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Resuscitation

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Clinical paper

Ventricular fibrillation waveform characteristics in out-of-hospital cardiac arrest and cardiovascular medication use



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Abstract

Background: Ventricular fibrillation (VF) waveform analyses are considered a reliable proxy for OHCA characteristics in out-of-hospital cardiac arrest (OHCA), but patient characteristics such as cardiovascular medication use might also be associated with changes in VF waveform measures.

Objectives: To assess associations between cardiovascular medication use and amplitude spectrum area (AMSA) of VF, while correcting for the presence of cardiovascular disease (CVD), CVD risk factors, and OHCA characteristics.

Methods: We included 990 VF patients from an OHCA registry in the Netherlands, with available information on medical history and cardiovascular medication use. Associations between cardiovascular medication use and AMSA were tested in a multivariate linear regression model, adjusting for CVD, CVD risk factors, and OHCA characteristics. Model performance was shown using R-square and R-change. We also calculated whether medication use was associated with faster dissolution of AMSA to lower values with increasing time delay.

Results: In the multivariate analysis, when corrected for CVD, CVD risk factors and OHCA characteristics, only potassium-sparing agents were associated with a lower AMSA when compared to patients using other cardiovascular medications (OR 0.46 [95% CI 0.10–0.81]; $P < 0.012$). The decrease in AMSA with increasing EMS-call-to-ECG delay was the same for patients with and without cardiovascular medication use (all $P > 0.05$). Only a small part of the variance in AMSA could be explained by medication use (R-square 0.003–0.026). Adding OHCA characteristics to the model resulted in the largest R square change (0.09–0.15).

Conclusions: It is unlikely that there is a strong and clinically relevant independent pharmacologic effect of cardiovascular medication use on AMSA. In OHCA, AMSA might be used as patient management tool without considering cardiovascular medication use.

Keywords: Heart arrest, Tachyarrhythmia, Ventricular fibrillation, Quantitative waveform measures, Pharmacotherapy

Introduction

The main predictor of favorable outcome from out-of-hospital cardiac arrest (OHCA) is the presence and defibrillation of ventricular fibrillation (VF).^{1,2} VF signals can be quantified by continuous VF

waveform measures, and these measures generally correlate well with shock success, and short- and long-term survival,^{3–8} as high amplitude, high frequency and coarse VF signals are considered a proxy for favorable OHCA characteristics.^{9,10} Nevertheless, the VF signal can also change by previous or acute myocardial infarction, heart failure, and increased left ventricular diameter or mass.^{4,11–19}

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<https://doi.org/10.1016/j.resuscitation.2020.02.027>

Also the use of beta blockers or angiotensin converting enzyme (ACE)-inhibitors has been associated with low frequency VF.^{4,20,21} The associations between VF waveform measures and medication may be driven by the underlying disease for which the medication was prescribed. If VF waveform measures are to be used to guide treatment in an OHCA setting, it is important to evaluate whether they are affected by use of cardiovascular medication. Likewise, when assessing the effect of cardiovascular medication on the VF signal, cardiovascular disease (CVD) and OHCA characteristics need to be accounted for.

In the present investigation, we studied the association between the amplitude spectrum area (AMSA) of the VF signal and the use of cardiovascular medications in relation to concomitant CVD, risk factors and OHCA characteristics.

Methods

Study design, setting and patient selection

The ARREST (AmsteRdam REsuscitation STudies) registry is an ongoing prospective registry of all resuscitation attempts in the North-Holland province of the Netherlands. This province has a population of 2.4 million people and covers 2671 km², including both urban and rural communities. For this study, we included all patients with ECG documented VF between July 2005 and December 2012, regardless of survival to hospital admission. We excluded patients with a clear non-cardiac cause of OHCA. Only patients with ECG recordings from LIFEPAK (Physio-Control, Redmond (WA), USA) automated external defibrillator (AED) (Lifepak 500, Lifepak 1000 and Lifepak CR plus) or manual defibrillator (Lifepak 12) (constituting more than 90% of all used defibrillators in the study region) were included. Patients with missing information on medical history or medication use data were excluded.

All data were collected according to the Utstein recommendations.²² Written informed consent was obtained from all participants who survived the OHCA. The Medical Ethics Review Board of the Academic Medical Center, Amsterdam, approved the study, including the use of data from patients who did not survive the OHCA.

Data collection

Data collection of the ARREST registry and a waveform analysis sub-study has been described in detail before.^{17,23} In short, for all EMS-calls with suspected OHCA, dispatch forms are collected from the dispatch center. In cases of OHCA, paramedics provide information regarding circumstances of the OHCA, OHCA characteristics and whether patients were transported to the hospital. If an AED was attached, research staff collected the ECG of the AED shortly thereafter. Manual defibrillator ECGs were transmitted electronically to the study center. If a patient was admitted to hospital, information regarding treatment during hospital stay was collected from hospital charts.

The timestamp of EMS call and time of initial rhythm recording (with synchronized clock times) from ambulance defibrillator or AED was used to calculate the time delay between EMS call and initial rhythm recording (call-to-ECG delay). The continuous ECGs and impedance signals with a sample rate of 125 Hz were analyzed with MATLAB (R2014B, the Mathwork Inc.). Two to five seconds of the first artifact free VF segments were manually selected for analysis. These

segments were band-pass filtered between 4 and 48 Hz and using a fast Fourier transformation transformed into the frequency domain.¹⁷ AMSA was calculated by summation of the frequencies in the VF signal weighted by their corresponding amplitudes.²⁴

In addition to call-to-ECG delay, OHCA characteristics that were included were location of collapse (home or public), bystander- or EMS-witnessed collapse and bystander cardiopulmonary resuscitation (CPR).

Complete drug history in the year preceding the OHCA was retrieved from the patient's pharmacy. These records are considered complete, as all patients in the Netherlands are registered at a single community pharmacy. These drug-dispensing records show all obtained prescriptions. Therefore medication that was prescribed by a physician but never obtained by the patient was not included in the database. Medical history was obtained from the patient's general practitioner (GP) by a study specific questionnaire or from hospital case files. In the Netherlands, every person has one single GP, and for non-life threatening medical problems the GP needs to be visited before seeking help from a medical specialist. If a patient is discharged from the hospital or visits a medical specialist, a discharge letter is sent to the GP, who is therefore aware of all medical history of the patient and records it in the patient's records.

Outcome and definitions

AMSA of the first analyzable VF segment was calculated as main outcome measure.

Drugs were classified according to the Anatomical Chemical Therapeutic (ATC) code of the World Health Organization.²⁵ Patients were considered to actively use medication during OHCA if its prescription date fell within a 30 days window before the OHCA date. We analyzed all ATC C (cardiovascular system) main groups and ATC C subgroups with more than 10 users. Fixed-dose combinations were shown as individual groups according to their ATC codes, and were excluded from the relevant comparator groups (e.g., fixed-dose combination of an ACE inhibitor and thiazide was excluded from the comparator group of ACE inhibitors as well as the thiazide group). In addition, we also included ATC B01 (anti-thrombotic agents) with subgroups, and A10 (diabetes medication). The use of any ATC C, B01 or A10 medication was defined as cardiovascular medication use.

For this study, CVD and CVD risk factors were considered to be present if this was indicated by the GP or described in the hospital documentation. CVD was defined as: history of heart failure, previous myocardial infarction, valve disorders, cardiomyopathy, and atrial or ventricular tachyarrhythmias. CVD risk factors were defined as: age >65 years, hypertension, dyslipidemia, obesity, smoking, diabetes type 1 or 2, and familial sudden cardiac death.

Data analysis

Descriptive statistics were shown as n (%) and mean (SD) where applicable. AMSA and time intervals had a non-normal distribution and were expressed as median (interquartile range; IQR). We compared the median AMSA of users of cardiovascular medication to two groups: (a) patients who used any other cardiovascular medication, (b) patients who did not use any cardiovascular medication at the time of OHCA. Overall differences between users and non-users of target cardiovascular medication were tested using Mann–Whitney U tests, with Bonferroni correction for multiple testing; $P < 0.025$ was required to reach statistical significance.

We tested differences in median AMSA between CVD and risk factors, demographics and OHCA characteristics, with Mann–Whitney U test and Student's T-test where applicable. Cardiovascular medication use that had an univariate significant association with change in AMSA, was included in multiple linear regression analyses. We computed three different models with log transformed AMSA (due to non-normal distribution) as outcome; a model including only medication, a second model correcting for the presence of CVD and risk factors (including age), and a third model correcting for presence of CVD, risk factors, demographics and OHCA characteristics (including call-to-ECG delay). Covariates were only included in the model if there was an univariate association with AMSA with $P < 0.10$. The use of beta blockers, ACE-inhibitors, a history of myocardial infarction and/or heart failure were included regardless of significance, because these have been reported to be associated with lower AMSA.^{12,17,20,21} As a sensitivity analysis, we also performed a multiple linear regression analysis including only covariates that had an univariate association with AMSA with $P < 0.05$. We calculated the R-square and R-square change to assess the contribution of cardiovascular medication use, CVD (and risk factors) and OHCA characteristics on explained variance of AMSA in each model.

We also tested whether cardiovascular medication use was associated with faster dissolution of VF into asystole, using an interaction term of medication use and call-to-ECG delay. An interaction of $P < 0.05$ shows significant differences between the slope of AMSA decrease with increasing call-to-ECG delay between users of a specific type of medication versus no cardiovascular medication use.

All statistical tests were two-sided. Statistics were performed in IBM SPSS Statistics (SPSS Statistics for Mac, Version 25.0. Armonk, NY: IBM Corp).

Results

Of the 11,759 patients with EMS-call for presumed OHCA, 6155 were OHCA with a presumed cardiac cause and resuscitation attempted, of whom 2401 patients had a resuscitation attempt for OHCA with initial rhythm VF, and analyzable ECG. Of these patients, for 990 patients both complete medical history and medication use were available; these patients were included in our analysis, regardless of admission to hospital or survival (Fig. 1). A missing case analysis is provided in Supplemental Table 1. Patients with missing medication data were younger ($P = 0.007$), collapsed more often in public ($P = 0.001$) and had less often an EMS-witnessed collapse ($P < 0.001$) than the patients without missing data. Patients with missing medical history had a longer call-to-ECG delay ($P < 0.001$). The mean age of included patients was 65.1 year (± 14.2), 770 patients (78%) were men. Any type of cardiovascular medication was used by 563 patients (57%). One, two, three, four or five cardiovascular medications were used by 109 (11%), 106 (11%), 108 (11%), 111 (11%), and 129 patients (13%), respectively.

When comparing to no use of cardiovascular medication, we found an association with significantly lower AMSA for use of cardiac therapy (6.8 mV-Hz (IQR 2.4–14.3); $P = 0.019$; mainly driven by antiarrhythmics and vasodilators), loop diuretics (5.7 mV-Hz (IQR 2.2–15.7); $P = 0.006$), potassium-sparing agents (4.6 mV-Hz (IQR 2.2–15.7); $P = 0.001$), ACE-inhibitors (6.3 mV-Hz (IQR 2.4–15.4); $P = 0.008$), anti-thrombotics (6.9 mV-Hz (IQR 2.8–15.8); $P = 0.019$), and vitamin K antagonists (ATC B01AA, 7.5 mV-Hz (IQR 2.9–16.3); $P = 0.017$) (Table 1). When compared to use of any other cardiovascular medication, only use of potassium-sparing agents ($P = 0.007$) was associated with lower AMSA (Supplemental Table 2).

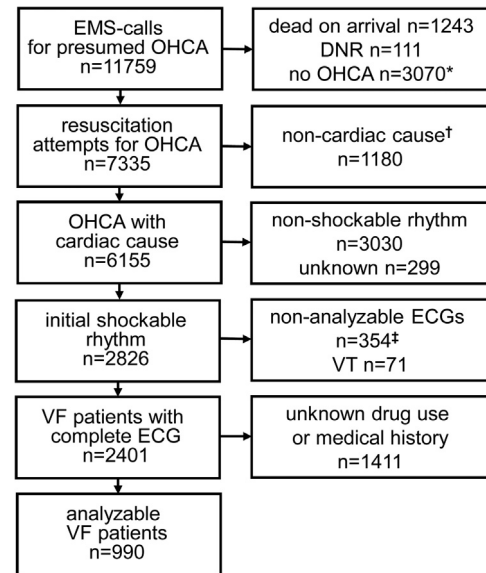


Fig. 1 – Flowchart of patient inclusion between July 4th 2005 and December 31st 2012.

***Including 4 patients with successful ICD shock.**

†Including 222 trauma cases, 79 drownings, 326 respiratory causes and 549 other non-cardiac causes (e.g. suicide, intoxications, neurologic, malignancies, aortic dissection/rupture etc.).

‡Including 181 non-LIFEPAK defibrillators, 114 paper tracings, 45 incomplete ECGs and 14 complete ECGs with artifacts such as pacemaker spikes or movement. DNR denotes do-not-resuscitate; EMS emergency medical history; Hx history; OHCA out-of-hospital cardiac arrest; VT ventricular tachycardia.

One or more known CVD risk factors were present in 80% of the patients, with hypertension ($n = 466$; 47%) and dyslipidemia ($n = 359$; 36%) as most prevalent risk factors. Only previous myocardial infarction ($P = 0.016$) was associated with a significantly lower AMSA. Familial sudden cardiac death was associated with a significantly higher AMSA ($P < 0.001$). All OHCA characteristics were associated with significant differences in AMSA, with lower AMSA for OHCA at home, longer call-to-ECG delay, absence of bystander or EMS-witnessed collapse, and absence of bystander CPR (Table 2).

Fig. 2 and Supplemental Table 2 show the results of the univariate and multivariate regression analysis showing associations of cardiovascular medication use with changes in AMSA. When adjusting for heart failure, myocardial infarction, obesity, familial sudden cardiac death and age in the model, there were no longer any statistically significant associations when compared to a control sample of patients using no CV medication. Further adjustment of the beta to zero (indicating no independent association) was observed when adding OHCA characteristics (location of collapse, call-to-ECG delay, EMS- or bystander witnessed collapse and bystander CPR) to the model. When compared to patients using any other cardiovascular medication, only use of potassium-sparing agents remained significantly associated with lower AMSA, also when adjusted for CVD and OHCA characteristics (Fig. 2). As a sensitivity analysis, we also calculated a model with only covariates that were significantly

Table 1 – AMSA in relation to target cardiovascular medication use when compared to no cardiovascular medication use.

All patients (N = 990)	(n (%))	AMSA (mV-Hz (IQR))	P*
No cardiovascular medication use (reference)	427 (43%)	8.7 (3.5–17.9)	N/A
<i>Any cardiovascular medication use</i>	563 (57%)	7.5 (2.7–16.1)	0.044
<i>C01: cardiac therapy</i>	151 (15%)	6.8 (2.4–14.3)	0.019 [†]
C01A: cardiac glycosides	56 (5.7%)	8.8 (2.4–16.2)	0.30
C01B: antiarrhythmics, class I/III	18 (1.8%)	4.9 (2.3–8.0)	0.069
C01D: vasodilators	97 (9.8%)	6.9 (2.7–15.0)	0.064
<i>C03: diuretics</i>	275 (28%)	7.2 (2.4–15.9)	0.030
C03A: thiazides	55 (5.6%)	8.4 (3.0–14.9)	0.38
C03B: low-ceiling diuretics, excl. thiazides	7 (0.7%)	9.9 (2.4–19.8)	0.85
C03C: high-ceiling (loop) diuretics	137 (14%)	5.7 (2.2–15.7)	0.006 [†]
C03D: potassium-sparing agents	54 (5.6%)	4.6 (1.3–10.3)	0.001 [†]
<i>C07: beta blockers</i>	287 (29%)	6.9 (2.4–16.8)	0.064
C07AA: beta blockers, non-selective	23 (2.3%)	6.5 (1.9–17.0)	0.33
C07AB: beta blockers, selective	245 (25%)	7.5 (2.4–16.1)	0.099
C07AG: alfa- and beta blockers	12 (1.2%)	6.7 (3.5–21.5)	0.73
<i>C08: calcium channel blockers</i>	125 (13%)	10.2 (3.4–19.0)	0.93
C08C: Ca-channel blocker, dihydropyridines	93 (9.4%)	8.4 (3.2–18.5)	0.87
C08D: Ca-channel blocker, non-dihydropyridines	33 (3.3%)	13.1 (4.6–21.4)	0.51
<i>C09: agents acting on renin-angiotensin-aldosterone system</i>	311 (31%)	6.8 (2.6–15.8)	0.033
C09A: ACE-inhibitors	185 (19%)	6.3 (2.4–15.4)	0.008 [†]
C09C: All-antagonists	84 (8.5%)	9.6 (3.4–17.3)	0.97
C09BA: ACE-inhibitors + thiazides	24 (2.4%)	6.3 (1.8–19.1)	0.43
C09D: All-antagonists + thiazides	29 (2.9%)	8.0 (2.8–12.8)	0.44
<i>C10: lipid modifying agents</i>	274 (28%)	7.4 (2.7–16.9)	0.11
<i>B01: anti-thrombotic therapy</i>	325 (33%)	6.9 (2.8–15.8)	0.019 [†]
B01AA: vitamin K antagonists	105 (11%)	6.6 (2.3–14.3)	0.017 [†]
B01AC: platelet aggregation inhibitors	230 (23%)	7.5 (2.9–16.3)	0.13
A10: drugs used in diabetes (n = 160)	126 (13%)	8.5 (2.8–15.1)	0.28

Table showing differences in AMSA between patients using target cardiovascular medication compared to patients using no cardiovascular medication (reference). Only showing groups with more than 10 users. As patients could use more than 1 type of medication, number of users in subgroups do not add up to number of main group users.

All denotes angiotensin II; ACE: angiotensin converting enzyme; AMSA: amplitude spectrum analysis; CV: cardiovascular; IQR: interquartile range.

* Difference in AMSA tested using Mann–Whitney U test. As we compared three groups (cardiovascular medication vs. no cardiovascular medication (this table) and target cardiovascular medication vs any other cardiovascular medication (Supplemental Table 1)), we applied Bonferroni correction; $P < 0.025$ was considered statistically significant.

† Statistically significant after Bonferroni correction.

associated with change in AMSA with $P < 0.05$. In this model, beta blocker use, obesity and heart failure were not included. The results of this model were similar to the results of our analysis with pre-defined variables (Supplemental Fig. 1). All additional analyses were performed in the model including the pre-specified variables.

Only a small part of the variance in AMSA could be explained by medication use (R-square 0.003–0.026) and CVD (R square 0.027–0.041); adding OHCA characteristics to the model resulted in the largest change of R square (0.09–0.15) (Supplemental Table 3).

There was no significant interaction between medication use and call-to-ECG delay in relation to AMSA; the decrease in AMSA with increasing EMS-call-to-ECG delay was the same for patients with and without cardiovascular medication use (all $P > 0.05$; Supplemental Tables 4 and 5).

Discussion

We have demonstrated that AMSA does not appear to be directly associated with cardiovascular medication use. When adjusted for underlying disease, most associations between cardiovascular

medication use and lower AMSA disappear, except for use of potassium-sparing agents. Also, the effect of medication, CVD risk factors and CVD are only modest when compared to the effect of the OHCA characteristics on AMSA. This suggests that when exploring the effect of AMSA-guided treatment during resuscitation, cardiovascular medication use may not need to be accounted for.

There are few studies exploring the effect of cardiovascular medication on AMSA or other VF waveform measures. We were not able to confirm the results of animal studies showing a lower AMSA associated with beta blocker use and ACE-inhibitors.^{20,21} In our study there was an univariate association with lower AMSA and ACE inhibitors, but this was not confirmed in the multivariate analysis. Shorter duration of VF (faster dissolution of VF to asystole) has been linked to the decline of incidence of VF during OHCA in the general population,^{20,26} but in this study we were not able to reproduce such an effect in relation to any cardiovascular medication use. As the absolute effect of CV medication on the VF signal was rather small, it is unlikely that this effect will be visible in relation to medication use in a population based study, as compared to isolated effects in an animal study.

Ristagno et al. studied the effect of cardiovascular medication use on AMSA in humans in a large cohort of OHCA patients.⁴ In that study,

Table 2 – AMSA in relation to cardiovascular disease, risk factors and OHCA characteristics.

	Yes n (%)	AMSA(IQR)	No n (%)	AMSA(IQR)	P ^a
<i>Cardiovascular disease (N=990)</i>					
Previous myocardial infarction	287 (29%)	5.9 (2.4–15.8)	689 (70%)	8.9 (3.2–17.0)	0.016
Heart failure	169 (8.0%)	7.2 (2.8–16.6)	794 (80%)	8.7 (3.0–17.0)	0.18
Valve disorders	139 (14%)	10.2 (2.9–19.3)	818 (83%)	7.9 (2.9–16.7)	0.10
Atrial tachyarrhythmias	166 (17%)	9.6 (2.8–16.9)	796 (80%)	7.8 (2.9–16.9)	0.73
Ventricular tachyarrhythmias	69 (7.0%)	9.7 (2.9–27.8)	890 (89%)	8.1 (2.9–16.7)	0.17
<i>Cardiovascular disease risk factors (N=990)</i>					
Age (>65 year)	513 (52%)	7.2 (2.9–15.3)	477 (48%)	9.1 (3.0–18.5)	0.053
Hypertension	466 (47%)	7.7 (2.9–16.6)	506 (51%)	8.5 (3.0–17.1)	0.65
Dyslipidemia	359 (36%)	7.9 (3.0–16.2)	611 (62%)	8.2 (2.9–17.2)	0.64
Obesity	190 (19%)	7.7 (2.8–14.8)	765 (77%)	8.4 (3.0–17.4)	0.08
Smoking	321 (32%)	8.9 (3.2–17.6)	642 (65%)	7.8 (2.9–16.6)	0.16
Diabetes type I	10 (1.0%)	8.1 (2.2–12.6)	957 (97%)	8.4 (3.0–17.1)	0.57
Diabetes type II	196 (20%)	7.6 (2.8–15.3)	777 (78%)	8.4 (3.0–17.3)	0.31
Familial sudden cardiac death	148 (14%)	12.6 (5.0–23.6)	809 (82%)	7.5 (2.8–15.9)	<0.001
<i>Demographics (N=990)</i>					
Male sex	770 (78%)	8.3 (2.9–16.4)	220 (22%)	8.0 (3.3–18.6)	0.29
<i>OHCA characteristics (N=990)</i>					
Location collapse home	614 (62%)	6.8 (2.4–15.9)	375 (38%)	10.1 (3.9–18.8)	<0.001
Call-to-ECG delay <8 min	582 (59%)	10.3 (4.5–19.8)	408 (41%)	4.7 (1.9–13.3)	<0.001
EMS-witnessed	106 (11%)	11.4 (5.6–24.6)	879 (89%)	7.5 (2.8–16.3)	<0.001
<i>Excluding EMS-witnessed collapse (N=879)</i>					
Bystander witnessed	737 (84%)	8.5 (3.0–17.3)	111 (13%)	3.4 (1.4–8.9)	<0.001
Bystander CPR	675 (77%)	8.4 (2.9–17.0)	167 (19%)	5.1 (1.9–14.8)	<0.001

Missing data: myocardial infarction n=14, heart failure n=27, valve disorders n=33, atrial tachyarrhythmias n=28, ventricular tachyarrhythmias n=69, hypertension n=18, dyslipidemia n=20, obesity n=35, smoking n=27, diabetes type 1 n=23, diabetes type 2 n=27, familial sudden cardiac death n=33, location of collapse n=1, bystander witness n=31, EMS-witnessed n=5, bystander CPR n=37.

AMSA denotes amplitude spectrum analysis; CPR: cardiopulmonary resuscitation; EMS: emergency medical services; IQR: interquartile range.

^a Differences tested using Mann–Whitney U Test.

a significantly lower AMSA was only observed in patients using centrally acting antihypertensives (used by less than 10 patients in our study) whereas no effect of use of beta blockers and ACE inhibitors on AMSA was noted. Differences in outcomes with our study might be explained by differences in control groups; almost half of our population did not use any cardiovascular medication, compared to only 30% in the study by Ristagno et al. This might attenuate the differences when testing differences between users and non-users of a specific type of medication.

No previous studies have shown an association between use of potassium-sparing agents and lower AMSA. Higher extracellular potassium levels are a known side-effect of potassium sparing agents. Antiarrhythmic drugs and higher potassium levels are known to lower the defibrillation threshold,²⁷ but whether higher potassium levels also relate to lower AMSA is yet unclear; we are not aware of human studies investigating this association. In an animal study it was shown that high extracellular potassium levels lower AMSA.²⁸ However, data on potassium levels in our patients at the time of the OHCA were not collected.

Remarkably, most medication that showed a univariate strong association with lower AMSA (loop diuretics, potassium-sparing agents, ACE inhibitors) might be used to treat heart failure. However, heart failure as reported by the GP was not significantly associated with lower AMSA. The study by Ristagno et al.⁴ did not show an association between heart failure and lower AMSA either. In our study, heart failure was reported by the GP without specification of severity. The combination of loop diuretics and ACE inhibitors with the addition of a potassium-sparing diuretic is rather specific for treatment of

symptomatic and more severe heart failure. As we were not informed of the severity of heart failure in patients reported by the GP, we could not evaluate the effect of disease severity on associations with lower AMSA, especially in relation to potassium-sparing agents.

Despite testing a wide range of CV medications, CVD, and risk factors, absolute differences in AMSA were only modest. By contrast, unfavorable OHCA characteristics had a much stronger AMSA lowering effect. Adding OHCA characteristics to the model had the largest effect on the explained variance of AMSA. This explains why AMSA remains a strong independent predictor for outcome of OHCA, also when corrected for medication use, CVD, and CVD risk factors.⁴ Therefore, any future use of AMSA during OHCA may not be constrained by patient characteristics such as previous CVD, CVD risk factors and concomitant cardiovascular medication use.

Limitations

There are limitations to this study. For a large number of patients, information on either medication use or medical history was missing. In the missing case analysis, we showed that patients with missing medication data were younger, collapsed more often in public and had less often an EMS-witnessed collapse. For patients collapsing in public places, especially when patients do not survive, sometimes the home-address is unknown or the community pharmacy/GP is unknown, which makes it impossible to retrieve the data. However, we do not believe that these differences materially change the (lack of) relation between AMSA and medication use and medical history.

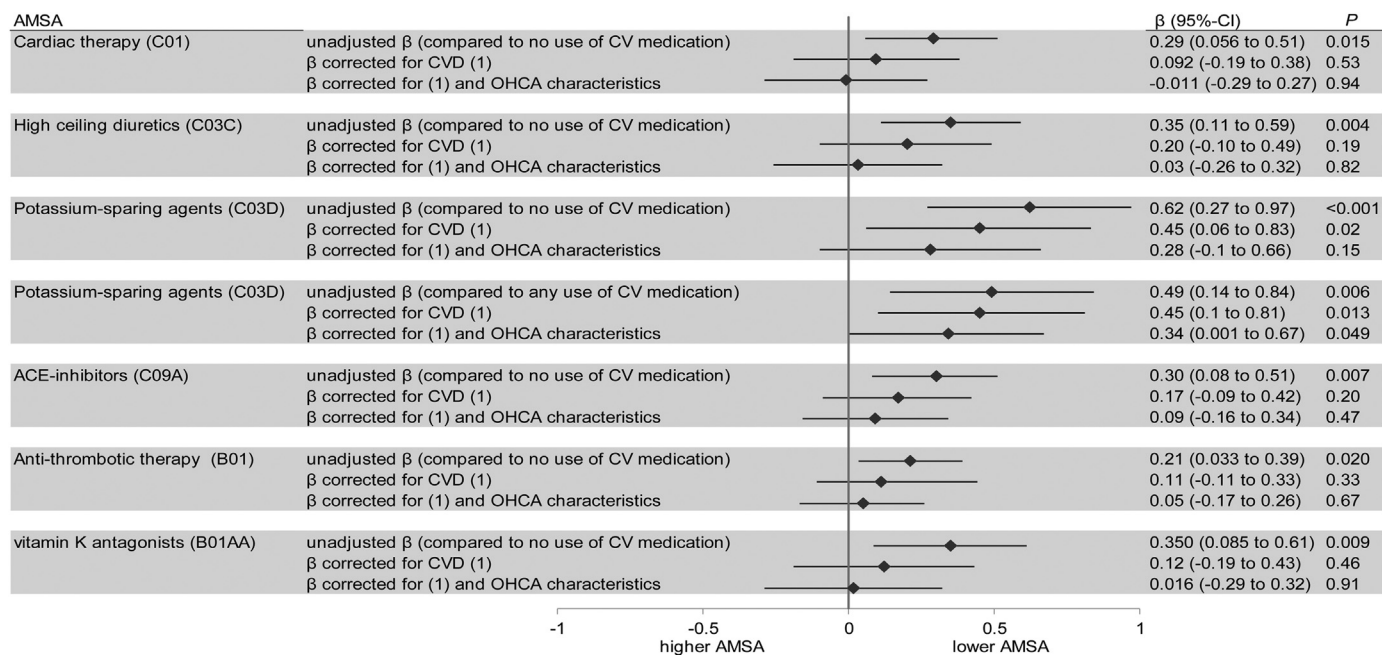


Fig. 2 – Forest plot showing associations between medication use and AMSA, when corrected for CVD, risk factors and OHCA characteristics in multivariate regression analysis.

Unadjusted β shows association of log transformed AMSA with cardiovascular medication use compared to patients using no CV medication; only includes ATC groups that univariately were associated with lower AMSA. As use of potassium-sparing agents was also associated with lower AMSA when compared to other CV medication use, this was also included. Using a multivariate linear regression model, β is adjusted for cardiovascular disease and risk factors (previous myocardial infarction, heart failure, obesity, age and familial sudden cardiac death; model 1) and subsequently adjusted for the variables from model 1 and OHCA characteristics (location of collapse, call-to-ECG delay, EMS- or bystander witnessed collapse and bystander CPR).

ACE denotes angiotensin converting enzyme; AMSA denotes amplitude spectrum analysis; CI: confidence interval; CPR: cardiopulmonary resuscitation; CVD: cardiovascular disease; EMS: emergency medical services.

More than 80% of patients using cardiovascular medication used more than 1 type of cardiovascular medication. Any pharmacologic effect is therefore for most patients a mixed effect of more types of cardiovascular medication. Furthermore, it is possible that patients collected, but did not take their prescribed medication. It has been estimated that only approximately 40% of patients are fully compliant to CV medication use.²⁹ This limitation is inherent to most medication studies, as in real world data medication use is unsupervised. CVD was assessed using a questionnaire completed by the GP after the OHCA. Severity of disease was not reported in this questionnaire, and information from other sources was not available.

AMSA is influenced by multiple factors, including the quality and quantity of chest compressions by bystanders as well as first responders and paramedics. Information on compression depth, chest recoil, pauses and other chest compression characteristics were not collected, and could not be accounted for in the multivariate regression analysis.

Conclusions

Cardiovascular medication use is not or only minimally associated with lower AMSA, when corrected for CVD, CVD risk factors and OHCA characteristics. It is unlikely that there is a strong and clinically relevant independent pharmacologic effect of any cardiovascular medication on AMSA. In OHCA, AMSA might be used as patient management tool without considering cardiovascular medication use.

Funding sources

M. Hulleman is supported by a grant from the Netherlands Heart Foundation (grant 2013T034). D.D. Salcido is supported by the following research grants; NHLBI1R01HL117979-01A1 (PI: Menegazzi, In-Kind), NHLBI 5K12HL109068-04 (PI: Yealy) and Laerdal Foundation Grant (PI: Salcido). H.L. Tan and M.T. Blom are supported by the European Union's Horizon 2020 research and innovation programme under acronym ESCAPE-NET, registered under grant agreement No 733381, and the Netherlands CardioVascular Research Initiative: the Dutch Heart Foundation, Dutch Federation of University Medical Centres, the Netherlands Organisation for Health Research and Development, and the Royal Netherlands Academy of Sciences (Predict-2 project).

The ARREST database is maintained by an unconditional grant of Physio Control Inc., part of Stryker, Redmond, WA. None of the funders were involved in the study design, data collection, analysis, interpretation or in writing of the manuscript.

Disclosures

R.W. Koster received the significant unconditional grant of Physio Control Inc., part of Stryker, Redmond (WA) for the data collection in the ARREST studies. The other authors report no relevant disclosures.

Acknowledgement

We thank all dispatch centers, ambulance services and first responders for their cooperation in the ongoing data collection.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.resuscitation.2020.02.027>.

REFERENCES

1. Wissenberg M, Lippert FK, Folke F, et al. Association of national initiatives to improve cardiac arrest management with rates of bystander intervention and patient survival after out-of-hospital cardiac arrest. *JAMA* 2013;310:1377–84.
2. Sasson C, Rogers MAM, Dahl J, Kellermann AL. Predictors of survival from out-of-hospital cardiac arrest: a systematic review and meta-analysis. *Circ Cardiovasc Qual Outcomes* 2010;3:63–81.
3. Ristagno G, Li Y, Fumagalli F, Finzi A, Quan W. Amplitude spectrum area to guide resuscitation—a retrospective analysis during out-of-hospital cardiopulmonary resuscitation in 609 patients with ventricular fibrillation cardiac arrest. *Resuscitation* 2013;84:1697–703.
4. Ristagno G, Mauri T, Cesana G, et al. Amplitude spectrum area to guide defibrillation: a validation on 1617 ventricular fibrillation patients. *Circulation* 2015;131:478–87.
5. Indik JH, Conover Z, McGovern M, et al. Association of amplitude spectral area of the ventricular fibrillation waveform with survival of out-of-hospital ventricular fibrillation cardiac arrest. *J Am Coll Cardiol* 2014;64:1362–9.
6. Indik JH, Conover Z, McGovern M, et al. Amplitude-spectral area and chest compression release velocity independently predict hospital discharge and good neurological outcome in ventricular fibrillation out-of-hospital cardiac arrest. *Resuscitation* 2015;92:122–8.
7. Goto Y, Suzuki I, Inaba H. Frequency of ventricular fibrillation as predictor of one-year survival from out-of-hospital cardiac arrests. *Am J Cardiol* 2003;92:457–9.
8. Jin D, Dai C, Gong Y, et al. Does the choice of definition for defibrillation and CPR success impact the predictability of ventricular fibrillation waveform analysis? *Resuscitation* 2017;111:48–54.
9. Callaway CW, Menegazzi JJ. Waveform analysis of ventricular fibrillation to predict defibrillation. *Curr Opin Crit Care* 2005;11:192–9.
10. Schoene P, Coult J, Murphy L, et al. Course of quantitative ventricular fibrillation waveform measure and outcome following out-of-hospital cardiac arrest. *Heart Rhythm* 2014;11:230–6.
11. Indik JH, Donnerstein RL, Hilwig RW, et al. The influence of myocardial substrate on ventricular fibrillation waveform: a swine model of acute and postmyocardial infarction. *Crit Care Med* 2008;36:2136–42.
12. Olasveengen TM, Eftestøl T, Gundersen K, Wik L, Sunde K. Acute ischemic heart disease alters ventricular fibrillation waveform characteristics in out-of hospital cardiac arrest. *Resuscitation* 2009;80:412–7.
13. Bonnes JL, Keuper W, Westra SW, et al. Characteristics of ventricular fibrillation in relation to cardiac aetiology and shock success: a waveform analysis study in ICD-patients. *Resuscitation* 2015;86:95–9.
14. Bonnes JL, Thannhauser J, Nas J, et al. Ventricular fibrillation waveform characteristics of the surface ECG: impact of the left ventricular diameter and mass. *Resuscitation* 2017;115:82–9.
15. Indik JH, Donnerstein RL, Berg RA, Hilwig RW, Berg MD, Kern KB. Ventricular fibrillation frequency characteristics are altered in acute myocardial infarction. *Crit Care Med* 2007;35:1133–8.
16. Sherman LD, Niemann JT, Rosborough JP, Menegazzi JJ. The effect of ischemia on ventricular fibrillation as measured by fractal dimension and frequency measures. *Resuscitation*. 2007;75:499–505.
17. Hulleman M, Salcido DD, Menegazzi JJ, et al. Predictive value of amplitude spectrum area of ventricular fibrillation waveform in patients with acute or previous myocardial infarction in out-of-hospital cardiac arrest. *Resuscitation* 2017;120:125–31.

18. Indik JH, Donnerstein RL, Kern KB, Goldman S, Gaballa MA, Berg RA. Ventricular fibrillation waveform characteristics are different in ischemic heart failure compared with structurally normal hearts. *Resuscitation* 2006;69:471–7.
19. Freese JP, Jorgenson DB, Liu P-Y, et al. Waveform analysis-guided treatment versus a standard shock-first protocol for the treatment of out-of-hospital cardiac arrest presenting in ventricular fibrillation: results of an international randomized, controlled trial. *Circulation* 2013;128:995–1002.
20. Wang H, Tang W, Ristagno G, et al. The potential mechanisms of reduced incidence of ventricular fibrillation as the presenting rhythm in sudden cardiac arrest. *Crit Care Med* 2009;37:26–31.
21. Sherman L, Niemann J, Youngquist ST, Shah AP, Rosborough JP. Beta-blockade causes a reduction in the frequency spectrum of VF but improves resuscitation outcome: a potential limitation of quantitative waveform measures. *Resuscitation* 2012;83:511–6.
22. Jacobs I, Nadkarni V, Bahr J, et al. Cardiac arrest and cardiopulmonary resuscitation outcome reports: update and simplification of the Utstein templates for resuscitation registries: a statement for healthcare professionals from a task force of the International Liaison Committee on Resuscitation (American Heart Association, European Resuscitation Council, Australian Resuscitation Council, New Zealand Resuscitation Council, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Councils of Southern Africa). *Circulation* 2004;110:3385–97.
23. Blom MT, van Hoeijen DA, Bardai A, 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.
24. Povoas HP, Bisera J. Electrocardiographic waveform analysis for predicting the success of defibrillation. *Crit Care Med* 2000;28:N210–1.
25. Who. The Anatomical Therapeutic Chemical Classification System with Defined Daily Doses (ATC/DDD).
26. Hulleman M, Zijlstra JA, Beesems SG, et al. Causes for the declining proportion of ventricular fibrillation in out-of-hospital cardiac arrest. *Resuscitation* 2015;96:23–9.
27. Babbs CF, Whistler SJ, Yim GK, Tacker WA, Geddes LA. Dependence of defibrillation threshold upon extracellular/intracellular K^+ concentrations. *J Electrocardiol* 1980;13:73–8.
28. Marill KA, Salcido DD, Sundermann ML, et al. Energy conserving chemical defibrillation of ventricular fibrillation: A randomized two phase controlled blinded trial. *Resuscitation* 2016;103:41–8.
29. Bansilal S, Castellano JM, Garrido E, et al. Assessing the impact of medication adherence on long-term cardiovascular outcomes. *J Am Coll Cardiol* 2016;68:789–801.