British Journal of Clinical Pharmacology

Br J Clin Pharmacol (2017) **83** 2541–2548 2541

PHARMACOEPIDEMIOLOGY

The impact of serum potassium-influencing antihypertensive drugs on the risk of out-of-hospital cardiac arrest: A case–control study

Correspondence Hanno L. Tan, MD, PhD, Department of Cardiology, Heart Center, Academic Medical Center, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands. Tel.: +31 20 5669111; Fax: +31 20 6975458; E-mail: h.l.tan@amc.uva.nl

Received 24 February 2017; **Revised** 17 May 2017; **Accepted** 14 June 2017

Fawaz F. Alharbi[1], Patrick C. Souverein[1], Mark C. H. de Groot[2], Marieke T. Blom[3], Anthonius de Boer[1], Olaf H. Klungel[1,4] and Hanno L. Tan[3]

[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 Cardiology, Heart Center, 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*

Keywords antihypertensive drugs, cardiac arrest, hyperkalaemia, hypokalaemia, potassium

AIMS

Sudden cardiac arrest (SCA) is a complex multifactorial event and most commonly caused by ventricular tachycardia/ fibrillation (VT/ VF). Some antihypertensive drugs could induce hypokalaemia or hyperkalaemia, which may increase susceptibility to VT/VF and SCA.

OBJECTIVE

To assess the association between different classes of antihypertensive drugs classified according to their potential impact on serum potassium levels and the occurrence of out-of-hospital cardiac arrest (OHCA) based on VT/VF.

METHODS

A case–control study was performed among current users of antihypertensive drugs. Cases were OHCA victims with electrocardiogram documented VT/VF drawn from the AmsteRdam REsuscitation STudies (ARREST) registry, and controls were non-OHCA individuals from the PHARMO database. Antihypertensive drugs were classified into: (i) antihypertensives with neutral effect on serum potassium levels; (ii) hypokalaemia-inducing antihypertensives; (iii) hyperkalaemia-inducing antihypertensives; (iv) combination of antihypertensives with hypo- and hyperkalaemic effects.

RESULTS

We included 1345 cases and 4145 controls. The risk of OHCA was significantly increased among users of hypokalaemia-inducing antihypertensives [adjusted odds ratio (OR) 1.39; 95% confidence interval (CI) 1.10–1.76] and among users of a combination of antihypertensives with hypo- and hyperkalaemic effects (adjusted OR 1.42; 95%CI 1.17–1.72) *vs.* users of antihypertensives with neutral effect. There was no difference in OHCA risk between users of hyperkalaemia-inducing antihypertensives *vs.* users of antihypertensive drugs with neutral effect (adjusted OR 1.15; 95%CI 0.95–1.40).

CONCLUSION

The risk of OHCA is significantly increased in patients who were current users of hypokalaemia-inducing antihypertensives and patients using a combination of antihypertensives with hypo- and hyperkalaemic effects.

DOI:10.1111/bcp.13356

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Sudden cardiac arrest (SCA) is a complex multifactorial event and most commonly caused by ventricular tachycardia/ fibrillation (VT/ VF).
- Some studies found an increased risk of SCA among users of hypokalaemia-inducing antihypertensives. However, these studies were limited by the fact that they used the definition of sudden death as proposed in the European Society of Cardiology guidelines in which the electrophysiological cause is not part of the definition.

WHAT THIS STUDY ADDS

- This is the first study that assessed the association between various antihypertensive drug classes stratified to their potential effects on serum potassium levels and the risk of out-of-hospital cardiac arrest (OHCA) in a large cohort in which electrocardiogram documentation of VT/VF was available.
- The risk of OHCA with VT/VF is significantly increased in patients who were current users of hypokalaemia-inducing antihypertensives and patients using a combination of antihypertensives with hypo- and hyperkalaemic effects.

Introduction

Over 50% of all cardiovascular deaths in industrialized countries are attributed to sudden death, most often due to sudden cardiac arrest (SCA) and occurring in the community (out-of-hospital cardiac arrest, OHCA). About 400 000 people annually are affected by SCA in Europe [1]. SCA is a complex multifactorial event and most commonly caused by ventricular tachycardia/fibrillation (VT/VF) [2]. Various cellular mechanisms may increase susceptibility to VT/VF and SCA. Accordingly, risk factors of SCA including coronary heart disease, congestive heart failure, diabetes mellitus, inherited factors [3], and electrolyte imbalances such as hypokalaemia [4, 5] and hyperkalaemia [6, 7] act by impacting on these mechanisms. Some drugs may also impact on these mechanisms, e.g. antihypertensive drugs which induce hypokalaemia or hyperkalaemia [7–9].

However, it has not been established whether use of antihypertensive drugs with such effects is associated with increased VT/VF risk in the community. A suggestion for such an association comes from studies which found an increased risk of sudden death among users of hypokalaemia-inducing antihypertensives [10–12]. These studies were, however, limited by the fact that they used the definition of sudden death as proposed in the European Society of Cardiology guidelines (*natural death due to cardiac causes, heralded by abrupt loss of consciousness within 1 hour of the onset of acute symptoms; pre-existing heart disease may have been known to be present, but the time and mode of death are unexpected*) [13]. This definition does not require electrocardiogram (ECG) documentation of VT/VF, thereby leaving the risk of misclassification of sudden death from other causes, e.g. stroke (a real possibility in patients with hypertension). Another limitation is that these studies did not analyse a possible association between hyperkalaemia-inducing antihypertensives and VT/VF. The aim of our study is to fill these knowledge gaps by studying a possible association between various antihypertensive drug classes stratified to their potential effects on serum potassium levels (both hypokalaemia and hyperkalaemia) in a large cohort in which ECG documentation of VT/VF was available to minimize the risk of misclassification.

Methods

Design and setting

A case–control study was performed to assess the association between the use of antihypertensive drugs classified by their potential impact on serum potassium levels and the risk of OHCA. Our cases and controls who were current users of antihypertensive drugs were selected from a matched case control set. In this matched set, cases are OHCA victims with electrocardiogram documented VT/VF from the AmsteRdam REsuscitation STudies (ARREST) registry in the period 5 July 2005–28 December 2011. Controls are non-OHCA individuals that were matched by age, sex and OHCA date (index date) to cases and were drawn from the Pharmaco-Morbidity Record Linkage System (PHARMO-RLS, www.pharmo.nl) database. The ARREST is an ongoing registry designed to study the risk factors of SCA in which all OHCA victims in the North Holland province of the Netherlands (>2.4 million inhabitants) are included. OHCA parameters, from ambulance dispatch to hospital discharge or patient death are recorded in the ARREST database. Moreover, ECG recordings from the ambulance monitor/defibrillator or automated external defibrillator are used to confirm the presence of VT/VF. One year of previous history for medication prescriptions before the date of OHCA occurrence are retrieved from community pharmacies. The ARREST registry recruitment was described in detail by Blom *et al.* [14]. The PHARMO database contains information about drug-dispensing histories of patients from community pharmacies (>3 million community-dwelling inhabitants in the Netherlands). The ARREST registry was conducted according to the principles expressed in the Declaration of Helsinki. Written informed consent was obtained from all participants who survived SCA. The Ethics Committee of the Academic Medical Center Amsterdam approved the use of data from people who did not survive SCA, and approved this study.

Case and control definition

For this study, we first selected 2518 cases from the ARREST registry who had an OHCA with ECG-documented VT/VF. The cases were matched by age, sex and OHCA (index date) up to 5 controls (10 597 patients) from the PHARMO

database. From these cases and matched controls, we selected adult patients (aged ≥18 years) who were current users of antihypertensive drugs (1345 cases and 4145 controls; Figure 1). These cases and controls were not matched any more. If we would have maintained the age, sex and OHCA date matching, we would have lost a substantial number of matched sets because of the criterion of the use of at least one antihypertensive drug at the index date. Antihypertensive drugs studied were: angiotensin-converting enzyme (ACE) inhibitors: ATC code C09A and C09B, angiotensin receptors blockers (ARBs): ATC code C09C and C09D, calcium channel blockers (CCBs): ATC code C08, β-blockers: ATC code C07, diuretics: ATC code C03 (thiazide or thiazide-like diuretics, loop diuretics and potassium-sparing diuretics) and miscellaneous antihypertensive agents: ATC code C02. We excluded the CCBs verapamil and diltiazem, and the beta-blocker sotalol from further analysis, because of their antiarrhythmic indication. We restricted the study population to current users of antihypertensive drugs on the index date to reduce the effect of confounding by indication and to be able to assess the risk of OHCA in patients with antihypertensives potentially influencing serum potassium levels *vs*. antihypertensives with neutral effect.

Exposure definition of antihypertensive drugs

Antihypertensive drug use was defined as current if the index date fell within the computed theoretical duration of the

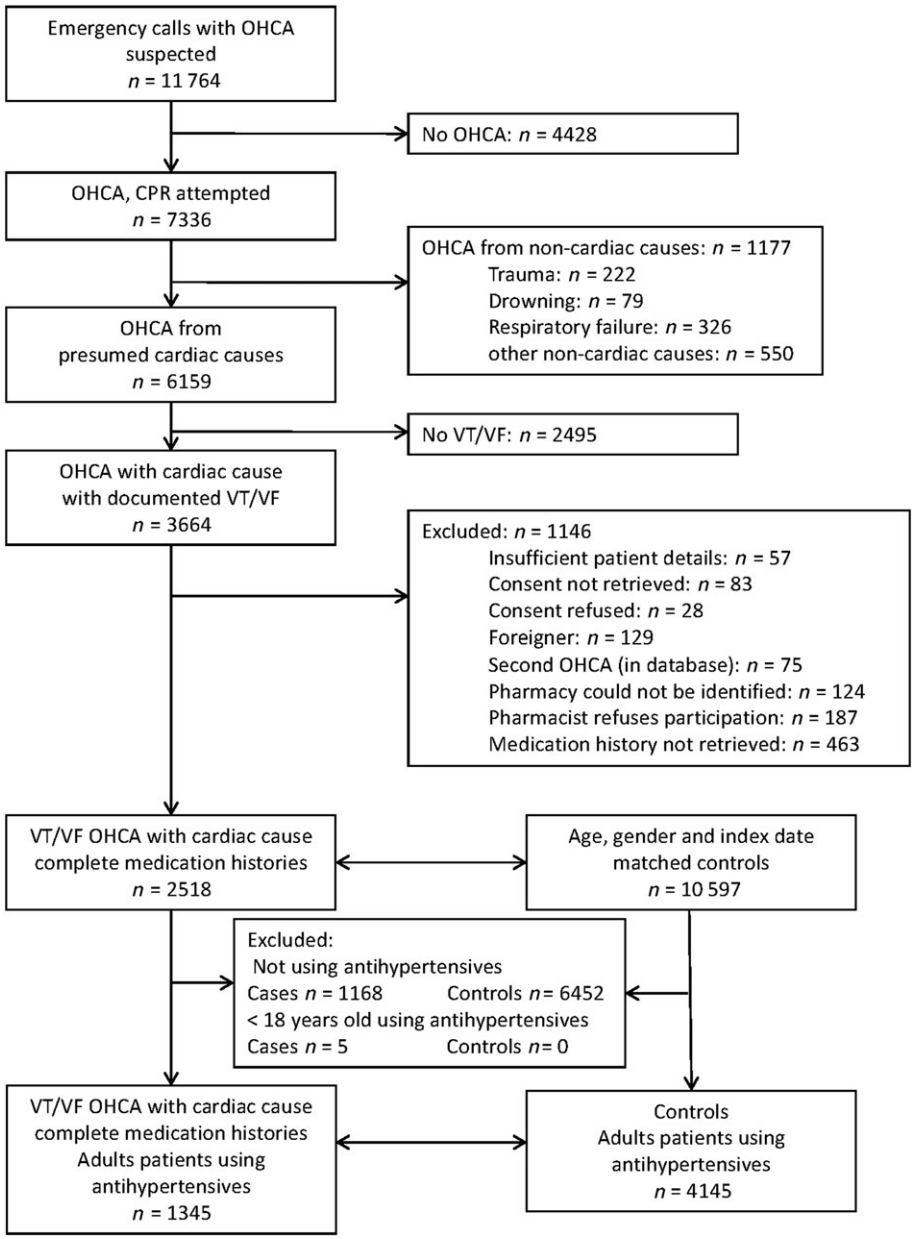

Figure 1
Flow chart

prescription (extended with 10% of that duration to take into account irregular drug use). We stratified current users of antihypertensive drugs into four drug classes according to the potential impact of the drugs on serum potassium levels: (i) antihypertensives with neutral effect (monotherapy of β-blockers or CCBs or miscellaneous antihypertensive drugs or a combination of at least two of such antihypertensives); (ii) hypokalaemia-inducing antihypertensives (monotherapy of loop diuretics or thiazide or thiazide-like diuretics or a combination of at least one of these drugs and antihypertensives with neutral effect); (iii) hyperkalaemia-inducing antihypertensives (monotherapy of ACE inhibitors or ARBs or potassium-sparing agents or a combination of at least one of these drugs and antihypertensives with neutral effect); and (iv) a combination of antihypertensives with hypo- and hyperkalaemic effects (at least one hypokalaemia-inducing antihypertensive combined with at least one hyperkalaemia-inducing antihypertensive with or without antihypertensives with neutral effect).

Covariates and risk factors

Age, sex, antiarrhythmic drugs (class I and III and other antiarrhythmic drugs), nonantiarrhythmic QT prolonging drugs, high cardiovascular risk-profile, and use of antidiabetic drugs or drugs for obstructive airway diseases were the available possible confounding factors for the association between the use of antihypertensive drugs and the risk of OHCA. High cardiovascular risk profile was defined as at least one prescription use of the following drugs: nitrates, platelet aggregation inhibitors, vitamin K antagonists and/or antilipidaemics within a period of 6 months before the index date. Antidiabetic medications users were defined as patients who filled at least one prescription of oral hypoglycaemic medications and/or insulin in the 6 months prior to the index date. Antiarrhythmic drugs class I and III were defined as at least one prescription of Vaughan–Williams class I and III medications. Other antiarrhythmic drugs were defined as at least one prescription use of the following drugs: verapamil, diltiazem, digoxin and/or ivabradine. Nonantiarrhythmic QT prolonging drugs were class 1 or 2 or 3 of QT-prolonging drugs derived from CredibleMeds® (http://crediblemeds.org/, accessed on April 13, 2014).

Statistical analysis

Our statistical analysis was performed using SPSS version 23. Age was summarized using mean ± standard deviation. Other baseline characteristics for cases and controls are presented as numbers and percentage. Student *t* test and chi-square 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 the use of antihypertensive drugs according to their potential impact on serum potassium levels and the risk of OHCA (crude) and to adjust for confounders (fully adjusted model). Based on our sample size of cases and controls, the power of this study was 92% to detect an odds ratio (OR) of 1.3 with an α of 5%.

Main analysis. Our main analysis consisted of two analyses. In the first analysis, we assessed the risk of OHCA with antihypertensives potentially influencing serum potassium levels *vs*. antihypertensives with neutral effect. In the second analysis, antihypertensives potentially influencing serum potassium levels were divided into three categories: hypokalaemia-inducing antihypertensives, hyperkalaemia-inducing antihypertensives, and a combination of antihypertensives with hypo- and hyperkalaemic effects; the risk of OHCA was compared to antihypertensives with neutral effect.

Analysis restricted to current users of maximally two antihypertensive drugs. We conducted an analysis restricted to those patients who were current users of a maximum of two antihypertensives. We did this for two reasons. Firstly, our reference group (antihypertensives with neutral effect) was mainly composed of patients with at most two antihypertensives. Secondly, we wanted to reduce the effect of confounding by indication by including only patients who were more likely to have mild or moderate hypertension since they were on one or two antihypertensives.

Sensitivity analysis. To test the robustness of our results we repeated both main analyses in sensitivity analyses by excluding patients who were taking at least one prescription of an antiarrhythmic drug and/or nonantiarrhythmic QT prolonging drugs.

Results

We included 1345 cases and 4145 controls (Figure 1). Their main characteristics are shown in Table 1. All comedications presented in Table 1 were significantly more frequently used among cases than among controls.

Main analysis

The relative risk of OHCA was significantly increased with antihypertensives potentially influencing serum potassium levels [adjusted OR 1.31; 95% confidence interval (CI) 1.10–1.55] compared to antihypertensives with neutral effect (Table 2A). After stratification by effect on serum potassium, a statistically significant increased risk of OHCA was observed with hypokalaemia-inducing antihypertensives (adjusted OR 1.39; 95%CI 1.10–1.76) and a combination of antihypertensives with hypo- and hyperkalaemic effects (adjusted OR 1.42; 95%CI 1.17–1.72) compared to antihypertensives with neutral effect. There was no difference in OHCA risk between hyperkalaemia-inducing antihypertensives (adjusted OR 1.15; 95%CI 0.95–1.40) compared to antihypertensives with neutral effect (Figure 2, Table 2B).

Restriction to a maximum of two antihypertensive drugs

We included 870 cases and 3048 controls exposed to a maximum of two antihypertensives at the index date. In our first restricted analysis, there was a nonsignificantly increased risk of OHCA with antihypertensives potentially influencing serum potassium levels *vs*. antihypertensives with neutral effect (adjusted OR 1.17; 95%CI 0.98–1.41; Table 3A). by contrast, in the second restricted analyses, we found that

Table 1

Baseline characteristics of cases and controls

	Cases (*n* = 1345)	Controls (*n* = 4145)	*P*-value
Mean age in years (standard deviation)	70.2 (11.5)	71.7 (10.5)	<0.0005
Male sex	1031 (76.7%)	3190 (77.0%)	0.817
Current use of antihypertensive drugs			
Monotherapy, total	426 (31.7%)	1630 (39.3%)	
- Beta-blockers	152 (35.7%)	578 (35.5%)	
- Calcium channel blockers	34 (8.0%)	166 (10.2%)	
- Miscellaneous antihypertensives	2 (0.5%)	1 (0.1%)	
- Thiazide or thiazide-like diuretics	46 (10.8%)	166 (10.2%)	
- Angiotensin converting enzyme inhibitors	93 (21.8%)	367 (22.5%)	
- Angiotensin receptor blockers	53 (12.4%)	257 (15.8%)	
- Potassium-sparing drugs	5 (1.2%)	9 (0.6%)	
- Loop diuretics	41 (9.6%)	86 (5.3%)	
Combination of 2 antihypertensive drugs	444 (33.0%)	1418 (34.2%)	
Combination of ≥ 3 antihypertensive drugs	475 (35.3%)	1097 (26.5%)	
High cardiovascular risk-profile	1047 (77.8%)	2792 (67.4%)	<0.0005
Nonantiarrhythmic QT prolonging drugs	107 (8.0%)	157 (3.8%)	<0.0005
Antiarrhythmic drugs class I and III	82 (6.1%)	79 (1.9%)	<0.0005
Other antiarrhythmic drugs	209 (15.5%)	108 (2.6%)	<0.0005
Antidiabetic drugs	322 (23.9%)	819 (19.8%)	0.001
Drugs for obstructive airway disease	141 (10.5%)	188 (4.5%)	<0.0005

Table 2

The use of antihypertensive drugs according to their potential impact on serum potassium levels and the risk of out-of-hospital cardiac arrest

A. First analysis				
	Cases (*n* = 1345) (100%)	**Controls (*n* = 4145) (100%)**	**Crude OR**	**Adjusted OR[a]**
Antihypertensives with neutral effect	214 (15.9%)	875 (21.1%)	1 (reference)	1 (reference)
Antihypertensives potentially influencing serum potassium levels	1131 (84.1%)	3270 (78.9%)	1.43 (1.22–1.69)	1.31 (1.10–1.55)
B. Second analysis				
	Cases (*n* = 1345) (100%)	**Controls (*n* = 4145) (100%)**	**Crude OR**	**Adjusted OR[a]**
Antihypertensives with neutral effect	214 (15.9%)	875 (21.1%)	1 (reference)	1 (reference)
Hypokalaemia-inducing antihypertensives	187 (13.9%)	579 (14.0%)	1.33 (1.07–1.66)	1.39 (1.10–1.76)
Hyperkalaemia-inducing antihypertensives	379 (28.2%)	1244 (30.0%)	1.27 (1.05–1.53)	1.15 (0.95–1.40)
Combination of antihypertensives with hypo- and hyperkalaemic effects	565 (42.0%)	1447 (34.9%)	1.62 (1.35–1.93)	1.42 (1.17–1.72)

[a]Adjusted for age, sex, anti-arrhythmic drugs class I and III, other antiarrhythmic drugs, nonantiarrhythmic QT prolonging drugs, high cardiovascular risk profile, antidiabetics, and drugs for obstructive airway disease.
OR, odds ratio

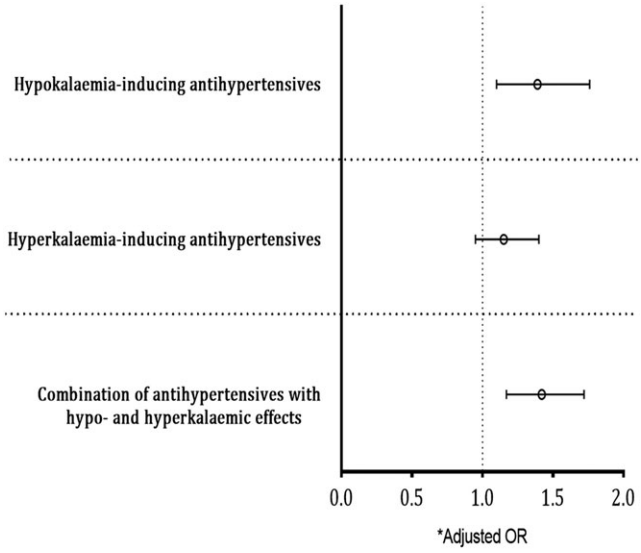

Figure 2

The use of antihypertensive drugs according to their potential impact on serum potassium levels and the risk of out-of-hospital cardiac arrest. OR, odds ratio

OHCA risk was increased significantly only with hypokalaemia-inducing antihypertensives compared to antihypertensives with neutral effect (adjusted OR 1.34; 95%CI 1.05–1.70, Table 3B).

Sensitivity analysis

In the sensitivity analyses in which we excluded patients with antiarrhythmic drugs and/or non-antiarrhythmic QT prolonging drugs, the results were consistent with our main analyses results (Table S1).

Discussion

Our study demonstrated that the risk of OHCA was significantly increased in patients who were current users of hypokalaemia-inducing antihypertensives and patients using a combination of antihypertensives with hypo- and hyperkalaemic effects compared to antihypertensives with neutral effect on serum potassium levels. There was no difference in OHCA risk between users of hyperkalaemia-inducing antihypertensives *vs*. users of antihypertensives with neutral effect.

To the best of our knowledge, our study is the first to assess the association between the use of antihypertensive drugs according to their potential impact on serum potassium levels and the risk of OHCA in which ECG documentation of VT/VF was used to limit the risk of misclassification.

Only a few studies addressed whether use of antihypertensive drugs is associated with increased SCA risk. In a meta-analysis of seven trials by Hoes *et al.* [10], the use of non-potassium-sparing diuretics increased the risk of SCA compared to placebo [risk ratio (RR) 1.5; 95%CI 1.1–2.0]. Moreover, a case–control study involving 114 cases of SCA found that the risk of SCA in hypertensive patients who used a thiazide with a potassium-sparing diuretic was lower than in hypertensive patients who used a thiazide diuretic without a potassium-sparing diuretic (adjusted OR 0.3; 95%CI 0.1–0.7). Furthermore, a case–control study conducted by Hoes *et al.* [12] found increased risks of sudden death in patients who used non-potassium-sparing diuretics (mainly hydrochlorothiazide, chlorthalidone and furosemide; adjusted RR 2.2; 95%CI 1.1–4.6), and in patients using β-blockers

Table 3

Use of antihypertensives according to their potential impact on serum potassium levels and the risk of out-of-hospital cardiac arrest among patients with at most two antihypertensive drugs

A. First analysis				
	Cases (*n* = 870) (100%)	**Controls (*n* = 3048) (100%)**	**Crude OR**	**Adjusted OR[a]**
Antihypertensives with neutral effect	214 (24.6%)	874 (28.7%)	1(reference)	1(reference)
Antihypertensives potentially influencing serum potassium levels	656 (75.4%)	2174 (71.3%)	1.24 (1.05–1.48)	1.17 (0.98–1.41)
B. Second analysis				
	Cases (*n* = 870) (100%)	**Controls (*n* = 3048) (100%)**	**Crude OR**	**Adjusted OR[a]**
Antihypertensives with neutral effect	214 (24.6%)	874 (28.7%)	1 (reference)	1 (reference)
Hypokalaemia-inducing antihypertensives	168 (19.3%)	537 (17.6%)	1.29 (1.02–1.62)	1.34 (1.05–1.70)
Hyperkalaemia-inducing antihypertensives	320 (36.8%)	1117 (36.6%)	1.18 (0.97–1.44)	1.08 (0.88–1.33)
Combination of antihypertensives with hypo- and hyperkalaemic effects	168 (19.3%)	520 (17.1%)	1.33 (1.06–1.67)	1.23 (0.96–1.57)

[a]Adjusted as in Table 2
OR, odds ratio

(adjusted RR 1.8; 95%CI 1.1–2.9) compared to patients receiving mainly potassium-sparing diuretics. Moreover, Hoes *et al*. [12] suggested a potential effect of hypokalaemia in increasing the risk of sudden death in patients who used non-potassium-sparing diuretics. In our study, the findings are consistent with these above studies, however, these studies had the limitation that ECG documentation of VT/VF of SCA was missing.

Many studies have confirmed the association between hypokalaemia and VT/VF [15–17]. However, the association between use of diuretics potentially inducing hypokalaemia and VT/VF is still controversial. Few studies suggested that use of diuretics inducing hypokalaemia was associated with an increased risk of ventricular arrhythmia [18, 19]. In contrast, other studies suggested that there is no association between the use of diuretics potentially inducing hypokalaemia and VT/VF [20–24]. In our opinion, most of these studies have limitations such as low sample size and short follow-up duration.

A recent Danish study reported a U-shaped relationship between all-cause mortality and serum potassium levels in hypertensive patients. Both serum potassium levels below and above the interval of 4.1–4.7 mmol l^{-1} were associated with increased mortality [25]. We think our study adds to these findings since in the Danish study all-cause mortality was studied, while we evaluated OHCA with ECG documented VT/VF, which, from the perspective of the biological mechanism by which potassium influences mortality, is more relevant. However, we found no increased risk of OHCA among users of hyperkalaemia-inducing antihypertensives and our study was limited by lacking of information on serum potassium levels. Therefore, further studies with availability of serum potassium levels are needed to assess the association between various antihypertensive drug classes stratified to their potential effects on serum potassium levels and the risk of VT/VF.

Several studies have established the benefits of antihypertensive drugs in reducing cardiovascular morbidity and mortality in patients with hypertension [26, 27]. However, a recent systematic review in hypertensive patients found that antihypertensive drugs (mainly thiazide diuretics) did not reduce SCA risk (RR 0.96; 95%CI 0.81–1.15), although these drugs did significantly reduce nonfatal and fatal myocardial infarction (MI) compared to placebo or no treatment [28]. However, this study had the limitation that the cause of SCA was unknown.

In our sensitivity analyses, we excluded patients who were taking antiarrhythmic drugs and/or non-antiarrhythmic QT prolonging drugs and we found that the risk of OHCA was still significantly increased with hypokalaemia-inducing antihypertensives and a combination of antihypertensives with hypo- and hyperkalaemic effects compared to antihypertensives with neutral effect. Moreover, we did a restricted analysis by including only patients who were current users of a maximum of two antihypertensives and found that OHCA risk was still significantly increased with hypokalaemia-inducing antihypertensives compared to antihypertensives with neutral effect. However, we also found that OHCA risk of a combination of antihypertensives with hypo- and hyperkalaemic effects was not significantly increased as we found in our main analysis. This may be caused by a loss of power and/or excluding from our analysis most patients who were more likely to have severe hypertension since they were on more than two antihypertensives.

There are some strengths and limitations of our study. A strong point is that our cases had ECG documented VT/VF. In the majority of previous studies, sudden death was the outcome without any distinction between VT/VF and asystole. A limitation is that some well-established risk factors for VT/VF such as socioeconomic status, comorbidities, occupation, region, drinking alcohol, smoking and body mass index were not available in our database. Another limitation is that our database lacks information on serum potassium levels. Interpretation of such levels analysed in serum samples drawn during and immediately following SCA is problematic, because, in this situation, serum acidosis is generally present, and impacts on serum potassium levels. Thus, serum samples drawn during this period may not reflect serum potassium levels immediately preceding OHCA. Given that OHCA occurrence can presently not be predicted, it is very difficult to collect information on serum potassium levels immediately preceding OHCA. Another limitation is that the indication for the use of antihypertensive drugs, the classification of the degree of hypertension, and blood pressure measurements were not available. To counteract confounding by indication as much as possible, we restricted our analysis to patients who were current users of a maximum of two antihypertensive drugs. Thereby, the patients were likely to have mild or moderate hypertension.

Conclusion

The risk of OHCA is significantly increased in patients who were current users of hypokalaemia-inducing antihypertensives and patients using a combination of antihypertensives with hypo- and hyperkalaemic effects.

Competing Interests

There are no competing interests to declare.

The ARREST registry is supported by the Netherlands Organization for Scientific Research (NWO, grant ZonMW Vici 918.86.616 to H.L.T.), the Dutch Medicines Evaluation Board (MEB/CBG), the Netherlands CardioVascular Research Initiative (Dutch Heart Foundation, Dutch Federation of University Medical Centres, Netherlands Organization for Health Research and Development, Royal Netherlands Academy of Sciences - CVON2012–10 Predict), and Biobanking and Biomolecular Research Infrastructure The Netherlands (BBMRI-NL).

Contributors

F.F.A. wrote the manuscript and performed the analysis; P.C. S. and M.T.B. obtained and worked up the original data to a data matrix ready for statistical analyses; F.F.A., P.C.S., M.d. G., M.T.B., A.d.B., O.H.K. and H.L.T. designed the research and critically revised and approved the manuscript.

References

1 Huikuri HV. Editorial: implantable cardioverter-defibrillator therapy and the total burden of sudden cardiac death. Europace 2009; 11: 1574.

2 Bardai A, Amin AS, Blom MT, Bezzina CR, Berdowski J, Langendijk PN, *et al*. Sudden cardiac arrest associated with use of a non-cardiac drug that reduces cardiac excitability: evidence from bench, bedside, and community. Eur Heart J 2013; 34: 1506–16.

3 Deo R, Albert CM. Epidemiology and genetics of sudden cardiac death. Circulation 2012; 125: 620–37.

4 Kjeldsen K. Hypokalemia and sudden cardiac death. Exp Clin Cardiol 2010; 15: e96–9.

5 Schulman M, Narins RG. Hypokalemia and cardiovascular disease. Am J Cardiol 1990; 65: E4–9.

6 Paice B, Gray JM, McBride D, Donnelly T, Lawson DH. Hyperkalaemia in patients in hospital. Br Med J (Clin Res Ed) 1983; 286: 1189–92.

7 Parham WA, Mehdirad AA, Biermann KM, Fredman CS. Hyperkalemia revisited. Tex Heart Inst J 2006; 33: 40–7.

8 Kuijvenhoven MA, Haak EAF, Gombert-Handoko KB, Crul M. Evaluation of the concurrent use of potassium-influencing drugs as risk factors for the development of hyperkalemia. Int J Clinical Pharm 2013; 1–6.

9 Macdonald JE, Struthers AD. What is the optimal serum potassium level in cardiovascular patients? J Am Coll Cardiol 2004; 43: 155–61.

10 Hoes AW, Grobbee DE, Lubsen J. Sudden cardiac death in patients with hypertension. An association with diuretics and β-blockers? Drug Saf 1997; 16: 233–41.

11 Siscovick DS, Raghunathan TE, Psaty BM, Koepsell TD, Wicklund KG, Lin X, *et al*. Diuretic therapy for hypertension and the risk of primary cardiac arrest. N Engl J Med 1994; 330: 1852–7.

12 Hoes AW, Grobbee DE, Lubsen J, Man in 'T Veld AJ, Van der Does E, Hofman A. Diuretics, β-blockers, and the risk for sudden cardiac death in hypertensive patients. Ann Intern Med 1995; 123: 481–7.

13 Priori SG, Aliot E, Blømstrom-Lundqvist C, Bossaert L, Breithardt G, Brugada P, *et al*. Task force on sudden cardiac death of the European Society of Cardiology. Eur Heart J 2001; 22: 1374–450.

14 Blom MT, Van Hoeijen DA, Bardai A, Berdowski J, Souverein PC, De Bruin ML, *et al*. Genetic, clinical and pharmacological determinants of out-of-hospital cardiac arrest: rationale and outline of the AmsteRdam resuscitation studies (ARREST) registry. Open Heart 2014; 1: e000112.

15 Solomon RJ, Cole AG. Importance of potassium in patients with acute myocardial infarction. Acta Med Scand 1981; 209: 87–93.

16 Nordrehaug JE, Johannessen KA, von der Lippe G. Serum potassium concentration as a risk factor of ventricular arrhythmias early in acute myocardial infarction. Circulation 1985; 71: 645–9.

17 Hulting J. In-hospital ventricular fibrillation and its relation to serum potassium. Acta Med Scand 1981; 209: 109–16.

18 Holland OB, Nixon J, Kuhnert L. Diuretic-induced ventricular ectopic activity. Am J Med 1981; 70: 762–8.

19 Hollifield JW, Slaton PE. Thiazide diuretics, hypokalemia and cardiac arrhythmias. Acta Med Scand 1981; 209 (S647): 67–73.

20 Papademetriou V, Burris JF, Notargiacomo A, Fletcher RD, Freis ED. Thiazide therapy is not a cause of arrhythmia in patients with systemic hypertension. Arch Intern Med 1988; 148: 1272–6.

21 Madias JE, Madias NE, Gavras HP. Nonarrhythmogenicity of diuretic-induced hypokalemia: [ill] ts evidence in patients with uncomplicated hypertension. Arch Intern Med 1984; 144: 2171–6.

22 Siegel D, Hulley SB, Black DM, Cheitlin MD, Sebastian A, Seeley DG, *et al*. Diuretics, serum and intracellular electrolyte levels, and ventricular arrhythmias in hypertensive men. JAMA 1992; 267: 1083–9.

23 Kostis JB, Lacy CR, Hall WD, Wilson AC, Borhani NO, Krieger SD, *et al*., SHEP Study Group. The effect of chlorthalidone on ventricular ectopic activity in patients with isolated systolic hypertension. Am J Cardiol 1994; 74: 464–7.

24 Narayan P, Papademetriou V. Effect of hydrochlorothiazide therapy on cardiac arrhythmias in African-American men with systemic hypertension and moderate to severe left ventricular hypertrophy. Am J Cardiol 1996; 78: 886–9.

25 Krogager ML, Torp-Pedersen C, Mortensen RN, Køber L, Gislason G, Søgaard P, *et al*. Short-term mortality risk of serum potassium levels in hypertension: a retrospective analysis of nationwide registry data. Eur Heart J 2017; 38: 104–12.

26 Gueyffier F, Bulpitt C, Boissel JP, Schron E, Ekbom T, Fagard R, *et al*. Antihypertensive drugs in very old people: a subgroup meta-analysis of randomised controlled trials. Lancet 1999; 353: 793–6.

27 Musini VM, Tejani AM, Bassett K, Wright JM. Pharmacotherapy for hypertension in the elderly. Cochrane Database Syst Rev 2009; 4: CD000028.

28 Taverny G, Mimouni Y, LeDigarcher A, Chevalier P, Thijs L, Wright JM, *et al*. Antihypertensive pharmacotherapy for prevention of sudden cardiac death in hypertensive individuals. Cochrane Database Syst Rev 2016; 3: CD011745.

Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article.

http://onlinelibrary.wiley.com/doi/10.1111/bcp.13356/suppinfo

Table S1 The use of antihypertensive drugs according to their potential impact on serum potassium levels and the risk of out-of-hospital cardiac arrest after exclusion of patients using antiarrhythmic drugs and/or nonantiarrhythmic QT-prolonging drugs