



Important New Evidence Service

In Partnership with The Centre for Medicines
Optimisation at Keele University

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Hypertension: Antihypertensives, serum potassium and sudden cardiac arrest

Sudden death accounts for over half of all cardiovascular deaths, often due to a cardiac arrest caused by ventricular tachycardia/ventricular fibrillation (VT/VF). Hypo- and hyperkalaemia are known risk factors for cardiac arrest, and a new study has investigated the association between antihypertensives, based on their potential impact on serum potassium, and an out-of-hospital cardiac arrest where VT/VF was documented. The risk was higher in users of hypokalaemia-inducing antihypertensives, and also in users of a combination of hypo- and hyperkalaemia-inducing antihypertensives, compared with users of antihypertensives with a neutral effect on serum potassium.

While this new evidence provides further insight into the possible triggers for a sudden cardiac arrest, the limitations of this study and the potential for uncontrolled confounding should be considered. These findings should in no way undermine the important role of antihypertensives in reducing the risk of cardiovascular events, and people with high blood pressure should be managed according to [NICE Guidance](#).

Reference: Alharbi FF, Souverein PC, de Groot MCH *et al.* [The impact of serum potassium-influencing antihypertensive drugs on the risk of out-of-hospital cardiac arrest: A case-control study](#). Br J Clin Pharmacol, 83: 2541–2548. doi: [10.1111/bcp.13356](#).

What do we know already?

- It is known that antihypertensives have different effects on serum potassium levels:
 - Hypokalaemia-inducing antihypertensives include loop diuretics, thiazide and thiazide-like diuretics.
 - Hyperkalaemia-inducing antihypertensives include angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and also potassium-sparing diuretics, such as spironolactone, eplerenone, amiloride and triamterene, which may be used alongside thiazide diuretics to prevent hypokalaemia.
 - Antihypertensives with a neutral effect include beta-blockers and calcium channel blockers (CCBs).
- Sudden cardiac arrest is a complex multifactorial event, most commonly caused by VT/VF. Electrolyte imbalances, including hypo- and hyperkalaemia, are known risk factors for sudden cardiac arrest.
- Previous studies have reported an increased risk of sudden death among users of hypokalaemia-inducing antihypertensives. However, the definition of 'sudden death' in these studies did not require electrocardiogram (ECG) confirmation of VT/VF. Thus misclassification is a possibility, with sudden death possibly resulting from other causes, such as stroke.
- A 2016 Cochrane review found no increased risk of sudden death with diuretic antihypertensives, although the authors cautioned that the paucity of data limited the quality of their analysis. This same review concluded that whilst antihypertensives reduce both fatal and non-fatal myocardial infarctions, they do not appear to reduce the risk of sudden cardiac death in hypertensive patients.
- Advice on the management of hypertension is set out in [NICE Clinical Guideline 127](#).

What does this evidence add?

- This is the first study to investigate a possible association between antihypertensives, stratified according to their potential effects on serum potassium levels, and the risk of an out-of-hospital cardiac arrest (OHCA), where an ECG has documented the occurrence of VT/VF.
- Compared with current users of antihypertensive drugs with a neutral effect on serum potassium (*see overleaf for classification*), the risk of OHCA was significantly higher in users of hypokalaemia-inducing antihypertensives ([Odds Ratio \[OR\]](#) 1.39, 95% [Confidence Interval \[CI\]](#) 1.10-1.76), and also users taking a combination of antihypertensives with hypo- and hyperkalaemic effects (OR 1.42, 95%CI 1.17-1.72).
- This study had a number of potential limitations. Data on other established risk factors for VT/VF, including smoking, drinking, comorbidities and BMI, were lacking. Indications for the use of antihypertensive drugs and

blood pressure measurements were also not available, as was neither serum potassium nor other electrolyte levels.

- More studies are needed to assess this association and these findings should not change current practice. Whilst not investigated in this study, the findings are perhaps a reminder about monitoring requirements for antihypertensives, which, according to recent [UK findings](#) (discussed in a previous [KINES](#)) are often poorly adhered to.
- Monitoring recommendations for antihypertensive drugs are available in a [NICE Clinical Knowledge Summary](#).

Study details

Study design:

- This case-control study was performed among current users of antihypertensive drugs. 'Cases' were patients that had suffered an out-of hospital cardiac arrest (OHCA) with ECG-documented VT/VF in the AmsteRdam Resuscitation Studies (ARREST) registry between 5th July 2005 and 28th December 2011. 'Controls' were non-OHCA individuals matched by age, sex and date, drawn from the Pharmaco-Morbidity Record Linkage System (PHARMACO-RLS) database.
- 2,518 cases from the ARREST registry were matched with up to 5 controls (10,597 patients) from the PHARMACO-RLS database. From these cases, adult patients (aged 18 and over) were selected who were current users of antihypertensive drugs (1,345 cases and 4,145 controls).
- Users of antihypertensive drugs were stratified into 4 drug classes according to their potential impact on serum potassium levels:
 - I. antihypertensives with neutral effect (monotherapy with beta-blockers or CCBs or miscellaneous drugs or a combination of at least two of these antihypertensives)
 - II. hypokalaemia-inducing antihypertensives (monotherapy with 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 with ACE inhibitors or ARBs or potassium-sparing diuretics or a combination of at least one of these drugs and antihypertensives with neutral effect)
 - 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)
- Users of verapamil, diltiazem and sotalol were excluded because of their antiarrhythmic indication.
- In their first analysis, the authors assessed the risk of OHCA, grouping antihypertensives potentially influencing serum potassium levels vs. antihypertensives with a neutral effect.
- In the second analysis, antihypertensives potentially influencing serum potassium levels were divided into 3 categories: hypokalaemia-inducing, hyperkalaemia-inducing, and a combination of antihypertensives with both effects. The risk of OHCA within these categories was compared to antihypertensives with a neutral effect.
- A further 'restricted analysis' was carried out selecting only people who were using of a maximum of 2 antihypertensive drugs. The intention of this was to reduce 'confounding by indication', by including only patients who were more likely to have mild or moderate hypertension.

Results:

- The risk of OHCA was significantly increased with antihypertensives potentially influencing serum potassium levels (adjusted OR 1.31; 95% CI 1.10 – 1.55) compared with antihypertensives with a neutral effect.
- A statistically significant increase in 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 with antihypertensives with a neutral effect.
- There was no difference in OHCA risk between hyperkalaemia-inducing antihypertensives (adjusted OR 1.15; 95% CI 0.95 – 1.40) compared with antihypertensives with a neutral effect.
- In the restricted analysis, which included 870 cases and 3,048 controls that were exposed to a maximum of 2 antihypertensives, OHCA risk was increased significantly only with hypokalaemia-inducing antihypertensives (adjusted OR 1.34; 95% CI 1.05 – 1.70) compared with antihypertensives with a neutral effect.

Level of evidence: Level 2 (limited quality patient-oriented evidence) according to the [SORT criteria](#).

Study funding: Various research organisations in Netherlands, and the Dutch Medicines Evaluation Board.