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ORIGINAL ARTICLE
Arrhythmia/electrophysiology

Differential effects on out-of-hospital cardiac arrest of dihydropyridines: real-world data from population-based cohorts across two European countries

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Aims Various drugs increase the risk of out-of-hospital cardiac arrest (OHCA) in the general population by impacting cardiac ion channels, thereby causing ventricular tachycardia/fibrillation (VT/VF). Dihydropyridines block L-type calcium channels, but their association with OHCA risk is unknown. We aimed to study whether nifedipine and/or amlodipine, often-used dihydropyridines, are associated with increased OHCA risk, and how these drugs impact on cardiac electrophysiology.

Methods and results We conducted a case–control study with VT/VF-documented OHCA cases with presumed cardiac cause from ongoing population-based OHCA registries in the Netherlands and Denmark, and age/sex/index date-matched non-OHCA controls (Netherlands: PHARMO Database Network, Denmark: Danish Civil Registration System). We included 2503 OHCA cases, 10 543 non-OHCA controls in Netherlands, and 8101 OHCA cases, 40 505 non-OHCA controls in Denmark. To examine drug effects on cardiac electrophysiology, we performed single-cell patch-clamp studies in human-induced pluripotent stem cell-derived cardiomyocytes. Use of high-dose nifedipine (≥60 mg/day), but not low-dose nifedipine (<60 mg/day) or amlodipine (any-dose), was associated with higher OHCA risk than non-use of dihydropyridines [Netherlands: adjusted odds ratios (OR_{adj}) 1.45 (95% confidence interval 1.02–2.07), Denmark: 1.96 (1.18–3.25)] or use of amlodipine [Netherlands: 2.31 (1.54–3.47), Denmark: 2.20 (1.32–3.67)]. Out-of-hospital cardiac arrest risk of (high-dose) nifedipine use was not further increased in patients using nitrates, or with a history of ischaemic heart disease. Nifedipine and amlodipine blocked L-type calcium channels at similar concentrations, but, at clinically used concentrations, nifedipine caused more L-type calcium current block, resulting in more action potential shortening.

Conclusion High-dose nifedipine, but not low-dose nifedipine or any-dose amlodipine, is associated with increased OHCA risk in the general population. Careful titration of nifedipine dose should be considered.

Keywords Sudden cardiac arrest • Nifedipine • Amlodipine • Epidemiology

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Introduction

Sudden cardiac arrest causes up to 50% of all cardiovascular deaths in industrialized countries[1] and most often occurs in the general population (out-of-hospital cardiac arrest, OHCA). OHCA predominantly results from lethal cardiac arrhythmias [ventricular tachycardia/ventricular fibrillation (VT/VF)] following disruptions in cardiac electrophysiology.[2] Numerous factors may cause such disruptions by impacting cardiac ion channels. Many commonly prescribed drugs, even those prescribed for non-cardiac disease, impact cardiac ion channels and are associated with increased OHCA risk.[3] The best-known risk drugs are drugs that block cardiac potassium channels, thereby impairing cardiac repolarization (QT-prolonging drugs).[4–9]

Emerging evidence also demonstrates the risk of non-cardiac drugs that impair cardiac depolarization[10] by blocking cardiac sodium-channels.[3,11,12] The possible OHCA risk of another type of depolarization-blocking drugs is less known: dihydropyridine calcium-channel blocking drugs. Dihydropyridines block L-type calcium-channels, primarily but not exclusively in vascular smooth muscle,[13] and are generally prescribed to treat ischaemic heart disease (IHD) or hypertension. Use of nifedipine has been associated with increased risk of all-cause mortality.[14] One proposed explanation was increased sympathetic stimulation and catecholamine release.[15] Although these changes may trigger VT/VF, it is unknown whether this excess mortality resulted from OHCA.

In this study, we aimed to establish whether use of nifedipine or amlodipine (the two most widely used dihydropyridines in the Netherlands) is associated with increased OHCA risk. We performed a case–control study in the Netherlands and a replication case–control study in Denmark, using population-based emergency medical services (EMS)-attended OHCA registries in both settings to study whether these drugs are associated with increased OHCA risk. We performed subgroup analyses to address confounding by indication of IHD and/or use of beta-blocking drugs. In addition, we assessed cellular electrophysiologic properties of nifedipine and amlodipine, by performing single-cell patch-clamp studies in human-induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs).

Methods

Design and setting

We used a case–control design with OHCA cases from ongoing population-based EMS-attended OHCA registries in the Netherlands (Amsterdam REsuscitation STudies, ARREST) and Denmark (replication cohort: Danish Cardiac Arrest Registry, DANCAR), and non-OHCA controls (Netherlands: PHARMO Database Network, Denmark: general population through the Danish Civil Registration System). Both OHCA registries are part of the ESCAPE-NET consortium that studies OHCA across Europe.[16] Cases were OHCA victims aged ≥18 years with documented VT/VF from presumed cardiac causes (excluding obvious non-cardiac causes). For both registries, each case was matched using exact matching on age at the date of OHCA (index-date), sex, and index-date with up to five controls who were alive on the index-date.

The study was approved by the Institutional Review Boards of the Academic Medical Center Amsterdam and the Danish Data Protection Agency (Ref.no. 2007-58-0015, local ref.no. GEH-2014-017, I-Suite.nr. 02735). In Denmark, ethical approval is not required for retrospective register-based studies in which individual patients cannot be identified.

The Netherlands

ARREST registry is an ongoing population-based observational registry that prospectively includes all OHCAs in one contiguous region of the Netherlands (2.4 million inhabitants, urban, and rural). Details of this registry are described elsewhere.[17] In short, the ARREST study centre is notified by the dispatch centre of every suspected OHCA in which EMS are involved. ECGs are collected from automated external defibrillators or EMS manual defibrillators, whichever defibrillated first. Complete drug-dispensing records 1 year before index-date are obtained from the community pharmacist. All OHCA cases from 1 June 2005 to 31 December 2011 were included. Non-OHCA controls were sampled from PHARMO Database Network, which contains drug-dispensing records from community pharmacies.[18] In the Netherlands, nearly all patients are registered at a single community pharmacy; therefore, medication records were considered complete.

Denmark

Out-of-hospital cardiac arrest cases were included in the DANCAR registry if they had attempts of resuscitation by a bystander or EMS. Capture of OHCA is nearly complete as the EMS are obliged to complete a case report form for every attended OHCA. Information on the first registered heart rhythm (shockable or non-shockable) was obtained from these forms, which constitute the DANCAR registry. Details of this registry are described elsewhere.[19] All OHCA cases from 1 June 2001 to 31 December 2014 were included. A unique and permanent civil registration number is assigned to all Danish citizens upon birth or immigration. This allows individual-level linkage of information between nationwide registries in Denmark. Information on age, sex, and vital status were obtained from the Danish Civil Registration System.[20] Data on hospital admissions were identified using the Danish National Patient Registry (one primary diagnosis and two or more secondary diagnoses if appropriate) according to the International Classification of Diseases (ICD); since 1994 the 10th revision (ICD-10) and before 1994 the 8th revision (ICD-8).[21] Causes of death according to the ICD classifications were determined using the National Causes of Death Registry.[22] Information on pharmacotherapy was obtained from The Danish Registry of Medicinal Product Statistics, which includes all drug-dispensing records from Danish pharmacies since 1995.[23]

Exposure definition

Current use was defined as a prescription starting in (ARREST) or covering (DANCAR) a period of maximally 90 days before the index-date. In DANCAR, daily dosage was estimated by calculating mean dosages from up to five consecutive prescriptions before the prescription of interest. Treatment duration was calculated by dividing the number of tablets in the prescription of interest by daily dosage, as described previously.[24] Dose-response analyses were examined using the defined daily dose (DDD, the recommended average maintenance daily dose for a medication used for its main indication).[25] Drug use was defined as low-dose (DDD < 2: nifedipine <60 mg/day, amlodipine <10 mg/day) or high-dose (DDD ≥ 2: nifedipine ≥60 mg/day, amlodipine ≥10 mg/day).

Covariates for out-of-hospital cardiac arrest risk

In both registries, covariates were assessed using cardiovascular drugs, drugs used for diabetes mellitus (used within 6 months before index date,

Table 1 Baseline characteristics of cases and controls

	ARREST			DANCAR		
	Cases	Controls	*P*-value	Cases	Controls	*P*-value
Total	2503	10 543		8101	40 505	
Age (years), median (interquartile range)	67.0 (57.0–77.0)	66.0 (57.0–76.0)	NA	68 (58–77)	68 (58–77)	NA
Male sex	1938 (77.4)	8167 (77.5)	NA	6435 (79.4)	32 175 (79.4)	NA
Concomitant drug use						
Beta-blockers	855 (34.2)	2338 (22.2)	<0.001	1948 (24.1)	5330 (13.2)	<0.001
Renin-angiotensin system inhibitors	1007 (40.2)	2778 (26.3)	<0.001	3339 (41.2)	9351 (23.1)	<0.001
Diuretics	890 (35.6)	2356 (22.3)	<0.001	3695 (45.6)	10 279 (25.4)	<0.001
Nitrates	358 (14.3)	574 (5.4)	<0.001	977 (12.1)	1343 (3.3)	<0.001
Statins	831 (33.2)	2613 (24.8)	<0.001	5649 (30.8)	7615 (18.8)	<0.001
Antithrombotics	1090 (43.5)	3004 (28.5)	<0.001	3713 (45.8)	10 136 (25.0)	<0.001
Non-dihyrdopyridine calcium antagonists	102 (4.1)	260 (2.5)	<0.001	397 (4.9)	824 (2.0)	<0.001
Antidiabetics	399 (15.9)	1135 (10.8)	<0.001	1034 (12.8)	2882 (7.1)	<0.001
Antiarrhythmic drugs class 1 and 3	54 (2.2)	41 (0.4)	<0.001	117 (1.4)	216 (0.5)	<0.001
Non-antiarrhythmic QT-prolonging drugs	133 (5.3)	331 (3.1)	<0.001	619 (7.6)	2597 (6.4)	<0.001
Comorbidities						
Peripheral vascular disease				808 (10.0)	1640 (4.1)	<0.001
Cerebral vascular disease				957 (11.8)	3064 (7.6)	<0.001
Ischaemic heart disease (including previous AMI)				2511 (31.0)	4609 (11.4)	<0.001
Atrial fibrillation				1440 (17.8)	2561 (6.3)	<0.001
Congestive heart failure				1718 (21.2)	1708 (4.2)	<0.001
Chronic kidney disease				384 (4.7)	799 (2.0)	<0.001
Chronic obstructive pulmonary disease				643 (7.9)	1721 (4.3)	<0.001

Numbers are expressed as *n* (%) unless indicated otherwise.
AMI, acute myocardial infarction; NA, not applicable.

listed in *Table 1*), and use (index-date within prescription duration) of Vaughan-Williams Class 1 or 3 antiarrhythmic drugs and/or common (≥1000 users/year) non-cardiac QT-prolonging drugs.[26] In DANCAR, covariates associated with OHCA risk were assessed using additional comorbidity information from diagnosis codes of hospital admissions up to 10 years before OHCA.

Cellular electrophysiologic studies

The current generated by L-type calcium-channels ($I_{Ca,L}$) and action potentials (APs) were measured in individual hiPSC-CMs, prepared as described previously.[27] Electrophysiologic measurements at 36 ± 0.2°C were performed 7–9 days after plating. $I_{Ca,L}$ was measured in response to depolarizing voltage clamp steps from -70 to 0 mV using the ruptured patch-clamp technique. Dose-response curves for nifedipine and amlodipine were fitted to the Hill equation: $I_{drug}/I_{control}=1/[1+(dose/IC_{50})^n]$, where $I_{drug}/I_{control}$ is normalized $I_{Ca,L}$, dose is bath concentration of the drug, IC_{50} is dose required for 50% current block, and n is the Hill coefficient. APs were measured in spontaneously beating hiPSC-CMs using the amphotericin-B-perforated patch-clamp technique. AP parameters analysed included: maximum diastolic potential, maximum AP-amplitude (APA_{max}), AP-duration at 20%, 50%, and 90% repolarization (APD_{20}, APD_{50}, and APD_{90}), maximal upstroke velocity (V_{max}), and plateau amplitude ($APA_{plateau}$). Averages were taken from 10 consecutive APs. The effects of nifedipine and amlodipine on $I_{Ca,L}$ were tested at steady-state (5 min after bath application), with increasing concentrations within one cell. More details are provided in Supplementary material online, *Methods*.

Statistical analysis

The χ^2 test was used to compare baseline characteristics between cases and controls, and between the various covariates of study drug users. The Mann–Whitney test was used to compare age between cases and controls. We used conditional logistic regression to determine associations between exposure of interest and OHCA risk, applying two models. In Model 1, crude odd ratios (OR_{crude}) were calculated. In Model 2, the OR was adjusted (OR_{adj}) for all confounders that were univariately significantly associated with OHCA and sufficiently powered (>5 exposed cases). Next, we performed stratified analyses regarding nitrate use (as proxy for IHD), beta-blocker use and history of IHD and/or previous acute myocardial infarction (AMI, only in DANCAR) and calculated $P_{interaction}$ using multivariable conditional logistic regression. Subgroup analysis were performed in subsets of patients classified by the presence of cardiovascular disease (in ARREST: defined as the use of any cardiovascular drugs listed in *Table 1*; in DANCAR: defined as patients who had a hospital contact for ≥1 cardiovascular disease up to 10 years before OHCA or the use of any cardiovascular drugs listed in *Table 1*). Paired and unpaired *t*-tests were used to test the effects of drugs and between drugs, respectively, on $I_{Ca,L}$ and APs. We considered a two-sided *P*-value <0.05 statistically significant. Data are presented as OR [95% confidence interval (CI)].

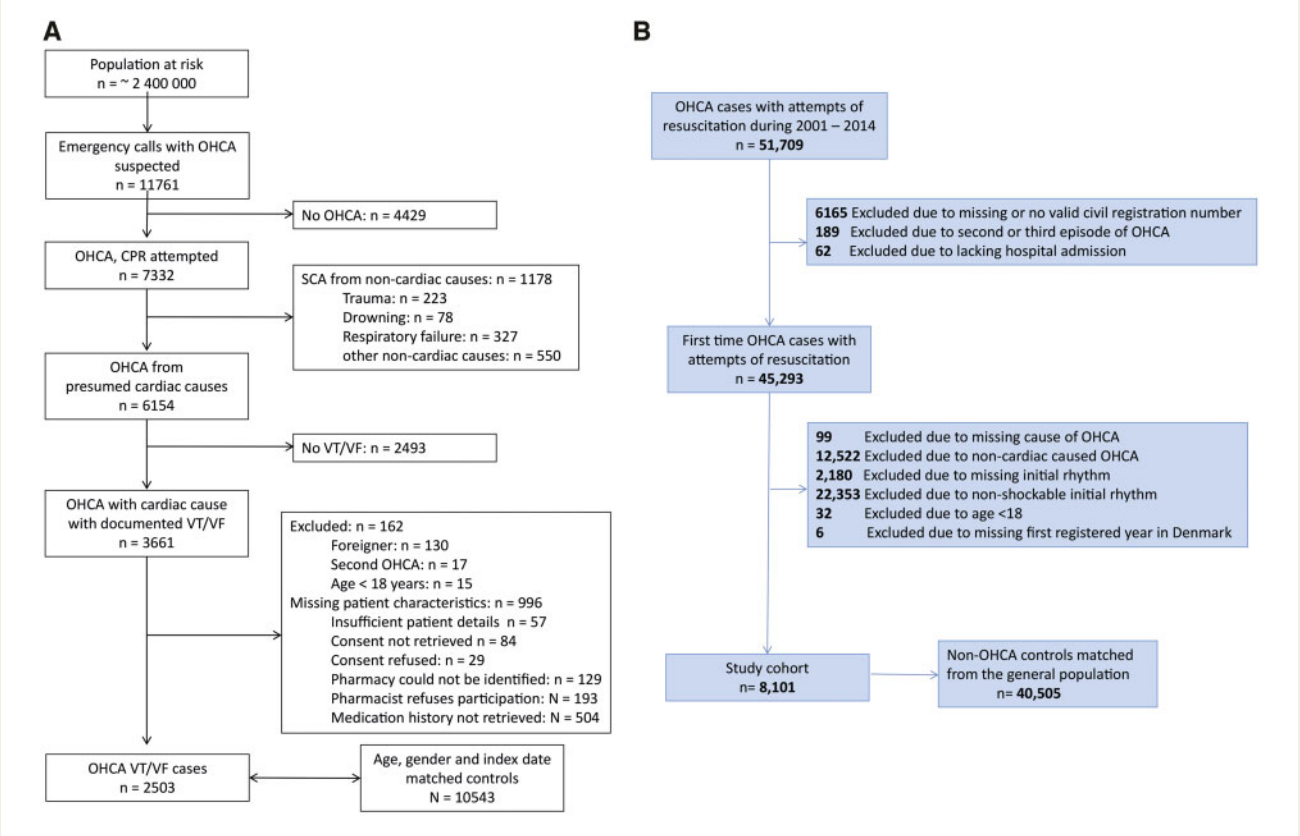

Figure 1 Flowchart of inclusion of out-of-hospital cardiac arrest cases. (*A*) ARREST registry. (*B*) DANCAR registry. CPR, cardiopulmonary resuscitation; OHCA, out-of-hospital cardiac arrest; VT/VF, ventricular tachycardia/ventricular fibrillation.

Results

Patient characteristics

In ARREST, from a total of 3661 OHCA cases with cardiac causes and documented VT/VF, complete medication histories were obtained in 2503; these cases (median age 67.0 years, 77.4% male) were matched to 10 543 controls (*Figure 1*). In DANCAR, 8101 OHCA cases (median age 68.0 years, 79.4% male), were matched to 40 505 controls (*Figure 1*). In both registries, use of all studied drug categories and comorbidities (in DANCAR) was more prevalent among cases than controls (*Table 1*).

Dihydropyridine use and out-of-hospital cardiac arrest risk

In ARREST, current use of any dihydropyridine was not associated with higher OHCA risk than no use of dihydropyridines [OR_{adj} 0.84 (0.71–0.99), *Figure 2*]. Increased OHCA risk occurred among current users of nifedipine compared to no use of dihydropyridines [OR_{adj} 1.28 (1.003–1.63), *Figure 2*] and was dose-dependent [low-dose OR_{adj} 1.15 (0.84–1.59), high-dose OR_{adj} 1.45 (1.02–2.07)]. In contrast, current use of amlodipine was associated with lower OHCA risk than no use of dihydropyridines [OR_{adj} 0.63 (0.50–0.79)], but this lower OHCA risk was not dose-dependent [low-dose OR_{adj} 0.57 (0.43–0.77), high-dose OR_{adj} 0.70 (0.50–0.97)]. Accordingly, current use of nifedipine was associated with higher OHCA risk than current use of amlodipine [any-dose OR_{adj} 2.03 (1.48–2.78), high-dose OR_{adj} 2.31 (1.54–3.47), *Figure 3*]. In DANCAR, these key findings were similar: current use of high-dose nifedipine was associated with higher OHCA risk than no use of dihydropyridines [OR_{adj} 1.96 (1.18–3.25), *Figure 2*] or current use of amlodipine [OR_{adj} 2.20 (1.32–3.67), *Figure 3*], while current use of amlodipine was associated with lower OHCA risk than no use of dihydropyridines [OR_{adj} 0.89 (0.82–0.97), *Figure 2*]. OR_{crude} is provided in Supplementary material online, *Table S1*.

To assess possible confounding, we studied whether concomitant medication use was different between nifedipine users and amlodipine users (Supplementary material online, *Table S2*). In both registries, there were no statistically significant differences. In DANCAR, there were also no statistically significant differences in comorbidities between nifedipine users and amlodipine users. In both registries, we found no statistically significant differences in concomitant medication use and comorbidities (in DANCAR) between low-dose and high-dose nifedipine users (Supplementary material online, *Table S3*). Moreover, in our subgroup analysis of patients with known cardiovascular disease, use of high-dose nifedipine was consistently associated with increased OHCA risk in both registries (Supplementary material online, *Table S4*).

We next studied whether OHCA risk was further increased in patients using nitrates (as proxy for IHD) by performing stratified

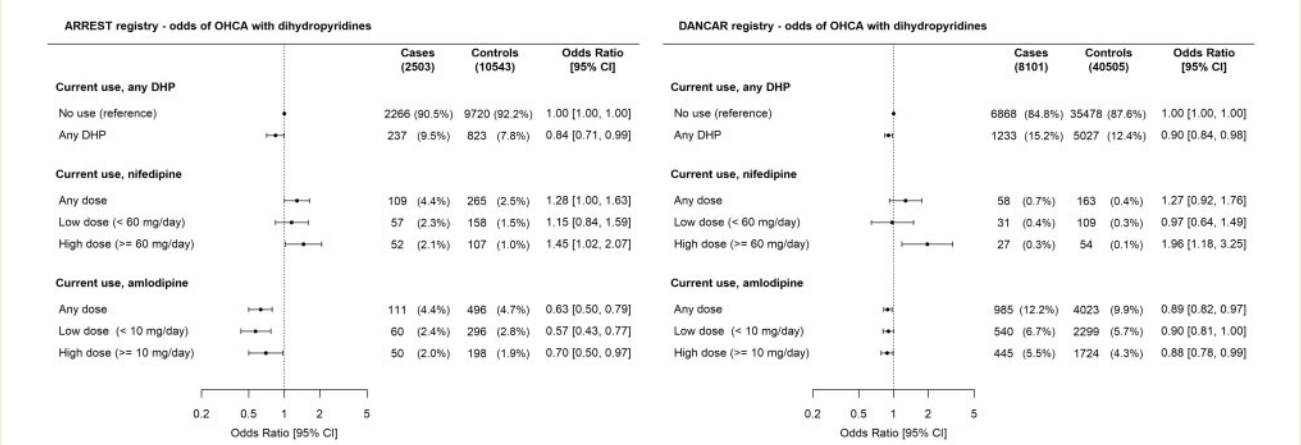

Figure 2 Current use of dihydropyridines, nifedipine, or amlodipine and out-of-hospital cardiac arrest risk compared with no use of any dihydropyridine. Numbers in table are *n* (%) unless indicated otherwise. Error bars denote 95% confidence interval. In ARREST, dose information was unavailable for one case and two controls; these individuals were not included in the Figure. CI, confidence interval; DHP, dihydropyridine.

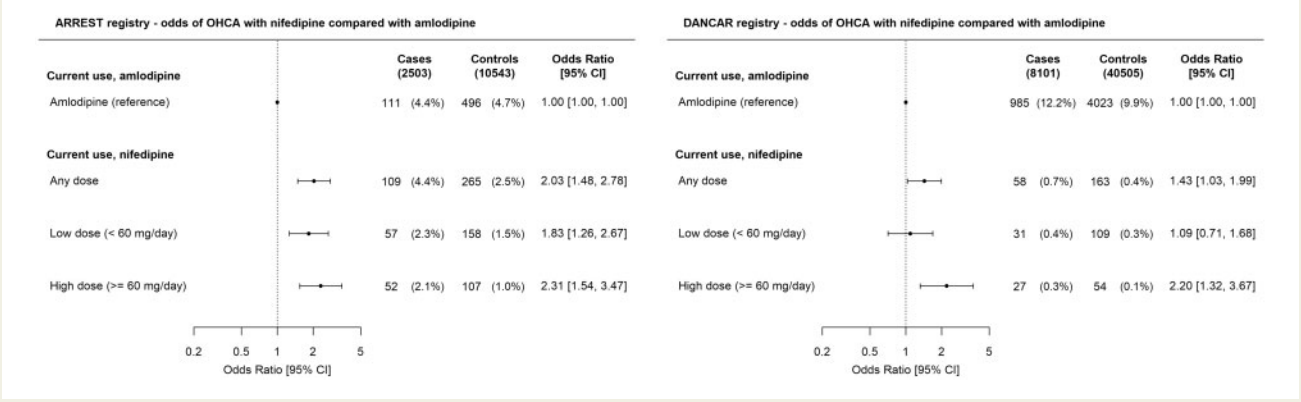

Figure 3 Current use of nifedipine and out-of-hospital cardiac arrest risk compared with current use of amlodipine. Numbers in table are *n* (%) unless indicated otherwise. Error bars denote 95% confidence interval. CI, confidence interval; OR, odds ratio.

analyses. We found that OHCA risk was not further increased in patients using nitrates (ARREST: any-dose nifedipine $P_{interaction}$ 0.098, high-dose nifedipine $P_{interaction}$ 0.050; DANCAR: any-dose nifedipine $P_{interaction}$ 0.546; high-dose nifedipine $P_{interaction}$ 0.857, Supplementary material online, *Figure S1*). Next, in DANCAR, we performed stratified analyses according to IHD or previous AMI status. We found that OHCA risk associated with any-dose nifedipine was not further increased in this group (DANCAR: any-dose nifedipine $P_{interaction}$ 0.079, high-dose nifedipine $P_{interaction}$ 0.949).

To study whether increased OHCA risk of nifedipine may be related to the effects of increased sympathetic stimulation, we conducted stratified analysis according to concomitant use of beta-blockers (which attenuate the effects of sympathetic stimulation). We found that OHCA risk associated with nifedipine was not altered in patients using beta-blockers (ARREST: any-dose nifedipine $P_{interaction}$ 0.405, high-dose nifedipine $P_{interaction}$ 0.226; DANCAR: any-dose nifedipine $P_{interaction}$ 0.766; high-dose nifedipine $P_{interaction}$ 0.796, Supplementary material online, *Figure S1*). Moreover, most nifedipine users among cases used its slow-release form (ARREST: $N = 106$ of 109, DANCAR: $N = 55$ of 58) which causes less sympathetic stimulation than short-acting nifedipine,[28] and there were no cases who used high-dose short-acting nifedipine.

Cellular electrophysiologic studies

We studied whether the disparate associations between nifedipine or amlodipine use and OHCA risk could be explained by differences in cardiac electrophysiologic properties between both drugs. First, we studied the effects of nifedipine and amlodipine on $I_{Ca,L}$. *Figure 4A* shows typical total $I_{Ca,L}$ recordings in the absence and presence of various nifedipine and amlodipine concentrations. Dose-response relationships of nifedipine and amlodipine (*Figure 4B*) were virtually overlapping [IC_{50} 104 ± 13 nmol/L (nifedipine, $n = 5$) vs. 64 ± 30 nmol/L (amlodipine, $n = 5$), $P = 0.22$; Hill coefficients

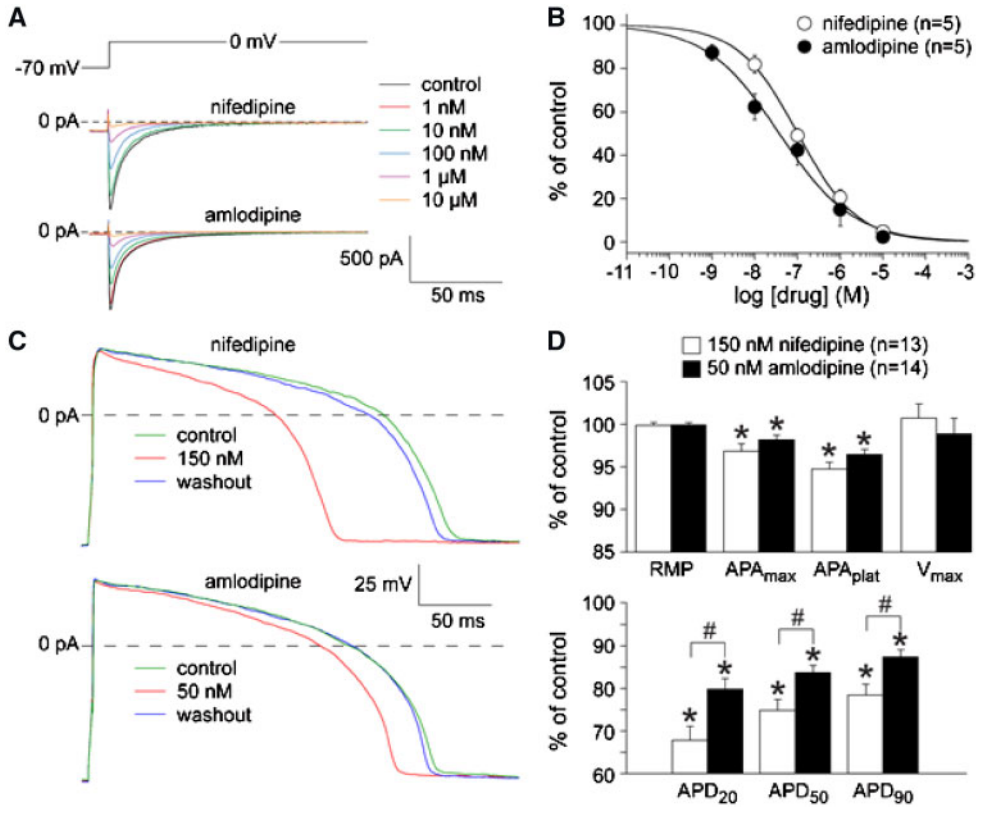

Figure 4 Effects of nifedipine and amlodipine on the L-type calcium current ($I_{Ca,L}$) and action potentials.(*A*) Typical $I_{Ca,L}$ recordings in absence and presence of nifedipine (top) and amlodipine (bottom). Inset: voltage clamp protocol. (*B*) Average dose-response curves of nifedipine and amlodipine on $I_{Ca,L}$. Note that currents are normalized to current before drug application. Solid lines: Hill equation fits of average data. (*C*) Typical examples of APs in absence and presence of 150 nM nifedipine (top) and 50 nM amlodipine (bottom). Both drugs caused reversible AP-shortening. (*D*) Average effects of nifedipine (150 nM) and amlodipine (50 nM) on AP-properties. *$P < 0.05$ control conditions vs. drugs; $^{\#}P < 0.05$ nifedipine vs. amlodipine.

0.66 ± 0.11 (nifedipine, $n = 5$) vs. 0.53 ± 0.05 (amlodipine, $n = 5$), $P = 0.25$]. Next, we tested the effects on APs of 150 nM nifedipine and 50 nM amlodipine (corresponding to maximal plasma concentrations of 60 mg/day nifedipine and 10 mg/day amlodipine, respectively[29,30]). *Figure 4C* shows typical APs, average effects are summarized in *Figure 4D*. Both drugs caused reversible AP-shortening and decrease of APA_{max} and $APA_{plateau}$ (*Figure 4C* and *D*), but these effects were larger for nifedipine (*Figure 4D*). For example, APD_{90} was reduced by 21.6 ± 2.5 and 12.7 ± 1.8% for nifedipine and amlodipine, respectively ($P = 0.006$).

Discussion

In this observational study with real-world data from two large independent population-based OHCA registries in different countries, high-dose nifedipine, but not low-dose nifedipine or any-dose amlodipine, was associated with increased OHCA risk, independent of concomitant medication use or comorbidities. OHCA risk was not further increased in the presence of IHD. Furthermore, at clinically used concentrations, nifedipine caused more L-type calcium current block, resulting in more action potential shortening.

Previous studies have raised serious concerns about the long-term safety of L-type calcium-channel blockers, mainly short-acting dihydropyridines.[15,31] Increased AMI risk upon use of high-dose short-acting calcium-channel blockers was reported among hypertension patients.[31] Also, increased total mortality risk was found among IHD patients using high-dose short-acting nifedipine.[15] One hypothesized mechanism for these findings is increased sympathetic tone,[15] most pronounced for short-acting nifedipine.[28] While reflex sympathetic activation during nifedipine use may have occurred secondary to rapid blood pressure drop among nifedipine users, we found that increased VT/VF risk still occurred among nifedipine users who concomitantly used beta-blockers (Supplementary material online, *Figure S1*); the latter drugs would block the effects of reflex sympathetic activation. Also, the vast majority of nifedipine users used its slow-release form; this form acts slowly and gradually, thereby not provoking rapid blood pressure drop and reflex stimulation of the sympathetic system. Supporting this notion, multiple randomized controlled trials were conducted to study the association between long-acting nifedipine and mortality risk,[32–35] but none found increased risk of (all-cause) mortality. Finally, the presence of coronary steal by collateral arteries has been described during nifedipine use,[36] but the results seem to be inconsistent.[37] For instance, one

study reported pro-ischaemic effects of nifedipine in chronic stable angina patients with good collateral flow and suggested that these findings could be mediated through coronary steal.[36] However, another study found opposite effects of nifedipine administration.[37] Also, while increased AMI risk was reported among users of short-acting calcium blockers,[31] multiple randomized controlled trials found no evidence for increased AMI risk among users of long-acting calcium channel antagonists, while the vast majority of nifedipine users among the OHCA cases in our study used its slow-release form. Our study indicates no further increased OHCA risk among patients with IHD. To our knowledge, no studies yet have investigated whether long-acting dihydropyridine use is associated with increased OHCA risk. Such studies require a dedicated study design, in particular, to ascertain that OHCA resulted from cardiac arrhythmia (VT/VF) rather than from non-cardiac causes. Thus, ECG documentation of VT/VF during OHCA is required, but this is extremely challenging, because OHCA occurs suddenly and unexpectedly, and VF dissolves into asystole within minutes if left untreated. The often-used pragmatic definition of OHCA (without requirement of ECG documentation) of the European Society of Cardiology ('event occurring within 1 h of symptom onset or, if unwitnessed, within 24 h of the victim being seen in good health'[38]) carries the risk of misclassification of non-cardiac causes. This is particularly relevant in our study, since hypertension patients (some of whom are treated with dihydropyridines) have increased risk of these non-cardiac causes (stroke, ruptured aneurysm). To overcome these difficulties, and to comprehensively study risk factors associated with OHCA, we set-up dedicated population-based OHCA registries (ARREST, DANCAR) and the ESCAPE-NET research network.[16] These efforts now allow us to study more reliably the risk of OHCA from cardiac arrhythmia associated with dihydropyridine use.

Our findings indicate that increased OHCA risk of high-dose nifedipine may be related to specific drug effects, rather than a class effect. While we found no evidence in our epidemiologic studies that increased sympathetic stimulation is involved, our cellular electrophysiologic studies provided possible clues. Different dihydropyridines have distinct potencies to inhibit L-type calcium-channels in vascular smooth muscle cells or myocardium. For example, nifedipine has ~10 times higher affinity for vascular cells than myocardium.[39] Although nifedipine and amlodipine are prescribed because of their effects on vascular L-type calcium-channels, we found that both drugs significantly block cardiac $I_{Ca,L}$, thereby shortening AP-duration. AP-shortening may provoke VT/VF by facilitating re-entrant excitation, the predominant electrophysiologic mechanism of VT/VF. This is most clearly demonstrated by the rare inherited Short-QT-syndrome, which is associated with a high risk of OHCA.[40] Conversely, AP-prolongation is the mechanism by which Classes IA and III antiarrhythmic drugs exert their therapeutic action. Thus, AP-shortening may contribute to the increase in OHCA risk of high-dose nifedipine. This may also explain why high-dose nifedipine, but not low-dose nifedipine or amlodipine, is associated with increased OHCA risk: high-dose nifedipine causes more AP-shortening than both other conditions. Of note, although amlodipine blocks cardiac L-type calcium-channels at similar concentrations as nifedipine, the extent of $I_{Ca,L}$ block in clinical practice is lower for amlodipine than for nifedipine, because prescribed dosages (and plasma-concentrations) are significantly lower for amlodipine.

Our findings provide clues for the design of preventive strategies against this adverse drug effect of nifedipine. Most strategies against OHCA risk of drugs that impact on cardiac electrophysiology focus strongly on identifying vulnerable individuals, e.g. individuals with (genetic) vulnerability to excessive QT-prolongation when prescription of QT-prolonging medication is considered. Similarly, guidelines state that anti-arrhythmic sodium-channel blockers such as flecainide should be withheld from patients with acquired causes of reduced cardiac excitability, e.g. cardiac ischaemia and/or heart failure. In the case of nifedipine, the strategy may have to focus both on identifying vulnerable individuals and on limiting the height of prescribed dosages. Although dose-dependent reduction in blood pressure was shown in patients with hypertension[41] and high-dose nifedipine was shown to better attenuate angina pectoris than low-dose nifedipine,[42] the dose-effect relationships of nifedipine strongly differ between patients.[43] Careful titration of nifedipine dose may have to be considered. Clearly, future studies are required to establish (i) whether nifedipine use confers higher OHCA risk than amlodipine use, (ii) whether vulnerable individuals are those who receive nifedipine for hypertension treatment, and (iii) whether lower dosages impact less on cardiac electrophysiology and OHCA risk, while retaining their beneficial effects on treatment for IHD and/or hypertension.

Strengths and limitations

A major strength of the ARREST and DANCAR registries is that documentation of VT/VF was present; this reduces risk of misclassification of patients who suffered OHCA from non-cardiac causes. Also, the population-based real-world design minimized selection bias by prospectively including every OHCA case in large contiguous regions representative for the community at large. Finally, our cellular electrophysiologic studies supported these epidemiologic findings by revealing differential effects on the AP that may explain these findings.

The observational nature of our epidemiologic studies comes with inherent limitations, e.g. the fact that we could only detect associations without proving causality. To gain more insight into a possible mechanistic explanation, we conducted cellular electrophysiologic studies using hiPSC-CMs. Although hiPSC-CMs are relatively immature compared to cardiomyocytes from an adult heart,[44] $I_{Ca,L}$ antagonists have similar effects in hiPSC-CMs to those observed in native cardiomyocytes.[45] Another limitation is the lack of completeness of data from the Dutch cohort since almost one-third of the OHCA cases was not included primarily due to lack of medication history (*Figure 1*). However, we expect that incomplete data were distributed proportionally between users and non-users of nifedipine. Also, while nifedipine was used by 38% of dihydropyridine users in the Netherlands, this was only the case in 4% in Denmark. As a consequence, we were able to identify only 27 users of high-dose nifedipine at the time of OHCA in the Danish registry, which is also reflected in the wide CI (*Figure 2*). Another limitation is that, although drug-dispensing data were complete, we had no information whether claimed medications were actually taken in both cohorts. In any case, drug-dispensing records, used in both cohorts, are already one important step closer to actual intake than drug prescription records.

Furthermore, we have no reason to assume that intake behaviour between nifedipine and amlodipine users would be different. Yet, possible misclassification arising from this was probably similarly distributed between cases and controls. To mitigate the limitations associated with use of medication proxies, we also used information on comorbidities in our multivariable analyses using DANCAR-data. This approach resulted in similar findings. Finally, there may have been confounding by indication, as cases and controls are different regarding concomitant drug use (*Table 1*), pointing towards cases in general having more comorbidity. However, it was very hard—if not practically impossible—to obtain data to prove that possible confounding was present or absent. We addressed this problem primarily by comparing OHCA risk of nifedipine use with amlodipine use. Moreover, we found no evidence that nifedipine users differed significantly from amlodipine users in demographic variables or their comorbidities (Supplementary material online, *Table S2*). In addition, the robustness of our findings regarding high-dose nifedipine was confirmed by a subgroup analysis in which we examined only patients with cardiovascular disease (Supplementary material online, *Table S4*). However, it is still possible that (unmeasured) residual confounders might have affected our observed associations.

Conclusion

High-dose nifedipine, but not low-dose nifedipine or any-dose of amlodipine, is associated with increased OHCA risk in the general population. Differences in cellular electrophysiologic properties of clinically used concentrations between both drugs were found.

Supplementary material

Supplementary material is available at *European Heart Journal – Cardiovascular Pharmacotherapy* online.

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