CHAPTER 13

General summary and discussion
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Sudden Cardiac Arrest (SCA) accounts for 15-20% of all natural deaths in Western Europe. SCA occurs predominantly in the general population and is often lethal. Although the largest part of out-of-hospital SCAs (~70%) has a cardiac cause, in ~50% of cases it is the first sign of a cardiovascular disease. In the general population, SCA is the culmination of multiple factors; a combination of inherited and/or acquired disorders, stressors and circumstantial triggers that eventually initiate an SCA.

In order to reduce the number of deaths due to SCA, two main approaches can be distinguished: 1) identify those at risk in order to prevent SCA, and 2) optimize out-of-hospital resuscitation care and in-hospital post-resuscitation care to improve survival after SCA. The risk of the occurrence of SCA itself can be studied, but also of markers of SCA risk, such as certain abnormalities on the electrocardiogram (ECG), in order to explore proposed mechanisms involved in SCA risk. Part I of this thesis presents four studies on SCA risk markers on the ECG, whereas Part II and Part III present studies on risk factors and outcome of out-of-hospital cardiac arrest and determinants thereof.

Part I: Markers of SCA risk on the ECG from non-cardiac risk factors

In a recent study, our group showed that people with epilepsy are at increased risk of SCA due to ventricular tachycardia/fibrillation (VT/VF). In chapter 2 we further explored this subject and determined whether ECG risk markers of SCA (abnormalities on the ECG that are associated with increased SCA risk) are more prevalent in people with epilepsy. In a cross-sectional, retrospective study, we analyzed the ECG recordings of 185 people with refractory epilepsy and 178 controls without epilepsy, and collected data on epilepsy characteristics, cardiac comorbidity, and drug use. Three markers of SCA risk were studied: QTc prolongation (male >450 ms, female >470 ms), the Brugada ECG pattern, and early repolarization pattern (ERP). QTc prolongation and ERP were more prevalent in patients with epilepsy (QTc prolongation: 5% vs. 0%; p=0.002; ERP: 34% vs. 13%, p<0.001), while the prevalence of the Brugada ECG pattern was comparable in both groups (2% vs. 1%, p=1). After adjustment for covariates, epilepsy remained associated with ERP (OR adj 2.4, 95% CI 1.1 to 5.5) and severe QTc prolongation (OR adj 9.9, 95% CI 1.1 to 1317.7). Our findings could not be explained by comorbidity or medication use.

Chapter 3 has a similar approach in a different patient group: patients with schizophrenia. SCA risk is increased in these patients, but the underlying causes are not fully resolved. In this study, we compared ECG markers of SCA risk, in particular, the Brugada ECG pattern and QTc prolongation, between patients with schizophrenia and community-dwelling non-schizophrenia controls. In a cross-sectional study, we analyzed ECGs of a cohort of 275 patients with schizophrenia, along with medication...
use. We compared the findings with non-schizophrenic individuals of comparable age (n=179) and, to account for assumed increased ageing rate in schizophrenia, with individuals 20 years older (n=1168). We found that the Brugada ECG pattern is significantly more prevalent in schizophrenia patients (11.6%) than in both control cohorts (1.1% and 2.4%). Importantly, the prevalence was also significantly increased in patients with schizophrenia who were not using sodium channel blocking drugs (notably antipsychotics). In contrast, although we also found a higher prevalence of QTc prolongation in schizophrenia patients (5.8% vs. 0% and 2.8%, p<0.05), QTc prolongation was largely explained by confounding factors, including the use of QTc prolonging (antipsychotics) drugs.

Our findings presented in Chapters 2 and 3 may give direction to further research aiming to explain why people with epilepsy and schizophrenia carry an increased risk of SCA. It is conceivable that variants in genes expressed in heart and brain might confer both a propensity for epilepsy or schizophrenia and an innate vulnerability to cardiac arrhythmias, thereby linking these diseases with ECG-markers of SCA risk. Nonetheless, although the use of sodium channel blocking or QTc prolonging drugs did not explain our ECG-findings, we consider it very likely that medication use and (cardiovascular) co-morbidity may considerably influence the risk of SCA in both patient groups. If confirmed, our findings warrant ECG recording as part of periodic cardiovascular screening in patients with schizophrenia or epilepsy and prudent prescription of drugs that affect the sodium channel or prolong the QT-interval (epilepsy), to minimize SCA risk.

Chapter 4 presents a study on the effects of low-dose haloperidol on the QTc-interval in an in-hospital population. Haloperidol has established QT-prolonging effects on the ECG by blocking cardiac potassium channels, but its influence in patients with multiple comorbidities is less well studied. We aimed to evaluate changes in QTc duration during low-dose haloperidol use, and determined associations between clinical variables and potentially dangerous QTc prolongation. In a retrospective single-center cohort study, we identified all 1788 hospitalized patients receiving haloperidol between 2005 and 2007; in 97 of these patients, ECG-recordings before, during and after haloperidol use were available. These patients were included in the final analysis. QTc was measured before, during and after haloperidol use. Clinical variables before haloperidol use (‘baseline’) and at the time of each ECG recording were retrieved from hospital records. We found that substantial QTc prolongation upon low-dose haloperidol use occurred predominantly in patients with normal baseline QTc duration. Conversely, in most patients with borderline or abnormal baseline QTc duration, an unexpected QTc shortening occurred. Importantly, 94% of patients with potentially dangerous QTc prolongation had a baseline QTc duration in the normal range. A rise in QTc duration to potentially dangerous levels (increase ≥50 ms or to ≥500 ms) was not
Chapter 13

only associated with baseline QTc duration, but also with surgery (increased risk) and signs of inflammation (decreased risk) before haloperidol use. Although patients with cardiovascular risk factors are reported to have a higher risk of QTc prolongation, we did not find significant associations in our study population.

In chapter 5 we further explored this subject in a study among old-aged hospitalized patients with multiple co-morbidities undergoing hip surgery. Haloperidol is often prescribed perioperatively to hip fracture patients. Since the study presented in chapter 4 identified surgery to be a risk factor for QTc prolongation, we aimed to determine (1) how QTc duration changes perioperatively, (2) whether low-dose haloperidol-use influences these changes, and (3) which clinical variables are associated with potentially dangerous perioperative QTc prolongation. We included 89 patients (mean age 84 years, 24% male), 39 of whom were treated with haloperidol, and analyzed their ECGs before, during and after hip surgery. Here, too, we found that perioperative QTc durations changed differentially, observing the same pattern as in chapter 4, with substantial QTc prolongation occurring predominantly in patients with normal baseline (before-surgery) QTc duration, and QTc shortening in most patients with abnormal baseline QTc duration. Changes in perioperative QTc duration were not influenced by low-dose haloperidol use or any of the other measured risk factors.

We consider it unlikely that QTc shortening in patients with a prolonged QTc interval prior to haloperidol use is due to the effects of haloperidol *per se*. A more plausible explanation might be that changes in the underlying condition occurred during haloperidol use, and that these changes caused QTc duration to shorten, despite haloperidol use. The assuring results presented in these studies need confirmation in other populations before a firm recommendation can be made to omit pre-haloperidol ECG recording as a standard measure in hospital care. We still recommend studying patient files for possible risk factors for QTc prolongation when prescribing haloperidol.

**Part II: Non-cardiac risk factors for SCA in the general community**

The second part of this thesis presents studies performed with data from the ARREST registry, and focuses on non-cardiac risk factors for SCA in the general community. Chapter 6 describes the rationale and outline of the part of ARREST that was set up to study genetic, clinical and pharmacological determinants of OHCA, providing examples of possible study designs.

Chapter 7 presents a review of the cardiac sodium channel and inherited electrophysiological disorders, and provides an overview on pharmacotherapy. The cardiac sodium channel plays a pivotal role in the propagation of electrical activity through the heart. The function of this ion channel may be modified by non-cardiac
conditions, e.g., the use of drugs prescribed for the treatment of non-cardiac disease, such as antidepressants and anti-epileptics.

Chapter 8 presents a study aiming to determine whether nortriptyline increases the risk for SCA, and to establish the underlying mechanisms. To this end, we studied QRS durations during rest/exercise in an index patient who experienced ventricular tachycardia during exercise while using nortriptyline, and compared them with those of 55 controls with/without nortriptyline and 24 controls with Brugada syndrome (BrS) without nortriptyline, who carried an SCN5A mutation. We performed molecular-genetic (exon-trapping) and functional (patch-clamp) experiments to unravel the mechanisms of QRS prolongation by nortriptyline and the SCN5A mutation found in the index patient. We conducted a prospective community-based study among 944 cases of SCA due to VT/VF (ARREST) and 4354-matched controls (PHARMO; a database including drug-dispensing records from community pharmacies of >3 million community-dwelling inhabitants in the Netherlands) to determine the risk for SCA associated with nortriptyline use. We showed that pharmacological (nortriptyline), genetic (loss-of-function SCN5A mutation), and/or functional (sodium channel inactivation at fast heart rates) factors conspire to reduce the cardiac sodium current and increase the risk for SCA. Nortriptyline use in the community was associated with a 4.5-fold increase in the risk for SCA [adjusted OR: 4.5 (95% CI: 1.1–19.5)]. We conclude that the arrhythmia causing combination of mechanisms blocking the cardiac sodium channel identified here has relevance in the general population. Nortriptyline increases the risk for SCA, particularly in the presence of genetic and/or non-genetic factors that decrease cardiac excitability. When prescribing or using a sodium channel blocking drug like nortriptyline we recommend to be conscious of other factors that may affect the sodium current (e.g., prolonged baseline QRS duration on the ECG, co-medication, ischemia or heart failure, high heart rates), analogous to the recommendations for QT prolonging medication.

Chapter 9 describes a community-based case-control study that aimed to determine whether patients with obstructive pulmonary disease (OPD) have an increased risk of SCA due to VT/VF, and whether this risk is mediated by cardiovascular risk-profile and/or respiratory drug use. We included 1310 SCA cases (ARREST) older than 40 years, and 5793 matched controls (PHARMO), and observed a higher risk of SCA in patients with OPD (n = 190 cases [15%], 622 controls [11%]) than in those without OPD (OR adjusted for cardiovascular risk-profile 1.4 [1.2–1.6]). In OPD patients with a high cardiovascular risk-profile, a higher risk of SCA was observed (OR 3.5 [2.7–4.4]) than in those with a low cardiovascular risk-profile (OR 1.3 [0.9–1.9]) The observed SCA risk was highest among OPD patients who received short-acting \( \beta \)-adrenoreceptor agonists (SABA) or anticholinergics (AC) at the time of SCA (SABA OR: 3.9 [1.7–8.8],
PART III: Survival after out-of-hospital cardiac arrest

The final part of this thesis presents three population-based cohort studies investigating outcome of resuscitation attempts after OHCA, and (non-cardiac) determinants thereof. Variability in survival rates is largely attributable to differences in the chain of survival: location of OHCA, presence of a witness, use of automated external defibrillator (AED), and time of onset of cardiopulmonary resuscitation (CPR), defibrillation, and advanced care. However, these factors do not entirely explain the variability in survival after OHCA; patient characteristics may also play an important role. Chapter 10 describes a community-based cohort study of 1172 patients with OHCA due to VT/VF between 2005 and 2008 that aimed to study whether patients with OPD have a lower survival rate after OHCA than non-OPD patients. We compared survival to Emergency Room (ER), to hospital admission, to hospital discharge, and at 30 days after OHCA, of OPD-patients and non-OPD patients. OPD patients (n = 178) and non-OPD patients (n = 994) had comparable survival to ER (75% vs. 78%, OR 0.9 [95% CI: 0.6–1.3]) and to hospital admission (56% vs. 57%, OR 1.0 [0.7–1.4]). However, survival to hospital discharge was significantly lower among OPD patients (21% vs. 33%, OR 0.6 [0.4–0.9]). In those patients who were admitted to hospital after OHCA (OPD: n = 100, no OPD: n = 561) OPD was an independent determinant of reduced 30-day survival rate (39% vs. 59%, adjusted OR 0.6 [0.4–1.0, p = 0.035]). Our findings suggest that in-hospital post-resuscitation care of OPD patients who suffered OHCA may need adaptation in order to close this mortality gap. We aim to raise awareness of the lower survival chances of OPD patients after OHCA; closer monitoring of these patients may provide insight into the pathophysiologic basis of this difference.

Chapter 11 addresses another aspect of survival after OHCA. We aimed to study whether access to and outcome after CPR differs between female and male OHCA patients. We performed a population-based cohort study of all cardiac OHCA patients aged >19 years (identified using death certificate data of the National Statistics service), and all emergency medical services-performed cardiac resuscitation attempts after OHCA in the Dutch province of North Holland between 2006-2012. We identified 22,443 OHCAs of cardiac cause (47.2% female), and recorded 6,038 resuscitation attempts by emergency medical services after cardiac OHCA (27.5% female). Women had a significantly lower chance of receiving a resuscitation attempt than men (OR 0.59, 95%CI 0.55-0.63, P< 0.001). Neurologically intact survival was significantly lower in women than in men (13.0% vs. 20.4%, odds ratio 0.58, 95%CI 0.50-0.69, P< 0.001).
The gender gap in survival was caused by a lower rate of a shockable initial rhythm in women (34.4% vs. 48.8%; odds ratio 0.55, 95%CI 0.48-0.63, P< .001). This difference is not explained by a longer time interval of emergency call to defibrillator connection, or other CPR characteristics. Also, female OHCAs were less likely to receive bystander CPR, even when OHCA was witnessed by bystanders. We conclude that women are less likely than men to receive CPR treatment by both EMS and bystanders in case of OHCA. When women do receive CPR, they have lower chance of survival. The survival disparity is gender related and can only partly be explained by CPR characteristics. We recommend raising awareness of SCA in women in order to increase recognition and improve access to resuscitation care.

Finally, in Chapter 12 we examine whether temporal trends can be distinguished in neurologically intact survival after OHCA, and, if so, whether a change in survival is attributable to increased AED use. Interventions aiming at improved bystander CPR and earlier defibrillation have been implemented in several communities, in order to increase survival rates after OHCA. In the Netherlands, national initiatives primarily aimed at decreasing time to first shock by more widespread use of the AED by dispatched rescuers (firefighter/police team) and by lay-rescuers using publicly available AEDs. We performed a population-based cohort study in the Netherlands, including all patients with OHCA from cardiac causes in the Dutch province of North Holland between 2006 and 2012, excluding EMS-witnessed arrests. Survival rates with favorable neurologic outcome after OHCA increased (16.2% to 19.7%, p for trend 0.021), though solely in patients presenting with a shockable rhythm (29.1% to 41.4%, p for trend <0.001). Survival rates increased at each stage of the resuscitation process; the strongest increase occurred in the pre-hospital phase. The proportion of surviving patients with favorable neurological outcome remained high throughout the study period (89.9% to 95.1%). Rates of AED-use almost tripled during the study period (21.4 to 59.3%, P for trend <0.001), thereby decreasing time from emergency-call to defibrillation-device connection (median 9.9 to 8.0 min, P<0.001), resulting in increased proportion of delivered shocks <6 minutes (9.2% to 21.7%, p<0.001). AED-use statistically explained increased survival with favorable neurologic outcome, by decreasing the OR of ‘year-of-resuscitation’ to a non-significant 1.04. We conclude that increased AED-use is associated with increased survival in patients with a shockable initial rhythm. We recommend continuous efforts to improve resuscitation care, with strong emphasis on introducing or extending AED programs, involving both dispatched AEDs and onsite AEDs.
Interpretations and conclusions

The studies presented in this thesis confirm the notion that SCA is a highly complex disease entity. In both the general population and in hospitalized patients, SCA, or markers thereof, results from a myriad of classically established indicators of high risk (e.g., coronary artery disease, heart failure), newly identified risk factors (epilepsy, schizophrenia, pathogenic mutations) and yet to be identified risk factors (other non-cardiac diseases, common genetic variants, environmental determinants). Because of the complexity of SCA risk, newly identified indicators of SCA risk should be interpreted critically.

Both the ECG studies and the ARREST studies presented in this thesis are based on observational data. This introduced challenges when aiming to separate the effects of the studied disease (obstructive pulmonary disease, schizophrenia, epilepsy) from the effects of the medication used to treat the diseases. Also, although we have attempted to address confounding in various ways, residual bias due to measured and unmeasured confounding cannot be ruled out. The problem of confounding holds for most if not all observational studies. In contrast, randomized clinical trials are generally considered the gold standard for identifying causal associations. However, randomized clinical trials in SCA are hard to set up due to the relatively rare occurrence of SCA (1:1000 person years on average in the general population): impractically large numbers of participants would be needed. Also, some SCA-risk factors (e.g. genetic factors, chronic disease) are not easily randomized. Although observational studies have disadvantages, they may yield more representative, real-life data than other study designs. Many real-life interactions between co-morbidities, drugs and other triggers may not occur in randomized trials, and hence cannot be studied.

For the future, much work remains to be done to identify risk indicators and to develop risk scores that are either applicable in the general population or in selected patient groups. This is a challenging task as the majority of SCA occurs in the general population in persons without a prior diagnosis of heart disease who are therefore not identified as being at risk of SCA. Identification of cardiac and non-cardiac risk indicators in the general population, their interactions and ultimately the mechanisms from which they arise is needed. Detection of risk factors is most likely to yield effective patient tailored prevention tools when the underlying mechanism is uncovered and targeted. To accomplish this, large registries with large numbers of well-phenotyped SCA cases (describing a multitude of possible risk factors and SCA triggers) are essential. This is especially so in the study of genetic risk factors and their interactions with drugs and acquired disease. ARREST aims to continue its registration of out-of-hospital SCA cases, nowadays in collaboration with other SCA cohorts worldwide.
Perhaps, at present, prevention of SCA is best achieved by raising awareness among physicians and patients that SCA is the result of a combination of factors that might be avoided. General risk scores help to identify people that need further treatment, or who will benefit most from adopting a healthier lifestyle, thereby motivating them to do so. The development of more fine tuned risk indicators and scores will facilitate more patient-tailored risk stratification tools.

Not only prevention of SCA, but also adequate resuscitation upon OHCA will remain important. Survival rate after a resuscitation attempt has increased significantly during the study period covered in this thesis. Adequate recognition and early access to early defibrillation and advanced care remain key elements to improve survival after OHCA. In this thesis, we have demonstrated the importance of AEDs to increase survival after OHCA in the general population. Furthermore, we have shown that patient characteristics (e.g., gender or co-morbidities) also influence one’s chances of access to and benefiting from resuscitation care.

We recommend continuous effort to improve resuscitation care, with strong emphasis on introducing or extending AED programs, involving both dispatched AEDs and onsite AEDs. The lay public will have an increasing role in timely recognizing OHCA and adequately providing resuscitation care.