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ORIGINAL ARTICLE

Risk of acute myocardial infarction after discontinuation of antihypertensive agents: a case–control study

FF Alharbi[1], PC Souverein[1], MC de Groot[2], AH Maitland-van der Zee[1,3], A de Boer[1] and OH Klungel[1,4]

We performed a nested case–control study in a cohort of antihypertensive drug users to assess the association between discontinuation of different antihypertensive agents and the risk of acute myocardial infarction (AMI). Cases and controls were drawn from the Utrecht Cardiovascular Pharmacogenetics database. Patients who were hospitalised for their first AMI were considered cases and controls were not hospitalised for AMI. Antihypertensive users were defined as current users if the index date (date of AMI) fell within the prescribed duration or as discontinuers if this date fell outside the prescribed duration. According to the recency of discontinuation, discontinuers were divided into the following: recent discontinuers (⩽90 days), intermediate-term discontinuers (91–180 days) and long-term discontinuers (>180 days). We found that the risk of AMI was significantly increased in discontinuers, regardless of time since discontinuation, of beta-blockers (adjusted odds ratio (OR) 1.54; 95% confidence interval (CI; 1.25–1.91), *P*-value < 0.0005), calcium channel blockers (CCBs; adjusted OR 2.25; 95% CI (1.53–3.30), *P*-value < 0.0005) and diuretics (adjusted OR 1.76; 95% CI (1.24–2.48), *P*-value = 0.002) compared to current users of these drugs. Moreover, the risk of AMI was significantly increased in long-term discontinuers (beta-blockers, CCBs, angiotensin-converting enzyme inhibitors and diuretics) and intermediate-term discontinuers (beta-blockers and CCBs) versus current users of these drugs. There was no difference in AMI risk between recent discontinuers of antihypertensive drugs versus current users of these drugs. In conclusion, discontinuation of antihypertensive drugs increases the risk of AMI after >90 days of discontinuation. This further underlines the importance of persistence to antihypertensive drug therapy to reduce the risk of AMI in patients with hypertension.

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INTRODUCTION

According to World Health Organization statistics, 31% of mortality in the world can be attributed to cardiovascular diseases (CVDs). CVDs are thereby the main cause of death worldwide. Hypertension is a major modifiable risk factor for CVD such as coronary heart disease (CHD) and cerebrovascular disease.[1] Therefore, treatment of hypertension by using different regimens of antihypertensive agents leads to a reduction of the risk of developing cardiovascular events.[2] The risk of stroke is significantly reduced by ~42% and the risk of CHD is reduced by ~15% when hypertension is adequately managed.[3] The increased risk of developing cardiovascular non-fatal events or cardiovascular mortality after discontinuation of antihypertensive agents was rarely observed in clinical practice and only addressed in some observational studies.[4,5] Furthermore, some antihypertensive agents after abrupt discontinuation may increase the risk of angina, acute myocardial infarction (AMI), hyper adrenergic crisis and stroke. This condition is called antihypertensive withdrawal syndrome (AWS).[6] Most studies have concluded that AWS is associated with sudden discontinuation of beta-blockers and centrally acting agents such as methyldopa and clonidine.[7–10] Moreover, some cases of AWS have been reported with calcium channel blockers (CCBs) and angiotensin-converting enzyme (ACE) inhibitors (lisinopril).[11–14] To the best of our knowledge, there are no published studies that assessed the association between discontinuation of ACE inhibitors and angiotensin receptors blockers (ARBs) and the risk of developing AMI. Moreover, there are no studies that evaluated the association between discontinuation of individual classes of antihypertensive drugs and the risk of developing AMI together in one population and at different time periods according to the recency of discontinuation. Therefore, the aim of the present study was to assess the association between discontinuation of different individual classes of antihypertensive drugs and the risk of AMI in daily practice.

MATERIALS AND METHODS

Design and setting

We performed a nested case–control study in the Utrecht Cardiovascular Pharmacogenetics (UCP) database to assess the association between the discontinuation of antihypertensive agents and the risk of AMI. This database consists of a high CVD risk population including patients with antihypertensive drugs,[15] use of statins and/or hypercholesterolaemia,[16] and diabetes.[17] These subjects were identified from the PHARMO Database Network, a population-based network of healthcare databases that combines the data from different healthcare settings in the Netherlands (www.pharmo.nl). For this study, dispensing data from community pharmacies and hospital discharge diagnoses were used. Drugs are coded using the Anatomical Therapeutic Chemical (ATC) classification system. For a subgroup of patients, we have information from questionnaires on important cardiovascular lifestyle risk factors and family history of CVDs.[18]

[1]Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands; [2]Department of Clinical Chemistry and Haematology, Division of Laboratory and Pharmacy, University Medical Center Utrecht, Utrecht, The Netherlands; [3]Department of Respiratory Disease, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands and [4]Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands. Correspondence: Professor OH Klungel, Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, PO Box 80 082, Utrecht 3508 TB, The Netherlands.
E-mail: O.H.Klungel@uu.nl
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Case and control definition

In the UCP database, all patients using antihypertensive agents (ACE inhibitors: ATC codes C09A and C09B; ARBs: ATC codes C09C and C09D; CCBs: ATC code C08; beta-blockers: ATC code C07; diuretics: ATC code C03; and miscellaneous antihypertensive agents: ATC code C02) were identified. Within these antihypertensive drug users, a case–control study was designed to assess the risk of AMI after discontinuation of antihypertensive agents. Subjects with a first hospital admission for AMI (International Classification of Diseases-9 code 410) in different hospitals in the Netherlands were selected as cases from the UCP database if they had at least one year of history in PHARMO, were at least 18-year old and had at least one antihypertensive drug prescription before the date of the AMI. The index date of the cases was defined as the date of first hospitalisation for AMI. The same inclusion criteria that were applied to the cases (at least 1 year of history in PHARMO, at least 18-year old and at least one antihypertensive drug prescription before the date of the index date (the date of the AMI of the corresponding case)) were met in controls not having developed an AMI. Controls were selected up to four per cases at the same index date from the UCP database by randomly selecting subjects. From these selected cases and controls, we included antihypertensive users who were dispensed only one antihypertensive drug at the index date or whose last dispensing was for one antihypertensive only before the index date.

Exposure definition of antihypertensive agents

According to the last prescription of an antihypertensive drug before the index date, patients were classified as current users if the index date fell between the dispensing date of an antihypertensive drug and the calculated theoretical end date as assessed by the number of tablets dispensed and the dose instruction. Patients were classified as discontinuer if this date fell outside the prescribed duration. In our study, we included only antihypertensive users with monotherapy who were specifically current users or discontinuers of one antihypertensive agent.

Covariates and risk factors

Age, sex, cardiovascular history, diabetes mellitus and hyperlipidemia were the available possible confounding factors for the association between discontinuation of antihypertensive agents and the risk of AMI. Cardiovascular history was defined as having any previous hospitalisation for CVDs (International Classification of Diseases-9 code 390–449) and/or at least one prescription of antiplatelet drugs or vitamin K antagonists or nitrates within a period of 6 months before the index date. Patients were considered to have diabetes mellitus when they filled at least one prescription of oral hypoglycemic medications and/or insulin in the 6 months before the index date and hyperlipidemia was defined in patients who filled at least one prescription of antilipidemic medications within 6 months before the index date. In addition to these confounders, for a subgroup of patients, cardiovascular risk factors such as smoking, use of alcohol, physical activity, family history of CVDs and body mass index at the time of the index date were available from questionnaires.

Statistical analysis

In our study, we analysed each antihypertensive drug class individually. This meant that for each antihypertensive drug class we restricted the study population to those subjects that either were current user of a specific antihypertensive agent (for example, beta-blocker) or were discontinuers of that same antihypertensive agent. Our statistical analysis was performed using Statistical Package for the Social Sciences (SPSS, IBM Corporation, Armonk, NY, USA) version 20. Age was summarised using mean ± s.d. Other baseline characteristics for cases and controls are presented as numbers and percentages. Student's *t*-test and χ^2-test were used to analyse differences of the baseline characteristics between cases and controls. We used unconditional logistic regression analysis to assess the association between discontinuation of antihypertensive agents and the risk of AMI, and to adjust for confounders.

Main analysis

Our main analysis consisted of two analyses. In the first analysis, we assessed the risk of AMI in discontinuers (regardless of time since discontinuation) of specific antihypertensive agents versus current users of the same agents. In the second analysis, discontinuers were divided according to the recency of discontinuation (the index date minus the theoretical end date of the last prescription) into three categories: recent discontinuers (⩽90 days), intermediate-term discontinuers (91–180 days) and long-term discontinuers (>180 days) to look at the potential risk of AMI at different time periods after discontinuation. Therefore, in the second analysis, we assessed the risk of AMI in recent, intermediate-term and long-term discontinuers of specific antihypertensive agents versus current users of the same agents.

Stratified analysis

We conducted stratified analyses to assess effect modification by history of CVD between discontinuation of antihypertensive agents and the risk of AMI.

Restricted analysis

We conducted a restricted analysis in those patients who had questionnaire data available for additional cardiovascular risk factors (smoking, drinking alcohol, physical activity, family history of CVDs and body mass index). Although the sample size was much smaller, this analysis was performed to assess the impact of controlling for these additional potential confounders on the association between discontinuers of antihypertensive agents and AMI. Also, from this restricted population, we conducted a subgroup analysis in patients with self-reported hypertension at the index date.

Sensitivity analysis

To test the robustness of our results, we repeated both main analyses in sensitivity analyses where use of antihypertensive drugs was based on treatment episodes rather than individual prescriptions. Treatment episodes of the same class of antihypertensive agents were defined by subsequent prescriptions, independent of switching of type and dose changes according to the method of Gardarsdottir *et al*.[19] The duration of a prescription was based on the amount of tablets dispensed and the prescribed dosage regimen. A new treatment episode was assumed when an interval of 90 days or more occurred between the theoretical end date of a prescription and the dispensing date of the subsequent prescription for the same patient. When a patient switched to another class of antihypertensives, a new treatment episode was assumed.

RESULTS

We included 1245 cases and 4994 controls who were current users or discontinuers of one antihypertensive agent from the UCP database with their index date between 19 November 1986 and 11 December 2009 in our analysis. The main characteristics of all cases and controls are shown in Table 1. A history of CVD was significantly more common among cases than controls. Moreover, antiplatelet drugs and nitrates were significantly more used among cases than controls.

Main analysis

The results of the first analysis show that the relative risk of AMI was significantly increased in discontinuers (regardless of time since discontinuation) of beta-blockers (adjusted odds ratio (OR) 1.54; 95% CI (1.25–1.91), *P*-value < 0.0005), CCBs (adjusted OR 2.25; 95% CI (1.53–3.30), *P*-value < 0.0005) and diuretics (adjusted OR 1.76; 95% CI (1.24–2.48), *P*-value = 0.002) compared to current users of these same agents (Table 2). In the second analysis, a statistically significant increased risk of AMI was only observed in intermediate-term discontinuers of beta-blockers (adjusted OR 5.18; 95% CI (2.18–12.3), *P*-value < 0.0005) and CCBs (adjusted OR 6.49; 95% CI (2.05–20.5), *P*-value = 0.001), and in long-term discontinuers of beta-blockers (adjusted OR 2.49; 95% CI (1.88–3.29), *P*-value < 0.0005), CCBs (adjusted OR: 3.50; 95% CI (1.93–6.34), *P*-value < 0.0005), ACE inhibitors (adjusted OR 2.96; 95% CI (1.43–6.14), *P*-value = 0.003) and diuretics (adjusted OR 2.26; 95%CI (1.44–3.56), *P*-value < 0.0005) compared to current users of the same agents. Moreover, there was no difference in AMI risk between recent discontinuers of antihypertensive agents versus current users of these agents (Figure 1; Table 3).

Table 1. Baseline characteristics of cases and controls

	Cases, n = *1245 (100%)*	*Controls*, n = *4994 (100%)*	P-*value*
Age (mean age in years (s.d.))	65.5 (11.4)	65.9 (11.7)	0.295
Gender			
Male	820 (65.9%)	3206 (64.2%)	0.272
Hyperlipidemia	338 (27.1%)	1387 (27.8%)	0.659
Diabetes mellitus	189 (15.2%)	660 (13.2%)	0.070
Cardiovascular history[a]	695 (55.8%)	2260 (45.3%)	< 0.0005
Previous cardiovascular hospitalisation (ICD-9 code 390–449)	225 (18.1%)	694 (13.9%)	< 0.0005
Co-medications			
●Statins	327 (26.3%)	1334 (26.7%)	0.750
● Non-statins cholesterol lowering drugs	30 (2.4%)	165 (3.3%)	0.105
● Insulin	69 (5.5%)	269 (5.4%)	0.828
● Oral hypoglycaemia medications	148 (11.9%)	517 (10.4%)	0.116
● Vitamin K antagonists	126 (10.1%)	507 (10.2%)	0.974
● Antiplatelet drugs	482 (38.7%)	1595 (31.9%)	< 0.0005
● Nitrates	425 (34.1%)	1057 (21.2%)	< 0.0005

Abbreviation: ICD, International Classification of Diseases. [a]Cardiovascular history is defined as any previous hospitalisation for CVD (ICD-9 code 390–449) and/or at least one prescription of antiplatelet drugs or vitamin K antagonists or nitrates within a period of 6 months before the index date.

Table 2. Discontinuers (regardless of time since discontinuation) versus current users of antihypertensive agents and the risk of AMI

Antihypertensive class	*Exposure*	*Cases*	*Controls*	*Crude OR (95% CI)*	*Adjusted OR (95% CI)*[a]	P-*value*
Beta-blockers	Current users	480 (75.0%)	1995 (82.3%)	1.00 (reference)	1.00 (reference)	
	Discontinuers	160 (25.0%)	430 (17.7%)	1.55 (1.26–1.91)	1.54 (1.25–1.91)	< 0.0005
CCBs	Current users	150 (71.8%)	488 (84.7%)	1.00 (reference)	1.00 (reference)	
	Discontinuers	59 (28.2%)	88 (15.3%)	2.23 (1.53–3.27)	2.25 (1.53–3.30)	< 0.0005
ACE inhibitors	Current users	122 (81.9%)	697 (85.7%)	1.00 (reference)	1.00 (reference)	
	Discontinuers	27 (18.1%)	116 (14.3%)	1.35 (0.85–2.14)	1.39 (0.87–2.21)	0.170
ARBs	Current users	32 (86.5%)	181 (89.6%)	1.00 (reference)	1.00 (reference)	
	Discontinuers	5 (13.5%)	21 (10.4%)	1.36 (0.48–3.87)	1.38 (0.46–4.10)	0.565
Diuretics	Current users	134 (68.4%)	748 (79.9%)	1.00 (reference)	1.00 (reference)	
	Discontinuers	62 (31.6%)	188 (20.1%)	1.77 (1.25–2.49)	1.76 (1.24–2.48)	0.002
Miscellaneous antihypertensives	Current users	8 (57.1%)	33 (78.6%)	1.00 (reference)	1.00 (reference)	
	Discontinuers	6 (42.9%)	9 (21.4%)	3.92 (0.91–16.9)	4.65 (0.95–22.8)	0.058

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptors blocker; CCB, calcium channel blocker; CI, confidence interval; OR, odds ratio. [a]Adjusted for age, gender, diabetes mellitus, hyperlipidemia and history of cardiovascular diseases.

Analysis stratified by history of CVD

The results of the stratified analyses with the history of CVD were consistent with our results obtained from the main analyses in both groups. However, in the subgroup of patients with a history of CVD, we found that there was no increased risk of AMI in discontinuers of beta-blockers versus current users of the same agents (adjusted OR 1.26; 95% CI (0.94–1.68), *P*-value = 0.118; Table 4). Furthermore, in patients without cardiovascular history, the risk of AMI was significantly increased in intermediate-term discontinuers of diuretics (adjusted OR 4.80; 95% CI (1.24–18.5), *P*-value = 0.023) and long-term discontinuers of ARBs versus current users of the same agents (adjusted OR 11.2; 95% CI (1.51–82.7), *P*-value = 0.018). We also found no difference in AMI risk between intermediate-term discontinuers of CCBs versus current users of the same agents in these patients without cardiovascular history (adjusted OR 3.06; 95% CI (0.49–19.2), *P*-value = 0.232) (Table 5).

Analysis restricted to subjects with additional information from questionnaires

We included 342 cases and 705 controls who had information from questionnaires on important cardiovascular lifestyle risk factors and family history of CVDs. In spite of the small sample size in this restricted analysis, the risk of AMI was significantly increased in discontinuers (regardless of time since discontinuation) of beta-blockers (adjusted OR 1.70; 95% CI (1.08–2.66), *P*-value = 0.021) and CCBs (adjusted OR 3.31; 95% CI (1.20–9.16), *P*-value = 0.021) compared to current users of the same agents. In this subgroup analysis, the percentage change in OR for the risk of AMI with and without controlling for those additional factors was 4.3% for beta-blockers, − 0.7% for diuretics, 21% for CCBs, − 29% for ACE inhibitors and 32% for ARBs (Supplementary Table 1). Also, from this restricted population, we conducted a subgroup analysis in patients with self-reported hypertension and we that found the results were consistent with our results obtained from the restricted analyses,

as the risk of AMI was still significantly increased in discontinuers (regardless of time since discontinuation) of beta-blockers (adjusted OR 1.98; 95% CI (1.06–3.69), *P*-value = 0.027) and CCBs (adjusted OR 11.1; 95% CI (1.79–68.7), *P*-value = 0.037) compared to current users of the same agents (Supplementary Table 2).

Sensitivity analysis

In our sensitivity analyses where exposure was based on treatment episodes, the results were consistent with our main analyses results but with slightly higher odd ratios. However, discontinuers (regardless of time since discontinuation) of most classes of antihypertensive agents had a significantly higher risk of AMI compared to current users of the same agents except for ARBs (adjusted OR 2.15; 95% CI (0.50–9.12), *P*-value = 0.302; Supplementary Table 3). Moreover, the risk of AMI was significantly increased in recent discontinuers of CCBs compared to current users of the same agents (adjusted OR 7.08; 95% CI (2.38–21.0), *P*-value < 0.0005), which was not seen in our main analyses (adjusted OR: 1.42; 95% CI (0.85–2.37), *P*-value = 0.181; Supplemental Table 4; Table 3).

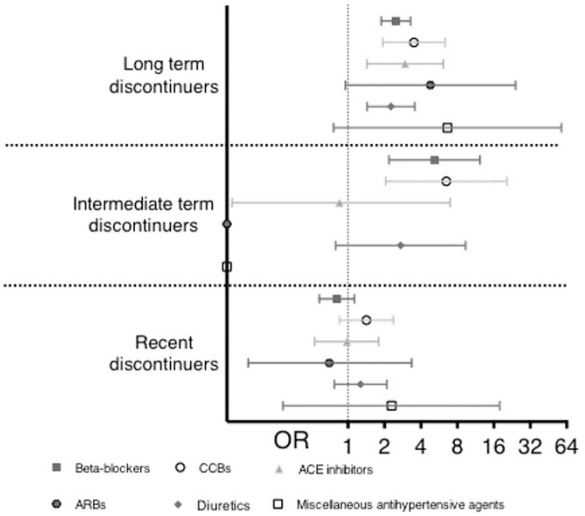

Figure 1. Recent, intermediate-term and long-term discontinuers versus current users of antihypertensive agents and the risk of AMI. A full colour version of this figure is available at the *Journal of Human Hypertension* journal online.

DISCUSSION

Our study demonstrated that the risk of AMI was significantly increased in discontinuers (regardless of time since discontinuation) of beta-blockers, CCBs and diuretics versus current users of the same agents. Especially, the risk of AMI was significantly increased in intermediate-term discontinuers (beta-blockers and CCBs) and long-term discontinuers (beta-blockers, CCBs, ACE inhibitors and diuretics) versus current users of the same agents. For recent discontinuers, there was no difference in AMI risk compared to current users of the same agents. Therefore, we concluded that the risk of AMI is increased after >90 days of discontinuation of antihypertensive agents. However, in our sensitivity analyses based on treatment episodes instead of individual prescriptions, the risk of AMI was significantly increased in recent discontinuers of CCBs compared to current users of the same agents. We defined exposure by aligning prescriptions in time. As in real life, patients may be sloppy in collecting their prescriptions at regular times, which may lead to misclassification of discontinuers. Therefore, we also defined exposure by creating treatment episodes according to the method by Gardarsdottir *et al.*[19] in a sensitivity analysis. These results were as to be expected very similar because of the 90 days grace time before a patient is considered a discontinuer.

Table 3. Recent, intermediate-term and long-term discontinuers versus current users of antihypertensive agents and the risk of AMI

Antihypertensive class	*Exposure*	*Cases*	*Controls*	*Crude OR (95% CI)*	*Adjusted OR (95% CI)*[a]	P-*value*
Beta-blockers	Current users	480 (75.0%)	1995 (82.3%)	1.00 (reference)	1.00 (reference)	
	Recent discontinuers (⩽90 days)	48 (7.5%)	244 (10.1%)	0.82 (0.59–1.13)	0.81 (0.58–1.13)	0.211
	Intermediate-term discontinuers (91–180 days)	12 (1.9%)	10 (0.4%)	5.22 (2.23–12.2)	5.18 (2.18–12.3)	< 0.0005
	Long-term discontinuers (>180 days)	100 (15.6%)	176 (7.3%)	2.47 (1.88–3.24)	2.49 (1.88–3.29)	< 0.0005
CCBs	Current users	150 (71.8%)	488 (84.7%)	1.00 (reference)	1.00 (reference)	
	Recent discontinuers (⩽90 days)	26 (12.4%)	55 (9.5%)	1.42 (0.86–2.36)	1.42 (0.85–2.37)	0.181
	Intermediate-term discontinuers (91–180 days)	8 (3.8%)	5 (0.9%)	6.19 (1.97–19.4)	6.49 (2.05–20.5)	0.001
	Long-term discontinuers (>180 days)	25 (12.0%)	28 (4.9%)	3.44 (1.91–6.19)	3.50 (1.93–6.34)	< 0.0005
ACE inhibitors	Current users	122 (81.9%)	697 (85.7%)	1.00 (reference)	1.00 (reference)	
	Recent discontinuers (⩽90 days)	14 (9.4%)	81 (10.0%)	0.95 (0.52–1.74)	0.98 (0.53–1.79)	0.938
	Intermediate-term discontinuers (91–180 days)	1 (0.7%)	8 (1.0%)	0.84 (0.10–6.80)	0.85 (0.11–6.97)	0.883
	Long-term discontinuers (>180 days)	12 (8.1%)	27 (3.3%)	2.86 (1.39–5.88)	2.96 (1.43–6.14)	0.003
ARBs	Current users	32 (86.5%)	181 (89.6%)	1.00 (reference)	1.00 (reference)	
	Recent discontinuers (⩽ 90 days)	2 (5.4%)	14 (6.9%)	0.75 (0.16–3.49)	0.70 (0.15–3.36)	0.659
	Intermediate-term discontinuers (91–180 days)	0 (0.0%)	2 (1.0%)	-	-	-
	Long-term discontinuers (>180 days)	3 (8.1%)	5 (2.5%)	3.81 (0.85–17.14)	4.79 (0.95–24.19)	0.058
Diuretics	Current users	134 (68.4%)	748 (79.9%)	1.00 (reference)	1.00 (reference)	
	Recent discontinuers (⩽90 days)	22 (11.2%)	99 (10.6%)	1.26 (0.76–2.07)	1.27 (0.77–2.09)	0.358
	Intermediate-term discontinuers (91–180 days)	4 (2.0%)	8 (0.9%)	2.63 (0.78–8.90)	2.72 (0.79–9.34)	0.111
	Long-term discontinuers (>180 days)	36 (18.4%)	81 (8.7%)	2.31 (1.48–3.61)	2.26 (1.44–3.56)	< 0.0005
Miscellaneous antihypertensives	Current users	8 (57.1%)	33 (78.6%)	1.00 (reference)	1.00 (reference)	
	Recent discontinuers (⩽ 90 days)	2 (14.3%)	4 (9.5%)	2.71 (0.38–19.2)	2.29 (0.29–17.9)	0.430
	Intermediate-term discontinuers (91–180 days)	1 (7.1%)	0 (0.0%)	-	-	-
	Long-term discontinuers (>180 days)	3 (21.4%)	5 (11.9%)	3.76 (0.61–23.2)	6.62 (0.76–57.8)	0.087

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptors blocker; CCB, calcium channel blocker; CI, confidence interval; OR, odds ratio.
[a]Adjusted for age, gender, diabetes mellitus, hyperlipidemia and history of cardiovascular diseases.

Table 4. Discontinuers (regardless of time since discontinuation) versus current users of antihypertensive agents and the risk of AMI in patients with or without cardiovascular history

Antihypertensive class	*Exposure*	*Cases*	*Controls*	*Crude OR (95% CI)*	*Adjusted OR (95% CI)*[a]	P-*value*
Patients with cardiovascular history						
Beta-blockers	Current users	324 (79.0%)	1030 (82.7%)	1.00 (reference)	1.00 (reference)	
	Discontinuers	86 (21.0%)	215 (17.3%)	1.35 (1.01–1.79)	1.26 (0.94–1.68)	0.118
CCBs	Current users	103 (71.5%)	309 (85.1%)	1.00 (reference)	1.00 (reference)	
	Discontinuers	41 (28.5%)	54 (14.9%)	2.35 (1.48–3.75)	2.34 (1.45–3.80)	0.001
ACE inhibitors	Current users	45 (81.8%)	239 (83.9%)	1.00 (reference)	1.00 (reference)	
	Discontinuers	10 (18.2%)	46 (16.1)%	1.16 (0.55–2.47)	1.22 (0.57–2.62)	0.612
ARBs	Current users	13 (86.7%)	61 (87.1%)	1.00 (reference)	1.00 (reference)	
	Discontinuers	2 (13.3%)	9 (12.9%)	1.04 (0.20–5.48)	0.87 (0.14–5.40)	0.877
Diuretics	Current users	47 (69.1%)	230 (81.3%)	1.00 (reference)	1.00 (reference)	
	Discontinuers	21 (30.9%)	53 (18.7%)	2.03 (1.09–3.76)	1.89 (1.01–3.55)	0.047
Miscellaneous antihypertensives	Current users	1 (33.3%)	10 (71.4%)	1.00 (reference)	1.00 (reference)	
	Discontinuers	2 (66.7%)	4 (28.6%)	4.99 (0.34–74)	6.28 (0.16–253)	0.330
Patients without cardiovascular history						
Beta-blockers	Current users	156 (67.8%)	965 (81.8%)	1.00 (reference)	1.00 (reference)	
	Discontinuers	74 (32.2%)	215 (18.2%)	2.10 (1.53–2.88)	2.05 (1.49–2.83)	< 0.0005
CCBs	Current users	47 (72.3%)	179 (84.0%)	1.00 (reference)	1.00 (reference)	
	Discontinuers	18 (27.7%)	34 (16.0%)	2.03 (1.05–3.92)	2.02 (1.04–3.91)	0.038
ACE inhibitors	Current users	77 (81.9%)	458 (86.7%)	1.00 (reference)	1.00 (reference)	
	Discontinuers	17 (18.1%)	70 (13.3%)	1.46 (0.82–2.63)	1.49 (0.82–2.68)	0.189
ARBs	Current users	19 (86.4%)	120 (90.9%)	1.00 (reference)	1.00 (reference)	
	Discontinuers	3 (13.6%)	12 (9.1%)	1.44 (0.36–5.66)	1.62 (0.35–7.51)	0.539
Diuretics	Current users	87 (68.0%)	518 (79.3%)	1.00 (reference)	1.00 (reference)	
	Discontinuers	41 (32.0%)	135 (20.7%)	1.74 (1.14–2.65)	1.74 (1.14–2.65)	0.010
Miscellaneous antihypertensives	Current users	7 (63.6%)	23 (82.1%)	1.00 (reference)	1.00 (reference)	
	Discontinuers	4 (36.4%)	5 (17.9%)	4.41 (0.68–28.6)	7.20 (0.90–57.8)	0.063

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptors blocker; CCB, calcium channel blocker; CI, confidence interval; OR, odds ratio.
[a]Adjusted for age, gender, diabetes mellitus and hyperlipidemia.

To our knowledge, our study is the first combined analysis that assessed the association between discontinuation of different individual antihypertensive drug classes and the risk of AMI together in one population and at different time periods according to the recency of discontinuation.

A cohort study conducted by Breekveldt-Postma *et al.*[5] found that non-persistent patients with antihypertensive agents had a higher risk of AMI with 15% (RR 1.15; 95% CI (1.00–1.33)) and higher risk of stroke with 28% (RR 1.28; 95% CI (1.15–1.45)) compared to persistent patients in daily clinical practice. This study included 77 193 patients followed for 2 years and the aim of the study was to investigate the association between the impact of early discontinuation of antihypertensive agents and the risk of AMI and stroke. They used the treatment episodes method with a gap < 60 days for the definition of the exposure as 2-year persistent or non-persistent of antihypertensive drugs. However, this study did not take into account the impact of individual classes of antihypertensive agents on the risk of AMI as we did in our study. Moreover, in our sensitivity analyses, we used the same method as Breekveldt-Postma *et al.*[5] with a gap of < 90 days to define exposure and found that our results were consistent as we found an increased risk of AMI in discontinuers of most antihypertensive drug classes. Moreover, Leite *et al.*[4] found in a population-based cohort study that the risk of cardiovascular mortality, defined as death by ischaemic heart disease, pulmonary heart disease, cerebrovascular disease, diseases of arteries, arterioles and capillaries, cardiovascular involvement in chronic Chagas' disease, and hypertensive diseases, was significantly increased in stoppers of antihypertensive agents versus current users in elderly populations ($\geqslant$60 years old; risk ratio 3.12; 95% CI (2.35–4.15)). However, this study only focused on cardiovascular mortality as outcome and only included elderly patients ($\geqslant$60 years). Moreover, this study did not study the effect of each individual class of antihypertensive agents on cardiovascular mortality. However, the results of this study and our study suggest that the persistence to antihypertensive agents should be encouraged to reduce the risk of cardiovascular events and cardiovascular mortality in patients with hypertension.

Several studies demonstrated that the risk of developing AWS is associated with sudden discontinuation of beta-blockers.[7,8] A case–control study conducted by Psaty *et al.*[7] included 248 cases and 737 controls with hypertension found that the risk of CHD was significantly higher in recent stoppers of beta-blockers (RR 4.5; 95% CI (1.1–18.5)). They defined recent stoppers as patients who had used their medications for at least 30 days and stopped using them within 30 days of the index date (the date of first event of CHD). However, this study had a small number of patients who were recent stoppers of beta-blockers (seven cases

Table 5. Recent, intermediate-term and long-term discontinuers versus current users of antihypertensive agents and the risk of AMI in patients with or without cardiovascular history

Antihypertensive class	*Exposure*	*Cases*	*Controls*	*Crude OR (95% CI)*	*Adjusted OR (95% CI)*[a]	P-*value*
Patients with cardiovascular history						
Beta-blockers	Current users	324 (79.0%)	1030 (82.7%)	1.00 (reference)	1.00 (reference)	
	Recent discontinuers (⩽90 days)	29 (7.1%)	111 (8.9%)	0.84 (0.55–1.28)	0.79 (0.51–1.22)	0.287
	Intermediate-term discontinuers (91–180 days)	7 (1.7%)	5 (0.4%)	5.08 (1.59–16.2)	4.48 (1.39–14.5)	0.012
	Long-term discontinuers (>180 days)	50 (12.2%)	99 (8.0%)	1.83 (1.25–2.66)	1.71 (1.17–2.50)	0.006
CCBs	Current users	103 (71.5%)	309 (85.1%)	1.00 (reference)	1.00 (reference)	
	Recent discontinuers (⩽90 days)	18 (12.5%)	37 (10.2%)	1.37 (0.74–2.53)	1.36 (0.73–2.55)	0.331
	Intermediate-term discontinuers (91–180 days)	6 (4.2%)	2 (0.6%)	11.12 (2.17–57)	11.62 (2.24–60.2)	0.003
	Long-term discontinuers (>180 days)	17 (11.8%)	15 (4.1%)	4.15 (1.95–8.82)	4.19 (1.93–9.08)	<0.0005
ACE inhibitors	Current users	45 (81.8%)	239 (83.9%)	1.00 (reference)	1.00 (reference)	
	Recent discontinuers (⩽90 days)	5 (9.1%)	31 (10.9%)	0.85 (0.31–2.31)	0.88 (0.32–2.41)	0.808
	Intermediate-term discontinuers (91–180 days)	0 (0.0%)	4 (1.4%)	-	-	-
	Long-term discontinuers (>180 days)	5 (9.1%)	11 (10.9%)	2.47 (0.81–7.53)	2.63 (0.85–8.16)	0.094
ARBs	Current users	13 (86.7%)	61 (87.1%)	1.00 (reference)	1.00 (reference)	
	Recent discontinuers (⩽ 90 days)	2 (13.3%)	6 (8.6%)	1.56 (0.28–8.61)	1.21 (0.19–7.83)	0.841
	Intermediate-term discontinuers (91–180 days)	0 (0.0%)	1 (1.4%)	-	-	-
	Long-term discontinuers (>180 days)	0 (0.0%)	2 (2.9%)	-	-	-
Diuretics	Current users	47 (69.1%)	230 (81.3%)	1.00 (reference)	1.00 (reference)	
	Recent discontinuers (⩽90 days)	9 (13.2%)	28 (9.9%)	1.60 (0.71–3.63)	1.57 (0.69–3.60)	0.285
	Intermediate-term discontinuers (91–180 days)	0 (0.0%)	3 (1.1%)	-	-	-
	Long-term discontinuers (>180 days)	12 (17.6%)	22 (7.8%)	2.98 (1.30–6.82)	2.66 (1.15–6.16)	0.023
Miscellaneous antihypertensives	Current users	1 (33.3%)	10 (71.4%)	1.00 (reference)	1.00 (reference)	
	Recent discontinuers (⩽90 days)	0 (0.0%)	1 (7.1%)	-	-	-
	Intermediate-term discontinuers (91–180 days)	1 (33.3%)	0 (0.0%)	-	-	-
	Long-term discontinuers (>180 days)	1 (33.3%)	3 (21.4%)	3.35 (0.15–76.1)	[b]	[b]
Patients without cardiovascular history						
Beta-blockers	Current users	156 (67.8%)	965 (81.8%)	1.00 (reference)	1.00 (reference)	
	Recent discontinuers (⩽ 90 days)	19 (8.3%)	133 (11.3%)	0.88 (0.53–1.47)	0.86 (0.52–1.44)	0.566
	Intermediate-term discontinuers (91–180 days)	5 (2.2%)	5 (0.4%)	6.34 (1.80–22.3)	6.79 (1.91–24.1)	0.003
	Long-term discontinuers (>180 days)	50 (21.7%)	77 (6.5%)	4.11 (2.73–6.18)	4.03 (2.67–6.10)	<0.0005
CCBs	Current users	47 (72.3%)	179 (84.0%)	1.00 (reference)	1.00 (reference)	
	Recent discontinuers (⩽90 days)	8 (12.3%)	18 (8.5%)	1.51 (0.61–3.75)	1.45 (0.58–3.62)	0.424
	Intermediate-term discontinuers (91–180 days)	2 (3.1%)	3 (1.4%)	2.89 (0.46–18)	3.06 (0.49–19.2)	0.232
	Long-term discontinuers (>180 days)	8 (12.3%)	13 (6.1%)	2.68 (1.03–6.99)	2.75(1.04–7.24)	0.041
ACE inhibitors	Current users	77 (81.9%)	458 (86.7%)	1.00 (reference)	1.00 (reference)	
	Recent discontinuers (⩽ 90 days)	9 (9.6%)	50 (9.5%)	0.99 (0.47–2.12)	1.02 (0.47–2.17)	0.970
	Intermediate-term discontinuers (91–180 days)	1 (1.1%)	4 (0.8%)	1.97 (0.21–18.1)	1.78 (0.19–16.8)	0.614
	Long-term discontinuers (>180 days)	7 (7.4%)	16 (3.0%)	3.20 (1.24–8.25)	3.30 (1.26–8.63)	0.015
ARBs	Current users	19 (86.4%)	120 (90.9%)	1.00 (reference)	1.00 (reference)	
	Recent discontinuers (⩽ 90 days)	0 (0.0%)	8 (6.1%)	-	-	-
	Intermediate-term discontinuers (91–180 days)	0 (0.0%)	1 (0.8%)	-	-	-
	Long-term discontinuers (>180 days)	3 (13.6%)	3 (2.3%)	7.43(1.35–41.1)	11.2(1.51–82.7)	0.018
Diuretics	Current users	87 (68.0%)	518 (79.3%)	1.00 (reference)	1.00 (reference)	
	Recent discontinuers (⩽ 90 days)	13 (10.2%)	71 (10.9%)	1.14 (0.60–2.15)	1.15 (0.61–2.19)	0.660
	Intermediate-term discontinuers (91–180 days)	4 (3.1%)	5 (0.8%)	4.44 (1.16–16.9)	4.80 (1.24–18.5)	0.023
	Long-term discontinuers (>180 days)	24 (18.8%)	59 (9.0%)	2.19 (1.28–3.76)	2.16 (1.25–3.71)	0.006
Miscellaneous antihypertensives	Current users	7 (63.6%)	23 (82.1%)	1.00 (reference)	1.00 (reference)	
	Recent discontinuers (⩽90 days)	2 (18.2%)	3 (10.7%)	3.47 (0.38–31.4)	4.56 (0.45–46.3)	0.199
	Intermediate-term discontinuers (91–180 days)	0 (0.0%)	0 (0.0%)	-	-	-
	Long-term discontinuers (>180 days)	2 (18.2%)	2 (7.1%)	6.10 (0.54–69.3)	22.1 (0.86–568)	0.062

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptors blocker; CCB, calcium channel blocker; CI, confidence interval; OR, odds ratio.
[a]Adjusted for age, gender, diabetes mellitus and hyperlipidemia. [b]The model is not converge.

and four controls). In our study, we defined recent discontinuers as antihypertensive users who discontinued using medications within 90 days of their index date (the date of first event of AMI for cases). The latency of increased risk of AMI in discontinuers of beta-blockers in our study after >90 days could have been caused by the fact that our patients had probably mild or moderate hypertension. Moreover, we noticed in our study that the risk of AMI was higher in intermediate-term discontinuers (beta-blockers and CCBs) compared to long-term discontinuers (beta-blockers and CCBs), and this was most pronounced in patients with cardiovascular events in the past.

We believe that the increased risk of AMI after discontinuation of antihypertensive agents in our study is most likely due to uncontrolled rebound hypertension in patients who discontinued their medications.[20,21] This hypothesis could, however, not be verified, as blood pressure measurements are not available in the UCP database. Moreover, in our study, patients who discontinued antihypertensive agents may also have discontinued their medications for primary and secondary prevention of CVDs that may lead to increasing the risk of AMI. Other general possible explaining factors for AWS after discontinuation of antihypertensive agents are increasing myocardial oxygen requirements,

increasing sympathetic tone, increasing levels of circulating catecholamines, increasing sensitivity of receptors to catecholamines, increasing renin–angiotensin system activity, and increasing platelet adhesiveness and aggregation.[22,23]

There are many factors that affect adherence to antihypertensive agents such as adverse effects of the medication, complex drug regimen, cost of drug, the patient's level of literacy and education, and lack of patient education on medications and CVDs. The adherence to antihypertensive agents can be improved by educating patients about high blood pressure and the importance of adherence to avoid the complications of hypertension, prescribing simple drug regimen, selecting drugs with less likely to develop adverse effects, and selecting effective and inexpensive drug.[24] Our study emphasises that the adherence and persistence to antihypertensive agents should be encouraged to adequately reduce the risk of AMI in patients with hypertension.

There are some strengths and limitations of our study. First, our cases are clearly defined by first diagnosis of AMI (International Classification of Diseases-9 code 410) from the Dutch National Medical Registry database. A validation of this code was done in a cohort of 21 148 subjects by linking incident cases of AMI, unstable angina pectoris and heart failure to causes in the death registry in Netherlands, the hospital discharge registry and the cardiology information system of the University Hospital Maastricht. The sensitivity for AMI hospital data was 84% and the positive predictive value was 97.1% using the cardiology information system-based registry as gold standard for the calculation.[25] Second, we included in our analyses only antihypertensive users who were specifically current users or discontinuers of one antihypertensive agent. These patients are more likely to suffer from mild or moderate hypertension. A limitation of our study is that some well-established risk factors such as smoking and body mass index for AMI were not available for all patients in our database. However, the subgroup analysis including these cardiovascular risk factors showed that the impact on percentage change of OR after controlling for these factors was considered acceptable especially for antihypertensive agents that had reasonable sample size such as beta-blockers. Another limitation is that our database lacks both the classification of degree of hypertension and blood pressure measurements. However, we included patients who more likely had mild or moderate hypertension, as they were on a single antihypertensive agent.

CONCLUSION

In summary, the study shows that the risk of AMI was increased after >90 days of discontinuation of antihypertensive agents in daily clinical practice. However, the study did not show that the risk of AMI was associated with recent discontinuation of antihypertensive agents. Our study emphasises again that the persistence to antihypertensive agents should be encouraged to adequately reduce the risk of AMI in patients with hypertension.

What is known about topic?

- AWS is associated with sudden discontinuation of beta-blockers and centrally acting agents such as methyldopa and clonidine.
- Some cases of AWS have been reported with CCBs and ACE inhibitors (lisinopril).
- Only a few studies assessed the effect of discontinuation of antihypertensive agents on risk of developing cardiovascular non-fatal events.

What this study adds?

- The risk of AMI was increased after >90 days of discontinuation antihypertensive agents in daily clinical practice.
- The persistence to antihypertensive agents should be encouraged to reduce the risk of AMI in patients with hypertension.

CONFLICT OF INTEREST

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