Acetylsalicylic acid use is associated with reduced risk of out-of-hospital cardiac arrest in the general population: Real-world data from a population-based study

Talip E. Eroglu1,2,3, Marieke T. Blom1, Patrick C. Souverein2, Alfi Yasmina4, Anthonius de Boer2, Hanno L. Tan1,5*, for the ESCAPE-NET investigators¶

1 Department of Cardiology, Heart Center, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands, 2 Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands, 3 Department of Cardiology, Copenhagen University Hospital–Herlev and Gentofte, Copenhagen, Denmark, 4 Department of Pharmacology, Faculty of Medicine, Lambung Mangkurat University, Banjarmasin, Indonesia, 5 Netherlands Heart Institute, Utrecht, The Netherlands

¶ The Complete Membership of the Author Group can be found in the Acknowledgements.

* h.l.tan@amc.nl

Abstract

Aim

Activated blood platelet products facilitate myocardial intracellular Ca\(^{2+}\) overload, thereby provoking afterdepolarizations and increasing susceptibility of ischemic myocardium to ventricular fibrillation (VF). These effects are counteracted \textit{in vitro} by acetylsalicylic acid (ASA), but no prior study investigated whether ASA is associated with decreased out-of-hospital cardiac arrest (OHCA) risk on a population level. Therefore, we studied whether ASA and other antiplatelet drugs (carbasalate calcium, clopidogrel) are associated with decreased risk of OHCA.

Methods

We conducted a population-based case-control study among individuals (772 OHCA-cases with documented VT/VF, 2444 non-OHCA-controls) who had used antiplatelet drugs in the year before index-date (OHCA-date), and studied the association between current antiplatelet drug use and OHCA-risk with multivariable logistic regression analysis.

Results

ASA use was associated with reduced OHCA-risk (adjusted odds ratio (OR\(_{\text{adj}}\)) 0.6 [0.5–0.8]), and more so in women (OR\(_{\text{adj}}\) 0.3 [0.2–0.6]) than in men (OR\(_{\text{adj}}\) 0.7 [0.5–0.95], \(P_{\text{interaction}}\) 0.021). Carbasalate calcium was associated with decreased OHCA-risk in women (OR\(_{\text{adj}}\) 0.5 [0.3–0.9]), but not in men (OR\(_{\text{adj}}\) 1.3 [0.96–1.7], \(P_{\text{interaction}}\) 0.005). Clopidogrel was not associated with reduction in OHCA-risk. Risk reduction associated with ASA in
patients with OHCA was similar in the presence of acute myocardial infarction (AMI) (OR adj 0.6 [0.4–0.9]) and in the absence of AMI (OR adj 0.7 [0.4–1.2]).

Conclusion

ASA use was associated with reduced OHCA-risk in both sexes, and more so in women, while carbasalate calcium only protected women. Clopidogrel was not associated with reduced OHCA-risk.

Introduction

Out-of-hospital cardiac arrest (OHCA) accounts for 50% of all deaths from cardiovascular disease [1], and is mostly caused by cardiac arrhythmia (ventricular tachycardia/ventricular fibrillation [VT/VF]), often triggered by acute myocardial infarction (AMI) [2]. Previously, we reported that substances released from activated blood platelets (activated blood platelet products [ABPPs]) impact cardiac electrophysiological properties. In particular, ABPPs facilitate intracellular Ca\(^{2+}\) overload by increasing intracellular calcium transients and L-type calcium current (without affecting sarcolemmal sodium or potassium currents) [3, 4]. These changes may increase susceptibility of ischemic myocardium to VF by provoking early afterdepolarizations (EADs) or delayed afterdepolarizations (DADs), but they were counteracted in vitro by acetylsalicylic acid (ASA) [4]. ASA derives its therapeutic action from inhibition of cyclooxygenase; this prevents the formation of cyclooxygenase products, such as thromboxane and prostaglandins (two types of ABPP). Given these observations, it is possible that ASA reduces the risk of VT/VF and OHCA. Women, in particular, may benefit from these antifibrillatory actions of ASA and, possibly, other antiplatelet drugs (carbasalate calcium, clopidogrel), because they are more vulnerable than men to the occurrence of EADs and DADs given their higher expression levels of cardiac L-type calcium currents [5]. However, it has not been studied yet whether or not ASA, carbasalate calcium or clopidogrel lower the risk for OHCA on a population level; to establish this was the aim of our present investigation. To do so, we performed a case-control study using data from population-based registries in the Netherlands. Because we expected that women, in particular, may benefit from the antifibrillatory actions of antiplatelet drugs, we stratified our analysis according to sex. Furthermore, expecting that OHCA risk reduction primarily occurs when ABPPs are formed, we studied the possible differential effects of antiplatelets in the presence or absence of ABPP formation. Taking acute myocardial infarction (AMI) as a situation in which ABPP formation is present, we performed subgroup analysis of OHCA cases who suffered OHCA in the presence or absence of AMI.

Methods

Design and setting

We performed a population-based case-control study. Cases were OHCA victims from cardiac causes with ECG-documented VT/VF enrolled in the AmsteRdam REsuscitation STudy (ARREST [6]) registry in 2005–2011. We excluded cases without complete drug-dispensing records one year prior to index-date (OHCA date), those with obvious non-cardiac causes (e.g., trauma, drowning), and those who suffered their second or subsequent OHCA episode. Controls were individuals who did not have OHCA at or before the index-date. For each case, up to five controls who were alive on the index-date were matched using exact matching based on age, sex,
and index-date. From this original case-control data set, individuals aged ≥18 years with coronary artery disease, defined by use of an antiplatelet drug in the 12 months before index-date, were included in the present analysis. Thus, the majority of cases and controls were treated for secondary prevention of cardiovascular disease, thereby increasing comparability with respect to underlying conditions. By sub-selecting all individuals who had used an antiplatelet drug in the year before the index-date from the original case-control data set, the original matching was lost. This study was conducted based on the principles outlined in the Declaration of Helsinki, and was approved by the Medical Ethics Committee of the Academic Medical Center, Amsterdam.

Data sources
Details of the ARREST registry are described elsewhere [6]. In brief, ARREST is an ongoing population-based registry that prospectively enrolls all suspected OHCAs in one contiguous region of the Netherlands (North Holland province, covering both urban and rural areas and containing approximately 2.4 million individuals) in collaboration with all dispatch centers, Emergency Medical Services (EMS) and hospitals in the study region. OHCA was defined as an EMS-attended resuscitation attempt for a cardiac arrest with presumed cardiac cause. After each suspected OHCA, EMS routinely provides the continuous ECG from their manual defibrillators. If an automated external defibrillator is used prior to EMS arrival, the ECG from the automated external defibrillator is obtained by the ARREST personnel. The presence or absence of VT/VF was verified from these ECGs [6]. Information regarding the immediate cause of VT/VF was obtained from hospital records and could only be obtained from patients who survived to hospital admission. The immediate cause of VT/VF was classified as AMI or no AMI (any other cardiac cause), or unknown. The diagnosis of AMI was established by the treating cardiologist and retrieved retrospectively from hospital records [6]. Information regarding drug-dispensing records one year prior to index-date was obtained by contacting the patient’s community pharmacy using standardized protocols. Controls were sampled from the PHARMO Database Network that contains, among other things, drug-dispensing records from community pharmacies [7]. We also obtained drug dispensing records one year prior to index-date from controls. As virtually all individuals in the Netherlands are registered at a single pharmacy, drug-dispensing records are considered as complete [8].

Exposure of interest and covariates
Current use of antiplatelet drugs was defined as having a drug-dispensing record within 90 days prior to index-date since, in the Netherlands, the average repeat prescription length for drugs used for chronic diseases is 90 days. We used the Anatomical Therapeutical Chemical (ATC) Classification System to define the use of antiplatelet drugs (B01AC). In order to estimate OHCA risk upon use of individual antiplatelet drugs, we included the most commonly used antiplatelet drugs in the Netherlands, i.e., ASA (B01AC06), carbasalate calcium (B01AC08), and clopidogrel (B01AC04). The association between other antiplatelet drugs (dipyridamole, ticlopidine) was not evaluated because the number of users was too small to yield meaningful results. High dose ASA used as analgesic has a different ATC code (N02BA01) than as antiplatelet drug (B01AC06) and was not included in this study. The association between individual antiplatelet drugs and OHCA risk could not be estimated in case of combinations of individual antiplatelet drugs, therefore these ORs are not reported.

Covariates
As covariates, we considered age, sex and pre-existing disease with known effects on OHCA risk (cardiovascular disease, diabetes mellitus) by using drug proxies (cardiovascular drugs
and antidiabetics, respectively, both defined as use within six months before index-date, listed in Table 1. We could not obtain diagnoses regarding pre-existing disease in the control group, but used drug use as proxies, as we did previously [9, 10]. Drugs used to define pre-existing disease are usually taken chronically. Also, medications with known effects on OHCA were evaluated: non-cardiac QT-prolonging drugs (from www.CredibleMeds.org [11, 12]) and antiarrhythmic drugs (Vaughan-Williams class 1 or 3). Use of non-cardiac QT-prolonging drugs and/or Vaughan-Williams class 1 or 3 antiarrhythmic drugs was defined as use within 90 days before index-date.

### Statistical analysis

The association between current antiplatelet drug use and OHCA risk was assessed by employing multivariable logistic regression analyses using 2 models. In model 1, estimates were adjusted for age and sex, and in model 2, estimates were additionally adjusted for use of cardiovascular drugs, antidiabetics, non-cardiac QT-prolonging drugs and/or antiarrhythmic drugs (listed in Table 1). By sub-selecting the original case-control data set to individuals who had used an antiplatelet drug in the year before the index-date, matching was lost. Therefore, we adjusted for age and sex in all analyses. First, we studied the association between current use of any antiplatelet drug and OHCA risk versus no current use of any antiplatelet drug. Second, we studied the association between current use of individual antiplatelet drugs (ASA, carbasalate calcium, clopidogrel) and OHCA risk compared to no current use of any antiplatelet drug in the whole group, and stratified according to sex. Third, we assessed risk of current use of antiplatelet drugs in the subgroups of OHCA cases who suffered OHCA in the presence or absence of AMI (compared to all controls). The presence of interaction on a multiplicative scale between sex and antiplatelet drugs was estimated by including the cross-product of the two factors as a variable in the model. Results are presented as odds ratio (OR) and 95% confidence interval (CI). Descriptive statistics are reported as mean (standard deviation) or number (percent) as indicated. Comparisons for continuous variables were made with independent t-test. Chi-square test was used when discrete variables were compared across groups. A two-sided p-value of <0.05 was considered statistically significant.

### Table 1. Baseline characteristics of cases and controls.

|                          | Cases     | Controls  | p-value |
|--------------------------|-----------|-----------|---------|
| Total                    | 772       | 2444      |         |
| Mean age, years (SD)     | 70.4 (11.5)| 73.1 (10.1)| <0.001 |
| Male sex                 | 623 (80.7)| 2033 (83.2)| 0.113  |
| Drugs used in the 6 months before index date |           |           |         |
| Beta-blockers            | 443 (57.4)| 1152 (47.1)| <0.001 |
| Calcium channel blockers | 203 (26.3)| 614 (25.1) | 0.514  |
| Renin angiotensin system inhibitors | 477 (61.8)| 1151 (47.1)| <0.001 |
| Diuretics                | 382 (49.5)| 838 (34.3) | <0.001 |
| Nitrates                 | 241 (31.2)| 441 (18.0) | <0.001 |
| Statins                  | 497 (64.4)| 1456 (59.6)| 0.017  |
| Antidiabetic drugs       | 193 (25.0)| 480 (19.6) | 0.001  |
| Antiarrhythmic drugs class 1 or 3 | 17 (2.2) | 12 (0.5) | <0.001 |
| Non-antiarrhythmic QT-prolonging drugs | 48 (6.2) | 88 (3.6) | 0.002  |

Numbers are number (%) unless indicated otherwise.

https://doi.org/10.1371/journal.pone.0267016.t001

and antidiabetics, respectively, both defined as use within six months before index-date, listed in Table 1. We could not obtain diagnoses regarding pre-existing disease in the control group, but used drug use as proxies, as we did previously [9, 10]. Drugs used to define pre-existing disease are usually taken chronically. Also, medications with known effects on OHCA were evaluated: non-cardiac QT-prolonging drugs (from www.CredibleMeds.org [11, 12]) and antiarrhythmic drugs (Vaughan-Williams class 1 or 3). Use of non-cardiac QT-prolonging drugs and/or Vaughan-Williams class 1 or 3 antiarrhythmic drugs was defined as use within 90 days before index-date.
Results
We identified 2503 OHCA-cases with cardiac causes, ECG-documented VT/VF, and complete drug-dispensing records; among these cases, 772 (mean age 70.4 years, 80.7% male, Table 1) used one or more antiplatelet drug in the year before OHCA-date (Fig 1). Among 10,543 non-OHCA controls with complete drug-dispensing records, 2444 (mean age 73.1 years, 83.2% male, Table 1) used one or more antiplatelet drug in the year before index-date (Fig 1).

When antiplatelet drugs were studied as a group, current use of any antiplatelet drug was not associated with OHCA risk (OR$^{adj}$ 0.9 [95% CI 0.7–1.1], Fig 2). When we studied individual drugs, we found that current ASA use was associated with decreased OHCA risk (OR$^{adj}$ 0.6 [95% CI 0.5–0.8]). This risk reduction was larger in women (OR$^{adj}$ 0.3 [95% CI 0.2–0.6]) than in men (OR$^{adj}$ 0.7 [95% CI 0.5–0.95], $P_{interaction}$ 0.021, Fig 3). Current carbasalate calcium use was associated with decreased OHCA risk in women (OR$^{adj}$ 0.5 [95% CI 0.3–0.9]), but not in men (OR$^{adj}$ 1.3 [95% CI 0.96–1.7], $P_{interaction}$ 0.005, Fig 3). Current clopidogrel use was not associated with reduced OHCA risk in the overall model with both sexes (OR$^{adj}$ 1.4 [CI 0.9–2.3], Fig 2). The risk reduction associated with current ASA use in patients who suffered OHCA following AMI (OR$^{adj}$ 0.6 [0.4–0.9], Fig 4) was similar as in patients who suffered OHCA without AMI (OR$^{adj}$ 0.7 [0.4–1.2], Fig 4).

To examine why reduced OHCA risk was observed among current ASA users (both sexes), but not among carbasalate calcium users, we assessed whether concomitant medication use was different between these groups. We found no such differences between ASA users and carbasalate calcium users (Table 2).

Discussion
In this observational study using real-world population-based data, we found that current ASA use was associated with reduced risk of OHCA. This protective effect was larger in women than in men. Carbasalate calcium use only reduced OHCA risk in women, but not in men. Clopidogrel use was not associated with reduced OHCA risk in either sex. Risk reduction by ASA among patients who suffered OHCA following AMI was similar to risk reduction among patients without AMI.

Previously, we demonstrated sex disparities in susceptibility to EADs by showing that ventricular myocytes of women are more susceptible to EADs than those of men. This could be explained by larger depolarizing L-type Ca$^{2+}$ current in conjunction with smaller transient outward potassium current in women than in men [13]; these observations were consistent with animal studies [14]. Given the importance of L-type Ca$^{2+}$ current during the action potential plateau, even mild increases in this current could lead to longer action potentials in women, rendering them more vulnerable to EADs than men. Accordingly, women may benefit more than men from the blocking effects of ASA and carbasalate calcium on ABPP-induced increase in L-type Ca$^{2+}$ current and intracellular Ca$^{2+}$ transients, explaining our observation that ASA and carbasalate calcium are associated with more OHCA risk reduction in women than in men.

Although these mechanisms might explain lower OHCA risk among ASA users, they do not explain why carbasalate calcium was associated with less reduction in OHCA risk than ASA in the overall model with both sexes (Fig 2). Carbasalate calcium is a calcium salt of ASA and is quickly metabolized to ASA after absorption [15]. Both drugs inhibit the conversion of arachidonic acid to prostaglandins and thromboxane by inhibiting cyclooxygenase. Given that we found no indications that the differences in observed effects between ASA and carbasalate calcium could be explained by specific drug properties, we studied whether patient differences may be responsible. When we studied concomitant medication use, we found no statistically
Fig 1. Flow chart of inclusion of out-of-hospital cardiac arrest cases. Abbreviations: OHCA, out-of-hospital cardiac arrest; VT/VF, ventricular tachycardia/ventricular fibrillation.
significant differences in concomitant medication use between ASA users and carbasalate calcium users, nor between men who used ASA or carbasalate calcium (S1 Table). We may speculate that residual confounders may play a role, since we lack important data on risk factors for OHCA such as left ventricular ejection fraction, smoking, BMI. Moreover, we may speculate that it could be that there may be a difference in the therapeutic indication for which the anti-platelet drugs were prescribed between subgroups (coronary artery disease, cerebrovascular events or peripheral artery disease), which may have affected the association with OHCA. However, we could not test this, since we have no information regarding therapeutic indications. In any case, carbasalate calcium is currently not recommended by the guidelines [16]. Consequently, the use of carbasalate calcium has declined by almost a half in the Netherlands between 2014 and 2018 [17]. Taken together, our results may support the use of ASA above carbasalate calcium when platelet inhibition is indicated.

Our findings are consistent with animal studies which showed that thrombotic coronary occlusion caused greater incidence of VT/VF than non-thrombotic occlusion, despite similar infarct sizes [18, 19], thereby suggesting that the intracoronary thrombus itself increases the vulnerability of ischemic myocardium to VT/VF above and beyond the effects of acute ischemia [18]. Supporting this hypothesis, various animal studies were conducted to examine the effects of ABPPs on cardiac electrophysiology [3, 20]. Increases of the inward L-type Ca\(^{2+}\) current and intracellular Ca\(^{2+}\) transients in cardiac myocytes were found after exposure of rabbit ventricular myocytes to ABPPs; this resulted in prolongation of action potential duration and the occurrence of EADs and DADs [3]. Moreover, platelets release various arrhythmogenic compounds during ischemia, such as thromboxane, which facilitate VF independently of their
ability to participate in the formation of an occlusive thrombus [20]. Accordingly, we provided evidence in a previous study that cyclooxygenase products of arachidonic acid, such as thromboxane and prostaglandins, are responsible for the increase in inward L-type Ca\(^{2+}\) current and intracellular Ca\(^{2+}\) transients in cardiac myocytes [4] by showing that ASA pretreatment significantly reduced the effects of ABPP on cellular calcium homeostasis [4]. Moreover, a previous study showed that all of the prostaglandins (i.e. PGD\(_2\), PGE\(_2\), PGF\(_2\alpha\)) derived from arachidonic acid are arrhythmogenic, of which PGF\(_2\alpha\) is the most potent to induce tachyarrhythmias in cultured neonatal rat myocytes [21]. Thus, reducing the effects of ABPP on inward L-type Ca\(^{2+}\) current and intracellular Ca\(^{2+}\) transients may contribute to the decrease in OHCA risk by ASA. This may be a mechanism underlying our observation that ASA reduces OHCA risk.

Previous studies found antiarrhythmic effects of treatment with ASA during ischemia in dogs [22], while intravenous administration of ASA reduced ischemia induced VF in rats [23].

Table 2. Characteristics of clopidogrel, acetylsalicylic acid and carbasalate calcium users.

|                     | clopidogrel | acetylsalicylic acid | carbasalate calcium | p-value |
|---------------------|------------|---------------------|--------------------|---------|
| Total               | 94         | 1301                | 1121               |         |
| Mean age, years (SD)| 71.3 (10.4)| 73.2 (10.2)         | 72.1 (10.4)        | 0.009   |
| Male sex            | 80 (85.1)  | 1070 (82.2)         | 922 (82.2)         | 0.775   |

Differences in the 6 months before index date:

| Drugs used in the 6 months before index date | clopidogrel | acetylsalicylic acid | carbasalate calcium | p-value |
|---------------------------------------------|------------|---------------------|--------------------|---------|
| Beta-blockers                               | 55 (58.5)  | 655 (50.3)          | 551 (49.2)         | 0.213   |
| Calcium channel blockers                    | 31 (33.0)  | 340 (26.1)          | 262 (23.4)         | 0.060   |
| Renin angiotensin system inhibitors         | 53 (56.4)  | 661 (50.8)          | 580 (51.7)         | 0.558   |
| Diuretics                                   | 41 (43.6)  | 484 (37.2)          | 430 (38.4)         | 0.434   |
| Nitrates                                    | 26 (27.7)  | 241 (18.5)          | 237 (21.1)         | 0.047   |
| Statins                                     | 62 (66.0)  | 836 (64.3)          | 677 (60.4)         | 0.116   |
| Antidiabetic drugs                          | 20 (21.3)  | 274 (21.1)          | 245 (21.9)         | 0.893   |
| Antiarrhythmic drugs class 1 or 3           | 0          | 7 (0.5)             | 11 (1.0)           | 0.306   |
| Non-antiarrhythmic QT-prolonging drugs      | 5 (5.3)    | 46 (3.5)            | 56 (5.0)           | 0.181   |

Numbers are number (%) unless indicated otherwise

https://doi.org/10.1371/journal.pone.0267016.t002
is in accordance with our findings which demonstrated reduced OHCA risk in the setting of AMI upon ASA use. Moreover, a study among patients with acute coronary syndrome found that patients who suffered pre-hospital cardiac arrest (without VT/VF documentation) were less frequently treated with ASA than patients without pre-hospital cardiac arrest [24]. However, the exposure window of ASA in that study was defined as the use of ASA prior to hospital presentation, which carries the risk of misclassification of ASA use by including past users (rather than current users) in the analysis.

Based on the described mechanism of platelet-derived products from the cyclooxygenase pathway and their relation with VF occurrence, it is expected that clopidogrel is not associated with lower OHCA risk [25–28]. ASA and clopidogrel act by different mechanisms. Clopidogrel attenuates the secondary response to adenosine diphosphate by blocking the P2Y\(_{12}\) receptor, thereby inhibiting thrombus formation, but not the production of thromboxane A2 and prostaglandins, two type of ABPPs that may elicit proarrythmic effects in vitro [3]. In contrast, ASA does inhibit the production of both compounds directly by inhibiting cyclooxygenase 1 [25–28]. Our findings were consistent with this expectation, and supported by an experimental study which showed that clopidogrel pre-treatment did not reduce ischemia-induced VF incidence [20], and a clinical report that, among patients with acute coronary syndrome, clopidogrel use was not different between those with or without pre-hospital cardiac arrest [24]. We observed an increased risk of OHCA in the setting of AMI upon use of clopidogrel. However, clopidogrel is usually given as secondary prevention to patients with acute coronary syndrome or percutaneous coronary intervention and after intracoronary stent implantation, and we acknowledge that the possibility of confounding by indication cannot be ruled out. Future studies are required to establish the molecular compounds responsible for the proarrhythmic effects of ABPPs; these studies may identify new targets for drug development for prevention of ischemia induced VF.

**Strengths and limitations**

A major strength of ARREST registry is the population-based real-world design in which every OHCA was obtained prospectively from the general population; this reduces the risk for selection bias. Furthermore, by studying the general population, including both urban and rural areas and capturing >90% of all OHCAs, our findings are representative for the community at large. Furthermore, to ascertain that OHCA resulted from cardiac causes, ECGs were obtained, and all OHCAs from obvious non-cardiac causes were excluded. Another strength is that information regarding drug use was based on drug-dispensing records in both cases and controls, an important step closer to the actual drug intake than only drug prescription records. Furthermore, we have no reason to assume that actual drug intake would be different between cases and controls, or between users of different antiplatelet drugs. Hence, any possible misclassification regarding drug intake is expected to be similarly distributed between cases and controls (non-differential misclassification). A limitation is that we had no information on relevant comorbidities for the majority of our cases and in all for the controls. Therefore, we could not perform direct adjustments for relevant comorbidities. To deal with this, we used as a proxy for disease drug-dispensing records obtained from community pharmacies, considered a reliable source for drug exposure [29]. Another limitation associated with the lack of data on comorbidities is that we had no information on therapeutic indication. Considering that antiplatelet drugs have a different range of indications (e.g., coronary artery disease, cerebrovascular events or peripheral artery disease), the underlying disease for which they are prescribed may have affected the association with OHCA. Secondly, confounding by indication might play a role in our study. To overcome this, we selected all patients who had at least
one antiplatelet drug prescription prior to index-date, so most of the patients were treated for secondary prevention of cardiovascular disease. However, it is still possible that (unmeasured) residual confounders might have affected our results, since data on several important risk factors such as left ventricular ejection fraction and systolic function were not available. Moreover, given the highly unpredictable way in which OHCA occurs, it is difficult, if not impossible, to obtain such data shortly before OHCA occurrence in a uniform manner across the study population. Another limitation is that we could only obtain AMI status for OHCA cases who survived to hospital admission. In OHCA cases who died before hospital admission, a diagnosis could not be made; these cases were therefore excluded from our subgroup analyses according to AMI status. We used documented AMI as a specific marker of ischemia during OHCA. Yet, the sensitivity of this marker may be low, and in some patients OHCA may have occurred during an ischemia episode that did not lead to AMI, e.g., because of spontaneous reperfusion by thrombus resolution and/or relaxation of the culprit vessel [30]. This might explain why we did not observe different associations in the AMI and non-AMI groups. Finally, the observational nature of our study allows for reporting statistical associations, and, as such, we could only detect associations without proving causality. Furthermore, our subgroup analysis was based on small sample sizes, which may have resulted in possible low statistical power. Hence, our findings should be interpreted with caution. Future studies with available data on therapeutic indication are needed to confirm and support our findings.

Conclusion
ASA use was associated with decreased risk of OHCA in both sexes, but was larger in women than in men, while carbasalate calcium use only reduced OHCA risk in women, but not in men. Clopidogrel use was not associated with reduction in OHCA risk.

Supporting information
S1 Table. Characteristics of males that used acetylsalicylic acid or carbasalate calcium. (DOCX)

Acknowledgments
The authors greatly appreciate the contributions of Paulien Homma, Remy Stieglis and Sandra de Haas for data management of the ARREST registry, and are greatly indebted to all participating EMS dispatch centers (Amsterdam, Haarlem and Alkmaar), regional ambulance services (Ambulance Amsterdam, GGD Kennemerland, Witte Kruis and Veiligheidsregio Noord-Holland Noord Ambulancezorg), fire brigades, and police departments in the study region for their contribution and support. The authors would also like to thank PHARMO Database Network, Stichting Farmaceutische Kerngetallen and the pharmacists for the participation in this study. TEE, MTB, PCS and HLT take full responsibility for the integrity of the data and the accuracy of the data analysis.

ESCAPE-NET (https://escape-net.eu/) consortium members are Hanno L. Tan, Marieke T. Blom, Talip E. Eroglu, Irene G.M. van Valkengoed, Aeilko H. Zwinderman, Elisabeth M. Lodder, Michael W.T. Tanck, Marcel M.A.M. Mannens, Peter Henneman, Laura H.P.I. van Dongen, Marieke A.R. Bak, Connie R. Bezzina, Dick L. Willems, Dominic S. Zimmerman, Lixia Jia, Ben P. van Nieuwenhuizen, Iris Oving, Remy Stieglis, Mette M. Ekkel, Vera G.M. van Eeden, Emma C. Linssen, Robin L.A. Smits, Jacob Tielt-Hansen, Gunnar Gislason, Fredrik Folke, Charlotte Glinge, Nertila Zylyftari, Simon Mathis Konig, Xavier Jouven, Jean-Philippe Empana, Mattias Ringh, Martin Jonsson, Ellinor Berglund, Peter J. Schwartz, Gaetano M. de
Ferrari, Lia Crotti, Veronica Dusi, Giuseppe Ristagno, Francesca Fumagalli, Simone Savastano, Enrico Baldi, Petra J.M. Elders, Peter P. Harms, Sabrina J.G.C. Welten, Anatolij Truhlar.

Author Contributions
Conceptualization: Talip E. Eroglu, Anthonius de Boer.
Data curation: Patrick C. Souverein.
Formal analysis: Talip E. Eroglu.
Funding acquisition: Hanno L. Tan.
Investigation: Talip E. Eroglu.
Methodology: Talip E. Eroglu, Marieke T. Blom, Anthonius de Boer, Hanno L. Tan.
Project administration: Talip E. Eroglu.
Supervision: Anthonius de Boer.
Visualization: Talip E. Eroglu.
Writing – original draft: Talip E. Eroglu.
Writing – review & editing: Marieke T. Blom, Alfi Yasmina, Anthonius de Boer, Hanno L. Tan.

References
1. Myerburg RJ, Castellanos A. Cardiac arrest and sudden cardiac death. In: Libby P, Bonow RO, Mann DL, Zipes DP. eds. Braunwald’s heart disease: a textbook of cardiovascular medicine. Oxford, UK: Elsevier, 2007:933–74.
2. Huikuri HV, Castellanos A, Myerburg RJ. Sudden death due to cardiac arrhythmias. N Engl J Med. 2001; 345(20):1473–82. https://doi.org/10.1056/NEJMra000650 PMID: 11794197
3. de Jong JS, Verkerk AO, van Borren MM, Zakharbova-Zwiauer OM, Nieuwland R, Meijers JC, et al. Activated human platelet products induce proarrhythmic effects in ventricular myocytes. J Mol Cell Cardiol. 2011; 51(3):347–56. https://doi.org/10.1016/j.yjmcc.2011.05.016 PMID: 21651913
4. Zakharbova-Zwiauer OM, Verkerk AO, de Jong JS, Sturk A, Nieuwland R, Tan HL. Acetylsaliclyc acid prevents platelet-induced proarrhythmic effects on intracellular Ca2+ homeostasis in ventricular myocytes. Int J Cardiol. 2013; 167(1):303–5. https://doi.org/10.1016/j.ijcard.2012.09.188 PMID: 23084818
5. Kalik ZM, Mike JL, Slipski C, Wright M, Jalics JZ, Womble MD. Sex and regional differences in rabbit right ventricular L-type calcium current levels and mathematical modelling of arrhythmia vulnerability. Exp Physiol. 2017; 102(7):804–17. https://doi.org/10.1113/EP085977 PMID: 28436171
6. 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(1):e000112. https://doi.org/10.1136/openhrt-2014-000112 PMID: 25332818
7. Herings R, Pedersen L. Pharmacy-based Medical Record Linkage Systems. In: Strom B, Kimmel S, editors. Pharmacoepidemiology 5ed: John Wiley & Sons, Ltd.;2012. P 270–86.
8. Buurma H, Bouvy M, De Smet P, Floor-Schreuder A, Leufkens H, Egberts A, et al. Prevalence and determinants of pharmacy shopping behaviour. J Clin Pharmacy. 2008; 33(1):17–23. https://doi.org/10.1111/j.1365-2710.2008.00878.x PMID: 18211612
9. Bardai A, Amin AS, Blom MT, Bezzina CR, Berdowski J, Langendijk PNJ, 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(20):1506–16. https://doi.org/10.1093/eurheartj/eht054 PMID: 23425522
10. Van Hoeijen DA, Blom MT, Bardai A, Souverein PC, De Boer A, Tan HL. Reduced pre-hospital and in-hospital survival rates after out-of-hospital cardiac arrest of patients with type-2 diabetes mellitus: an observational prospective community-based study. Europace. 2015; 17(5):753–60. https://doi.org/10.1093/europace/euv014 PMID: 25755289
11. Straus SM, Sturkenboom MC, Bleumink GS, Dieleman JP, van der Lei J, de Graeff PA, et al. Non-cardiac QTc-prolonging drugs and the risk of sudden cardiac death. Eur Heart J. 2005; 26(19):2007–12. https://doi.org/10.1093/eurheartj/ehs312 PMID: 15888497

12. Woosley, RL, Heise, CW and Romero, KA. Available at: www.crediblemeds.org, QTdrugs List, Accession Date: 2-11-2017, AZCERT, Inc. 1822 Innovation Park Dr., Oro Valley, AZ 85755.

13. Verkerk AO, Wilders R, Veldkamp MW, de Geringel W, Kirkels JH, Tan HL. Gender disparities in cardiac cellular electrophysiology and arrhythmia susceptibility in human failing ventricular myocytes. Int Heart J. 2005; 46(6):1105–18. https://doi.org/10.1536/ihj.46.1105 PMID: 16394606

14. Pham TV, Robinson RB, Danilo P Jr, Rosen MR. Effects of gonadal steroids on gender-related differences in transmural dispersion of L-type calcium current. Cardiovasc Res. 2002; 53(3):752–62. https://doi.org/10.1016/s0008-6363 (01)00449-7 PMID: 11861045

15. Wang X, Huang LL, Chen DM, Ihsan A, Yuan ZH. Analytical determination and pharmacokinetics of major metabolites of carbasalate calcium in broilers following oral administration. J Veterin Pharmacol Therap. 2011; 34(4):410–6. https://doi.org/10.1111/j.1365-2885.2010.01250.x PMID: 21091728

16. Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes: The Task Force for the diagnosis and management of chronic coronary syndromes of the European Society of Cardiology (ESC). Eur Heart J. 2020; 41(3):407–7. https://doi.org/10.1093/eurheartj/ehz425 PMID: 31504439

17. Zorginstituut Nederland. Aantal gebruikers 2014–2018 voor ATC-subgroep B01AC: Trombocytenantaggregatieinhibitors excl heparine. Available from: https://www.gipdatabank.nl/ [Accessed 1 January 2020].

18. Goldstein JA, Butterfield MC, Ohnishi Y, Shelton TJ, Corr PB. Arrhythmogenic influence of intracoronary thrombus during acute myocardial ischemia. Circulation 1994; 90:139–47. https://doi.org/10.1161/01.cir.90.1.139 PMID: 8025989

19. Coronel R, Wilms-Schopman FJG, Janse MJ. Profibrillatory effects of intracoronary thrombus in acute regional ischemia of the in situ porcine heart. Circulation 1997; 96:3985–91. https://doi.org/10.1161/01.cir.96.11.3985 PMID: 9403623

20. Dhanjal TS, Medina RA, Leem J, Clark JE, Southworth R, Curtis MJ. Trapped platelets activated in ischemia initiate ventricular fibrillation. Circ Arrhythm Electrophysiolo. 2013; 6(5):995–1001. https://doi.org/10.1016/j.circarr.2013.03.007 PMID: 23995251

21. Li Y, Kang JX, Leaf A. Differential effects of various eicosanoids on the production or prevention of arrhythmias in cultured neonatal rat cardiac myocytes. Prostaglandins. 1997; 54(2):511–30. https://doi.org/10.1016/s0090-6980(97)00122-6 PMID: 9380795

22. Moschos CB, Haider B, De La Cruz C, Lyons MM Jr, Regan TJ. Antiarrhythmic effects of aspirin during nonthrombotic coronary occlusion. Circulation 1978; 57:681–4. https://doi.org/10.1161/01.cir.57.4.681 PMID: 630676

23. Fagbemi SO. The effect of aspirin, indomethacin and sodium meclofenamate on coronary artery ligation arrhythmias in anaesthetized rats. Eur J Pharmacol. 1984; 97:283–287. https://doi.org/10.1016/0014-2999(84)90461-8 PMID: 6705826

24. Li Q, Goodman SG, Yan RT, Gore JM, Polasek P, Lai K, et al. Pre-hospital cardiac arrest in acute coronary syndromes: insights from the global registry of acute coronary events and the Canadian registry of acute coronary events. Cardiology 2013; 126(1):27–34. https://doi.org/10.1159/000353365 PMID: 23860213

25. Hall R, Mazer CD. Antiplatelet Drugs. Anesthesia & Analgesia. 2011; 112(2):292–318.

26. Rang HP, Dale MM. Rang and Dale’s Pharmacology. Edinburgh: Elsevier/Churchill Livingstone, 2012. 413–16.

27. Schafer AI. Antiplatelet therapy. Am J Med. 1996; 101(2):199–209. https://doi.org/10.1016/s0002-9343 (96)80077-5 PMID: 8757361

28. Jneid H, Bhatt DL, Corti R, Badimon JJ, Fuster V, Francis GS. Aspirin and clopidogrel in acute coronary syndromes: therapeutic insights from the CURE study. Arch Intern Med. 2003; 163(10):1145–53. https://doi.org/10.1001/archinte.163.10.1145 PMID: 12767950

29. Lau HS, de Boer A, Beuning KS, Porsius A. Validation of pharmacy records in drug exposure assessment. J Clin Epidemiol 1997; 50(5):619–25. https://doi.org/10.1016/s0895-4356(97)00040-1 PMID: 9180655

30. Bentzon JF, Otsuka F, Virmani R, Falk E. Mechanisms of Plaque Formation and Rupture. Circ Res 2014; 114(12):1852–1866. https://doi.org/10.1161/CIRCRESAHA.114.302721 PMID: 24902970