**Aalborg Universitet**

AALBORG UNIVERSITY
DENMARK

# Association of beta-blockers and first-registered heart rhythm in out-of-hospital cardiac arrest

*real-world data from population-based cohorts across two European countries*

Barcella, Carlo A; Eroglu, Talip E; Hulleman, Michiel; Granfeldt, Asger; Souverein, Patrick C; Mohr, Grimur H; Koster, Rudolph W; Wissenberg, Mads; de Boer, Anthonius; Torp-Pedersen, Christian; Folke, Fredrik; Blom, Marieke T; Gislason, Gunnar H; Tan, Hanno L; ESCAPE-NET Investigators

*Published in:*
Europace

*DOI (link to publication from Publisher):*
10.1093/europace/euaa124

*Creative Commons License*
CC BY-NC 4.0

*Publication date:*
2020

*Document Version*
Publisher's PDF, also known as Version of record

Link to publication from Aalborg University

*Citation for published version (APA):*
Barcella, C. A., Eroglu, T. E., Hulleman, M., Granfeldt, A., Souverein, P. C., Mohr, G. H., Koster, R. W., Wissenberg, M., de Boer, A., Torp-Pedersen, C., Folke, F., Blom, M. T., Gislason, G. H., Tan, H. L., & ESCAPE-NET Investigators (2020). Association of beta-blockers and first-registered heart rhythm in out-of-hospital cardiac arrest: real-world data from population-based cohorts across two European countries. *Europace*, *22*(8), 1206-1215. https://doi.org/10.1093/europace/euaa124

**General rights**
Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal -

ESC European Society of Cardiology

Europace (2020) **22**, 1206–1215
doi:10.1093/europace/euaa124

**CLINICAL RESEARCH**
*Sudden death and ICDs*

# Association of beta-blockers and first-registered heart rhythm in out-of-hospital cardiac arrest: real-world data from population-based cohorts across two European countries

**Carlo A. Barcella [1*†], Talip E. Eroglu[2†], Michiel Hulleman[2], Asger Granfeldt[3], Patrick C. Souverein[4], Grimur H. Mohr[1], Rudolph W. Koster[2], Mads Wissenberg[1], Anthonius de Boer[4], Christian Torp-Pedersen[5,6], Fredrik Folke[1], Marieke T. Blom[2], Gunnar H. Gislason[1,7], and Hanno L. Tan[2,8]; for the ESCAPE-NET Investigators**

[1]Department of Cardiology, Herlev and Gentofte Hospital, University of Copenhagen, Gentofte, Denmark; [2]Department of Cardiology, Heart Center, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands; [3]Department of Intensive Care, Aarhus University Hospital, Aarhus, Denmark; [4]Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands; [5]Unit of Epidemiology and Biostatistics, Aalborg University Hospital, Aalborg, Denmark; [6]Department of Clinical Investigation and Cardiology, Nordsjaellands Hospital, Hillerød, Denmark; [7]The Danish Heart Foundation, Copenhagen, Denmark; and [8]Netherlands Heart Institute, Utrecht, The Netherlands

*Received 3 February 2020; editorial decision 24 April 2020; accepted after revision 28 April 2020; online publish-ahead-of-print 28 June 2020*

**Aims** Conflicting results have been reported regarding the effect of beta-blockers on first-registered heart rhythm in out-of-hospital cardiac arrest (OHCA). We aimed to establish whether the use of beta-blockers influences first-registered rhythm in OHCA.

**Methods and results** We included patients with OHCA of presumed cardiac cause from two large independent OHCA-registries from Denmark and the Netherlands. Beta-blocker use was defined as exposure to either non-selective beta-blockers, β1-selective beta-blockers, or α-β-dual-receptor blockers within 90 days prior to OHCA. We calculated odds ratios (ORs) for the association of beta-blockers with first-registered heart rhythm using multivariable logistic regression. We identified 23 834 OHCA-patients in Denmark and 1584 in the Netherlands: 7022 (29.5%) and 519 (32.8%) were treated with beta-blockers, respectively. Use of non-selective beta-blockers, but not β1-selective blockers, was more often associated with non-shockable rhythm than no use of beta-blockers [Denmark: OR 1.93, 95% confidence interval (CI) 1.48–2.52; the Netherlands: OR 2.52, 95% CI 1.15–5.49]. Non-selective beta-blocker use was associated with higher proportion of pulseless electrical activity (PEA) than of shockable rhythm (OR 2.38, 95% CI 1.01–5.65); the association with asystole was of similar magnitude, although not statistically significant compared with shockable rhythm (OR 2.34, 95% CI 0.89–6.18; data on PEA and asystole were only available in the Netherlands). Use of α-β-dual-receptor blockers was significantly associated with non-shockable rhythm in Denmark (OR 1.21; 95% CI 1.03–1.42) and not significantly in the Netherlands (OR 1.37; 95% CI 0.61–3.07).

**Conclusion** Non-selective beta-blockers, but not β1-selective beta-blockers, are associated with non-shockable rhythm in OHCA.

**Keywords** Out-of-hospital cardiac arrest • Beta-blockers • First-registered heart rhythm • Non-shockable heart rhythm • Pulseless electrical activity • Asystole • ESCAPE-NET

* Corresponding author. Tel: +45 50 25 97 57. *E-mail address*: carlo.alberto.barcella@regionh.dk

† The first two authors contributed equally to the study.

© The Author(s) 2020. Published by Oxford University Press on behalf of the European Society of Cardiology.
This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/4.0/), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com

## What's new?

- The use of beta-blockers prior to out-of-hospital cardiac (OHCA) arrest may influence the first-registered heart rhythm.
- The different classes of beta-blockers have different effects on the first-registered heart rhythm in OHCA.
- The use of non-selective beta-blockers is associated with non-shockable heart rhythm in OHCA, particularly with pulseless electrical activity.
- The use of $\beta$1-selective beta-blockers is not associated with non-shockable heart rhythm in OHCA.
- When we considered differences in baseline comorbidities, the use of non-selective beta-blockers persisted associated with non-shockable heart rhythm.

# Introduction

The incidence of shockable rhythm [ventricular tachycardia (VT), ventricular fibrillation (VF)] as first-registered heart rhythm in out-of-hospital cardiac arrest (OHCA) has exhibited an absolute and relative decline worldwide compared with non-shockable rhythm [pulseless electrical activity (PEA) and asystole] during the last decades.[1–3] Several causes for this decreased incidence have been suggested, such as decline in mortality from ischaemic heart disease (IHD), increased use of implantable cardiac defibrillators, and improvements in heart failure management,[1] with beta-blockers as cornerstone of the medical therapy.[4] The chronic use of beta-blockers has increased significantly during the last decades primarily because of their favourable effects on mortality after myocardial infarction and in congestive heart failure (CHF).[5] This increase has been suggested as one of the contributing factors for the decline of shockable rhythm in OHCA, considering the antifibrillatory and anti-arrhythmic properties of these drugs.[2] Previous studies have shown that beta-blocker use may influence first-registered heart rhythm, but these studies have yielded conflicting results.[6–9] Given the importance of the first-registered heart rhythm in post-resuscitation treatment and prognosis,[10] we aimed to clarify this controversy by analysing real-world data from two large independent population-based OHCA-registries from Denmark and the Netherlands. We studied whether use of beta-blockers at the time of OHCA influenced the first-registered heart rhythm in OHCA (shockable vs. non-shockable). We distinguished between use of non-selective beta-blockers, β1-selective beta-blockers, and α-β-dual-receptor blockers, because these drug classes impact differently on various relevant cardiac and extracardiac functional properties.

# Methods

## Data availability

The data and study materials are not available to other researchers for purposes of reproducing the results or replicating the procedure.

## Study design and setting

We performed a population-based cohort study using data from two large ongoing Emergency Medical Services (EMS) attended OHCA-registries in Denmark and the Netherlands. Both registries are part of the ESCAPE-NET project that aims to study the causes and to develop effective treatments for OHCA across 10 European countries.[11] From both cohorts, we included adult patients with OHCA of presumed cardiac cause (*Figure 1*). We excluded patients with (i) unknown first-registered heart rhythm, (ii) presumed non-cardiac cause of OHCA (e.g. drowning, trauma, asphyxia), (iii) missing estimated time interval from recognition of OHCA to rhythm analysis by EMS, (iv) estimated time of arrival by EMS ≥30 min, or (v) incomplete drug dispensing records (this last condition only applied to the Dutch registry). This study was conducted according to the principles described in the Declaration of Helsinki and was approved by the Ethical Committee of the Academic Medical Center, Amsterdam, and the Danish Data Protection Agency (2007-58-0015, internal reference GEH-2014-017, I-Suite No. 02,735). In Denmark, ethical approval is not required for observational, registry-based studies where patients remain anonymous.

### *Denmark*

The population-based Danish Cardiac Arrest Register (DANCAR) includes all OHCAs across Denmark for which EMS were dispatched and where resuscitation efforts, either by a bystander or EMS personnel, have been attempted (2001–2014). The EMS is activated for all medical emergencies in Denmark, and EMS-personnel is required to fill out a case report form for every OHCA: the first-registered heart rhythm is reported in such case reports as a binary variable (non-shockable or shockable rhythm). The causes of OHCA were extrapolated from the death certificates and discharge diagnoses from the index hospitalization. When the cause of the underlying OHCA was cardiac disease, unknown disease, or unexpected collapse, the arrest was classified as of presumed cardiac cause. DANCAR has been described in detail elsewhere.[12] All residents in Denmark have a unique and permanent personal civil registration number that allows individual-level linkage across nationwide registries. All admissions to Danish hospitals are registered since 1978 in the Danish National Patient Registry: diagnoses are classified according to the *International Classification of Diseases* (ICD). The National Prescription Register contains information on all dispensed drug prescriptions since 1995, classified according to the Anatomical Therapeutic Chemical (ATC) system. The Danish Civil Registration System provides data about patient's age and gender; the Danish Register of Causes of Death holds information about vital status and causes of death, including primary and contributing causes.

### The Netherlands

The population-based AmsteRdam REsuscitation STudies (ARREST) registry is an ongoing observational study that prospectively includes all OHCAs in one contiguous region of the Netherlands (North Holland province). This study region has a population of ∼2.6 million and covers 2404 km$^2$, both rural and urban areas. A detailed description of ARREST is provided elsewhere.[13] In short, the ARREST study centre is notified by the dispatch centre when there is a suspected OHCA in which EMS is involved. Electrocardiograms from EMS manual defibrillator or automated external defibrillation, whichever defibrillated first, were obtained to establish the first-registered heart rhythm. The first-registered heart rhythm was categorized as shockable (VT, VF) or non-shockable (asystole, PEA). For this study, data from 2009 to 2012 was used. To establish medication use, drug dispensing records 1 year prior to OHCA were obtained by contacting the patient's community pharmacy. These records were considered complete, since nearly all patients in the Netherlands are registered at a single community pharmacy. Medical

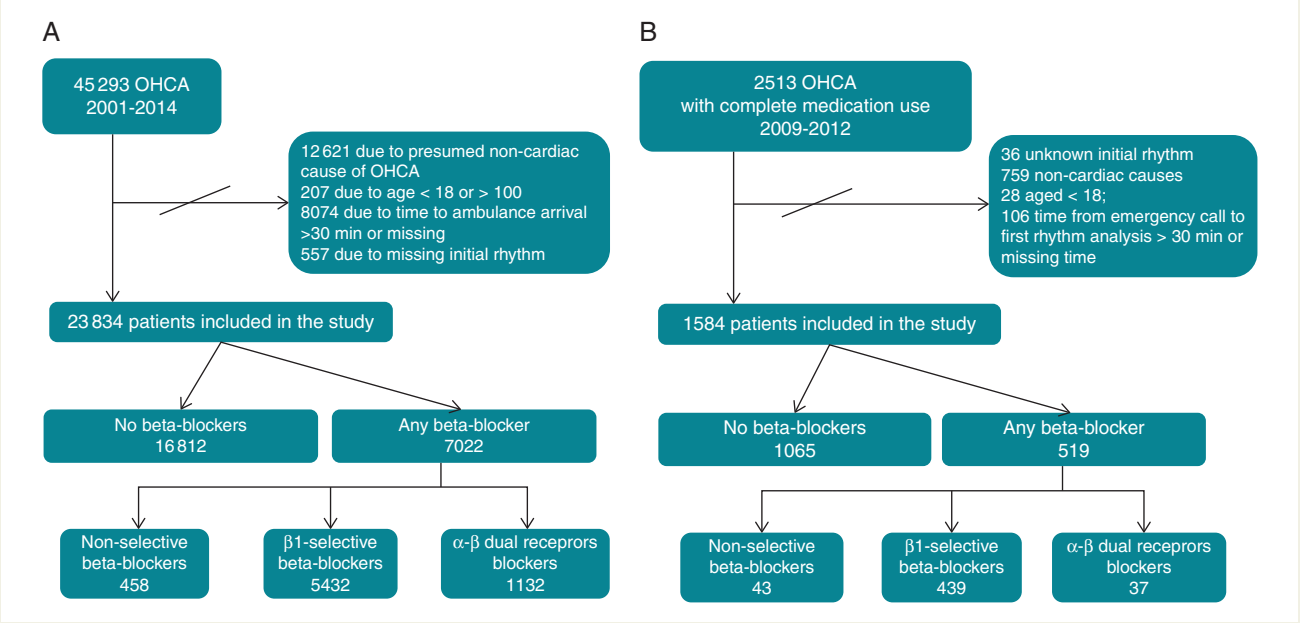



**Figure 1** Patient flow chart. (*A*) DANCAR registry. (*B*) ARREST registry. OHCA, out-of-hospital cardiac arrest.

history was obtained by contacting the hospital of admission and the general practitioner (GP). The GPs were asked to fill out a questionnaire to identify whether patients were diagnosed with any medical condition before their OHCA. Also, GP records contain information on hospital admissions and related diagnoses.[13]

## Exposure of interest

Beta-blocker use was defined as starting in (ARREST) or covering (DANCAR) a period of maximum 90 days prior to OHCA (see Supplementary material online, *Table S1* for ATC codes). In DANCAR, the treatment duration was calculated by dividing the number of tablets from the prescription of interest by daily dosage. We determined the daily dosage estimating the mean dosage from up to five consecutive prescriptions before the prescription of interest.[14] If more than one beta-blocker was prescribed within 90 days prior to OHCA, beta-blocker use was defined according to the most recent prescription. Moreover, in DANCAR, we stratified analyses according to the daily dosage (low/high) of beta-blockers (see Supplementary material online, *Table S1* for the classification of doses).

Similarly, we examined the association between angiotensin-converting enzyme (ACE) inhibitors, which have similar indications as beta-blockers, and first-registered heart rhythm to assess possible confounding by indication (see Supplementary material online, *Table S2* for ATC codes).

## Covariates

We identified baseline comorbidity up to 10 years before OHCA from the Danish National Patient Register (complete ICD codes are provided in Supplementary material online, *Table S3*). In ARREST, the same comorbidities were identified by contacting the hospital of admission and the GP. Also, use of medications with potential effects on first-registered heart rhythm was evaluated.[9] Use of these medications were defined as having a drug dispensing record up to 180 days prior to OHCA. (ATC-codes are provided in Supplementary material online, *Table S4*).

## Statistical analysis

In both cohorts, the association between beta-blocker use and first-registered heart rhythm was studied using logistic regression analysis. Furthermore, in ARREST, we studied the association between beta-blocker use and specific first-registered heart rhythm—distinguishing between PEA and asystole—by multinomial logistic regression analysis using complete cases. We calculated both crude estimates (unadjusted analysis) and multivariable analysis adjusted for age, sex, OHCA-related parameters [location of OHCA, presence/absence of bystander cardiopulmonary resuscitation (CPR) or EMS-witnessed OHCA, and time from recognition of OHCA to EMS arrival], year of OHCA (only in DANCAR, because in ARREST we could only include OHCAs from 2009 to 2012) and all comorbidities and medications listed in *Table 1*. Analyses were conducted for the overall use of any beta-blocker (reference: no use of any beta-blocker), and separately for different classes of beta-blockers (reference: no use of any beta-blocker). Subgroup analysis was performed (i) among witnessed OHCAs (bystander or EMS witnessed) with estimated time to rhythm analysis ≤10 min and (ii) in subsets of patients classified by the presence of certain comorbidities at baseline: CHF, IHD, atrial fibrillation (AF), hypertension, and individuals without cardiovascular disease (absence of IHD, CHF, AF, or use of digoxin or antiarrhythmic drugs). Finally, we examined the association between ACE inhibitors and first-registered heart rhythm. Results are presented as odds ratios (ORs) with 95% confidence intervals (CIs). Categorical data are presented as absolute numbers and percentages, and continuous data as mean and standard deviation or medians together with their associated quartiles.

# Results

## Patient characteristics

From DANCAR, we included 23 834 OHCA-patients (mean age 70.3, 68.4% male, *Figure 1*). Of these, 7022 (29.5%) used a beta-blocker within 90 days before OHCA (*Table 1*), including 458 who

**Table 1 Baseline characteristics of subjects with out-of-hospital cardiac arrest stratified into beta-blocker users and non-users**

| | DANCAR | | | ARREST | | |
|---|---|---|---|---|---|---|
| | Any beta-blocker | No beta-blockers | Missing data | Any beta-blocker | No beta-blockers | Missing data |
| Total | 7022 (29.5) | 16 812 (70.5) | | 519 (32.8) | 1065 (67.2) | |
| Age (years), mean (SD) | 72.7 (11.7) | 69.2 (14.2) | NA | 72.43 (10.9) | 66.17 (14.4) | NA |
| Male sex | 4845 (69.0) | 11 447 (68.1) | NA | 371 (71.5) | 773 (72.6) | NA |
| Resuscitation factors | | | | | | |
| OHCA in private home | 4644 (74.2) | 10 161 (69.3) | 2920 (12.2) | 403 (77.6) | 773 (72.7) | 2 (0.1) |
| Witnessed status | 3586 (51.2) | 8550 (51.1) | | | | |
| Bystander-witnessed OHCA | 1012 (14.5) | 2389 (14.3) | 106 (0.5) | 337 (65.7) | 704 (66.5) | 12 (0.8) |
| EMS-witnessed OHCA | 2397 (34.3) | 5794 (34.6) | | 56 (10.9) | 98 (9.3) | |
| Unwitnessed OHCA | | | | 120 (23.4) | 257 (24.3) | |
| CPR status | | | | | | |
| Bystander CPR | 2645 (37.7) | 6328 (37.7) | 57 (0.2) | 332 (65.0) | 722 (68.7) | 22 (1.4) |
| EMS-witnessed OHCA | 1012 (14.4) | 2389 (14.3) | | 56 (10.9) | 98 (9.3) | |
| Neither bystander CPR nor EMS-witnessed OHCA | 3352 (47.9) | 8051 (48.0) | | 123 (24.1) | 231 (22.0) | |
| Median time from recognition of OHCA to EMS arrival, min (IQR)[a] | 9 (4–15) | 9 (4–14) | NA | 8.2 (5.7–11.2) | 8.1 (5.8–11.1) | NA |
| Comorbidity | | | | | | |
| Ischaemic heart disease[b] | 3704 (52.8) | 2810 (16.7) | NA | 219 (43.0) | 165 (16.2) | 55 (3.5) |
| Congestive heart failure | 2706 (38.5) | 2059 (12.3) | NA | 195 (38.7) | 129 (12.7) | 67 (4.2) |
| Atrial fibrillation | 2211 (31.5) | 1830 (10.9) | NA | 147 (29.3) | 123 (12.2) | 70 (4.4) |
| Chronic obstructive pulmonary disease | 1072 (15.3) | 2286 (13.6) | NA | 83 (16.7) | 147 (14.6) | 77 (4.9) |
| Diabetes mellitus | 1783 (25.4) | 2359 (14.0) | NA | 167 (32.7) | 173 (16.7) | 51 (3.2) |
| Cerebrovascular disease | 1239 (17.6) | 2004 (11.9) | NA | 94 (18.8) | 115 (11.4) | 78 (4.9) |
| Hypertension | 2155 (30.7) | 2363 (14.1) | NA | 334 (65.5) | 421 (41.3) | 55 (3.5) |
| Dyslipidaemia | 3354 (47.8) | 3093 (18.4) | NA | 217 (42.7) | 275 (27.0) | 58 (3.7) |
| Chronic kidney disease | 802 (11.4) | 684 (4.1) | NA | 98 (19.8) | 71 (7.1) | 89 (5.6) |
| Liver disease | 131 (1.9) | 353 (2.1) | NA | 19 (3.8) | 30 (3.0) | 89 (5.6) |
| Concomitant medication | | | | | | |
| Antipsychotics | 394 (5.6) | 1334 (7.9) | NA | 14 (2.7) | 32 (3.0) | NA |
| Antidepressants | 1356 (19.3) | 2873 (17.1) | NA | 33 (6.4) | 64 (6.0) | NA |
| Anxiolytics/hypnotics | 1831 (26.1) | 3550 (21.1) | NA | 102 (19.7) | 134 (12.6) | NA |
| Corticosteroids | 759 (10.8) | 1753 (10.4) | NA | 35 (6.7) | 73 (6.9) | NA |
| Digoxin | 1411 (20.1) | 1571 (9.4) | NA | 59 (11.4) | 36 (3.4) | NA |
| Antiarrhythmic drugs, Class I and III | 287 (4.1) | 184 (1.1) | NA | 27 (5.2) | 18 (1.7) | NA |

Numbers are number (%) unless indicated otherwise.
*Note*: In the calculation of percentages, observations with missing value for the covariate involved in calculation were excluded.
CPR, cardiopulmonary resuscitation; EMS, emergency medical system; IQR, interquartile range; NA, not applicable; OHCA; out-of-hospital cardiac arrest; SD, standard deviation.
[a]EMS-witnessed excluded.
[b]Acute myocardial infarction included.

used non-selective beta-blockers, 5432 who used β1-selective beta-blockers, and 1132 who used α-β-dual-receptor blockers (*Table 2*). From ARREST, we included 1584 OHCA-patients (mean age 68.2, 72.2% male, *Figure 1*). Of these, 519 (32.8%) used a beta-blocker within 90 days before OHCA (*Table 1*), including 43 who used non-selective beta-blockers, 439 who used β1-selective beta-blockers, and 37 who used α-β-dual-receptor blockers (*Table 2*).

## Beta-blocker use and first-registered heart rhythm

In DANCAR, the overall use of beta-blockers was associated with increased odds of non-shockable rhythm [$OR_{adj}$ 1.16 (1.07–1.26), *Figure 2*] compared with no use of any beta-blocker. We found a significant association between non-shockable rhythm and use of non-selective beta-blockers [$OR_{adj}$ 1.93 (1.48–2.52)] or α-

**Table 2** Baseline characteristics of subjects with out-of-hospital cardiac arrest divided into users of non-selective beta-blockers, β1-selective beta-blockers, and α-β-dual-receptor blockers

| | DANCAR | | | | ARREST | | | |
|---|---|---|---|---|---|---|---|---|
| | Non-selective beta-blockers | β1-selective beta-blockers | α-β-dual-receptor blockers | Missing data[a] | Non-selective beta-blockers | β1-selective beta-blockers | α-β-dual-receptor blockers | Missing data[a] |
| Total | 458 (6.5) | 5432 (77.4) | 1132 (16.1) | | 43 (8.3) | 439 (84.6) | 37 (7.1) | |
| Age (years), mean (SD) | 72.3 (11.9) | 73.2 (11.6) | 70.6 (11.7) | NA | 73.32 (12.7) | 72.69 (10.6) | 68.33 (12.0) | NA |
| Male sex | 271 (59.2) | 3707 (68.2) | 867 (76.6) | NA | 30 (69.8) | 318 (72.4) | 23 (62.2) | NA |
| Resuscitation factors | | | | | | | | |
| OHCA in private home, *n* (%) | 309 (78.4) | 3547 (73.5) | 788 (75.7) | 765 (10.9) | 37 (86.0) | 332 (75.6) | 34 (91.9) | NA |
| Witnessed status | 210 (46.1) | 2783 (51.4) | | | | | | |
| Bystander-witnessed OHCA | 68 (14.9) | 801 (14.8) | 593 (52.6) | 27 (0.4) | 27 (65.9) | 288 (66.1) | 22 (61.1) | 6 (1.2) |
| EMS-witnessed OHCA | 178 (39.0) | 1827 (33.8) | 143 (12.7) | | 8 (19.5) | 41 (9.4) | 7 (19.4) | |
| Unwitnessed OHCA | | | 392 (34.7) | | 6 (14.6) | 107 (24.5) | 7 (19.4) | |
| CPR status | | | | | | | | |
| Bystander CPR | 149 (32.6) | 2056 (37.9) | 440 (38.9) | 13 (0.2) | 24 (60.0) | 288 (66.2) | 20 (55.6) | 8 (1.5) |
| EMS-witnessed OHCA | 68 (14.7) | 801 (14.8) | 143 (12.6) | | 8 (20.0) | 41 (9.4) | 7 (19.4) | |
| Neither bystander CPR nor EMS-witnessed OHCA | 241 (52.7) | 2563 (47.3) | 548 (48.5) | | 8 (20.0) | 106 (24.4) | 7 (19.4) | |
| Median time from recognition of OHCA to EMS arrival, min (IQR)[b] | 9 (3–15) | 9 (4–15) | 10 (4–15) | NA | 9.4 (4.6–13.0) | 8.2 (5.9–11.2) | 7.3 (4.0–10.1) | NA |
| Comorbidity | | | | | | | | |
| Ischaemic heart disease[c] | 132 (28.8) | 2855 (52.6) | 717 (63.3) | NA | 21 (48.8) | 178 (41.4) | 20 (55.6) | 10 (1.9) |
| Congestive heart failure | 75 (16.4) | 1777 (32.7) | 854 (75.4) | NA | 14 (34.1) | 155 (36.4) | 26 (70.3) | 15 (2.9) |
| Atrial fibrillation | 125 (27.3) | 1718 (36.6) | 368 (32.5) | NA | 14 (34.1) | 122 (28.7) | 11 (30.6) | 17 (3.3) |
| Chronic obstructive pulmonary disease | 66 (14.4) | 817 (15.0) | 189 (16.7) | NA | 12 (28.6) | 63 (14.9) | 8 (23.5) | 21 (4.0) |
| Diabetes mellitus | 97 (21.2) | 1339 (24.7) | 347 (30.7) | NA | 13 (31.0) | 137 (31.7) | 17 (47.2) | 9 (1.7) |
| Cerebrovascular disease | 68 (14.9) | 973 (17.9) | 198 (17.5) | NA | 11 (26.2) | 75 (17.7) | 8 (23.5) | 19 (3.7) |
| Hypertension | 109 (23.8) | 1655 (30.5) | 391 (34.5) | NA | 22 (51.2) | 286 (66.2) | 26 (74.3) | 9 (1.7) |
| Dyslipidaemia | 100 (21.8) | 2608 (48.0) | 646 (57.1) | NA | 21 (48.8) | 180 (41.9) | 16 (45.7) | 11 (2.1) |
| Chronic kidney disease | 21 (4.6) | 583 (10.7) | 198 (17.5) | NA | 9 (22.0) | 78 (18.6) | 11 (32.4) | 25 (4.8) |
| Liver disease | 25 (5.5) | 77 (1.4) | 29 (2.6) | NA | 4 (9.8) | 12 (2.9) | 3 (8.8) | 24 (4.6) |
| Concomitant medication | | | | | | | | |
| Antipsychotics | 48 (10.5) | 293 (5.4) | 53 (4.7) | NA | 0 | 14 (3.2) | 0 | NA |
| Antidepressants | 124 (27.1) | 1016 (18.7) | 216 (19.1) | NA | 4 (9.3) | 24 (5.5) | 5 (13.5) | NA |
| Anxiolytics/hypnotics | 151 (33.0) | 1369 (25.2) | 311 (27.5) | NA | 9 (20.9) | 81 (18.5) | 12 (32.4) | NA |
| Corticosteroids | 50 (10.9) | 585 (10.8) | 124 (11.0) | NA | 4 (9.3) | 30 (6.8) | 1 (2.7) | NA |
| Digoxin | 70 (15.3) | 1055 (19.4) | 286 (25.3) | NA | 3 (7.0) | 49 (11.2) | 7 (18.9) | NA |
| Antiarrhythmic drugs, Class I and III | 9 (2.0) | 188 (3.5) | 89 (7.9) | NA | 3 (7.0) | 19 (4.3) | 5 (13.5) | NA |

Numbers are number (%) unless indicated otherwise.

*Note:* In the calculation of percentages, observations with missing value for the covariate involved in calculation were excluded.

CPR, cardiopulmonary resuscitation; EMS, emergency medical system; IQR, interquartile range; NA, not applicable; OHCA; out-of-hospital cardiac arrest; SD, standard deviation.

[a]Percentage of the total number of patients using beta-blockers.

[b]EMS-witnessed excluded.

[c]Acute myocardial infarction included.

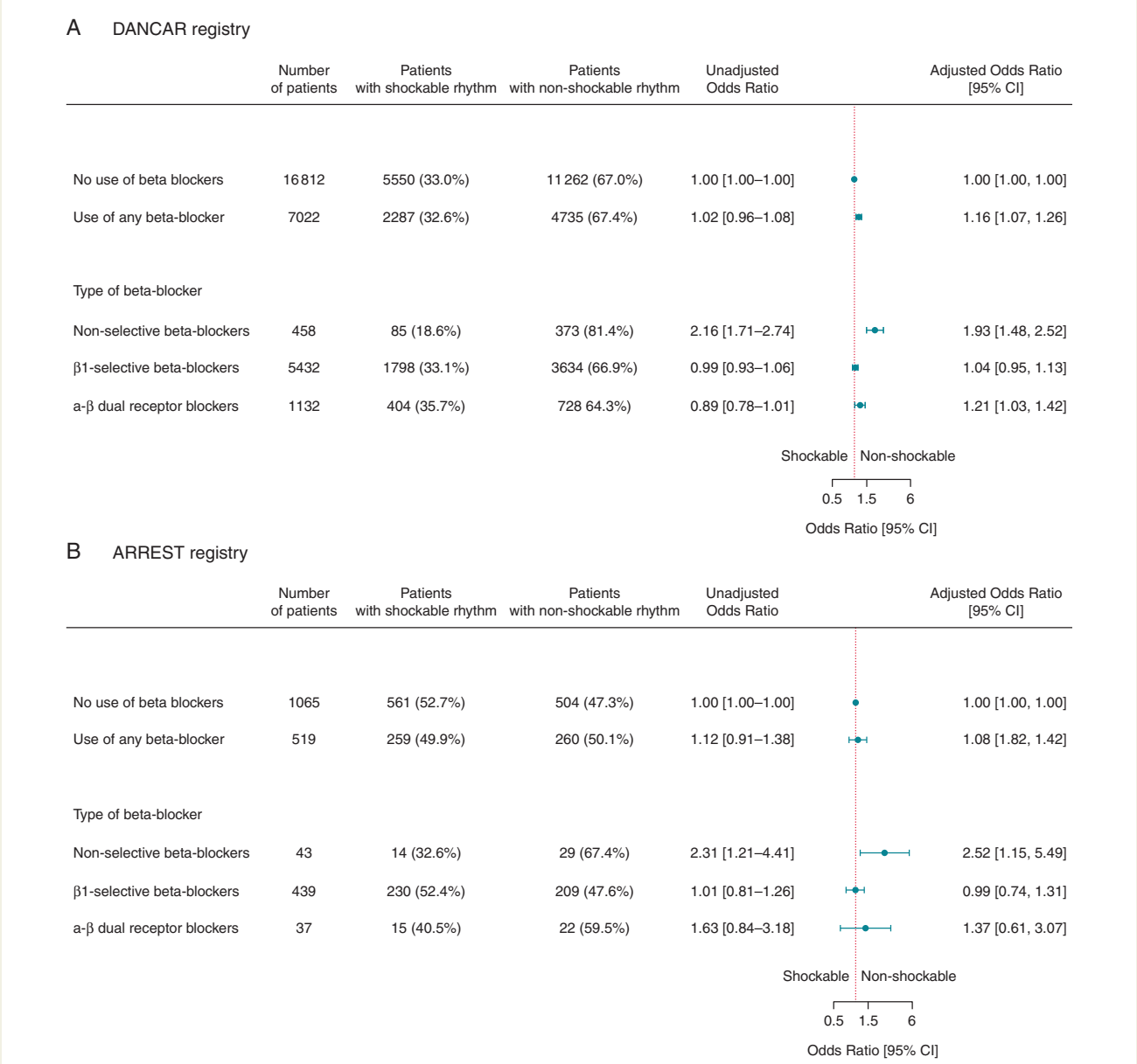



**Figure 2** Use of beta-blockers and odds of first-registered heart rhythm being non-shockable. (*A*) DANCAR registry. (*B*) ARREST registry. CI, confidence interval; DHP, dihydropyridine. Numbers in table are number (%) unless indicated otherwise. Error bars denote 95% confidence interval. The results are adjusted for all the covariates listed in *Table 1*.

β-dual-receptor blockers [$OR_{adj}$ 1.21 (1.03–1.42)], but not β1-selective beta-blockers [$OR_{adj}$ 1.04 (0.95–1.13)]. In ARREST, the overall use of beta-blockers was not associated with increased odds of non-shockable rhythm [$OR_{adj}$ 1.08 (0.82–1.42), *Figure 2*]. The other key findings in DANCAR were reproduced in ARREST: increased odds of non-shockable rhythm was associated with use of non-selective beta-blockers [$OR_{adj}$ 2.52 (1.15–5.49)], but not β1-selective beta-blockers [$OR_{adj}$ 0.99 (0.74–1.31)]. Use of α-β-dual-receptor blockers was not significantly associated with non-shockable rhythm [$OR_{adj}$ 1.37 (0.61–3.07), *Figure 2*]. We also found that non-selective beta-blocker use was associated with PEA [$OR_{adj}$ 2.38 (1.01–5.65)], but not asystole [$OR_{adj}$ 2.34 (0.89–6.18)] when compared with shockable rhythm (*Figure 3*). Neither use of β1-selective beta-blockers nor α-β-dual-receptor blockers was associated with PEA or asystole compared with VT/VF (*Figure 3*). The results for the individual beta-blockers for both registries are listed in the Supplementary material online, *Table S5*.

When we stratified the analyses according to the dosage, we found that only high dose of any beta-blocker, non-selective, and α-β-dual-receptor blockers were associated with increased likelihood of non-shockable rhythm (Supplementary material online, *Figure S1*).

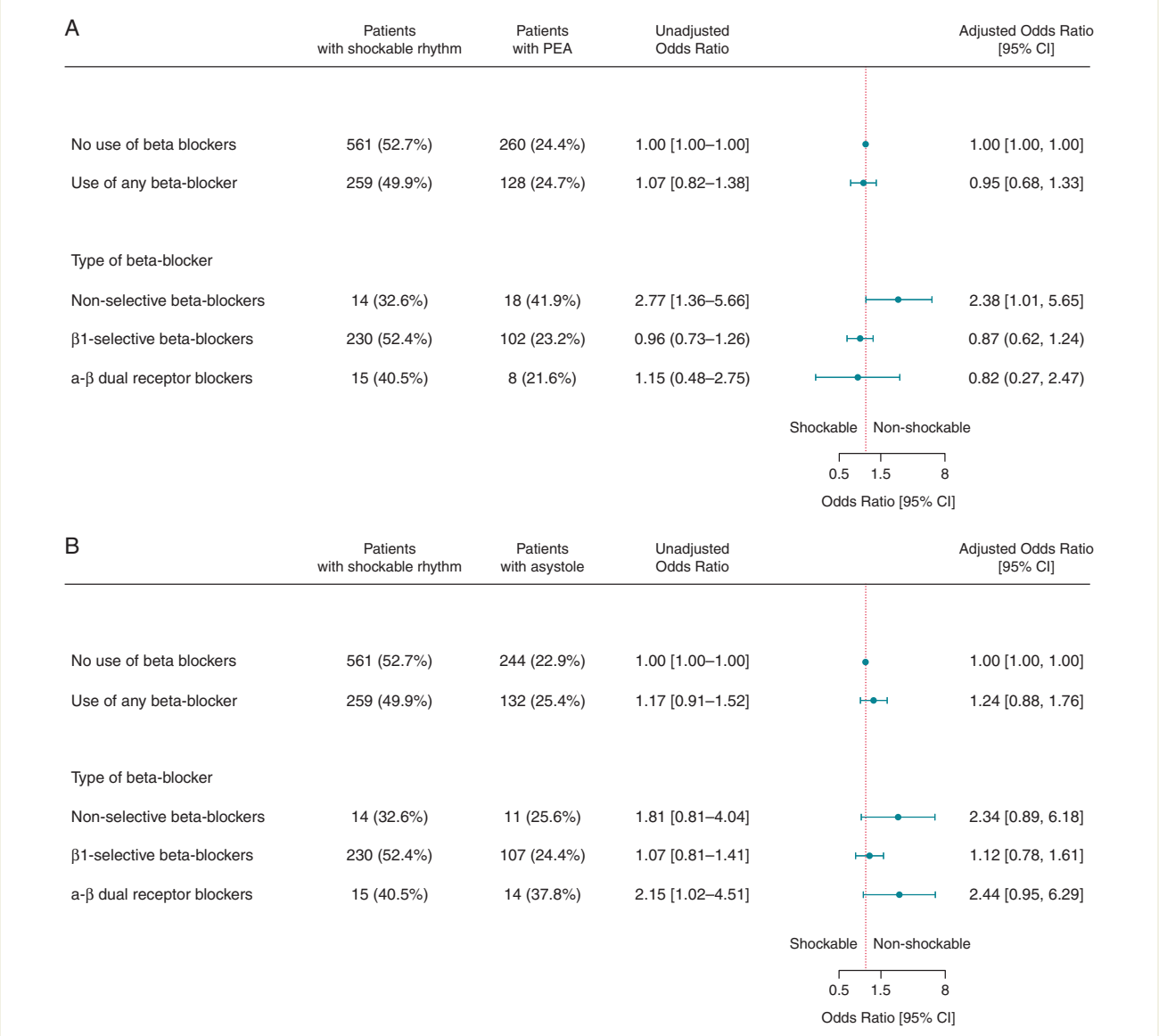



**Figure 3** Use of beta-blockers and odds of PEA vs. VT/VF and asystole vs. VT/VF. (*A*) PEA versus VT/VF. (*B*) Asystole vs. VT/VF, PEA vs. asystole. Data on PEA and asystole only available in ARREST. Numbers in table are number (%) unless indicated otherwise. Error bars denote 95% confidence interval. The results are adjusted for all the covariates listed in *Table 1*. CI, confidence interval; PEA, pulseless electrical activity; VT/VF, ventricular tachycardia/ ventricular fibrillation.

## Subgroup analysis—witnessed out-of-hospital cardiac arrest with estimated time to rhythm analysis ≤10 min

In both cohorts, the main results were confirmed by subgroup analysis including only witnessed OHCAs (bystander or EMS witnessed) with estimated time to rhythm analysis ≤10 min: use of non-selective beta-blockers was associated with increased odds of non-shockable rhythm [DANCAR: $OR_{adj}$ 1.94 (1.33–2.83), ARREST: $OR_{adj}$ 6.79 (2.25–20.50)], while use of β1-selective beta-blockers or α-β-dual-receptor blockers was not (Supplementary material online, *Figure S2*).

## Subgroup analysis—baseline comorbidity

In DANCAR, in subgroup analyses based on the presence of certain comorbidities, use of non-selective beta-blockers was consistently associated with higher odds of non-shockable rhythm compared with no use of any beta-blocker, even among patients without cardiac comorbidity (Supplementary material online, *Table S6*). We found a significant association between α-β-blockers and non-shockable heart rhythm only among patients with IHD and in patients without cardiac disease (Supplementary material online, *Table S6*). No association in any subgroup was seen for β1-selective blockers. Subgroup analyses

for ARREST were not reported because of too small numbers to get meaningful results.

### Sensitivity analysis angiotensin-converting enzyme inhibitors in relation to shockable rhythm

In both registries, we found no increased odds of non-shockable rhythm upon use of ACE inhibitors (Supplementary material online, *Figure S3*).

## Discussion

In this observational study using real-world data from two independent population-based OHCA-registries, we found that use of non-selective beta-blockers, but not β1-selective beta-blockers, was associated with non-shockable rhythm. The use of α-β dual receptor blocker was significantly associated with non-shockable rhythm in DANCAR—albeit to a lesser extent than non-selective beta-blockers—and not significantly in ARREST.

Previous studies have investigated the association between use of beta-blockers and first-registered heart rhythm in OHCA patients, but obtained conflicting results.[6–9,15] In one single-centre study, a five-fold increased likelihood of presenting with PEA in patients treated with beta-blockers was observed.[6] The authors hypothesized that the attenuation of the compensatory catecholaminergic vasoconstriction in the setting of myocardial dysfunction due to an acute coronary occlusion could result in circulatory collapse and a low blood pressure characteristic of PEA; this effect may be more plausible in case of non-selective drugs with concomitant α-blockade.[6] However, the small number of cases included in the study ($N = 179$) and the high number of cases excluded due to unknown beta-blocker status (25%) limit the reliability of these results. Conversely, another study with a larger cohort including 8266 OHCAs found that use of beta-blockers was not associated with an increased risk of non-shockable heart rhythm.[7] The fact that this study only investigated the overall effect of beta-blockers on first-registered heart rhythm without distinguishing among the different classes may explain why those results differed from ours. While we observed an association of non-shockable rhythm with the overall use of beta-blockers in the larger DANCAR registry (but not in the ARREST registry), this association was modest, and mainly driven by non-selective beta-blockers. In neither registry did we find an association of non-shockable rhythm with β1-selective beta-blockers, which represent almost 85% of the prescribed beta-blockers in ARREST.

The classes of beta-blockers differ substantially between each other in several important pharmacodynamic and pharmacokinetic properties, particularly their affinity and selectivity for the distinct adrenoceptors.[16] Correspondingly, they have distinct clinical indications.[17] Hence, the observed association of non-selective beta-blockers with non-shockable rhythm may, in addition to their pharmacological effect, be related to the underlying disease for which these drugs are prescribed, e.g. prevention of variceal haemorrhage in patients with liver disease, which is independently related to non-shockable rhythm.[9] Nonetheless, non-selective beta-blockers remained significantly associated with non-shockable rhythm when comorbidities were taken into account.

Similarly, we found that patients taking β1-selective beta-blockers had a high burden of cardiac diseases such as IHD and CHF or were treated with digoxin or class I and III antiarrhythmic drugs. All these conditions have been related to shockable rhythm, and hence they may have masked the association with non-shockable rhythm.[9,18] Accordingly, we did not observe an association with non-shockable rhythm for sotalol, which is classified as non-selective beta-blocker according to the ATC classification and is used as an antiarrhythmic drug in cardiac patients. Besides, due to our study design, we lacked information about important clinical features, such as left ventricular ejection fraction. Therefore, we cannot exclude that confounding by indication or unmeasured confounders have driven our results. To try to address these issues, we conducted subgroup analyses only including patients with similar baseline characteristics which are known to influence the use of beta-blockers and the first-registered rhythm in OHCA such as IHD and CHF,[4,9,18] and in patients without baseline cardiovascular comorbidities. Our main results were confirmed in these subgroup analyses. Thus, we found no evidence that differences in patient profiles accounted for differential effects on first-registered heart rhythm upon use of beta-blockers.

It may be also highlighted that animal studies have demonstrated that pre-arrest therapy with various types of beta-blockers have different effects on the characteristics of the first-registered heart rhythm and the probability of achieving return of spontaneous circulation.[15,19] For instance, some non-selective beta-blockers such as timolol and propranolol were found to have a higher beta-blockade potency and a larger antifibrillatory potency compared with other type of beta-blockers.[20] Similarly, in the analyses stratified by the dosage, we observed a trend towards increasing odds of non-shockable rhythm with increasing dosage only for non-selective drugs, suggesting a causal relationship.

Whatever the mechanism, it must be emphasized that beta-blockers remain among the very few drugs that reduce the incidence of VT/VF because of their antiarrhythmic and antifibrillatory properties. Thus, use of beta-blockers remains favourable because it is likely to prevent the occurrence of VT/VF and OHCA in the first place in many patients, although patients who still experience OHCA while on beta-blockers are more likely to have non-shockable rhythm.

Considering the importance of the first-registered heart rhythm during resuscitation attempts and its influence on post-resuscitation management,[10] future studies are required to shed light on the physiological mechanisms which link non-selective beta-blockers to non-shockable rhythm.

### Strengths and limitations

A major strength is that DANCAR and ARREST are specifically designed to study the incidence, outcomes and determinants of OHCA, which allows accurate data collection from every OHCA patient. Also, the population-based design minimized selection bias by prospectively including every OHCA, rendering our findings representative for the community at large. The main limitation is inherent to the observational nature of our study, i.e. we could only detect associations, and conclusions on causality should be made with caution. As previously discussed, confounding by indication may have

driven our results. Nevertheless, when we repeated the analysis for ACE inhibitors, which have similar indications as beta-blockers and whose users had similar differences in baseline characteristics compared with non-users, we did not find an association with any type of first-registered heart rhythm, rendering it unlikely that residual confounding alone may have driven our results.

In both registries, the time to rhythm analysis by EMS was only an estimate, which may be particularly inaccurate in case of unwitnessed OHCAs. However, restricting the analyses to witnessed OHCAs with estimated time to rhythm analysis ≤10 min did not alter the results.

Another limitation is that data on pre-existing disease were missing in 7.6% of all OHCA patients from ARREST, but the missing data were distributed proportionally between users and non-users of beta-blockers. Furthermore, in both registries, we did not have information about the therapeutic indication for the use of beta-blockers. Lastly, it should be acknowledged that the association between non-selective beta-blockers and PEA was barely significant (lower 95% CI is 1.01) in the ARREST registry.

# Conclusions

Non-selective beta-blockers, but not β1-selective beta-blockers, are associated with non-shockable rhythm in OHCA.

# Supplementary material

Supplementary material is available at *Europace* online.

## Acknowledgements

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 centres (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 ARREST study region for their contribution and support. The authors would also like to thank the pharmacists and Stichting Farmaceutische Kerngetallen. For completion of the case reports which form the Danish Cardiac Arrest Registry, the authors thank the Danish Emergency Medical Services.

## Funding

This work was supported by the European Union's Horizon 2020 research and innovation programme under the acronym ESCAPE-NET, registered under grant agreement No 733381 (C.B., T.E.E., M.T.B., and H.L.T.), and the Netherlands CardioVascular Research Initiative (Dutch Heart Foundation, Dutch Federation of University Medical Centers, Netherlands Organization for Health Research and Development, and Royal Netherlands Academy of Sciences) grant CVON-2018-30 Predict 2 (M.T.B. and H.L.T.) and CVON-2017-15 RESCUED (H.L.T.). M.H. is supported by a grant from the Netherlands Heart Foundation (2013T034). The ARREST registry is supported by Stryker (Redmond, WA, USA). The Danish Cardiac Arrest Registry is supported by Trygfonden.

**Conflict of interest:** C.A.B. reports grant from European Union (European Union's Horizon 2020 research and innovation programme under the acronym ESCAPE-NET), during the conduct of the study. M.T.B. reports grant from European Union (European Union's Horizon 2020 research and innovation programme under the acronym ESCAPE-NET), during the conduct of the study. T.E.E. reports grant from European Union (European Union's Horizon 2020 research and innovation programme under the acronym ESCAPE-NET), during the conduct of the study. M.H. is supported by a grant from the Netherlands Heart Foundation. R.W.K. reports grants and non-financial support from Stryker, during the conduct of the study; personal fees from Stryker, personal fees from HeartSine, outside the submitted work. H.L.T. reports grant from European Union (European Union's Horizon 2020 research and innovation programme under the acronym ESCAPE-NET), during the conduct of the study. C.T.-P. reports grants from Bayer, grants from Novo-Nordisk, outside the submitted work. All other authors declared no conflict of interest.

## References

1. Cobb LA, Fahrenbruch CE, Olsufka M, Copass MK. Changing incidence of out-of-hospital ventricular fibrillation, 1980-2000. *JAMA* 2002;**288**:3008–13.
2. Hulleman M, Zijlstra JA, Beesems SG, Blom MT, van Hoeijen DA, Waalewijn RA *et al.* Causes for the declining proportion of ventricular fibrillation in out-of-hospital cardiac arrest. *Resuscitation* 2015;**96**:23–9.
3. Herlitz J, Engdahl J, Svensson L, Young M, Angquist K-A, Holmberg S. Decrease in the occurrence of ventricular fibrillation as the initially observed arrhythmia after out-of-hospital cardiac arrest during 11 years in Sweden. *Resuscitation* 2004;**60**:283–90.
4. López-Sendón J, Swedberg K, McMurray J, Tamargo J, Maggioni AP, Dargie H *et al.*; Task ForceOn Beta-Blockers of the European Society of Cardiology. Expert consensus document on beta-adrenergic receptor blockers. *Eur Heart J* 2004;**25**:1341–62.
5. Gislason GH, Abildstrom SZ, Rasmussen JN, Rasmussen S, Buch P, Gustafsson I *et al.* Nationwide trends in the prescription of beta-blockers and angiotensin-converting enzyme inhibitors after myocardial infarction in Denmark, 1995-2002. *Scand Cardiovasc J* 2005;**39**:42–9.
6. Youngquist ST, Kaji AH, Niemann JT. Beta-blocker use and the changing epidemiology of out-of-hospital cardiac arrest rhythms. *Resuscitation* 2008;**76**:376–80.
7. Czarnecki A, Morrison LJ, Qiu F, Cheskes S, Koh M, Wijeysundera HC *et al.* Association of prior β-blocker use and the outcomes of patients with out-of-hospital cardiac arrest. *Am Heart J* 2015;**170**:1018–24.e2.
8. Teodorescu C, Reinier K, Uy-Evanado A, Chugh H, Gunson K, Jui J *et al.* Antipsychotic drugs are associated with pulseless electrical activity: the Oregon Sudden Unexpected Death Study. *Heart Rhythm* 2013;**10**:526–30.
9. Granfeldt A, Wissenberg M, Hansen SM, Lippert FK, Lang-Jensen T, Hendriksen OM *et al.* Clinical predictors of shockable versus non-shockable rhythms in patients with out-of-hospital cardiac arrest. *Resuscitation* 2016;**108**:40–7.
10. Rajan S, Folke F, Hansen SM, Hansen CM, Kragholm K, Gerds TA *et al.* Incidence and survival outcome according to heart rhythm during resuscitation attempt in out-of-hospital cardiac arrest patients with presumed cardiac etiology. *Resuscitation* 2017;**114**:157–63.
11. Tan HL, Dagres N, Böttiger BW, Schwartz PJ; ESCAPE-NET Investigators. European Sudden Cardiac Arrest network: towards Prevention, Education and New Effective Treatments (ESCAPE-NET). *Eur Heart J* 2018;**39**:86–8.
12. Wissenberg M, Hansen CM, Folke F, Lippert FK, Weeke P, Karlsson L *et al.* Survival after out-of-hospital cardiac arrest in relation to sex: a nationwide registry-based study. *Resuscitation* 2014;**85**:1212–8.
13. 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.
14. Eroglu TE, Mohr GH, Blom MT, Verkerk AO, Souverein PC, Torp-Pedersen C *et al.* Differential effects on out-of-hospital cardiac arrest of dihydropyridines: real-world data from population-based cohorts across two European countries. *Eur Heart J Cardiovasc Pharmacother* 2019;doi:10.1093/ehjcvp/pvz038.
15. 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.

16. Reiter MJ. Cardiovascular drug class specificity: beta-blockers. *Prog Cardiovasc Dis* 2004;**47**:11–33.
17. do Vale GT, Ceron CS, Gonzaga NA, Simplicio JA, Padovan JC. Three generations of β-blockers: history, class differences and clinical applicability. *Curr Hypertens Rev* 2019;**15**:22–31.
18. Granfeldt A, Adelborg K, Wissenberg M, Møller Hansen S, Torp-Pedersen C, Christensen EF *et al*. Severity of ischemic heart disease and presenting rhythm in patients with out-of-hospital cardiac arrest. *Resuscitation* 2018;**130**:174–81.
19. de Oliveira FC, Feitosa-Filho GS, Ritt L. Use of beta-blockers for the treatment of cardiac arrest due to ventricular fibrillation/pulseless ventricular tachycardia: a systematic review. *Resuscitation* 2012;**83**:674–83.
20. Anderson JL, Rodier HE, Green LS. Comparative effects of beta-adrenergic blocking drugs on experimental ventricular fibrillation threshold. *Am J Cardiol* 1983;**51**:1196–202.

**EP CASE EXPRESS**

doi:10.1093/europace/euaa122

# Left bundle branch pacing in a patient with mirror image dextrocardia and persistent right superior vena cava

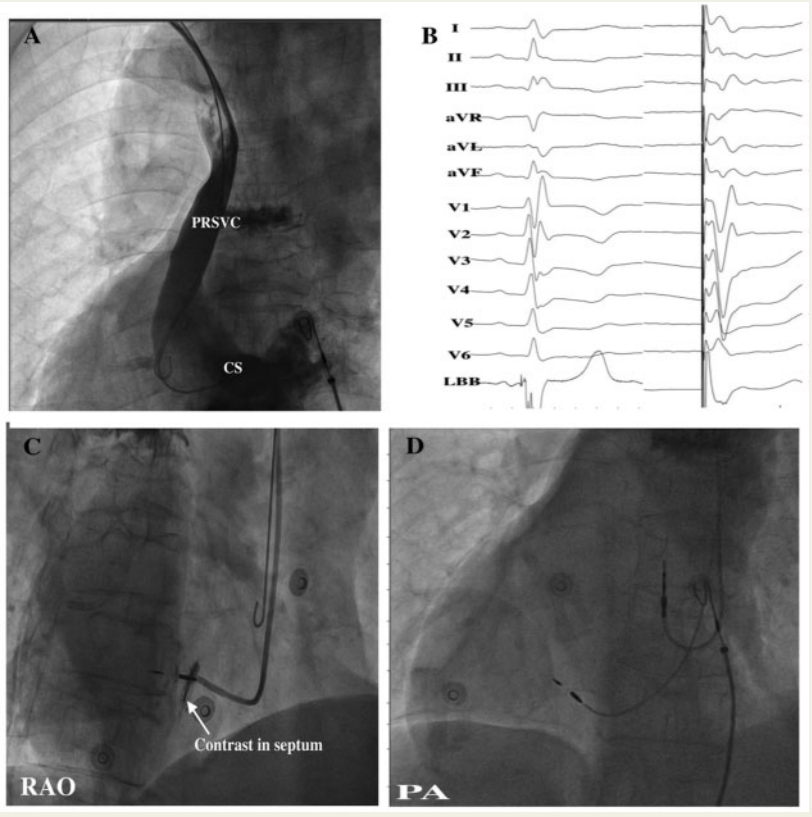
**Hui-Qiang Wei, Hui Li, Yumei Xue, Shulin Wu, and Xianhong Fang***

Department of Cardiology, Guangdong Cardiovascular Institute, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Science, Guangzhou, China

* Corresponding author. Tel: +8613710608335. *E-mail address:* drfangxh@163.com

An 80-year-old female presented with symptomatic bradycardia and mirror image dextrocardia. Vascular access was initiated via the right axillary vein, a common site for such a procedure. However, it was noted that the initial guidewire did not take the anticipated course across the mid-line but instead repeatedly coursed caudally on the right side of the mediastinum. Angiography via the right axillary vein revealed the presence of persistent right superior vena cava (PRSVC). The complex anatomical structure posed great challenge for pacemaker implantation. The left axillary vein was obtained and the guidewire was successfully passed through the inferior vena cava. The delivery sheath was reshaped to reverse-curved position. The pacing lead was successfully placed in the left bundle branch area, and left bundle branch potential was recorded with a low capture threshold of 0.5 V/0.5 ms (*Panel B*). Left bundle branch pacing could be successfully accomplished in the setting of mirror image dextrocardia and PRSVC (*Panel D*).

The full-length version of this report can be viewed at: https://www.escardio.org/Education/E-Learning/Clinical-cases/Electrophysiology.




Published on behalf of the European Society of Cardiology. All rights reserved. © The Author(s) 2020. For permissions, please email: journals.permissions@oup.com.