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Use of prescription medications with cardiovascular adverse effects among older adults in the United States

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Abstract

Background: Many commonly used prescription medications have cardiovascular adverse effects, yet the cumulative risk of cardiovascular events associated with the concurrent use of these medications is unknown. We examined the association between the concurrent use of prescription medications with known risk of a major adverse cardiovascular event (MACE) ("MACE medications") and the risk of such events among older adults.

Methods: A multi-center, population-based study from the Atherosclerosis Risk in Communities (ARIC) study of a cohort of 3669 community-dwelling adults aged 61–86 years with no history of cardiovascular disease who reported the use of at least one medication between September 2006 and August 2013 were followed up until August 2015. Exposure defined as time-varying and time-fixed use of 1, 2 or ≥3 MACE medications with non-MACE medications serving as negative control. Primary outcome was incident MACE defined as coronary artery revascularization, myocardial infarction, fatal coronary heart disease, stroke, cardiac arrest, or death.

Results: In fully adjusted models, there was an increased risk of MACE associated with use of 1, 2, or ≥3 MACE medications (1 MACE: hazards ratio [HR], 1.21; 95% confidence interval [CI], 0.94–1.57); 2 MACE: HR 1.89, CI 1.42–2.53; ≥3 MACE: HR 2.22, CI 1.61–3.07) compared to use of non-MACE medications. These associations persisted in propensity score-matched analyses and among new users of MACE medications, never users of cardiovascular medications and subgroups of participants with increased risk of MACE. There was no association between the number of non-MACE medications used and MACE.

Conclusions and Relevance: In this community-based cohort of older adults with no prior cardiovascular disease, the use of MACE medications was independently and consistently associated with an increased risk of such events in a dose–response fashion.

KEYWORDS
adverse effects, major adverse cardiovascular events, polypharmacy

Key Points

- The association between the concurrent use of medications with a known risk of a major adverse cardiovascular event and the risk of such events among older adults is not known.
- In this community-based, primary prevention cohort study of 3669 older adults, we found that the concurrent use of multiple MACE medications is associated with a statistically significant two-fold increase in the risk of MACE.
- There was no association between the number of non-MACE medications used and MACE.
- Clinicians may need to consider the additive risk of MACE for patients that use multiple medications across different therapeutic classes and consider alternate treatment options to reduce the risk of outcomes such as myocardial infarction, stroke, and death.

Plain Language Summary

Although many commonly used prescription medications are associated with cardiovascular adverse effects, the impact of the concurrent use of these medications is not known. We investigated the extent to which the use of multiple medications associated with adverse cardiovascular effects increase the risk of experiencing major adverse cardiovascular events (e.g., heart attack, stroke, sudden cardiac death, fatal heart disease) among older adults without cardiovascular disease. We found that the concurrent use of multiple medications with known cardiovascular risks or adverse effects is associated with a two-fold increase in the risk of major adverse cardiovascular events. We found no association between the use of multiple medications that do not have these cardiovascular adverse effects and the risk of major adverse cardiovascular events. Therefore, clinicians may need to consider the additive risk of prescription medications with cardiovascular side effects for patients that use multiple medications across different therapeutic classes and consider alternate treatment options to reduce the risk of outcomes such as myocardial infarction, stroke, and death.

1 | INTRODUCTION

Prescription and over-the-counter medications are commonly used in the United States, particularly among older adults.[1] While most medications are associated with any number of potential adverse effects,[2] many commonly used medication classes, including non-steroidal anti-inflammatory drugs (NSAIDs),[3–6] proton pump inhibitors (PPIs),[7–9] and bronchodilators,[10–12] have established cardiovascular risks.[13,14] Such risks may be especially relevant to the elderly, many of whom may have preexisting cardiovascular disease (CVD).[15,16]

Numerous scientific investigations have characterized the potential cardiovascular risks of specific products,[17–19] and many others have quantified the association between specific therapeutic classes and CVD, including myocardial infarction (MI), stroke, and sudden cardiac death.[3,4,7–12,20–22] For example, non-aspirin NSAIDs have been consistently associated with CVD, with a 15%–44% increased risk of MI and stroke among treated patients.[3,6] By contrast, evidence linking PPIs and bronchodilators to MI and sudden cardiac death is more variable.[23–26] Despite the insights from these and other studies, far less is known regarding the concurrent use of multiple medications with a potential for major adverse cardiovascular events (MACE), including their impact on cardiovascular health and survival.

We used an ongoing, population-based, prospective cohort of middle aged and older adults to comprehensively evaluate the association between all medications with a potential for MACE, including MI, stroke, fatal coronary heart disease (CHD), acute coronary syndrome, or death. We hypothesized that the concurrent use of medications that carry potential risk of MACE is independently associated with increased risk of incident MACE.

2 | METHODS

2.1 | Data and cohort

We used publicly available data from the Atherosclerosis Risk in Communities (ARIC) study. The ARIC study is a prospective community-based cohort study that initially enrolled 15 792 adults aged 45–64 years from four U.S. communities (Forsyth County, North Carolina; Jackson County, Mississippi; suburban Minneapolis, Minnesota; and Washington County, Maryland) between January 1987 and March 1990.[27] Follow up visits were conducted over 3-year intervals until Visit #4 (February 1996–January 1999), with a 15-year gap until Visit #5 (June 2011–August 2013; Figure S1). Between Visits #4 and #5, participants responded to annual follow-up questionnaires by telephone where they were asked about health status updates and, beginning in September 2006, medication use. Death and cardiovascular events were continuously identified using the National Death Index, local newspaper obituaries, state death records and a review of community hospital discharge lists.

2.2 | Study design and follow-up

Our study spanned 9 years beginning in September 2006, when the first annual follow-up survey recorded medication use, through August 2015, 2-years after the last Visit #5 questionnaire was administered (Figure S1). We included participants that reported the use of at least one medication during annual follow-up surveys and Visit #5 ($n = 9235$; Figure S2). We excluded 603 individuals who did not participate in Visit #4 and 2431 participants with a history of MI, CHD, stroke, coronary artery revascularization, cardiac arrest, heart failure, atrial fibrillation, venous thromboembolism/pulmonary embolism, and peripheral artery disease prior to cohort entry. We identified prevalent CVD through a combination of self-report, *International Classification of Diseases, Ninth Revision* (ICD-9) codes associated with hospitalizations, and variables within the ARIC dataset that reflect medical record review or adjudicated events (Box S1). To mitigate potential confounding by indication, we further excluded participants treated with medications indicated for the treatment of CVD (Box S2) at cohort entry ($n = 2316$). Following these exclusions, 3669 participants were included in our final cohort (Figure S2). Participants entered the cohort at their first reported medication use during annual follow-up or Visit #5. They exited the cohort at the earliest occurrence of (1) MACE event, (2) death, or the (3) end of follow-up. The end of follow-up was defined as 2-years after the last ARIC questionnaire within the study period.

2.2.1 | Time-varying and time-fixed analyses

Due to ARIC's proactive surveillance and event identification, we found a wide variation (i.e., ranging from less than 1 year to 9 years) in the elapsed person-time between an ARIC questionnaire and event. To reduce misclassification of exposure and person-time in our time-varying analyses, we restricted exposure windows following ARIC questionnaires to 2 years. Time-varying analyses only included person-time with current medication use identified by the preceding ARIC questionnaire; person-time where individuals used no medications was excluded. Our time-fixed analysis approximated an intention-to-treat analysis. In this analysis, participants' exposure at cohort entry was carried through until they exited the cohort.

2.3 | Prescription medication use

Based on our prior approach,[28] we used Micromedex (Truven Health Analytics) to identify medications with the potential for MACE ("MACE medications") which included the following adverse effects: MI; stroke; CHD; cardiac arrest; or death (Box S3). To identify potential severity of any adverse effect, we further classified medications with a MACE adverse effect listed as a black-box warning (BBW). The validity, comprehensiveness, and utility of Micromedex in identifying adverse effects based on FDA labels and post-marketing studies has been previously established.[29,30] Specifically, a study found that Micromedex had a sensitivity of 93% and positive predictive value (PPV) of 99% in reporting BBWs.[29] A separate study that evaluated software for drug–drug interactions, found Micromedex ranked the highest in accuracy relative to similar software, with a sensitivity of 95%, specificity of 100%, PPV of 100%, and negative predictive value (NPV) of 95%.[30]

Recent medication use (≤2 weeks) was collected during annual follow-up visits beginning in September 2006 and during Visit #5. Prescriptions and over-the-counter medicines were identified by direct visual inspection of medication containers during Visit #5 and by participants reading labels over the phone during annual follow-up visits.

We aggregated the number of MACE medications used into four exposure levels (0, 1, 2, and ≥3). To assess the specificity of the association between MACE medications with incident MACE events, we also identified medications *without* MACE ("non-MACE medications") as a negative control and aggregated these into four levels (0, 1, 2, and ≥3). We considered non-MACE medications a negative control because MACE and non-MACE medications within single therapeutic classes share common indications (Box S3 and Table S1), such as antidepressants, non-narcotic analgesics, antihypertensives, or antidiabetics. Additionally, under a null hypothesis, the number of MACE medications would carry the same level of risk as the comparable number of non-MACE medications. Under this reasoning, we also modeled the use of non-MACE medications among never-users of MACE medications as a negative control. Analyses with MACE ever- and never-use were determined by time-varying ever-use of MACE medications; MACE never-use includes person-time of continuous non-MACE medication use and initial MACE medication use determines MACE ever-use.

2.4 | Outcomes

Incident MACE represented a composite of cardiovascular events and death. Since over half of identified MACE medications carry more than one cardiovascular adverse effect, incident cardiovascular events encompassed fatal or non-fatal MI, fatal or non-fatal stroke, fatal CHD, coronary artery revascularization, sudden death, or cardiac arrest, and were identified using ARIC variables that indicated adjudicated events or events identified from record abstraction (Box S1). We included all-cause mortality in our MACE definition, because it captures out-of-hospital fatal cardiovascular events (e.g., fatal MI, fatal stroke, sudden cardiac death, and cardiac arrest). Additionally, we treated death from a non-cardiovascular cause as a competing event for cardiovascular events in our statistical models.

2.5 | Covariates

We selected demographic characteristics, socioeconomic status, comorbidities, health behaviors, and measures of cardiovascular risk that might confound the association between use of MACE medications and MACE. All these variables are presented in Table 1. In the

TABLE 1 Baseline characteristics of study population overall and by use of MACE medications ($n = 3669$)

Characteristic	Number of participants (%)			
		Use of MACE medications at cohort entry		
	Overall	None	Any	*p*-value[a]
Overall no. of participants	3669 (100)	1829 (49.9)	1840 (50.1)	
Follow-up, years				
Mean (SD)	5.2 (1.8)	5.1 (1.7)	5.2 (1.8)	0.41
Median (range)	5.4 (0.01–8.3)	5.3 (0.01–8.2)	5.4 (0.07–8.3)	
No. of MACE medications				
0	1829 (49.8)	1829 (100)	–	<0.001
1	1165 (31.8)	–	1165 (63.3)	
2	446 (12.2)	–	446 (24.2)	
≥3	229 (6.2)	–	229 (12.5)	
No. of non-MACE medications				
0	273 (7.4)	–	273 (14.8)	<0.001
1	1172 (31.9)	774 (42.3)	398 (21.6)	
2	894 (24.4)	502 (27.5)	392 (21.3)	
≥3	1330 (36.3)	553 (30.2)	777 (42.2)	
Gender				
Men	1411 (38.5)	823 (45.0)	588 (32.0)	<0.001
Women	2258 (61.5)	1006 (55.0)	1252 (68.0)	
Race				
White	2986 (81.4)	1485 (81.2)	1501 (81.6)	0.77
Black	683 (18.6)	344 (18.8)	339 (18.4)	
Age, years[b]				
Mean (SD)	71.4 (5.4)	71.5 (5.4)	71.4 (5.5)	0.58
Median (range)	71 (61–86)	71 (62–85)	71 (61–86)	
Marital status[c]				
Not married	2846 (78.1)	1445 (79.6)	1401 (76.7)	0.04
Married	797 (21.9)	371 (20.4)	426 (23.3)	
Educational attainment				
<High school	504 (13.8)	247 (13.5)	257 (14.0)	0.44
High school	1203 (32.8)	582 (31.9)	621 (33.8)	
College/Vocational	1457 (39.7)	735 (40.2)	722 (39.3)	
Graduate/Professional	502 (13.7)	263 (14.4)	239 (13.0)	
Family income				
<$25 000	830 (23.5)	394 (22.5)	436 (24.5)	0.14
≥$25 000	2701 (76.5)	1361 (77.5)	1340 (75.5)	
Insurance type[d]				
Private	2272 (65.2)	1154 (66.4)	1118 (64.1)	0.18
Public	964 (27.7)	457 (26.3)	507 (29.1)	
Other	247 (7.1)	128 (7.4)	119 (6.8)	
Charlson comorbidity index				
Mean (SD)	0.1 (0.4)	0.1 (0.4)	0.2 (0.5)	0.002
Median (range)	0 (0–4)	0 (0–4)	0 (0–3)	
BMI, kg/m^2				
Normal (<25)	1075 (29.4)	542 (29.7)	533 (29.0)	0.59
Overweight (25–29.9)	1493 (40.8)	752 (41.2)	741 (40.3)	
Obese (≥30)	1094 (29.9)	531 (29.1)	563 (30.7)	

TABLE 1 (Continued)

Characteristic	Number of participants (%)			
		Use of MACE medications at cohort entry		
	Overall	None	Any	*p*-value[a]
COPD	78 (2.1)	23 (1.3)	55 (3.0)	<0.001
Diabetic[e]	381 (10.5)	170 (9.4)	211 (11.6)	0.03
Antidiabetic use	469 (12.8)	192 (10.5)	277 (15.1)	<0.001
Hypertensive[f]	1017 (27.8)	444 (24.4)	573 (31.2)	<0.001
Antihypertensives use	1634 (44.5)	792 (43.3)	842 (45.8)	0.13
Statin use	1304 (35.5)	690 (37.7)	614 (33.4)	0.006
CHD risk score, categorized[g]				
Low (<5)	2191 (60.6)	1042 (57.8)	1149 (63.5)	0.002
Medium (5–<10)	795 (22.0)	423 (23.4)	372 (20.6)	
High (≥10)	627 (17.4)	339 (18.8)	288 (15.9)	
Smoking status				
Current	468 (12.8)	226 (12.4)	242 (13.3)	0.30
Former	1504 (41.3)	773 (42.5)	731 (40.0)	
Never	1671 (45.9)	818 (45.0)	853 (46.7)	
Alcohol drinker				
Current	2026 (55.6)	1037 (57.0)	989 (54.1)	0.06
Former	916 (25.1)	458 (25.2)	458 (25.1)	
Never	703 (19.3)	323 (17.8)	380 (20.8)	

Abbreviations: BBW, black-box warning; BMI, body mass index (calculated as weight [kilograms] divided by height [meters] squared); CHD, coronary heart disease; CI, confidence interval; COPD, chronic obstructive pulmonary disease; MACE, major adverse cardiovascular effects; NSAIDs, nonsteroidal anti-inflammatory drugs; SD, standard deviation.

[a]*p*-value tests for difference in prevalence between none and any use of MACE medications.

[b]Age at cohort entry.

[c]"Not married" includes widowed, divorced, separated, and never married.

[d]"Public" health insurance includes Medicaid and Medicare.

[e]Diabetes was identified through self-report, recent antidiabetic medication use, a fasting (≥8 h) blood glucose level of ≥126 mg/dl, or a nonfasting glucose of ≥200 mg/dl.

[f]Hypertension (ARIC "Definition 5") at Visit #4 was identified through self-report, recent antihypertensive medication use, systolic blood pressure ≥140 mm Hg, or diastolic blood pressure ≥90 mm Hg.

[g]CHD 10-year risk score at Visit #4, calculated using gender, race (black/white), age, systolic blood pressure, current cigarette use, total cholesterol, high-density lipoprotein, self-reported medication use for hypertension, and self-reported diabetes status.

time-varying model, the Charlson Comorbidity Index (CCI) was updated with comorbidities identified during follow up. In the time-fixed model, the CCI included comorbidities identified by the cohort entry date.[31,32] Lastly, we also included chronic obstructive pulmonary disease (COPD), identified using the following ICD-9 codes: 416.8; 146.9; 491.x–496.x; and 500–505. The 10-year CHD risk score is a risk assessment metric within the ARIC dataset and was modeled as a continuous variable. Among those that do not have heart disease, it predicts the probability of having a heart attack within the next 10 years.[33,34]

2.6 | Statistical analyses

We used descriptive statistics to evaluate the characteristics of participants at baseline. We conducted separate time-varying and time-fixed analysis of the association between MACE medications and MACE. In time-varying models, individuals contribute person-time to different exposure levels (0, 1, 2, or ≥3 MACE medications) as the number of MACE medications used changed over time. Crude incidence rates were generated per 1000 person-years (PY). We used Cox proportional hazard models to estimate hazard ratios (HRs) and 95% confidence intervals (CI) for the association between the use of MACE medications and incident MACE.

In addition to our MACE never-user analyses that used time-fixed or time-varying exposure to non-MACE medications as a negative control, we also controlled for potential prevalent user bias by approximating a new-user study design after excluding users of MACE medications at cohort entry. To further address potential confounding by indication, we conducted a series of subgroup analyses, including by 10-year CHD risk score. In order to evaluate whether specific MACE medications or therapeutic classes carried a greater risk of MACE

relative to other MACE medications, we evaluated the association between common MACE medications by therapeutic class and two-way combinations of MACE medications with MACE compared to the use of one MACE medication.

We conducted cause-specific hazards in order to evaluate the effect of competing events in the association of MACE and non-MACE medications with cardiovascular events, and separately, death (Table S2).[35] All analyses were performed using Stata Statistical Software: Release 14 (StataCorp LC).

2.7 | Sensitivity analyses

We performed several sensitivity analyses to confirm the robustness of our findings. First, we conducted a propensity score matched analysis of MACE and non-MACE users at cohort entry in order to control for unobserved confounders that are correlated with covariates included in the propensity score. Additionally, in order to create exposure groups that were comparable by weighting based on confounding factors, we conducted three separate analyses with three different inverse probability of treatment weights (IPTW). The time-varying IPTW modeled the likelihood of attrition following cohort entry (Table S11).

To address additional confounding by indication and identify potential effect modification, we evaluated the association of MACE medications and MACE among never-users of CVD medications. We further analyzed MACE medications and non-MACE medications across the time-varying ever-use of specific medications and therapeutic classes that carry a higher risk of MACE (opioid analgesics; antidepressants; NSAIDs or cyclooxygenase-2 [COX-2] inhibitors; bronchodilators and PPIs). We sought to address residual confounding associated with the cumulative exposure to medications by controlling for the total number of medications as a covariate instead of the number of non-MACE medications. Additionally, we evaluated the effect of using continuous instead of categorical values for the number of medications.

We also evaluated the sensitivity of the association between MACE medications and CV events using more restrictive CV outcome definition that included only "definite" and "probable" outcomes from adjudicated MI, stroke, and fatal CHD events.

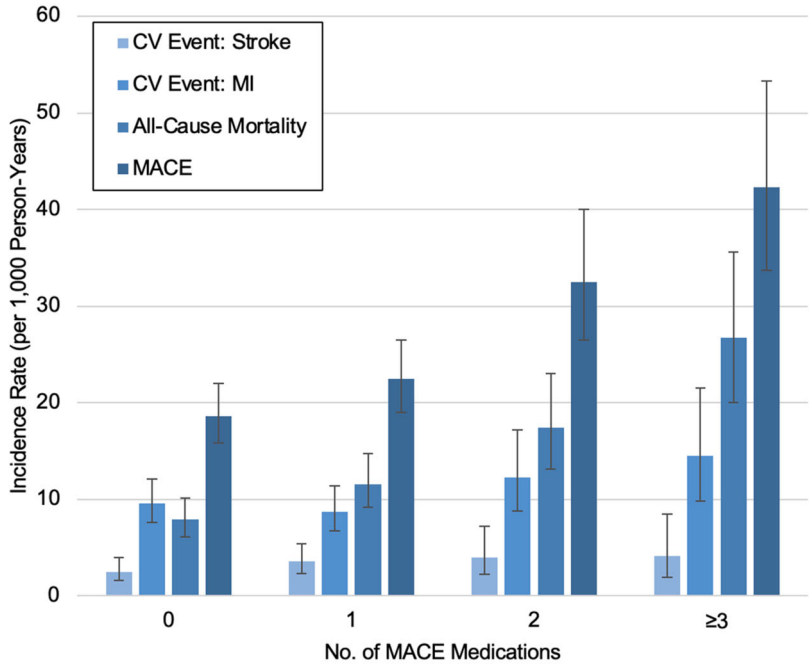
3 | RESULTS

3.1 | Cohort characteristics

Overall, the mean (SD) age at cohort entry was 71.4 (5.4) years, 61.5% were women, and 81.4% were white (Table 1). Of 3669 participants, 1829 (49.9%) did not use MACE medications and 1840 (50.1%) used at least one MACE medication at cohort entry. Of the 231 MACE medications identified in the ARIC datasets, 51.5% carried more than one cardiovascular adverse effect; most commonly MI or stroke. Except for MACE medications, MACE ever- and never-users used similar medications overall, including aspirin; antihypertensives; statins; and antidiabetics (Table S1).

3.2 | Incidence of MACE by number of MACE medications

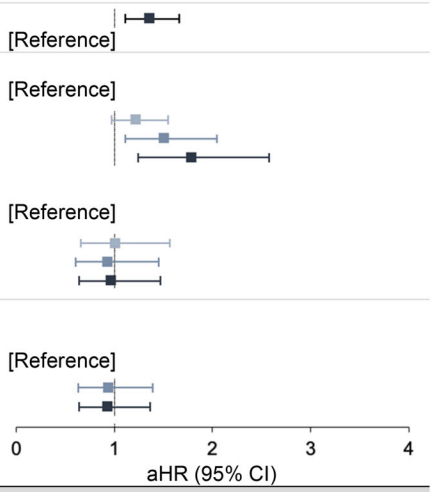
Risk of stroke, MI, and death increased with the number of MACE medications (Figure 1). The unadjusted incidence of MACE increased

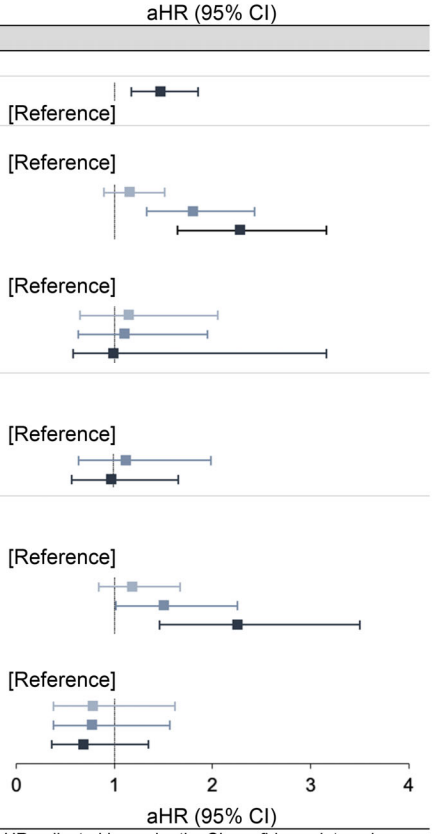


Cardiac arrest/sudden death not shown due to small number of events. Bars indicate 95% confidence limits.

FIGURE 1 Incidence rate of outcomes by the number of MACE medications concurrently used ($n = 3669$). MACE, major adverse cardiovascular effects

	Person Years	MACE[a] Events	IR[b]	aHR (95% CI)
Time-Fixed[c]				
Overall	18,934	458	24.2	
MACE users	9,539	263	27.6	
Non-MACE users	9,395	195	20.8	[Reference]
No. of MACE medications				
0	9,395	195	20.8	[Reference]
1	6,027	154	25.6	
2	2,331	67	28.7	
≥3	1,181	42	35.6	
No. of Non-MACE medications				
0	1,366	29	21.2	[Reference]
1	5,897	131	22.2	
2	4,659	108	23.2	
≥3	7,012	190	27.1	
Non-MACE Users	9,395	195	20.8	
No. of Non-MACE medications				
1	3,835	76	19.8	[Reference]
2	2,611	53	20.3	
≥3	2,948	66	22.4	
Time-Varying[d]				
Overall	18,190	442	24.3	
MACE use	10,675	302	28.3	
Non-MACE use	7,515	140	18.6	[Reference]
No. of MACE medications				
0	7,515	140	18.6	[Reference]
1	6,185	139	22.5	
2	2,766	90	32.5	
≥3	1,724	73	42.3	
No. of Non-MACE medications				
0	869	16	18.4	[Reference]
1	3,695	79	21.4	
2	3,987	89	22.3	
≥3	9,639	258	26.8	
MACE Never Users[e]	6,084	109	17.9	
No. of Non-MACE medications				
1	1,813	31	17.1	[Reference]
2	1,664	31	18.6	
≥3	2,607	47	18.0	
MACE New Users	15,004	237	15.8	
No. of MACE medications				
0	6,291	80	12.7	[Reference]
1	5,018	79	15.7	
2	2,317	42	18.1	
≥3	1,379	36	26.1	
No. of Non-MACE medications				
0	538	10	18.6	[Reference]
1	2,576	34	13.2	
2	3,210	50	15.6	
≥3	8,680	143	16.5	





Abbreviations: IR, incidence rate; MACE, major adverse cardiovascular events; aHR, adjusted hazard ratio; CI, confidence interval.
Note: Expanded Figure 2 in eTable 2 in Supplement. [a] MACE include: fatal coronary heart disease, fatal and non-fatal myocardial infarction, fatal and non-fatal stroke (ischemic and hemorrhagic), cardiac arrest, and sudden cardiac death. [b] Crude incidence rate per 1,000 person-years. [c] Variables included in adjusted model (from Visit #4, unless otherwise stated): 10-year CHD risk score, Charlson Comorbidity Index (at cohort entry), insurance type, body-mass index, smoking status, alcohol use, age (at cohort entry), center, education attainment, marital status, and family income within previous 12-months. [d] Number of MACE medications is time-varying exposure and number of non-MACE medications is modeled as a time-varying covariate. Other variables included in adjusted model (from Visit #4, unless otherwise stated): 10-year CHD risk score, Charlson Comorbidity Index (time-varying), insurance type, body-mass index, smoking status, alcohol use, age (at cohort entry), center, education attainment, marital status, and family income within previous 12-months. [e] Time-varying never use: participants were considered MACE "never users" until their initial use of a MACE medication where they became MACE "ever users".

FIGURE 2 Association between the use of MACE medications and the incident risk of MACE ($n = 3669$). MACE, major adverse cardiovascular effects

substantially with the number of MACE medications (1 MACE medication: 22.5 per 1000 PY; 2 MACE medications: 32.5 per 1000 PY; and, ≥3 MACE medications: 42.3 per 1000 PY). Among participants that never used a MACE medication, the unadjusted incidence of MACE remained similar across the number of medications (1 non-MACE medication: 28.4 per 1000 PY; 2 non-MACE medications: 31.2 per

1000 PY; and, ≥3 non-MACE medications: 30.1 per 1000 PY) (Figure 2).

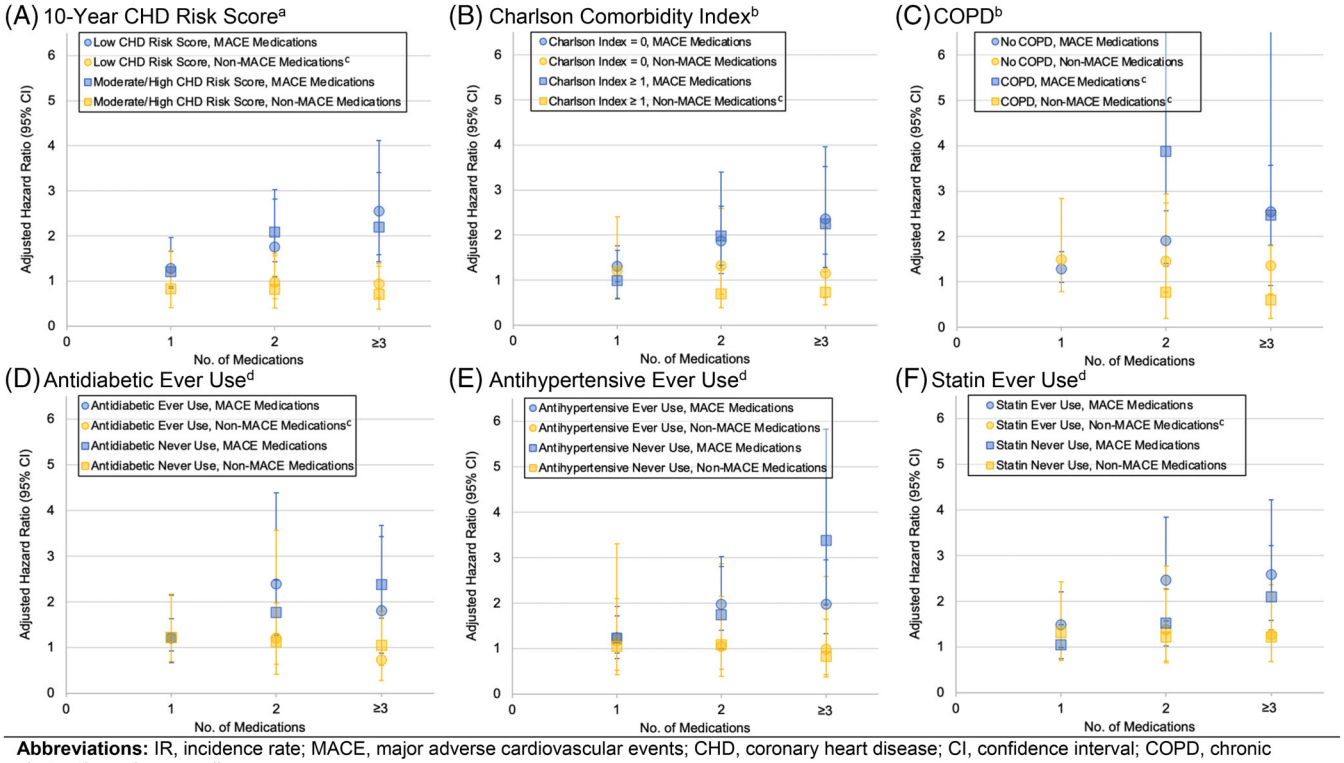
3.3 | Association between number of MACE medications and MACE

After adjustment, users of MACE medications at cohort entry had significantly greater risk of incident MACE (adjusted hazard ratio [aHR], 1.22 [95% CI, 0.97–1.55] for 1 MACE medication, 1.51 [95% CI, 1.11–2.04] for 2 MACE medications, and 1.79 [95% CI, 1.24–2.58] for ≥3 MACE medications) than non-users (Figure 2; Table S2). The number of non-MACE medications was not associated with an increased risk of MACE.

In the time-varying models, the risk of MACE increased with the number of concurrently used MACE medications (aHR, 1.89 [95% CI, 1.42–2.53] for 2 MACE medications and 2.22 [95% CI, 1.61–3.07] for ≥3 MACE medications), compared to non-use (Figure 2; Table S2). Our findings persisted among new users of MACE medications. In negative control analyses, there was no association between non-MACE medications and MACE among participants that never used a MACE medication. The risk of CV events increased with the number of MACE medications and decreased with the number of non-MACE medications (Table S2). These findings persisted across sensitivity analyses, including: use of more restrictive criteria for CV events (Table S3); use of continuous and categorical variables for the number of MACE and non-MACE medications (Table S4); and adjustment for the total number of medications instead of the number of non-MACE medications (Table S5).

3.3.1 | Variation in risk of MACE across different subgroups

The exclusive association between MACE medications and MACE persisted across demographic, cardiovascular and clinical subgroups (Figure 3; Tables S6 and S7). For example, there was a similar magnitude of association across participants with varying 10-year CHD-risk scores. Analyses that stratified by ever-use of antidiabetics, antihypertensives, statins, and bronchodilators displayed a higher risk of MACE events associated with the use of multiple MACE medications (Figure 3; Table S6).



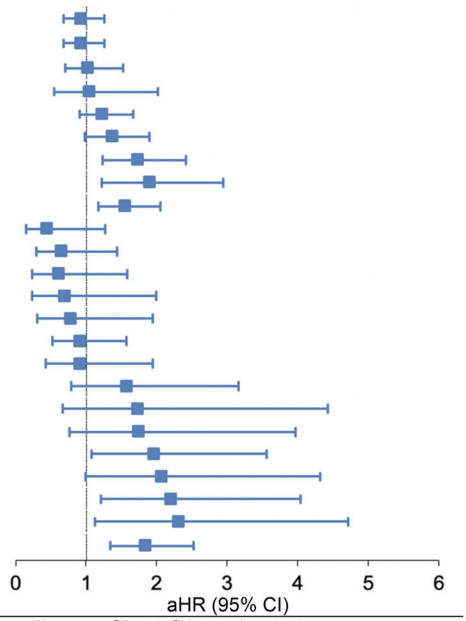
Abbreviations: IR, incidence rate; MACE, major adverse cardiovascular events; CHD, coronary heart disease; CI, confidence interval; COPD, chronic obstructive pulmonary disease

[a] Ten-year CHD Risk identified at Visit #4, scores <5 are considered "low," scores 5 to <10 are "moderate," and scores ≥10 are "high". CHD 10-year risk score at visit 4, calculated using gender, race (black/white), age, systolic blood pressure, current cigarette use, total cholesterol, high-density lipoprotein, self-reported medication use for hypertension, and self-reported diabetes status. [b] Charlson Comorbidity Index and COPD are time-varying. [c] Categories for zero and one medication were collapsed due to sample size; the referent group was "0 or 1" medications. [d] Ever use of therapeutic classes is time-varying: participants were considered "never users" until their initial use of a medication in the therapeutic class where they became "ever users".

Variables included in adjusted model: number of non-MACE medications (time-varying), 10-year CHD risk score (excluded from CHD Risk Score subgroup analysis), Charlson Comorbidity Index (time-varying; excluded from Charlson subgroup analysis), insurance type, body-mass index, smoking status, alcohol use, age (at cohort entry), center, education attainment, marital status, and family income within previous 12-months.

FIGURE 3 Association between the use of MACE medications and MACE events stratified by cardiovascular subgroups ($n = 3669$). MACE, major adverse cardiovascular effects

MACE Medications	Person Years	Crude IR[a]	Adjusted[b] Hazard Ratio (95% CI)
Any MACE Use	10,675	28.3	
One	6,185	22.5	[Reference]
Antihypertensives	2,523	28.5	0.93 (0.68 – 1.26)
Levothyroxine	2,737	21.9	0.93 (0.68 – 1.26)
Bronchodilators	1,019	44.2	1.03 (0.70 – 1.52)
Antidiabetic	377	26.5	1.05 (0.55 – 2.02)
NSAIDs	2,219	25.2	1.23 (0.91 – 1.67)
Antidepressants	1,550	29.7	1.37 (0.98 – 1.90)
Opioid Analgesics	1,089	50.5	1.73 (1.24 – 2.41)
Corticosteroids	423	56.7	1.90 (1.22 – 2.95)
Two	2,766	32.5	1.56 (1.18 – 2.06)
Bronchodilators-Antihypertensives	141	35.6	0.44 (0.15 – 1.27)
Levothyroxine-Antihypertensives	351	22.8	0.65 (0.30 – 1.44)
Antihypertensives-Opioid Analgesics	203	24.6	0.61 (0.24 – 1.58)
Bronchodilators-NSAIDs	140	28.6	0.70 (0.24 – 1.99)
Levothyroxine-Opioid Analgesics	204	24.5	0.78 (0.31 – 1.95)
Bronchodilators-Bronchodilators	300	53.3	0.91 (0.53 – 1.57)
NSAIDs-Antihypertensives	310	25.8	0.91 (0.43 – 1.95)
Antidepressants-NSAIDs	252	35.8	1.58 (0.79 – 3.16)
Antihypertensives-Antihypertensives	98	82.0	1.73 (0.67 – 4.43)
Corticosteroids-Opioid Analgesics	91	77.0	1.75 (0.77 – 3.97)
Opioid Analgesic-NSAIDs	258	54.2	1.96 (1.08 – 3.56)
Antidepressants-Bronchodilators	114	87.8	2.07 (0.99 – 4.32)
Antidepressants-Opioid Analgesics	194	66.9	2.21 (1.21 – 4.04)
Bronchodilators-Opioid Analgesics	108	111.2	2.31 (1.13 – 4.72)
Three or more	1,724	42.3	1.84 (1.34 – 2.52)



Abbreviations: IR, incidence rate; MACE, major adverse cardiovascular events; CHD, coronary heart disease; CI, confidence interval
MACE include: fatal coronary heart disease, fatal and non-fatal myocardial infarction, fatal and non-fatal stroke (ischemic and hemorrhagic), cardiac arrest, and sudden cardiac death. [a] Crude incidence rate per 1,000 person-years. [b] Each medication or pair is modeled as a time varying exposure (in separate models). The additional number of medications with MACE adverse effects (if applicable) and number of medications without MACE adverse effect are modeled as time-varying covariates. Other variables included in adjusted model (from Visit #4, unless otherwise stated): 10-year CHD risk score, Charlson Comorbidity Index (time-varying), insurance type, body-mass index, smoking status, alcohol use, age (at cohort entry), center, education attainment, marital status, and family income within previous 12-months.

FIGURE 4 Most commonly used MACE medications and two-way combinations associated with MACE among those exposed to MACE medications. MACE, major adverse cardiovascular effects

3.3.2 | Variation in risk of MACE across different therapeutic classes

There was variation in the risk of MACE across therapeutic classes and specific two-way combinations of MACE medications (Figure 4). Use of opioid analgesics or corticosteroids was associated with nearly a two-times higher risk of MACE relative to the use of other MACE medications (aHR, 1.73 [95% CI, 1.24–2.41] and 1.90 [95% CI, 1.22–2.95], respectively). Relative to the use of other MACE medications, the risk of MACE was two-times higher for common two-way combinations, including opioid analgesics-NSAIDs (aHR, 1.96 [95% CI, 1.08–3.56]); antidepressants-opioid analgesics (aHR, 2.21 [95% CI, 1.21–4.04]); and, bronchodilators-opioid analgesics (aHR, 2.31 [95% CI, 1.13–4.72]). We also observed variation within therapeutic class (Table S8).

3.4 | Sensitivity analyses

In propensity score-matched analyses, there was an increase in the risk of MACE associated with the use of MACE medications at cohort entry (aHR, 1.38 [95% CI, 1.12–1.71]) compared to non-MACE users (Table S9). Participants that never used CVD medications had an increased rate of MACE with the use of 2 and ≥3 MACE medications (aHR, 1.83 [95% CI, 1.30–2.59] and 2.43 [95% CI, 1.64–3.60], respectively) and did not have an increased risk among non-MACE medications (Table S10). Our findings were consistent across analyses that restricted to: (1) participants that entered the cohort at the first annual follow-up regardless of medication use (Table S12); and (2) that were weighted based on likelihood of attrition (Table S13).

4 | DISCUSSION

Although the cardiovascular risks of many prescription medications have been well characterized, such investigations have typically focused on a specific products or therapeutic classes,[3,4,7–12,20–22] rather than quantifying the cumulative cardiovascular risk posed by the concurrent use of medications. In this large and diverse prospective population-based cohort, concurrent use of medications with a potential for MACE was independently and consistently associated with increased risk of MACE in a dose dependent manner. Older adults using multiple MACE medications, had on average, double or triple the risk of incident MACE compared to those that do not use such medications. Conversely, individuals using multiple non-MACE medications did not have an increased risk of MACE associated with their medications. These findings build on prior studies focusing on individual products and suggest the additive risk associated with the

use of two or more medications with major adverse cardiovascular effects.

Our findings are important because of their plausibility, magnitude, and relevance to many adults who regularly use multiple prescription medications.[36,37] While many studies have investigated potential cardiovascular risks of individual medicines no known study has investigated the risk associated with the use of multiple medications and MACE. However, these findings are plausible, as the cardiovascular risk of these products has been described based on randomized controlled trials, included on the FDA approved product label, and/or demonstrated in post-marketing studies.

Our results persisted across subgroups with varying levels of underlying cardiovascular risk and among those taking antihypertensives, antidiabetic agents, and statins. For example, the risk of MACE associated with the concurrent use of MACE medications is similar between statin users and non-users. This finding may suggest that the use of medications that carry a risk for MACE may undermine the effectiveness of medications intended to reduce cardiovascular risk. Cardiovascular prevention efforts among older adults, including hypertension, diabetes, and statin treatment guidelines should consider incorporating information on the cardiovascular safety profiles of medications. As suggested by our analyses that demonstrated a higher risk of MACE among MACE medications without a BBW, further research is needed to evaluate the mechanism through which the risk of MACE medications is reduced among users of medications with BBW when compared to those without such warnings that still carry a risk for MACE.

The risk of incident MACE varied across and within therapeutic classes and drug combinations. For example, the risk of MACE associated with the use of specific bronchodilators or NSAIDs was higher than the risk associated with use of any medication in those therapeutic classes as a whole. Specifically, the increased risk of MACE was only observed among ipratropium (bronchodilator) and meloxicam (NSAID) users. This highlights the need for clinicians to weigh the additive cardiovascular risk for patients that use multiple medications across different therapeutic classes and consider alternate treatment options to improve quality of care.

Among older adults taking MACE medications, we found that the concurrent use of opioid analgesics with other MACE medications is associated with the greatest MACE risk. For example, the concurrent use of opioid analgesics in combination with bronchodilators displayed a higher risk of MACE than the concurrently use of opioid analgesics and NSAIDs.

Our study was not designed to assess the risk–benefit balance of specific products or combinations, and many of the products that we included have demonstrable efficacy, and effectiveness, in the management and treatment of health conditions, including hypertension, depression and diabetes. Thus, our findings highlight, at a population-level, what is known with varying degrees of certainty at an individual product level—that many prescription drugs have cardiovascular risks—and that these risks translate into an increased occurrence of outcomes such as MI, stroke, and death among concurrent users of these products compared to non-users.

Our study also has several limitations. First, sample size limited our statistical analyses. However, this longitudinal, population-based cohort, with historical information on sociodemographic and health behaviors addressed many limitations associated with claims data. Second, as this is an observation study there is a risk of unmeasured confounding. We attempted to address this through a series of sensitivity analyses and by using a propensity-score matched cohort. Unmeasured confounding may still occur if the use of non-MACE medications does not adequately mirror the confounding structure of MACE medications. Third, as this is an observational and exploratory study we did not adjust for multiplicity. Fourth, our exposure measure was based on an annual medication use of both MACE and non-MACE medications and does not capture dose, duration of use, or adherence. Time-lags between study time points may have resulted in misclassified person-time. We attempted to mitigate this by restricting the exposure windows following a questionnaire to 2-years. Fifth, we do not incorporate information on several cardiovascular risk factors, including both clinical and subclinical (e.g., heart failure, QT prolongation, CRP, Troponin, and Coronary Artery Calcium [CAC] score). However, we did leverage the active cardiovascular screening and follow up conducted by ARIC investigators and excluded participants with an increased risk of CVD. Finally, we limit our analyses to MACE medications and therefore do not know whether and how medications with other cardiovascular risks, including arrhythmias and heart failure, may influence our findings.

Despite these limitations, our analyses were robust to numerous sensitivity analyses that varied assumptions regarding confounding by indication, selection bias, and misclassification of person-time. Although causal inference can be limited in observational studies, our analysis has several features that support its credibility, including findings that persist across the treatment propensity-score matched cohort, new-users of MACE medications, MACE never-use analyses (negative control), and multiple sensitivity analyses. Across specific subgroups associated with an increased risk of MACE, the specificity of MACE with MACE medications held. Additional strengths of this analysis include its use of physician-reviewed and adjudicated event variables, longitudinal study design, and inclusion of both time-fixed and time-varying exposure measurement which reinforced the temporality of the association.

5 | CONCLUSIONS

Findings from this cohort study indicate that the concurrent use of prescription medications associated with adverse cardiovascular effects is associated with an increased risk for MACE among older adults. Many commonly used therapeutic classes (e.g., NSAIDs, antidepressants, bronchodilators, and opioids) carried an elevated risk of MACE and this risk increases when these medications are used together.

CONFLICTS OF INTEREST

Dr. Qato serves as a consultant for Public Citizen's Health Research Group. Dr. Alexander is past Chair and a current member of FDA's

Peripheral and Central Nervous System Advisory Committee; is a co-founding Principal and equity holder in Monument Analytics, a health care consultancy whose clients include the life sciences industry as well as plaintiffs in opioid litigation; and is a past member of OptumRx's National P&T Committee. This arrangement has been reviewed and approved by Johns Hopkins University in accordance with its conflict of interest policies.

ETHICS STATEMENT

This study was exempt from institutional review board approval because the University of Southern California Office for the Protection of Research Subjects determined it did not constitute human subject research.

REFERENCES

1. Hales CM, Servais J, Martin CB, Kohen D. *Prescription Drug Use Among Adults Aged 40–79 in the United States and Canada Key Findings Data from the National Health and Nutrition Examination Survey and the Canadian Health Measures Survey*.
2. Hampton LM, Daubresse M, Chang HY, Alexander GC, Budnitz DS. Emergency department visits by adults for psychiatric medication adverse events. *JAMA Psychiat*. 2014;71(9):1006-1014. doi:10.1001/jamapsychiatry.2014.436
3. Ray WA, Stein CM, Hall K, Daugherty JR, Griffin MR. Non-steroidal anti-inflammatory drugs and risk of serious coronary heart disease: an observational cohort study. *Lancet*. 2002;359(9301):118-123. doi:10.1016/S0140-6736(02)07370-1
4. Graham DJ, Campen D, Hui R, et al. Risk of acute myocardial infarction and sudden cardiac death in patients treated with cyclo-oxygenase 2 selective and non-selective non-steroidal anti-inflammatory drugs: nested case-control study. *The Lancet*. 2005;365(9458):475-481. doi:10.1016/s0140-6736(05)17864-7
5. Trelle S, Reichenbach S, Wandel S, et al. Cardiovascular safety of non-steroidal anti-inflammatory drugs: network meta-analysis. *BMJ*. 2011;342(7789):154. doi:10.1136/bmj.c7086
6. Baigent C, Bhala N, Emberson J, et al. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. *The Lancet*. 2013;382(9894):769-779. doi:10.1016/S0140-6736(13)60900-9
7. Charlot M, Grove EL, Hansen PR, et al. Proton pump inhibitor use and risk of adverse cardiovascular events in aspirin treated patients with first time myocardial infarction: Nationwide propensity score matched study. *BMJ*. 2011;342(7807):d2690. doi:10.1136/bmj.d2690
8. Shah NH, LePendu P, Bauer-Mehren A, et al. Proton pump inhibitor usage and the risk of myocardial infarction in the general population. *PLoS ONE*. 2015;10(6):e0124653. doi:10.1371/journal.pone.0124653
9. Shih CJ, Chen YT, Ou SM, Li SY, Chen TJ, Wang SJ. Proton pump inhibitor use represents an independent risk factor for myocardial infarction. *Int J Cardiol*. 2014;177(1):292-297. doi:10.1016/j.ijcard.2014.09.036
10. Gershon A, Croxford R, Calzavara A, et al. Cardiovascular safety of inhaled long-acting bronchodilators in individuals with chronic obstructive pulmonary disease. *JAMA Intern Med*. 2013;173(13):1175-1184. doi:10.1001/jamainternmed.2013.1016
11. Wang MT, Liou JT, Lin CW, et al. Association of cardiovascular risk with inhaled long-acting bronchodilators in patients with chronic obstructive pulmonary disease: a nested case-control study. *JAMA Intern Med*. 2018;178(2):229-238. doi:10.1001/jamainternmed.2017.7720
12. Lee CH, Choi S, Jang EJ, et al. Inhaled bronchodilators and acute myocardial infarction: a nested case-control study. *Sci Rep*. 2017;7(1):17915. doi:10.1038/s41598-017-17890-1
13. Wang PS, Schneeweiss S, Avorn J, et al. Risk of death in elderly users of conventional vs. atypical antipsychotic medications. *N Engl J Med*. 2005;353(22):2335-2341. doi:10.1056/nejmoa052827
14. Weintraub D, Chiang C, Kim HM, et al. Association of antipsychotic use with mortality risk in patients with Parkinson disease. *JAMA Neurol*. 2016;73(5):535-541. doi:10.1001/jamaneurol.2016.0031
15. Benjamin EJ, Muntner P, Alonso A, et al. Heart disease and stroke statistics-2019 update: a report from the American Heart Association. *Circulation*. 2019;139(10):e56-e528. doi:10.1161/CIR.0000000000000659
16. Centers for Disease Control (CDC). *Heart Disease Facts*; 2019. Accessed December 11, 2019. https://www.cdc.gov/heartdisease/facts.htm
17. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *N Engl J Med*. 2007;356(24):2457-2471. doi:10.1056/NEJMoa072761
18. Nissen SE, Wolski K. Rosiglitazone revisited: an updated meta-analysis of risk for myocardial infarction and cardiovascular mortality. *Arch Intern Med*. 2010;170(14):1191-1201. doi:10.1001/archinternmed.2010.207
19. Wallach JD, Wang K, Zhang AD, et al. Updating insights into rosiglitazone and cardiovascular risk through shared data: individual patient and summary level. *BMJ*. 2020;368(8232):1-19. doi:10.1136/bmj.l7078
20. Jackson JW, Schneeweiss S, VanderWeele TJ, Blacker D. Quantifying the role of adverse events in the mortality difference between first and second-generation antipsychotics in older adults: systematic review and meta-synthesis. *PLoS ONE*. 2014;9(8):e105376. doi:10.1371/journal.pone.0105376
21. Cohen HW, Gibson G, Alderman MH. Excess risk of myocardial infarction in patients treated with antidepressant medications: association with use of tricyclic agents. *Am J Med*. 2000;108(1):2-8. doi:10.1016/S0002-9343(99)00301-0
22. Tata LJ, West J, Smith C, et al. General population based study of the impact of tricyclic and selective serotonin reuptake inhibitor antidepressants on the risk of acute myocardial infarction. *Heart*. 2005;91(4):465-471. doi:10.1136/hrt.2004.037457
23. Ray WA, Meredith S, Thapa PB, Hall K, Murray KT. Cyclic antidepressants and the risk of sudden cardiac death. *Clin Pharmacol Ther*. 2004;75(3):234-241. doi:10.1016/j.clpt.2003.09.019
24. Wang MT, Lai JH, Tsai CL, Liou JT. Risk of adverse cardiovascular events with use of inhaled long-acting bronchodilators in management of chronic obstructive pulmonary disease. *J Food Drug Anal*. 2019;27(3):657-670. doi:10.1016/j.jfda.2018.12.006
25. Suissa S, Dell'Aniello S, Ernst P. Concurrent use of long-acting bronchodilators in COPD and the risk of adverse cardiovascular events. *Eur Respir J*. 2017;49(5):1602245. doi:10.1183/13993003.02245-2016
26. Martinez C, Assimes TL, Mines D, Dell'Aniello S, Suissa S. Use of venlafaxine compared with other antidepressants and the risk of sudden cardiac death or near death: a nested case-control study. *BMJ*. 2010;340(7742):352. doi:10.1136/bmj.c249
27. INVESTIGATORS TA. The atherosclerosis risk in communities (ARIC) study: design and objectives. *Am J Epidemiol*. 1989;129(4):687-702. doi:10.1093/oxfordjournals.aje.a115184
28. Qato DM, Ozenberger K, Olfson M. Prevalence of prescription medications with depression as a potential adverse effect among adults in the United States. *JAMA*. 2018;319(22):2289-2298. doi:10.1001/jama.2018.6741
29. Cheng CM, Guglielmo BJ, Judy M, Auerbach AD. Coverage of FDA medication boxed warnings in commonly used drug information resources. *Arch Intern Med*. 2010;170(9):831-833. doi:10.1001/archinternmed.2010.91
30. Barrons R. Evaluation of personal digital assistant software for drug interactions. *Am J Health Syst Pharm*. 2004;61(4):380-385. doi:10.1093/ajhp/61.4.380

31. Charlson M, Szatrowski TP, Peterson J, Gold J. Validation of a combined comorbidity index. *J Clin Epidemiol*. 1994;47(11):1245-1251. doi:10.1016/0895-4356(94)90129-5
32. Quan H, Li B, Couris CM, et al. Updating and validating the charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. *Am J Epidemiol*. 2011;173(6):676-682. doi:10.1093/aje/kwq433
33. Carnahan RM, Lund BC, Perry PJ, Pollock BG, Gulp KR. The anticholinergic drug scale as a measure of drug-related anticholinergic burden: associations with serum anticholinergic activity. *J Clin Pharmacol*. 2006;46(12):1481-1486. doi:10.1177/0091270006292126
34. Emeny RT, Chang CH, Skinner J, et al. Association of receiving multiple, concurrent fracture-associated drugs with hip fracture risk. *JAMA Netw Open*. 2019;2(11):e1915348. doi:10.1001/jamanetworkopen.2019.15348
35. Varadhan R, Weiss CO, Segal JB, Wu AW, Scharfstein D, Boyd C. Evaluating health outcomes in the presence of competing risks. *Med Care*. 2010;48(6):S96-S105. doi:10.1097/MLR.0b013e3181d99107
36. Qato DM, Wilder J, Schumm LP, Gillet V, Alexander GC. Changes in prescription and over-the-counter medication and dietary supplement use among older adults in the United States, 2005 vs 2011. *JAMA Intern Med*. 2016;176(4):473-482. doi:10.1001/jamainternmed.2015.8581
37. Kantor ED, Rehm CD, Haas JS, Chan AT, Giovannucci EL. Trends in prescription drug use among adults in the United States from 1999-2012. *JAMA*. 2015;314(17):1818-1831. doi:10.1001/jama.2015.13766

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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