, 95% CI: [2.60 - 3.61], $p < 0.001$) or HF (HR: 3.84, 95% CI: [3.47 - 4.24], $p < 0.001$) had a worse prognosis.

Table 3. Comorbidities-adjusted mortality risk of antidiabetic and cardiovascular medications.

Comorbidities	Biguanide	Sulphonylurea	Insulin	ACEI/ARB	Beta Blockers	CCB	Lipid-lowering Agent
CHD	0.49 (0.47 - 0.51)	1.01 (0.98 - 1.05)	2.06 (1.98 - 2.13)	1.63 (1.57 - 1.69)	1.93 (1.86 - 2.00)	1.06 (1.02 - 1.09)	2.50 (2.42 - 2.59)
AF	0.48 (0.45 - 0.50)	1.03 (0.97 - 1.09)	1.45 (1.36 - 1.54)	1.57 (1.49 - 1.66)	1.36 (1.29 - 1.43)	1.00 (0.95 - 1.05)	1.31 (1.24 - 1.38)
HF	0.37 (0.35 - 0.38)	0.89 (0.85 - 0.93)	2.31 (2.21 - 2.41)	2.19 (2.09 - 2.30)	1.49 (1.43 - 1.56)	0.95 (0.91 - 0.99)	1.93 (1.85 - 2.01)
CHD-HF	0.30 (0.27 - 0.32)	0.95 (0.88 - 1.03)	2.47 (2.29 - 2.67)	2.70 (2.48 - 2.94)	2.21 (2.05 - 2.38)	0.78 (0.73 - 0.84)	3.89 (3.61 - 4.19)
CHD-AF	0.38 (0.34 - 0.42)	1.02 (0.90 - 1.15)	1.46 (1.28 - 1.66)	2.30 (2.04 - 2.60)	1.81 (1.62 - 2.01)	0.86 (0.78 - 0.96)	2.62 (2.35 - 2.91)
HF-CHD	0.39 (0.35 - 0.43)	0.75 (0.67 - 0.83)	3.84 (3.47 - 4.24)	2.65 (2.36 - 2.99)	2.24 (2.03 - 2.48)	0.84 (0.76 - 0.92)	3.81 (3.45 - 4.22)
HF-AF	0.44 (0.38 - 0.50)	0.90 (0.78 - 1.05)	2.45 (2.12 - 2.83)	2.47 (2.11 - 2.89)	1.44 (1.26 - 1.65)	0.88 (0.77 - 1.01)	1.46 (1.27 - 1.68)
AF-CHD	0.48 (0.41 - 0.56)	0.79 (0.67 - 0.94)	3.06 (2.60 - 3.61)	2.19 (1.83 - 2.63)	1.94 (1.65 - 2.28)	1.05 (0.90 - 1.24)	2.67 (2.28 - 3.13)
AF-HF	0.35 (0.32 - 0.39)	1.02 (0.91 - 1.14)	1.51 (1.34 - 1.70)	2.48 (2.20 - 2.79)	1.33 (1.21 - 1.47)	0.85 (0.77 - 0.94)	1.57 (1.41 - 1.74)
CHD-HF-AF	0.30 (0.22 - 0.41)	1.09 (0.76 - 1.56)	2.39 (1.70 - 3.36)	3.12 (2.11 - 4.63)	1.91 (1.39 - 2.63)	0.76 (0.55 - 1.04)	2.65 (1.94 - 3.64)
CHD-AF-HF	0.28 (0.23 - 0.34)	1.16 (0.93 - 1.44)	1.24 (0.98 - 1.58)	2.89 (2.29 - 3.64)	1.61 (1.33 - 1.94)	0.74 (0.61 - 0.89)	2.61 (2.16 - 3.16)
HF-CHD-AF	0.37 (0.27 - 0.50)	0.72 (0.52 - 0.98)	3.03 (2.23 - 4.13)	2.19 (1.56 - 3.08)	1.86 (1.37 - 2.52)	0.86 (0.64 - 1.16)	2.24 (1.66 - 3.02)
AF-CHD-HF	0.36 (0.25 - 0.52)	0.94 (0.64 - 1.40)	4.63 (3.24 - 6.63)	2.40 (1.58 - 3.64)	2.32 (1.60 - 3.36)	0.85 (0.60 - 1.22)	3.22 (2.24 - 4.61)
HF-AF-CHD	0.46 (0.31 - 0.66)	0.74 (0.50 - 1.10)	3.13 (2.13 - 4.60)	4.29 (2.56 - 7.19)	1.28 (0.88 - 1.86)	1.01 (0.69 - 1.46)	2.49 (1.71 - 3.62)
AF-HF-CHD	0.42 (0.30 - 0.58)	0.80 (0.56 - 1.13)	3.18 (2.27 - 4.44)	2.68 (1.82 - 3.95)	1.78 (1.28 - 2.46)	1.10 (0.79 - 1.53)	3.71 (2.66 - 5.16)

ACEI/ ARB: Angiotensin-converting enzyme inhibitor/ angiotensin receptor blocker; CCB: calcium channel blocker

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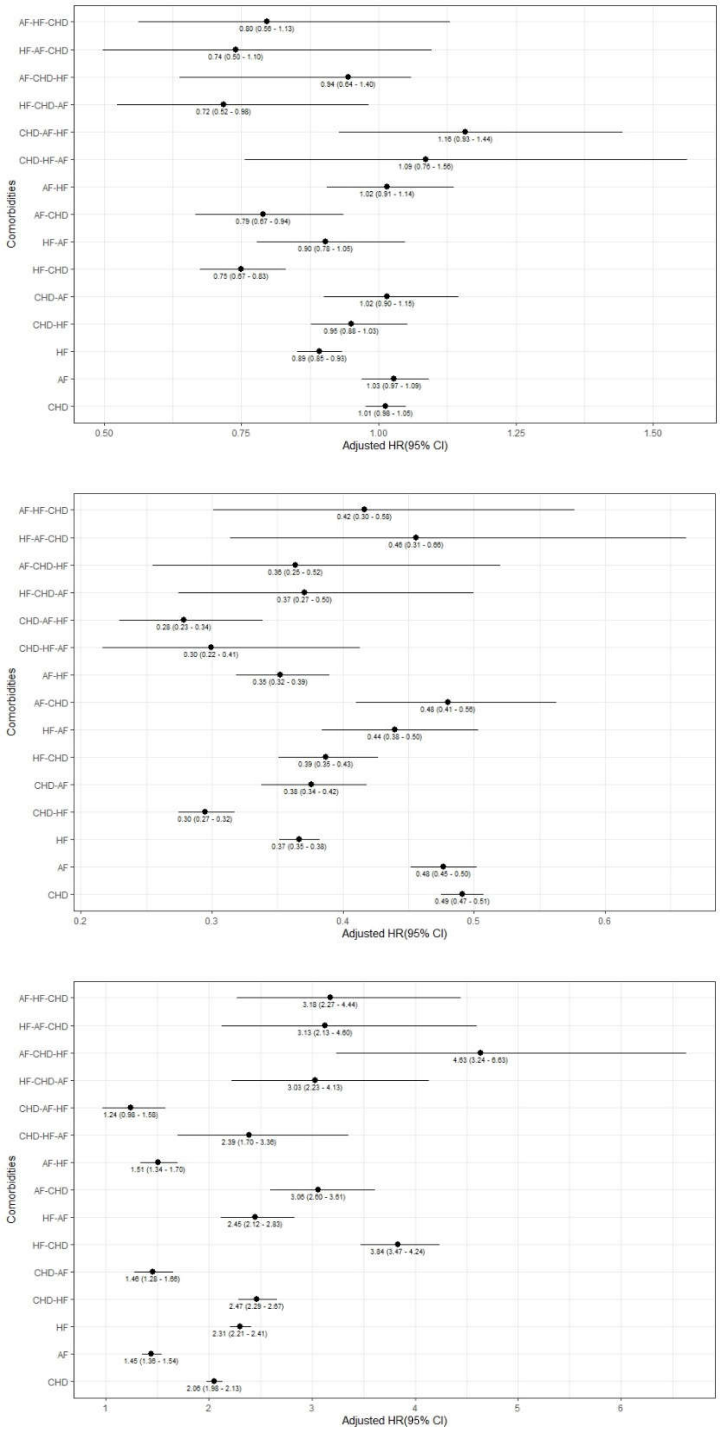

Figure 1. Forest plot of all comorbidities-adjusted mortality risk of antidiabetic medications (first panel: biguanide vs. no biguanide; second panel: sulphonylurea vs no sulphonylurea; third panel: insulin vs. no insulin).

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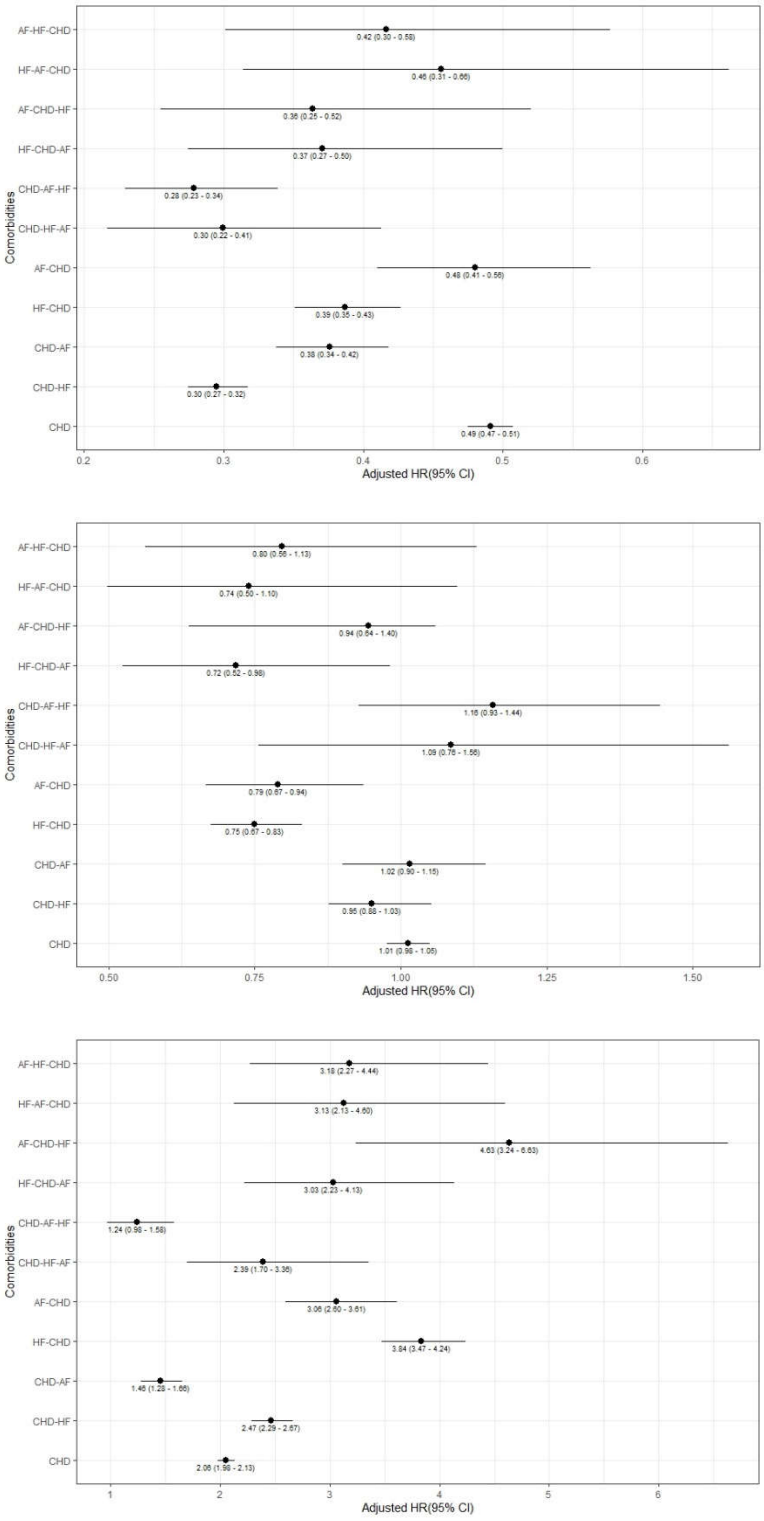

Figure 2. Forest plot of coronary heart disease-involving comorbidities-adjusted mortality risk of antidiabetic medications (first panel: biguanide vs. no biguanide; second panel: sulphonylurea vs no sulphonylurea; third panel: insulin vs. no insulin).

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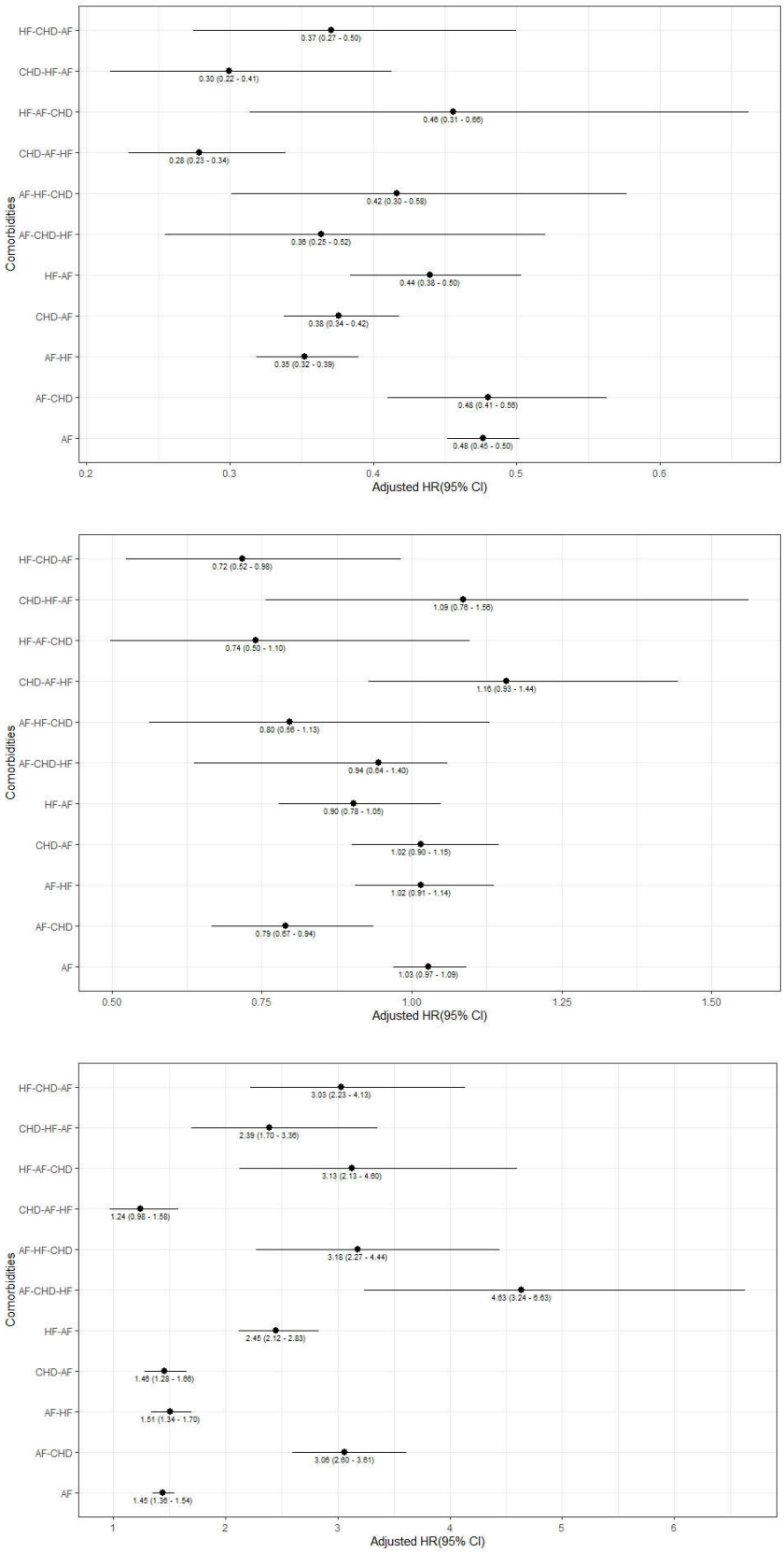

Figure 3. Forest plot of atrial fibrillation-involving comorbidities-adjusted mortality risk of antidiabetic medications (first panel: biguanide vs. no biguanide; second panel: sulphonylurea vs no sulphonylurea; third panel: insulin vs. no insulin).

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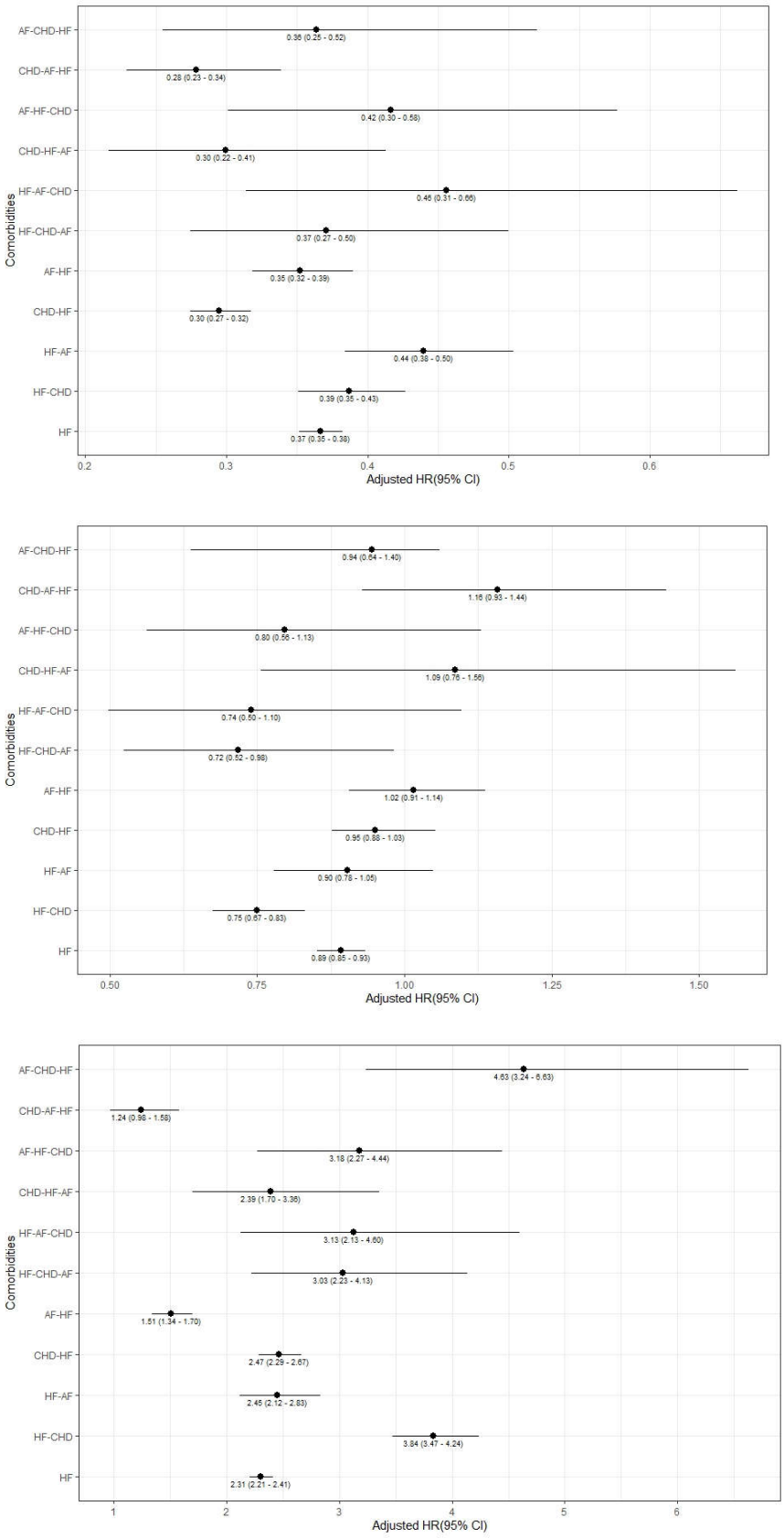
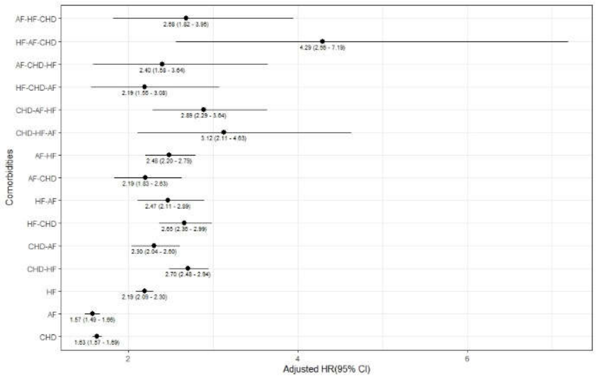
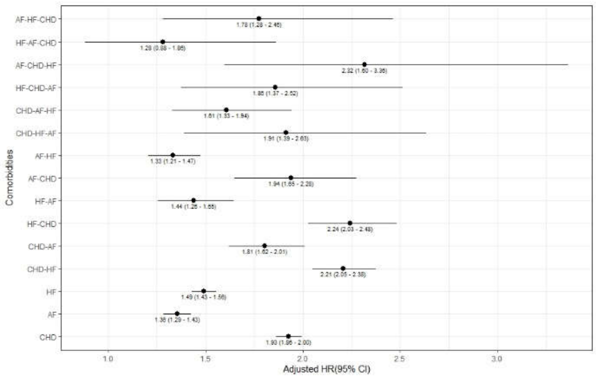
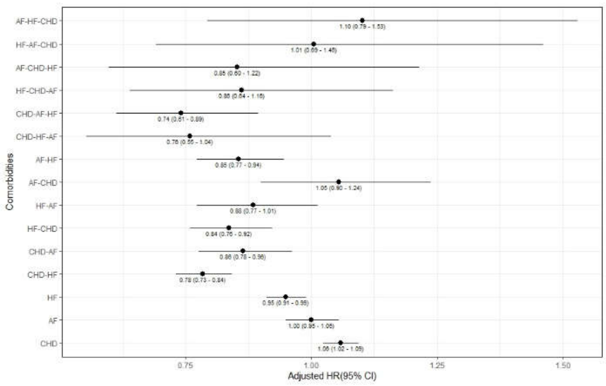


Figure 4. Forest plot of heart failure-involving comorbidities-adjusted mortality risk of antidiabetic medications (first panel: biguanide vs. no biguanide; second panel: sulphonylurea vs no sulphonylurea; third panel: insulin vs. no insulin).

Forest plots of comorbidity sequences amongst users of cardiovascular medications, stratified by the development of AF, HF and CHD, were illustrated in **Figures 5-8**. Interestingly, the number and sequence of comorbidity development had little effect on the mortality risk amongst ACEI/ ARB and CCB users. The presence of CHD in the sequence of comorbidities increases the mortality risk for patients on lipid lowering agents and beta-blockers. In users of lipid lowering agents who developed all three comorbidities, those with preceding AF had a greater risk of mortality (AF-CHD-HF: HR: 3.22, 95% CI: [2.24 - 4.61], p < 0.001; AF-HF-CHD: HR: 3.71, 95% CI: [2.66 - 5.16], p < 0.001).







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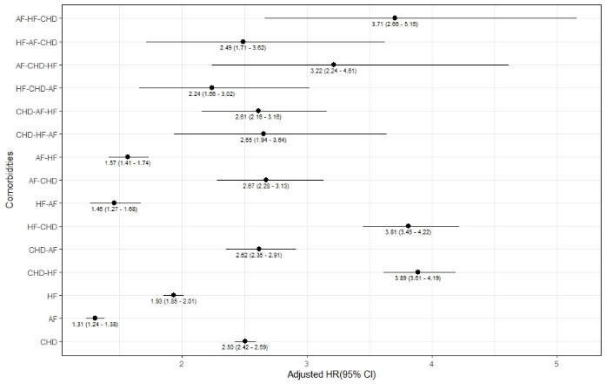
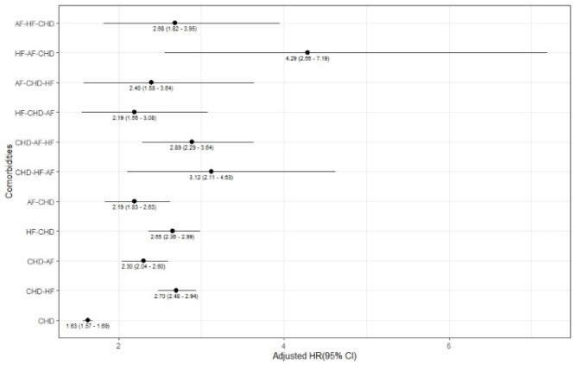
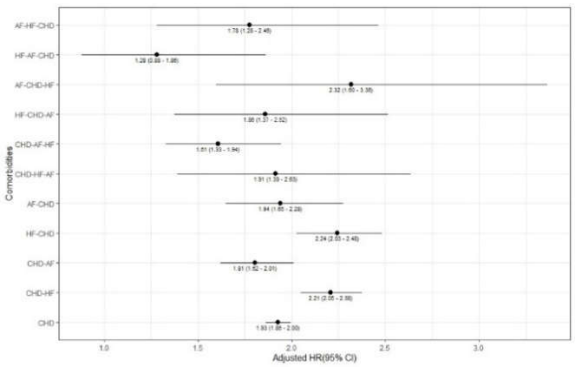
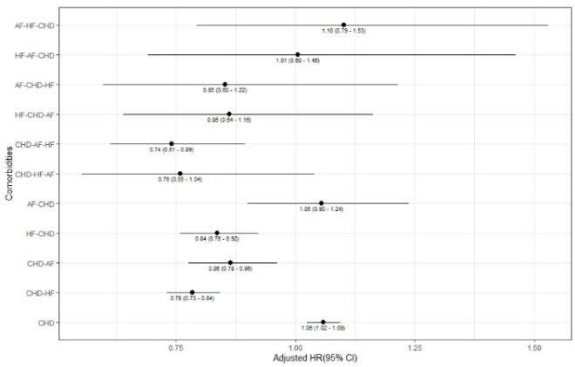


Figure 5. Forest plot of all comorbidities-adjusted mortality risk of cardiovascular medications (first panel: angiotensin-converting enzyme inhibitor/angiotensin receptor blocker vs. no angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; second panel: beta blocker vs. no beta blocker; third panel: calcium channel blocker vs. no calcium channel blocker; fourth panel: lipid lowering agent vs. no lipid lower agent).







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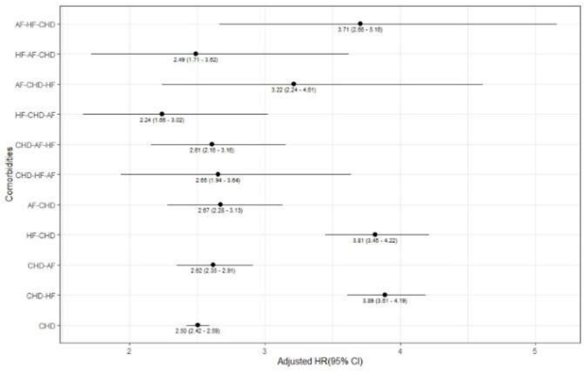
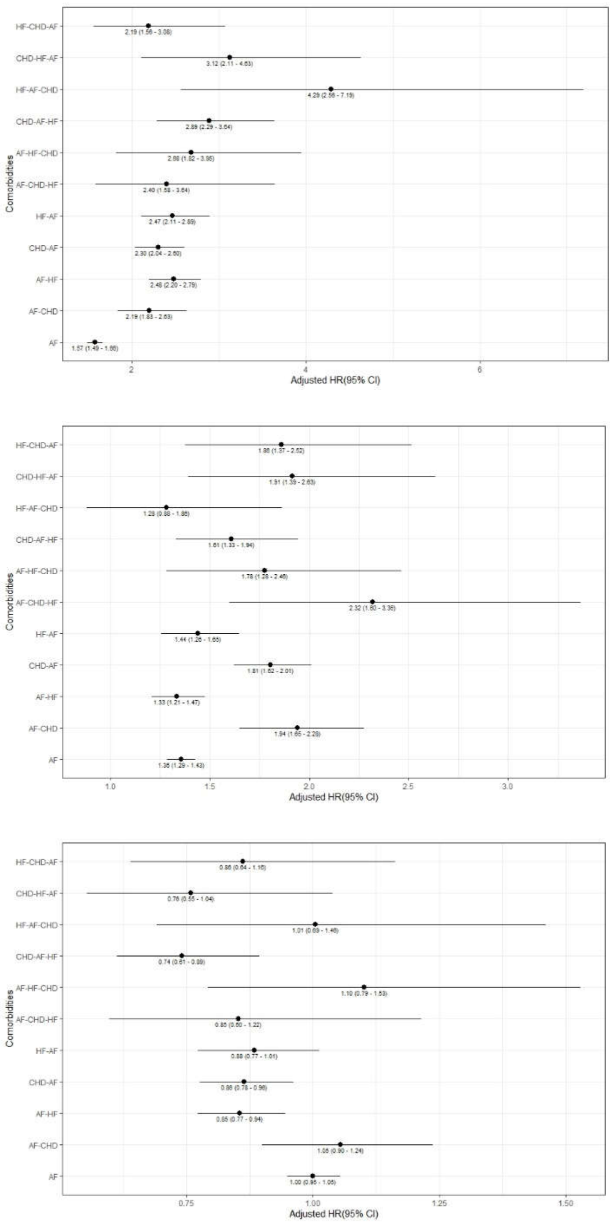


Figure 6. Forest plot of coronary heart disease-involving comorbidities-adjusted mortality risk of cardiovascular medications (first panel: angiotensin-converting enzyme inhibitor/angiotensin receptor blocker vs. no angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; second panel: beta blocker vs. no beta blocker; third panel: calcium channel blocker vs. no calcium channel blocker; fourth panel: lipid lowering agent vs. no lipid lower agent).



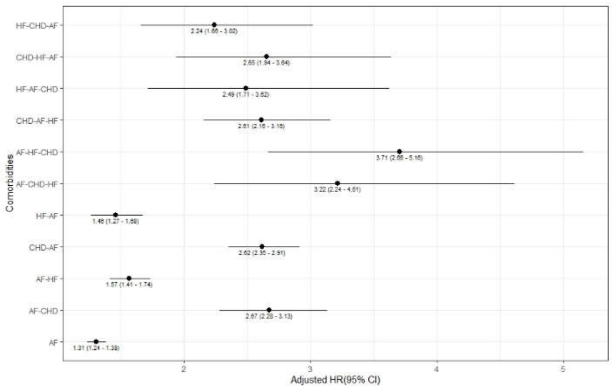
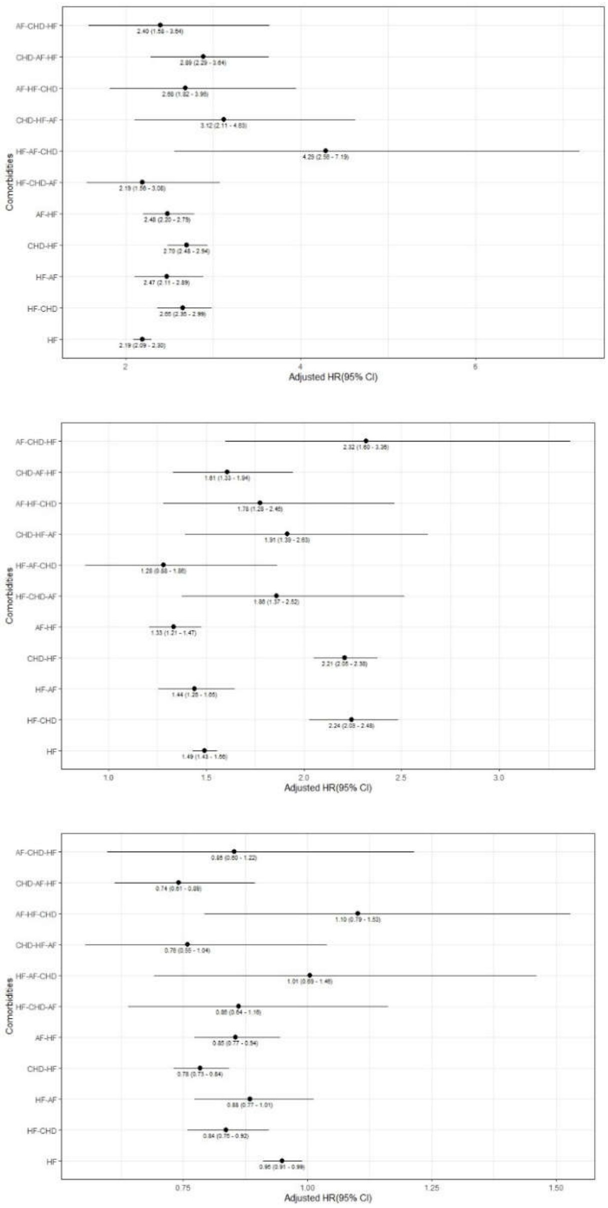


Figure 7. Forest plot of atrial fibrillation-involving comorbidities-adjusted mortality risk of cardiovascular medications (first panel: angiotensin-converting enzyme inhibitor/angiotensin receptor blocker vs. no angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; second panel: beta blocker vs. no beta blocker; third panel: calcium channel blocker vs. no calcium channel blocker; fourth panel: lipid lowering agent vs. no lipid lower agent).



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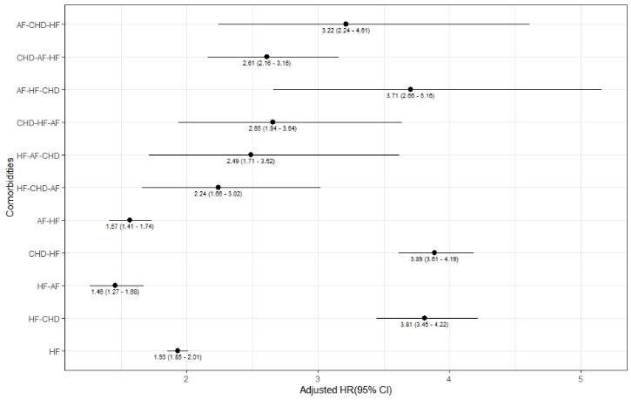

Figure 8. Forest plot of heart failure-involving comorbidities-adjusted mortality risk of cardiovascular medications (first panel: angiotensin-converting enzyme inhibitor/angiotensin receptor blocker vs. no angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; second panel: beta blocker vs. no beta blocker; third panel: calcium channel blocker vs. no calcium channel blocker; fourth panel: lipid lowering agent vs. no lipid lower agent).

4. Discussion

To the best of our knowledge, this is the first study that examines the effect of cardiovascular comorbidities sequence on the risk of mortality. There are several notable findings from the present study: 1) the number and sequence of cardiovascular comorbidities development affect the mortality risk to a varying degree between different medications; 2) the increase in the number of cardiovascular comorbidities does not always translate into an increase in mortality risk, depending on the type of cardiovascular comorbidities involved and the sequence of development; 3) sequences of cardiovascular comorbidities have a different effect on mortality risk amongst patients on different medications.

Although it seems intuitive that the increase in the number of comorbidities directly translates into an increase in mortality risk, existing studies have reported otherwise. A study on the association between guideline-recommended drugs and mortality amongst elderlies with multiple comorbidities reported similar mortality risk amongst patients with AF, CHD, HF, hyperlipidemia and hypertension in isolation and combination. [16] In a recent study on the effects of multi-comorbidity on the mortality of patients with chronic obstructive pulmonary disease, whilst multi-comorbidity is an independent marker for mortality, only some comorbidities affect mortality. [17] Long term comorbidities that are associated with frailty are more likely to increase the risk of mortality. [15,18] For example, the mortality risk of patients with dementia is increased after adjusting for the comorbidity load. [19] Thus, the earlier intervention of these comorbidities may help to delay the progression of frailty and therefore reduce the risk of mortality.

The variable effects of comorbidities sequence on the mortality risk of patients prescribed different medications are contributed by a multitude of factors. For example, patients' response to medications varies based on the presence of different comorbidities. Unlike HF patients who are in sinus rhythm, the efficacy of beta-blockers in HF patients with AF remained controversial in terms of the benefits on survival. [20] It has been reported that amongst women on beta-blockers with CHD, there is an increased risk of new-onset HF, which is associated with increased 30-day mortality. [21] Moreover, the difference in the indication of medication prescription between diseases may have contributed to the difference in mortality risk. A recent meta-analysis on more than 100000 AF patients reported that statin therapy can result in a 10% absolute reduction in the all-cause mortality risk. [22] However, unlike CHD and HF, AF patients were not routinely started on lipid-lowering therapy under the current guidelines. The delay in treatment initiation may have resulted in a greater risk of mortality in AF patients who subsequently developed other cardiovascular complications.

The sequence of comorbidity development is both a marker of disease severity and the window of opportunity for intervention to improve patient outcomes. In the present

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study, the development of CHD earlier in the disease course marks a lower mortality risk amongst insulin users, but a higher risk amongst sulphonylurea users. Since insulin is prescribed to patients with more advanced diabetes mellitus, an earlier diagnosis of CHD allows for early intervention and potential early diagnosis of other cardiovascular complications, thus improving their overall survival. Similar findings were demonstrated in the higher mortality risk amongst first-presentation ST-elevation myocardial infarction patients free of modifiable cardiovascular risk factors than their counterparts with pre-existing risk factors, where the risks were attenuated after adjusting for the application of guideline-directed therapy. [23] Current studies that demonstrate a higher cardiovascular adverse event and mortality risk amongst insulin users randomized patients with diabetes mellitus into insulin provision and insulin sensitization groups, which did not reflect the more advanced disease state amongst typical insulin users in real life. [24,25] However, given sulphonylurea is a second-line agent, the earlier development of CHD marks for early macrovascular involvement, therefore reflecting a poorer disease prognosis. In addition, the cardioprotective effect of sulphonylurea is relatively weak compared to other antidiabetic agents, hence further increasing the mortality risk. [26,27] Indeed, many observational studies have reported higher risks of adverse cardiovascular events in sulphonylurea users. [28-30]

Given the shared risk factors for and pathophysiological mechanisms underlying CHD, AF and HF, it is common for the three conditions to co-exist and create a vicious cycle of deterioration amongst patients. [31] Studies have reported that there is a greater increase in mortality risk amongst AF patients with HF of ischemic origin. Since AF has been reported to increase oxidative stress and endothelial dysfunction [32,33], it exacerbates the myocardial ischemia under the already reduced coronary perfusion in CHD, resulting in more severe HF and earlier mortality. [34] By contrast, atrial ischemia promotes the generation of arrhythmogenic substrates in the atrium, resulting in the development of AF. [35] AF itself is a known risk factor for acute myocardial infarction due to increased myocardial oxygen consumption and adverse cardiac remodeling. [36-38] Ultimately, the extent to which the sequence of the cardiovascular complication development affects patient prognosis requires further elucidation.

Limitations

Several limitations should be noted in the present study. Firstly, the observational nature of the present study makes it susceptible to documentation errors. Secondly, potential treatment non-compliance affects the accuracy in the use of medication prescription as a surrogate marker for medication exposure. Thirdly, due to limitations of the electronic healthcare database, there is a lack of electrocardiographic and echocardiographic data that can be used for patient prognostication. Finally, data on lifestyle cardiovascular risk factors such as obesity, smoking and alcoholism were unavailable.

5. Conclusion

To conclude, the sequence of comorbidity development affects the risk of all-cause mortality to varying degrees in users of different cardiovascular and antidiabetic agents. Further study is needed to elucidate the underlying mechanisms and modifications to current management guidelines to improve patient prognosis.

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