Out-of-hospital cardiac arrest

A pharmacoepidemiological approach

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Part IV

Summary, discussion and future perpsectives

DISCUSSION AND FUTURE PERSPECTIVES

In this thesis we investigated the risk of out-of-hospital cardiac arrest (OHCA) associated with the use of repolarization blocking drugs, depolarization blocking drugs and sulfonylurea drugs (SU-drugs), and studied the influence of beta-blockers on first-registered heart rhythm during OHCA. In this Chapter the findings of the presented studies in this thesis and the methodological considerations will be discussed. Finally, several directions for future research will be discussed.

Repolarization blocking drugs and OHCA risk

In Chapter 2 we showed that use of cardiac QT-prolonging drugs confers lower OHCA risk than use of non-cardiac QT-prolonging drugs. In order to understand the study findings, we compared patient characteristics and drug properties between users of both drug types that may result in differences in *a priori* OHCA risk between users of cardiac and non-cardiac QT-prolonging drugs. We found that users of cardiac QT-prolonging drugs had more cardiovascular disease and drug-dispensing records for cardiovascular drugs, while psychiatric disorders were more common among users of non-cardiac QT-prolonging drugs. Both observations are not surprising, since users of cardiac QT-prolonging drugs (i.e., sotalol, amiodarone, flecainide) have cardiovascular diseases and many of the non-cardiac QT-prolonging drugs are psychoactive substances. Next, we compared the relative magnitude of the cardiac potassium current I_{Kr} blocking effects of the most commonly used drugs in our study by determining the ratio of effective free therapeutic plasma concentration ($ETCP_{unbound}$) over the concentration that inhibits 50% of I_{Kr} channels (IC50).[1] Cardiac QT-prolonging drugs exhibit higher I_{Kr} inhibition at therapeutic concentrations compared to the most frequently used non-cardiac QT-prolonging drugs in our study. This finding was in line with our expectation, since cardiac QT-prolonging drugs are specifically designed to block the cardiac potassium channel, while being an off-target effect of non-cardiac QT-prolonging drugs. Therefore, differences in patient characteristics or drug properties do not appear to explain our findings. One possibility for our study finding might be differences in behavior of prescribers of both drug classes resulting in differences in risk-mitigations measures taken. We assume that cardiac QT-prolonging drugs were mostly prescribed by cardiologists, and non-cardiac QT-prolonging drugs by other physicians. Prescribers of non-cardiac QT-prolonging drugs may lack easy access to methods for risk monitoring such as ECG monitoring, may have less awareness of the potential life-threatening arrhythmia risk of non-cardiac QT-prolonging drugs or may have limited knowledge to utilize appropriate risk-mitigating actions when they consider prescription of these drugs. In Chapter 3 we studied OHCA risk of non-cardiac QT-prolonging drugs, which was classified into category 1 drugs ('known risk of Torsade de Pointes [TdP]') and category 2 drugs ('possible risk of Torsade de Pointes') according to the clinically widely used CredibleMeds website.[2,3,4]

We found that both categories were associated with an increased risk of OHCA, which indicates that risk mitigation measures should also be applied to category 2 drugs.

Depolarization blocking drugs and OHCA risk

In Chapter 4 we observed increased OHCA risk upon use of non-cardiac depolarization-blocking drugs. As we lack information on important OHCA risk factors such as cardiovascular diseases[5] we cannot rule out the possibility that our results, at least in part, are driven by confounding. To deal with the absence of information regarding cardiovascular diseases, we used drug use as proxy for cardiovascular disease for confounder adjustment in the analyses. Our association persisted in patients without use of cardiovascular drugs. Moreover, we had no information regarding other clinical diagnoses that have been associated with OHCA, such as depression.[6] Considering that some of the non-cardiac DB-drugs are antidepressants,[7] we cannot rule out that our results may have been driven by confounding by indication. Therefore, future studies with data on this comorbidity is needed to further explore the association between non-cardiac DB-drugs and OHCA risk. Lastly, it could be speculated that the association between non-cardiac DB-drugs and OHCA risk when non-ventricular tachycardia/ventricular fibrillation (VT/VF), but not VT/VF, was the first-registered rhythm, is influenced by resuscitation characteristics. We observed longer time from emergency medical services call to defibrillator connection and that OHCA occurred less often at a public location in OHCA-cases, which are both associated with non-VT/VF,[8] among users of non-cardiac DB-drugs compared to those who did not use non-cardiac DB-drugs.

In Chapter 5 we observed that high-dose nifedipine (≥60 mg/day) was associated with increased risk of OHCA compared to no use of dihydropyridines. Despite our efforts to adjust for important OHCA risk factors such as cardiovascular disease we cannot rule out the possibility that this result is driven by confounding by disease severity, in particular coronary artery disease, since nifedipine high-dose but not low-dose was associated with OHCA. The fact that high-dose amlodipine, which is used for similar indications, was not associated with increased OHCA risk may suggest that this association is not a class effect but a specific drug effect. Therefore, while keeping the study limitations in mind, these data suggest that careful titration should be considered when prescribing nifedipine.

Other drug categories and OHCA

The findings in Chapter 6 indicate that the OHCA reducing effect of SU-drugs is drug-specific, rather than a class effect. Moreover, our cellular electrophysiological study provided no evidence that our epidemiological findings on SU-drugs could be explained by the effect of SU-drugs to counteract ischemia-induced shortening of action potential duration. Furthermore, differences between SU-drugs could not be explained by differences in pa-

tient characteristics. However, it is possible that our study was not powered to detect actual differences in OHCA risk between individual SU-drugs. Further studies are warranted to further assess the OHCA risk of individual SU drugs.

Results in Chapter 7 suggest that non-selective beta-blocker use, but not β1-selective beta-blocker use, increases the risk of non-shockable rhythm in OHCA. As users of β1-selective beta-blockers had higher prevalence of diseases associated with shockable rhythm such as ischemic heart disease and congestive heart failure,[8] we cannot rule out that a possible association with non-shockable rhythm may have been masked.

Methodological considerations

The random allocation of individuals into intervention or a control group in randomized clinical trials (RCTs), ensures that measured and unmeasured confounders are equally distributed among the two groups. If the RCT is sufficiently powered the risk of random and systematic error is substantially reduced resulting in high internal validity. Therefore, RCTs are considered as the gold standard and are the preferred research design to assess causality between an exposure and outcome. However, this type of study design is not ideal to study OHCA as an outcome considering the ethical and practical issues. Moreover, not all research questions can be addressed by RCTs because many interactions between drugs and co-morbidities or other triggers may not occur in RCTs. Observational studies, utilizing existing registries with information regarding drug-dispensing records and comorbidities offer an alternative method to investigate drug-induced arrhythmias in large unselected cohorts. However, observational studies have their own limitations. Due to lack of randomization, confounding bias may affect the internal validity of study results. Therefore, in the included studies in this thesis the risk of bias should always be considered when interpreting the results. Another issue is that some variables of interest were not available to include in the analyses. Data on risk factors of OHCA such as lifestyle factors (BMI, smoking, alcohol use), left ventricular ejection fraction and familial predisposition to OHCA were lacking. However, given the highly unpredictable way in which OHCA occurs it is hard to obtain clinical information just before OHCA occurrence. Furthermore, in some of our OHCA patients and in all non-OHCA individuals, comorbidities of interest such as cardiovascular diseases were not available to include in the analyses. Therefore, we could not perform direct adjustments for comorbidities. To deal with this, we used drug use as a proxy for comorbidities which we included in the analyses. This may result in misclassification of disease severity because patients with different disease stages may use the same drugs. For instance, a patient with heart failure with decreased left ventricular ejection fraction at the time of OHCA may use renin-angiotensin-aldosterone system inhibitor, while another patient with heart failure but with normalized left ventricular ejection fraction at the time of OHCA may use the same medication. On the other hand, it is also possible that left ventricular ejection

fraction is normalized because of the prescribed medication, while the patient started with low left ventricular ejection fraction. Furthermore, we had no information regarding the therapeutic indication. Considering that cardiovascular drugs have a wide range of indications (for instance renin-angiotensin-aldosterone system inhibitor to treat heart failure and/or hypertension), misclassification of the disease may have occurred. We used in Chapter 2, 5 and 7 the Danish registries in which information regarding comorbidities were available. In the Danish registries, information on comorbidities was based on hospital diagnoses[9] and thus information regarding patients that are exclusively treated by the general practitioner was not available. However, considering that most of the included cardiovascular diseases (e.g., ischemic heart disease, heart failure, atrial fibrillation) in our analyses are diagnosed in hospitals we expect that this issue only partially affected our results. However, it must be taken in mind that this approach does not take disease severity into account since the information on the presence of comorbidity is a binary variable, which makes it hard to adjust properly for diseases such as heart failure and diabetes mellitus that have a large spectrum of disease severities.

Our close collaboration in ARREST with dispatch centers, emergency medical services and the hospitals in the study area enables us to capture virtually all emergency medical services attended OHCAs in the study region.[10] Another way to obtain data on OHCA is to use diagnosis based on emergency department and in-hospital diagnosis, as done in other studies.[11,12] However, that approach may result in selection bias because patients who died before hospital admission could not be included in the study. This may be relevant in our study presented in chapter 6 regarding the association between SU-drugs and OHCA risk, since diabetes is associated with reduced pre-hospital survival.[13] Our population-based design in which both OHCA patients who survived to hospital admission and those who died pre-hospital were included minimizes this selection bias.[10] In Chapter 6 we could not identify the duration of diabetes mellitus, since we had drug-dispensing records only for one year prior to index-date (OHCA-date). Therefore, we had no information about the first-ever initiation of antidiabetic treatment. Therefore, we could not adjust for diabetes duration. To deal with diabetes severity, we created a study population with a similar disease severity by excluding insulin users which could be considered as a proxy for advanced stage of type 2 diabetes.

FUTURE PERSPECTIVES

Our finding that OHCA risk associated with non-cardiac DB-drugs was greatest among youngest patients (≤ 50 years) in whom comorbidities including myocardial ischemia/infarction are likely not yet have developed, seems to suggest that genetic factors may

contribute to this risk (chapter 4). Additionally, a recent study demonstrated that common genetic variants importantly drive an individual's sensitivity to the electrophysiological effects of DB-drugs.[14] In this light, future studies are needed to identify new genes associated with OHCA during use of DB-drugs. So far, genetic studies primarily focused on subgroups of OHCA patients who suffered OHCA in the presence of acute myocardial infarction.[15] However, future genetic studies should also focus on OHCA patients who suffered OHCA during use of risk drugs, i.e., QT-prolonging drugs and DB-drugs, considering the growing evidence linking genetic factors to drug induced arrhythmia.[16,17] OHCA cohorts from the general population with well-phenotyped patient groups may help to find new genes associated with OHCA during use of QT-prolonging drugs and DB-drugs. Second, more studies are required to identify individuals at high risk of OHCA during use of DB-drugs. Important clinical features (e.g. congestive heart failure, female sex, electrolyte abnormalities) that prolong the QT-interval and predispose to cardiac arrhythmia in the presence of QT-prolonging drugs are well-established,[18] while risk factors that predispose to cardiac arrhythmia in the presence of DB-drugs are less known, especially for non-cardiac DB-drugs. The identified genetic and clinical risk factors can be used to design a risk score for OHCA occurrence during use of these risk drugs, which will lead to a more patient-tailored treatment strategy. To accomplish this goal, large study cohorts of well-phenotyped OHCA patients are essential. This risk score can be incorporated into a clinical decision support system that warns the physician when prescription of a QT-prolonging drugs or DB-drugs is considered. This will help to increase the physician's awareness and will lead to safer use of these risk drugs. In chapter 2 we demonstrated that use of cardiac QT-prolong drugs is associated with lower OHCA risk than use of non-cardiac QT-prolonging drugs in the general population, although users of cardiac QT-prolonging drugs had higher cardiovascular disease burden compared to users of non-cardiac QT-prolonging drugs. This seems to suggest that perhaps, at present, prevention of drug-induced arrhythmia is best achieved by increasing awareness of the life-threatening potential of these risk drugs (QT-prolonging drugs, DB-drugs) among prescribers of these drugs.

CONCLUSIONS

The six epidemiological studies included in this thesis provide novel insights into the role of drugs in the occurrence of OHCA. Based on the six main findings, we can conclude that:

- Cardiac QT-prolonging drugs confer lower OHCA risk than non-cardiac QT-prolonging drugs. Furthermore, non-cardiac QT-prolonging drugs classified as conferring possible risk of TdP also increase OHCA risk.
- Use of non-cardiac DB-drugs is associated with increased risk of OHCA compared with no use of any non-cardiac DB-drugs. This increased risk occurs in patients in whom non-

VT/VF (asystole) is the first-registered rhythm, and it occurs in both sexes, and more strongly in younger patients (≤50 years). These findings indicate that risk-mitigation measures should be taken when non-cardiac DB-blocking drugs are prescribed.

- High-dose nifedipine (≥60 mg/day), but not low-dose nifedipine or amlodipine (low and high dose), is associated with increased OHCA risk. Our data suggest that careful titration should be considered when prescribing nifedipine.
- SU-drugs are associated with reduced OHCA risk compared to metformin monotherapy. Our findings indicate that OHCA reducing effects of SU-drugs are drug-specific rather than a class effect. We did not find any evidence to suggest that the differences are explained by differential effects on action potential duration.
- Non-selective beta-blocker use, but not β1-selective beta-blocker, are associated with non-shockable rhythm in OHCA.

REFERENCES

1. De Bruin ML, Pettersson M, Meyboom RH, Hoes AW, Leufkens HG. Anti-HERG activity and the risk of drug-induced arrhythmias and sudden death. Eur Heart J. 2005;26(6):590-7.
2. Schwartz PJ, Woosley RL. Predicting the Unpredictable: Drug-Induced QT Prolongation and Torsades de Pointes. J Am Coll Cardiol. 2016;67(13):1639-50.
3. Woosley RL, Black K, Heise CW, Romero K. CredibleMeds.org: What does it offer? Trends Cardiovasc Med. 2018;28(2):94-9.
4. Woosley RL, Heise CW, Gallo T, Tate J, Woosley D and Romero KA, www.CredibleMeds.org, Qtdrugs List, [Accession Date: 8-5-2021], AZCERT, Inc. 1822 Innovation Park Dr., Oro Valley, AZ 85755.
5. Huikuri HV, Castellanos A, Myerburg RJ. Sudden death due to cardiac arrhythmias. N Engl J Med. 2001;345(20):1473-82.
6. Empana JP, Jouven X, Lemaitre RN, Sotoodehnia N, Rea T, Raghunathan TE, et al. Clinical depression and risk of out-of-hospital cardiac arrest. Arch Intern Med. 2006;166(2):195-200.
7. Postema PG, Wolpert C, Amin AS, Probst V, Borggrefe M, Roden DM, et al. Drugs and Brugada syndrome patients: review of the literature, recommendations, and an up-to-date website (www.brugadadrugs.org). Heart Rhythm. 2009;6(9):1335-41.
8. 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.
9. Schmidt M, Schmidt SA, Sandegaard JL, Ehrenstein V, Pedersen L, Sørensen HT. The Danish National Patient Registry: a review of content, data quality, and research potential. Clin Epidemiol. 2015;7:449-90.
10. 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.
11. Leonard CE, Brensinger CM, Aquilante CL, Bilker WB, Boudreau DM, Deo R, et al. Comparative Safety of Sulfonylureas and the Risk of Sudden Cardiac Arrest and Ventricular Arrhythmia. Diabetes Care. 2018;41(4):713-22.
12. Leonard CE, Bilker WB, Newcomb C, Kimmel SE, Hennessy S. Antidepressants and the risk of sudden cardiac death and ventricular arrhythmia. Pharmacoepidemiol Drug Saf. 2011;20(9):903-13.
13. 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.
14. Tadros R, Tan HL, El Mathari S, Kors JA, Postema PG, Lahrouchi N, et al. Predicting cardiac electrical response to sodium-channel blockade and Brugada syndrome using polygenic risk scores. Eur Heart J. 2019;40(37):3097-107.
15. Bezzina CR, Pazoki R, Bardai A, Marsman RF, de Jong J, Blom MT, et al. Genome-wide association study identifies a susceptibility locus at 21q21 for ventricular fibrillation in acute myocardial infarction. Nat Genet. 2010;42(8):688-91.

16. Napolitano C, Schwartz PJ, Brown AM, Ronchetti E, Bianchi L, Pinnavaia A, et al. Evidence for a cardiac ion channel mutation underlying drug-induced QT prolongation and life-threatening arrhythmias. J Cardiovasc Electrophysiol. 2000;11(6):691-6.

17. Itoh H, Crotti L, Aiba T, Spazzolini C, Denjoy I, Fressart V, et al. The genetics underlying acquired long QT syndrome: impact for genetic screening. Eur Heart J. 2016;37(18):1456-64.

18. Heist EK, Ruskin JN. Drug-induced arrhythmia. Circulation. 2010;122(14):1426-35.

OUT-OF-HOSPITAL CARDIAC ARREST: A PHARMACOEPIDEMIOLOGICAL APPROACH

Summary

Part 1 of this thesis presents two studies aimed to study whether cardiac repolarization blocking drugs increase the risk of out-of-hospital cardiac (OHCA) arrest. Part 2 presents two studies aimed to determine whether cardiac depolarization blocking drugs increase the risk of OHCA. Part 3 describes a study aimed to determine whether sulfonylurea drugs (SU-drugs) decreases the risk of OHCA, and presents another study aimed to investigate a possible association of beta-blockers with non-ventricular tachycardia/ventricular fibrillation [VT/VF] during OHCA.

PART I: Repolarization blocking drugs and OHCA risk

Chapter 2 presents a case-control study that aimed to determine whether use of cardiac and non-cardiac QT-prolonging drugs from category 1, which is defined as drugs with known risk of torsades de pointes (TdP) according to the CredibleMeds list (a list in which drugs are classified into four risk categories based on their potential to cause TdP), increases the risk of OHCA compared with no use of QT-prolonging drugs from category 1. We included 2503 OHCA cases and 10543 matched non-OHCA controls from the Netherlands, and 8101 OHCA cases and 40505 matched non-OHCA controls from Denmark. Use of non-cardiac QT-prolonging drugs was associated with increased risk of OHCA (Netherlands: odds ratio (OR) 1.37 [95% confidence interval (CI):1.03-1.81]; Denmark: OR 1.63 [95% CI:1.57-1.70]). We found that the association between cardiac QT-prolonging drugs and OHCA was weaker (Netherlands: OR 1.17 [95% CI:0.92-1.50]; Denmark: OR 1.21 [95% CI:1.09-1.33]), although the prevalence of cardiovascular disease and cardiovascular drug use was higher among users of cardiac QT-prolonging drugs compared to users of non-cardiac QT-prolonging drugs. **Chapter 3** describes a case-control study that aimed to determine whether the use of non-cardiac QT-prolonging drugs, classified as category 1 drugs ['drugs with known risk of TdP'] and category 2 drugs ['drugs with possible risk of TdP']) according to the CredibleMeds list, increases the risk of OHCA. We included 5473 OHCA cases and matched 20866 non-OHCA controls. Use of non-cardiac QT-prolonging drugs from both categories 1 and 2 was associated with increased risk of OHCA (category 1: OR 1.7 [95% CI:1.3-2.1]); category 2: OR 1.4 [95% CI:1.2-1.6]) compared with no use of non-cardiac QT-prolonging drugs. Our findings showed that the difference between non-cardiac QT-prolonging drugs from category 1 and 2 on OHCA risk is modest. Our findings indicate that risk mitigation measures should also be applied when drugs category 2 are prescribed in order to reduce OHCA-risk.

PART II: Depolarization blocking drugs and OHCA risk

Chapter 4 describes a case-control study that aimed to determine whether non-cardiac depolarization-blocking drugs (DB-drugs) increases the risk of OHCA. We included 5473 OHCA cases and 21866 matched non-OHCA controls, and observed a higher risk of OHCA upon use of non-cardiac DB-drugs compared to no use of any non-cardiac DB-drugs (OR 1.6 [95% CI:1.4-1.9]). The increased risk was more prominently among women and more strongly in younger patients (≤50 years). Furthermore, stratification according to first-registered heart rhythm (VT/VF vs. non-VT/VF) revealed that increased OHCA risk applied to OHCA with non-VT/VF, but not with VT/VF. **Chapter 5** presents a study aiming to determine whether nifedipine and/or amlodipine use increases the risk of OHCA, and to establish the underlying mechanisms. We performed functional (patch-clamp) experiments to investigate how these drugs influence the cardiac electrophysiology. We conducted a case-control study to determine the risk for OHCA with nifedipine and amlodipine using data from ARREST and DANCAR, a Danish OHCA registry. We included 2503 OHCA cases and 10543 matched non-OHCA controls from the Netherlands, and 8101 OHCA cases and 40505 matched non-OHCA controls from Denmark. In both registries, use of high-dose nifedipine (≥60 mg/day), but not low-dose nifedipine (<60 mg/day), was associated with increased OHCA risk compared to non-use of dihydropyridines (Netherlands: OR 1.45 [95% CI:1.02–2.07], Denmark: 1.96 [95% CI:1.18–3.25]). Use of amlodipine in high and low dose was not associated with increased risk for OHCA. Functional experiments showed at clinically used concentrations, nifedipine caused more L-type calcium current block than amlodipine, resulting in more action potential shortening.

PART III: Other drug categories and OHCA

Chapter 6 describes a study aiming to determine whether use of SU-drugs decreases the risk of OHCA, and to study the underlying mechanisms. We performed functional (patch-clamp) experiments to investigate the effects of individual SU-drugs on action potential duration (APD) during simulated ischemia. Furthermore, we conducted an epidemiological case-control study to determine the risk for OHCA with sulfonylurea drugs. We included 219 OHCA cases with diabetes and 697 non-OHCA controls with diabetes, and observed a lower risk of OHCA upon use of SU-drugs monotherapy or in combination with metformin compared to use of metformin monotherapy ($OR_{SUdrugs\text{-}monotherapy}$ 0.6 [95% CI:0.4-0.9], $OR_{SUdrugs+metformin}$ 0.6 [95% CI:0.4-0.9]). Gliclazide (OR 0.5 [95% CI:0.3-0.9]) and tolbutamide (OR 0.6 [95% CI:0.3-1.002]) use was associated with reduced risk of OHCA compared to glimerpide, although tolbutamide failed to reach statistical significance. Glibenclamide was not associated with reduced OHCA risk (OR 1.3 [95% CI:0.6-2.7]). Functional experiments showed that only glibenclamide resulted in significantly less APD shortening after 15 minutes. Functional experiments provided no evidence that our epidemiological findings could be explained by the effects of SU-drugs on APD shortening. In **Chapter 7** the associa-

tion between use of beta-blockers and first registered heart rhythm during a resuscitation attempt for OHCA was studied using ARREST and DANCAR. We included 23346 OHCA patients from DANCAR and 1584 OHCA patients from ARREST. Use of non-selective beta-blockers was associated with increased risk of non-VT/VF as initial rhythm in both registries (DANCAR: OR 1.93 [95% CI:1.48–2.52], ARREST: OR 2.52 [95%-CI:1.15–5.49]). In ARREST we could further specify non-shockable rhythm into pulseless electrical activity (PEA) and asystole; PEA but not asystole was associated with non-selective beta-blocker use. Use of β1-selective beta-blockers was not associated with an increased risk of non-VT/VF.

HARTSTILSTAND: EEN PHARMACOEPIDEMIOLOGISCHE BENADERING

Nederlandse samenvatting

Deel 1 van dit proefschrift beschrijft twee studies die tot doel hebben om te onderzoeken of cardiale repolarisatie blokkerende geneesmiddelen het risico op plotselinge hartstilstand verhogen. Deel 2 beschrijft twee studies die tot doel hebben om vast te stellen of cardiale depolarisatie blokkerende geneesmiddelen het risico op plotselinge hartstilstand verhogen. Deel 3 beschrijft een studie die tot doel heeft om vast te stellen of sulfonylurea medicijnen het risico op plotselinge hartstilstand verlagen, en beschrijft een andere studie die tot doel heeft om een mogelijke associatie van bètablokkers met non-ventriculaire tachycardie/ventriculaire fibrillatie [VT/VF] tijdens plotselinge hartstilstand te onderzoeken.

DEEL I: Repolarisatie blokkerende geneesmiddelen en het risico op plotselinge hartstilstand

Hoofdstuk 2 beschrijft een case-control studie met als doel om vast te stellen of het gebruik van cardiale en niet-cardiale QT-verlengende geneesmiddelen uit categorie 1, die volgens de CredibleMeds lijst (een lijst waarin geneesmiddelen zijn geclassificeerd in vier categorieën op basis van hun potentiaal om torsades de pointes [TdP] te veroorzaken) geclassificeerd zijn als geneesmiddelen met bekend risico op torsades de pointes (TdP), het risico verhoogd op plotselinge hartstilstand vergeleken met geen gebruik van QT-verlengende geneesmiddelen uit categorie 1. We includeerden 2503 cases met plotselinge hartstilstand en 10543 gematchte controles zonder plotselinge hartstilstand uit Nederland, en 8101 cases met plotselinge hartstilstand, en 40505 gematchte controles zonder plotselinge hartstilstand uit Denemarken. Gebruik van niet-cardiale QT-verlengende geneesmiddelen was geassocieerd met verhoogd risico op plotselinge hartstilstand (Nederland: odds ratio (OR) 1.37 [95%-betrouwbaarheidsinterval (BI):1.03-1.81]; Denemarken: OR 1.63 [95% BI:1.57-1.70]). We vonden dat de associatie tussen cardiale QT-verlengende geneesmiddelen en plotselinge hartstilstand zwakker was (Nederland: OR 1.17 [95% BI:0.92-1.50]; Denemarken: OR 1.21 [95% BI:1.09-1.33]), terwijl de prevalentie van cardiovasculaire aandoeningen en cardiovasculaire medicatie gebruik hoger was onder gebruikers van cardiale QT-verlengende geneesmiddelen vergeleken met gebruikers van niet-QT-verlengende geneesmiddelen. **Hoofdstuk 3** beschrijft een case-control studie met als doel om vast te stellen of het gebruik niet-cardiale QT-verlengende geneesmiddelen, die volgens de CredibleMeds lijst zijn geclassificeerd als categorie 1 geneesmiddelen ['geneesmiddelen met bekend risico op TdP'] en categorie 2 geneesmiddelen ['geneesmiddelen met mogelijk risico op TdP'], het risico verhoogd op plotselinge hartstilstand onderzocht. We includeerden 5473 cases met plotselinge hartstilstand en 21866 gematchte controles zonder plotselinge hartstilstand. Gebruik van zowel categorie 1 als categorie 2 was geassocieerd met een verhoogd risico op plotselinge hartstilstand

vergeleken met geen gebruik van niet-cardiale QT-verlengende geneesmiddelen (categorie 1: OR 1.7 [95% BI:1.3-2.1]); categorie 2: OR 1.4 [95% BI:1.2-1.6]). Onze bevindingen lieten zien dat het verschil tussen niet-cardiale QT-verlengende geneesmiddelen van categorie 1 en 2 op plotselinge hartstilstand risico bescheiden is. Onze bevindingen wijzen erop dat er ook maatregelen genomen moeten worden bij het voorschrijven van geneesmiddelen uit categorie 2 om het risico op plotselinge hartstilstand te verminderen.

DEEL II: Depolarisatie blokkerende geneesmiddelen en het risico op plotselinge hartstilstand

Hoofdstuk 4 beschrijft een case-control studie met als doel vast te stellen of niet-cardiale depolarisatie blokkerende geneesmiddelen het risico verhoogd op plotselinge hartstilstand. We includeerden 5473 cases met plotselinge hartstilstand en 21866 gematchte controles zonder plotselinge hartstilstand, en vonden een hoger risico van plotselinge hartstilstand bij gebruik van niet-cardiale depolarisatie blokkerende geneesmiddelen ten opzichte van geen gebruik van niet-cardiale depolarisatie blokkerende geneesmiddelen (OR 1.6 [95% BI:1.4-1.9]). Het risico was hoger bij vrouwen en in jonge patiënten (≤50 jaar). Stratificatie naar het eerste geregistreerde hartritme liet zien dat het verhoogde risico van toepassing was wanneer niet-VT/VF het eerste hartritme tijdens de plotselinge hartstilstand is, maar niet wanneer het eerste hartritme VT/VF is. **Hoofdstuk 5** beschrijft een studie naar de associatie van nifedipine en/of amlodipine gebruik en het risico op plotselinge hartstilstand, en mogelijke onderliggende mechanismen. We voerden functionele (patch-clamp) experimenten uit om te onderzoeken hoe deze geneesmiddelen de cardiale elektrofysiologie beïnvloeden. We voerden een case-control studie uit om het risico van nifedipine en amlodipine gebruik voor plotselinge hartstilstand vast te stellen door gebruik te maken van gegevens uit ARREST en DANCAR, een Deense reanimatieregistratie. We includeerden 2503 cases met plotselinge hartstilstand en 10543 gematchte controles zonder plotselinge hartstilstand uit Nederland, en 8101 cases met plotselinge hartstilstand en 40505 gematchte controles zonder plotselinge hartstilstand uit Denemarken. We vonden een hoger risico van plotselinge hartstilstand bij het gebruik van nifedipine in hoge dosering (≥60 mg/dag), maar niet bij lage dosering, ten opzichte van geen gebruik van dihydropyridines in beide registraties (ARREST: OR 1.45 [95% BI:1.02–2.07], DANCAR: OR 1.96 [95% BI:1.18–3.25]). Amlodipine-gebruik in hoge en lage dosering was niet geassocieerd met toename van het risico voor plotselinge hartstilstand. Functionele experimenten lieten zien dat nifedipine bij klinische concentraties resulteert in meer actiepotentiaalverkorting dan amlodipine.

DEEL III: Andere geneesmiddelcategorieën en plotselinge hartstilstand

Hoofdstuk 6 beschrijft een studie naar de associatie van sulfonylureagebruik en het risico op plotselinge hartstilstand, en om de onderliggende mechanismen te onderzoeken. We voerden functionele (patch-clamp) experimenten uit om de effecten van sulfonylurea op de

duur van de actiepotentiaal tijdens gesimuleerde ischemie te onderzoeken. We voerden een epidemiologische case-control studie uit om het risico van sulfonylurea voor plotselinge hartstilstand vast te stellen. We includeerden 219 cases met plotselinge hartstilstand met diabetes, en 697 controles zonder plotselinge hartstilstand met diabetes, en vonden een lager risico van plotselinge hartstilstand bij gebruik van sulfonylureas in monotherapie of in combinatie met metformine ten opzichte van het gebruik van metformine in monotherapie ($OR_{sulfonylurea\text{-}monotherapy}$ 0.6 [95% BI:0.4-0.9], $OR_{sulfonylurea+metformine}$ 0.6 [95% BI:0.4-0.9]). Gliclazide (OR 0.5 [95% BI:0.3-0.9]) en tolbutmide (OR 0.6 [95%-BI:0.3-1.002]) gebruik was geassocieerd met een afname van het risico voor plotselinge hartstilstand vergeleken met glimepiride gebruik, alhoewel dit niet statistisch significant was voor tolbutamide. Functionele experimenten lieten zien dat alleen glibenclamide resulteerde in significant minder verkorting van de duur van de actiepotentiaal na 15 minuten. Functionele experimenten leverden geen bewijs dat onze epidemiologische bevindingen verklaard kon worden door de effecten van sulfonylureas op de duur van de actiepotentiaal verkorting. In **hoofdstuk 7** werd de associatie van het gebruik van bètablokkers en eerste geregistreerde hartritme tijdens een reanimatiepoging voor plotselinge hartstilstand onderzocht in ARREST en DANCAR. We includeerden 23346 patiënten met plotselinge hartstilstand uit DANCAR en 1584 patiënten met plotselinge hartstilstand uit ARREST. Gebruik van niet-selectieve bètablokkers was geassocieerd met een verhoogd risico op non-VT/VF als initieel ritme in beide registraties (DANCAR: OR 1.93 [95% BI:1.48–2.52], ARREST: OR 2.52[95% BI:1.15–5.49]). In ARREST konden we niet-schokbare ritme verder specificeren in polsloze elektrische activiteit (PEA) en asystolie; PEA maar niet asystolie was geassocieerd met niet-selectieve bètablokker gebruik. Gebruik van β1-selective bètablokkers was niet geassocieerd met een verhoogd risico op non-VT/VF.