DRUGS, QTc PROLONGATION AND SUDDEN CARDIAC DEATH

Sabine Straus

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CONTENTS

❤ 'Ik heb in mijn hele leven nog nooit een origineel idee gehad' zei hij met nadruk 'en toch heb ik een proefschrift geschreven. Wat laat, en ik denk ook niet dat iemand het gelezen heeft, behalve mijn promotor natuurlijk, maar ik ben Onze Lieve Heer nog iedere dag dankbaar dat ik het af heb mogen maken.' ❤

(Uit: Het Bureau van J.J. Voskuil)

CHAPTER 1

GENERAL INTRODUCTION

HISTORICAL PERSPECTIVE OF SUDDEN CARDIAC DEATH

The term sudden cardiac death pertains to an unexpected death from cardiac causes within a short time period and has been described throughout history.[1]

The ancient Egyptians inscribed on the tomb of a nobleman some 4500 years ago that he had died suddenly and without apparent cause.

Another early case of sudden death was Phidippides, the young Greek messenger, who collapsed and died after he ran 26.2 miles from Marathon to Athens to deliver the news of the Greek victory over the Persians in 460 BC.

It has been hypothesised that Hippocrates in his writings provided the first medical description (approximately 400 BC) of sudden cardiac death: "Those who are subject to frequent and severe fainting attacks without obvious cause die suddenly".[1,2]

Sudden (cardiac) death was originally ascribed to supernatural causes. In the bible Ananias and his wife Sapphira were punished for their deceit by sudden death *"When Ananias heard this, he fell down and died. And great fear seized all who heard what had happened. About three hours later his wife came in, not knowing what had happened. Peter asked her, "Tell me, is this the price you and Ananias got for the land?" "Yes," she said, "that is the price." Peter said to her, "How could you agree to test the Spirit of the Lord? Look! The feet of the men who buried your husband are at the door, and they will carry you out also." At that moment she fell down at his feet and died. Then the young men came in and, finding her dead, carried her out and buried her beside her husband.* (ACTS 4:32-5:11).

Even when medical science advanced to a stage where autopsies became available many sudden cardiac deaths remained unexplained.

Only recently, it has been hypothesized that Napoleon might have died due cardiac arrhythmias induced by drugs the Emperor was using at that time.[3]

DEFINITION OF SUDDEN CARDIAC DEATH

Efforts to understand sudden cardiac death and its underlying mechanism, treatment, and, ultimately, prevention have been complicated by the multiplicity of definitions used to characterize it.[4] Recently the European Society of Cardiology Task force on Sudden Cardiac Death has suggested the use of the Meyerburg Castellanos definition as follows: [5] "natural

death due to cardiac causes, heralded by abrupt loss of consciousness within one hour of the onset of acute symptoms; preexisting heart disease may have been known to be present, but the time and the mode of death are unexpected." A difficult issue is the classification of deaths that occur unwitnessed, for instance when a patient is found dead in bed. Most authors have classified such events as sudden cardiac deaths. The clinical presentation of sudden cardiac death is frequently used as a surrogate implying that a specific mechanism is involved. [5] Ventricular tachy-arrhythmia is the final fatal mechanism in approximately 85% of all sudden cardiac deaths. Brady-arrhythmias and pulse-less electrical activity occur less frequently and generally in hearts with more advanced disease.

MAGNITUDE OF THE PROBLEM

Sudden cardiac death remains a major public health problem. Cardiovascular disease is the leading cause of death in the western world. [6] [7] Sudden cardiac death accounts for almost half of these cardiovascular deaths, constituting the largest component of coronary heart disease mortality. Approximately 30% of the cases of sudden cardiac death have cardiac arrest as the first and only manifestation of cardiovascular disease. [7] [8] The commonly used estimate of 300,000 sudden cardiac deaths in the United States has not been based on any epidemiological studies, but has rather been derived from the estimation that there were 600,000 cardiovascular deaths annually, of which 50% were sudden. [9]

Because the majority of patients who suffer sudden cardiac death have coronary artery disease, the epidemiology of sudden cardiac death to a great extent parallels that of coronary heart disease. [10] For many years, clinicians have considered risk factors for coronary heart disease as similar to those for sudden cardiac death. [11] The risk factors for sudden cardiac death include, in line with cardiovascular risk factors: age, sex, hypertension, left ventricular function, elevated serum cholesterol, diabetes mellitus, body mass index, conduction disturbances, smoking, alcohol abuse and a family history of sudden cardiac death. [10] [12]

Sudden cardiac death is among the most common causes of death in the developed world. [13] It is estimated that more than 3 million people die yearly from sudden cardiac death. It is estimated that cardiac arrest has a survival rate of less than 5 %.

Although there has been a reduction in total cardiac mortality the percentage of deaths that are sudden has increased from 38% to 47%. This increase is primarily due to an increase in out of hospital cardiac arrest. The magnitude can be understood by noting that sudden cardiac death accounts for more deaths annually than AIDS, breast cancer, lung cancer and stroke together. [13]

The incidence rate of sudden cardiac death varies between 0.5-2 per 1000 persons annually, depending on definitions used and populations studied. [5] [14-16] A generally assumed risk of 0.1-0.2% per year in the population of 18 years and older, is an average figure across that

age spectrum. The most marked increase occurs in the age group of 40-65 years of age, predominantly in association with coronary artery disease.[11]

ETIOLOGY OF SUDDEN CARDIAC DEATH

Ventricular arrhythmias are present in 80-85% of the cases.[13 17 18] Most commonly sudden cardiac death is caused by the onset of a rapid monomorphic ventricular tachycardia that degenerates into ventricular fibrillation. Less frequently it is initiated by polymorphic ventricular tachycardias and ventricular fibrillation directly. In only a few cases ST segment changes suggestive of ischemia precede the initiation of the terminal event. Polymorphic ventricular arrhythmias are the most common initiating event. Sudden cardiac death associated with brady-arrhythmias usually represents end stage heart failure.

A major, if not the major, unanswered question in sudden cardiac death is, what is the immediate precipitating event that causes the arrhythmia, leading to sudden cardiac death in an otherwise stable patient? [19] Most of the stable risk factors (e.g. hypertension, heart failure) lack sufficient sensitivity, specificity and predictive value to permit using a specific intervention in a particular patient before the actual event. This probably relates, at least in part to the transient nature of many risk factors, such as myocardial ischemia; abnormality in electrolytes, such as low potassium; and the transient effects of toxins, such as drugs or alcohol.[10]

Evidence is accumulating that the occurrence of an abrupt ventricular arrhythmia is a multi-factorial, time dependent process involving a changing complex interplay of myocardial scar, ischemia, adrenergic factors, electrical heterogeneity, time, and possibly genetic factors, all superimposed on a vulnerable myocardial substrate that is acquired as a result of occlusive and progressive coronary artery disease.

To simplify our understanding the factors involved in sudden cardiac death are sometimes categorized into 3 groups: substrate, modulator and trigger.[17]

Substrate is commonly used for factors that damage the normal structure of the myocardium, the more stable risk factors. Major factors in this group are myocardial infarction (leaving scarred myocardial tissue), heart failure (leading to remodeling of myocardium) and genetic predisposition. These factors have in common that they are permanent, thus creating a surrounding (substrate) in which ventricular fibrillation can more readily occur.[10 17 20] In recent years, genetic studies began to reveal how mutations in ion channel genes predispose patients to certain cardiac arrhythmias.[21]

Modulators are those risk factors that temporarily increase the risk of sudden cardiac death, such as plaque rupture, acute ischemia, autonomic nerve influences, electrolyte disturbances or drugs.

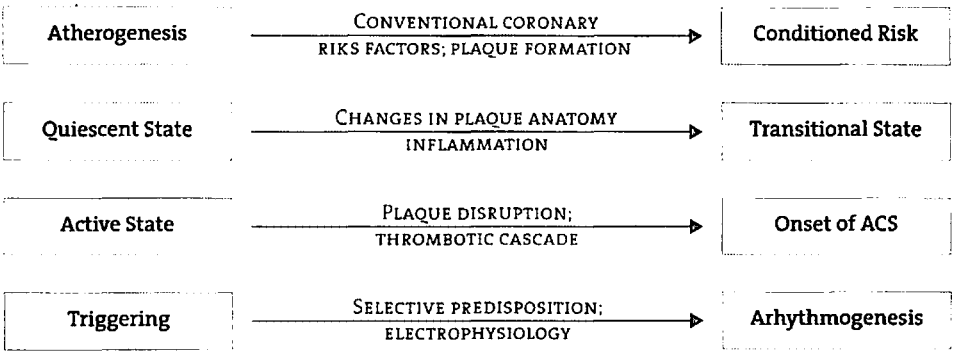
The trigger is the event, the critically timed premature stimulus (e.g. ventricular extrasystole), which initiates the ventricular fibrillation.

Ischemic Heart Disease

Coronary artery disease with or without myocardial infarction is by far the most common underlying substrate for sudden cardiac death in the Western world, being responsible for 65 to 70% of all cases.[11 10 13 15 22]

The modulator thought to be responsible for converting chronic coronary artery disease into acute cardiac events is termed plaque rupture. [23 24] Plaque rupture is probably the most common lesion underlying acute coronary syndromes. [25] The frequency of unstable plaques and coronary thrombosis in sudden cardiac death is extremely variable and the reported percentages of active coronary lesions observed at autopsy in sudden cardiac death victims ranges from less than 20% to more than 80%.[26] It is estimated that sudden cardiac death accounts for at least 36% to 50% of all mortality after myocardial infarction and new ischemia may be an important modulator. [27 28]

Any type of atherosclerosis related myocardial injury, such as ischemia, an old or new myocardial infarction, inflammation and or fibrosis, potentially increases the patient's vulnerability to arrhythmia and sudden cardiac death. [23 24] The greatest risk of sudden cardiac death seems to be in the first 6 to 12 months after the myocardial infarction [29], especially in high-risk patients. Recent studies, however, showed that the risk remains increased with time after a myocardial infarction in patients using beta blocking therapy.[28]



Cascade from conventional risk factors to arrhytmogenesis in sudden cardiac death due to coronary heart disease. The cascade indentifies four levels of evolution of risk, beginning with lesion initiation at development, progressing to onset of an active state, to onset of acute coronary syndromes (ACS), and finally the specific expression of life-threatening cardiac arrhythmias. Multiple factors enter at each level, including specific risk based on genetic profiles of individual patients.

A possible cascade for the development of coronary artery disease and acute coronary events is shown here. It cites four levels of evolution, beginning with atherogenesis, driven by conventional coronary risk factors, which leads to the presence of coronary artery disease that is the conditioning factor for future events.[9]

Heart failure

The incidence and prevalence of heart failure, an important substrate of sudden cardiac death, has continued to increase with the ageing population.[19] [30] Despite remarkable improvements in therapy, the prognosis of patients with heart failure remains poor. Arrhythmic death is a common mode of death in heart failure, occurring in approximately half of the cases. [8] It has been estimated that patients with heart failure have 6 to 9 times the rate of sudden cardiac death of the general population.[19] Sudden cardiac death most likely results from a cascade of events that create an electrically unstable heart, that most often is manifested by a ventricular tachy-arrhythmia.[19] What is certain about sudden cardiac death in the setting of heart failure is, that there are a number of structural and functional changes in the heart and a genetic predisposition that may contribute to an increased risk of dying suddenly. Sudden death in patients with heart failure is a complex phenotypic expression of a systemic disease that most often results from the unfortunate confluence of a number of factors. These include: a hospitable substrate, the results of remodeling membrane properties of the heart, altered neurohumoral signaling, myocardial ischemia and a genetic predisposition to electrical instability. [20]

The risk of sudden cardiac death varies over time, reflecting temporal heterogeneity of both the myocardial substrate and triggers.[19]

Autonomic nervous system

Enhanced activity of the sympathetic nervous system is a modulator associated with the occurrence of sudden cardiac death. Autonomic function is often linked to sudden cardiac death but the exact mechanism is subject to debate as there are many points of interaction. Autonomic tone could play a role in initiating the transient ischemia. The interaction between autonomic tone and thrombosis might play an important link in the pathogenesis of sudden cardiac death.[31] A mechanism that also received attention recently is the nerve sprouting hypothesis.[32] The nerve sprouting hypothesis of sudden cardiac death suggests that myocardial infarction results in nerve injury [33], followed by nerve sprouting and regional myocardial hyperinnervation. It is known that sympathetic stimulation is important in the generation of sudden cardiac death. Sympathetic nerve sprouting may be an important determinant of sudden cardiac death in chronic ischemia.[33]

The sympathetic imbalance has also been implicated in the prolongation of the QT interval.

Research has indicated that reduced parasympathetic nervous system activity increases the likelihood of ventricular fibrillation.[34]

Deranged cardiac autonomic activity is associated with an increased burden of cardiovascular mortality, including arrhythmias and sudden cardiac death.[35]

Genetic factors

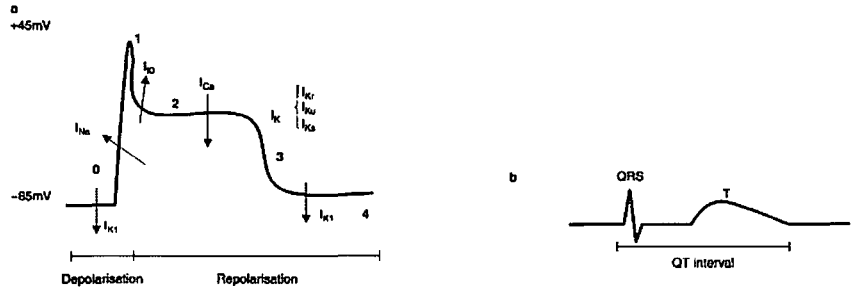
There are inherited diseases leading to genetically determined cardiac arrhythmias and sudden cardiac death. In the last decade, genetic studies began to reveal how mutations in ion channels cause arrhythmias in patients and increase the likelihood of ventricular fibrillation and sudden cardiac death.[21] [36]

The identification of the genes responsible for the long QT syndrome led to the discovery that they all encode ion channels. All the encoded ion channels are involved in the control of repolarization and this fostered the concept that LQTS may represent an unique model for the study of genotype-phenotype correlation in hereditary arrhythmogenic disorders. [37] Mutations identified in these genes produce either gain or loss of function, resulting in an excess inward sodium current or in reduced potassium outward current.[37] The ionic alterations lengthen the action potential and explain the prolonged QT interval characteristic of the Long QT Syndrome (LQTS), which can be either congenital or acquired.

A brief overview of the normal electrophysiology of the heart is necessary to better understand the mechanism underlying the Long QT Syndrome.

Normal electrophysiology

The normal regular beating of the heart is accompanied by cyclic changes in the membrane potential of cardiac cells.[38] The electrical activity of each cardiac cell is made possible by electrochemical currents, carried by ion channels and exchangers, which give rise to the action potential.[39] As with many other excitable cells the resting potential of cardiac cells is largely determined by the concentration gradient for potassium ions across the cell membrane whereas the rapid potential change during pulse initiation depends on the concentration gradient for sodium ions. The rapid depolarization is caused by a large inward current of sodium ions (Phase 0). Repolarization consists of three phases: the rapid repolarization phase is carried by a transient surge of outward current of potassium ions (Phase 1). This is followed by a plateau phase (Phase 2), which duration is determined by a delicate balance between inward and outward currents through competing ion channels and exchangers (mainly calcium and sodium). Phase 3 of the repolarization process is caused mainly by inactivation of inward calcium currents and increasing potassium outward currents. Outward potassium currents carry the repolarization plateau. The delayed rectifier current is the most important repolarizing current and has at least 3 distinct components: I_{kur} (ultra rapidly activating delayed rectifier current), I_{kr} (rapidly activating delayed rectifier current) and I_{ks} (slowly activating delayed rectifier current).[40]



The cardiac action potential: (a) action potential showing the phases of cardiac depolarisation and repolarisation with ion current directions during activation of the different ion channels; (b) ECG. I_{Ca} = calcium current; I_K = potassium current; I_{K1} = inwardly rectifying potassium current; I_{Na} = depolarising sodium current; I_{to} = transient outward potassium current; I_{Kr} = rapidly activating delayed rectifier potassium current; I_{Ks} = slowly activating delayed rectifier potassium current; I_{Ku} = ultra rapidly activating delayed rectifier potassium current. (Reprinted with permission)

Congenital Long QT Syndrome

The long QT syndrome is an inherited arrhythmogenic disease characterized by susceptibility to life threatening arrhythmias, often but not always occurring in the setting of high adrenergic activity e.g. physical or emotional stress.[41]

Two phenotypic variants have been initially identified: the more common autosomal dominant Romano Ward syndrome and the autosomal recessive Jervell and Lange Nielsen syndrome, in which the cardiac phenotype is associated with neurosensory deafness.[38 41 42]

Prolonged ventricular repolarization (i.e. prolonged QT interval) is the electrocardiographic marker of LQTS. The QT interval of the ECG reflects the duration of the action potential that is determined by the delicate balance between inward and outward currents.[39]

Syncope and fainting are the typical manifestations of LQTS and are often precipitated by vigorous exercise, stress or strong emotions.

There is a great diversity in genes that control the expression of potassium channels.[39] The ultra-rapidly activating I_{kur} is mediated by KCNA.[5]

Four HERG (human ether a go-go gene) alpha subunits assemble to form I_{kr} (rapidly activating delayed rectifier current) and four subunits assemble with beta subunits to form I_{ks} (slowly activating delayed rectifier current). Mutations of these subunits lead to dysfunctional channels, reduced I_{kr} and I_{ks} current and a clinical syndrome of prolonged QT interval. The evidence that there are least 6 genes, for which at least 5 encode for channel proteins responsible for LQTS, implies that the classification into two phenotypes was insufficient to completely describe the disease.[41] Subsequently more findings have led to the conclusion that LQTS is not only a channelopathy but may also be caused by mutation of intracellular proteins. Therefore genetic heterogeneity and multiplicity of mechanisms are distinguishing features of LQTS. Furthermore besides the remarkable number of mutations reported so far it is also evident that the clinical manifestations may

span from completely asymptomatic individuals to fully penetrant and symptomatic forms, even among patients harboring the same mutations.[41] This phenomenon is defined as variable penetrance, and it represents an important feature of LQTS.

Acquired Long QT Syndrome

Reduction in the major outward current, mediated by the rapid component of the delayed rectifier potassium channels (I_{kr}), results in the prolongation of the QT interval. The most frequent cause of reduction of the potassium outward current at present is the administration of many clinically useful drugs.[39]

Drugs reduce this current, mainly by their effect on the alpha subunits of human ether a go- go related gene of the I_{kr} channel. In the past decade one of the most frequent causes of withdrawal or restriction of the use of drugs has been the prolongation of the QT interval associated with Torsade de Pointes, which can be fatal.[43] Current evidence suggests that 5 to 10 % of persons in whom Torsade de Pointes develops on exposure to QT interval prolonging drugs may harbour mutations associated with the Long QT syndrome and can therefore be viewed as having sub-clinical forms of the congenital syndrome.[43 44]

Despite progress in clinical profiling and interventions sudden cardiac death remains a major clinical and public health problem. There remain important unresolved issues that are a challenge for future progress. Among these are a better understanding of the magnitude of the problem and methods of profiling risk for individuals, the etiology and mechanisms of sudden cardiac death in individuals with and without previously identified structural heart disease and strategies for prevention of sudden cardiac death.[45]

As has been illustrated in these introductory notes many causes of sudden cardiac death are known, yet seldom is one single cause sufficient to provoke a life threatening arrhythmia. Sudden cardiac death is a multifactorial process and we are most likely dealing with a probabilistic event in which each of the risk factors identifies only a small fraction of the multifactorial process.[46]

SCOPE AND OUTLINE OF THIS THESIS

This thesis comprises a number of epidemiological studies aimed at gaining more insight into the problem of sudden cardiac death in a general population, and the role of drugs in the occurrence of sudden cardiac death. We have focused on drugs associated with an increased risk of sudden cardiac death, drugs as a cause of QTc prolongation and QTc prolongation as a risk factor for sudden cardiac death.

Most studies presented in this thesis used data from the Integrated Primary Care Information (IPCI) project in the Netherlands.[47] The IPCI project is a general practice research database,

containing the complete medical records on approximately 500,000 patients. The electronic records contain coded and anonymous data on patient demographics, symptoms (in free text), diagnoses (using the International Classification for Primary Care and free text) from GPs and specialists, referrals, laboratory findings, hospitalizations, and drug prescriptions, including their indications and dosage regimen. To maximize completeness of the data, general practitioners participating in the IPCI project are not allowed to maintain a system of paper-based records besides the electronic medical records.

The two studies evaluating the QTc interval were performed in the Rotterdam study, a large prospective population-based cohort study among 7983 inhabitants of Ommoord, a suburb of Rotterdam, who were 55 years of age or older.[48] This study provides an excellent setting for observational studies.

In Chapter 2 of this thesis, the incidence of sudden cardiac death in a general population was assessed. Chapter 3 focuses on the value of the QTc interval in predicting the risk of sudden cardiac death in a general population of older adults, using the data from the Rotterdam study. In Chapter 4 the association between the current use of drugs, reported to be associated with Torsade de Pointes, and the duration of the QTc interval was explored.

Chapter 5 and 6 describe the results of a case control study examining antipsychotic drugs and non-cardiac QTc prolonging drugs as risk factor for sudden cardiac death. In Chapter 7 the effect of current use of brochodilator medication and the risk of sudden cardiac death is discussed. Finally in the general discussion presented in Chapter 8 we discuss the main findings of this thesis in the context of current scientific knowledge and suggestions for future research are provided.

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❤ 'Would you tell me,
please, which way
I ought to go from here?' ❤

(Uit: Alice's adventures in wonderland
van Lewis Carroll)

CHAPTER 2

INCIDENCE OF SUDDEN CARDIAC DEATH

ABSTRACT

Objective: Sudden cardiac death (SCD) is a major clinical and public health issue. We conducted a cohort study within the Integrated Primary Care Information database (IPCI) in the Netherlands to determine the incidence of sudden cardiac death in the general population.

Methods and results: The study population consisted of a dynamic cohort of all subjects of 18 years and older without a diagnosis of cancer, registered with the General Practitioner (GP) during the period between 1995-2001. SCD was defined as death within one hour after the onset of the terminal event or an unwitnessed death, if the subject was seen alive and well sometime during the preceding 24 hours. The cause was attributed to cardiac disorders unless other causes were apparent. The study population comprised 249,126 subjects with a mean follow-up of 2.54 years. During follow up we identified 4892 deaths, of which 582 cases were classified as probable SCD. The overall incidence of SCD in this population was 0.92 cases per 1000 person-years (py) (95% CI: 0.85-0.99), was 2.3 fold higher in men than in women and increased with age: from 0.1/1000 py (95% CI: 0.07-0.13) for the people aged under 50 up to 7.9/1000 py (95% CI: 6.8-9.2) for subjects above 80 years of age. The incidence of SCD peaked in October: 1.36/1000 py (95% CI: 1.07-1.69) and was lowest in August 0.6/1000 py (95% CI: 0.45-0.87).

Conclusions: The incidence of SCD in the general Dutch population was almost 1 per 1000 person- years per year during the period January 1, 1995 to April 1, 2001. Most of the cases occurred at home.

INTRODUCTION

Cardiovascular disease still remains the most common cause of natural death in developed countries, despite a substantial reduction in age-adjusted rates of death from cardiovascular causes over the past decades. Of all cardiac deaths approximately 50% is estimated to be of sudden nature.[1 2] Sudden cardiac death is defined as natural death due to cardiac causes, heralded by abrupt loss of consciousness within one hour after the onset of acute

symptoms. Although pre-existing heart disease may be present, the time and mode of death are unexpected by definition.[3] The time interval between the onset of symptoms and death initially was 24 hours, but has subsequently been reduced to 1 hour.[3 4] A difficult issue in the assessment of sudden death is the classification of deaths, which occur unwitnessed, for instance if somebody is found dead in bed. Most authors have preferred to classify such events as sudden cardiac death, even though the delay between onset of symptoms and death is unknown.[5-9] Due to the variation in required time delay definitions, inclusion or exclusion of unwitnessed deaths and the type of population, the reported incidence rates vary largely.[5 6 10-12] In this study we aimed to estimate the incidence of sudden cardiac death in the general population, since up until now there are no incidence studies that were conducted in a well-defined general population by using the current definitions and guidelines of sudden death.[3]

METHODS

Setting

The Integrated Primary Care Information (IPCI) database is a longitudinal observational database, which contains information from computer-based records of general practitioners (GPs) in the Netherlands. Details of the database have been described elsewhere.[13 14] The database contains the full medical electronic records of approximately 500,000 patients. The electronic records contain information on patient demographics, symptoms (in free text), diagnoses (using the International Classification for Primary Care), drug prescriptions plus their ICPC coded indication, and hospitalisations.[15] Summaries of the hospital discharge letters or information from specialists are entered in a free text format and copies can be provided upon request. To maximise completeness of the data, GPs who participate in the IPCI project are not allowed to use paper-based records. The system complies with European Union guidelines on the use of medical data for medical research and has been proven valid for epidemiological research.[14]

Study population

The study population consisted of a dynamic population of subjects 18 years and older who had a valid history of at least 1 year in the IPCI database. Subjects with a diagnosis of cancer were excluded, because in these patients the cause of death is often difficult to assess even in case of acute deaths. The study period started on January 1, 1995 and ended on April 1, 2001. Subjects were followed until death, transferral out of practice, last data draw- down or end of the study period, whichever came first.

Case definition

All subjects who died during the study period were identified by an automated database search. Cases were classified "probable" sudden cardiac death if the medical record indicated that death occurred within one hour after the onset of cardiovascular symptoms or if the following wording was found: "sudden cardiac death", "acute cardiac death", "mors subita", "sudden death", "died suddenly", "died unexpectedly" or if this was an unexpected death of someone seen in "good health" or in a stable medical condition less than 24 hours previously. Our definition included unwitnessed deaths. The cause of death was supposed to be of cardiac origin unless the patient's (medical) history suggested otherwise (e.g. pneumonia, cerebrovascular accident etc).

All cases of death were assessed manually and validated independently by two physicians as probable or no sudden cardiac death. In case of discrepancy (n=13) a third physician arbitrated.

Statistical analysis

The incidence of sudden cardiac death was determined by dividing the total number of cases of (probable) sudden cardiac death by the total number of person-years accumulated by the study population.

Incidence estimates were calculated per age category (5 years categories), calendar year, calendar month and gender. 95% confidence intervals were calculated based on a Poisson distribution. Differences in age were tested by means of the Mann Whitney test. The number of cases of sudden cardiac death per week day was assessed and 95% confidence intervals were calculated based on the normal distribution.[16] To extrapolate our data to the Dutch population we standardised our incidence estimates of sudden cardiac death directly to the data from the Central Bureau for Statistics (CBS, www.cbs.nl).

RESULTS

The source population consisted of 431,942 subjects of whom 253,500 were 18 years of age or older and had a valid history of at least 365 days in the IPCI database. After exclusion of patients with a diagnosis of cancer the study population comprised 249,126 subjects. The median age of the study population was 40 years (Inter-Quartile Range, IQR 29- 55) and 49.1% were males. Males were younger than females (median age of 39, IQR 29-53 versus 41, IQR 29-57). Within this population 4892 deaths were identified, 582 of which were classified as probable sudden cardiac death. The mean age of the cases was 72±13 years and the majority (59.3%) were male. The mean age of male cases was significantly lower than that of female cases (69±13 years versus 76±11 years, $p<0.01$). Of the 582 cases 228 (39.2%) were unwitnessed deaths. The unwitnessed cases were significantly older than the witnessed cases (75±12 years versus 70± 14 years $p<0.01$). Sudden unwitnessed cardiac deaths occured more frequently in females (48.9%) than in males (32.5%, $p<0.01$). The unwitnessed cases were significantly older than the witnessed

cases (median age 75 years [IQR: 66–81] vs. 70 years [IQR: 61–78], P<.01). Of the witnessed cases (n=354), the majority (75.9%) occurred at home, 14.1% occurred in a public place or during sport, 5.4% on the way to the hospital or upon arrival at the hospital, and in 4.6% the site where sudden cardiac death occurred was not specified (TABLE 1).

The overall incidence of sudden cardiac death in this population was 0.92 /1000 person years (95% CI: 0.85-0.99) (TABLE 2).

TABLE 1 : **SITE OF OCCURRENCE OF WITNESSED CASES OF SUDDEN CARDIAC DEATH (*n*=354)**

Location	Cases
Home	269 (75.9%)
Public places	50 (14.1%)
Street	16
Hotel/Camping	9
Sport	8
Work	5
Church	3
Car	3
Library	1
Railway station	1
Market	1
Shop	1
GP office	1
Café	1
Ambulance	5 (1.4%)
UAH[a]	14 (4.0%)
Not Specified	16 (4.6%)

[a] Upon arrival at the hospital.

TABLE 2 : **INCIDENCE OF SUDDEN CARDIAC DEATH BY CALENDAR YEAR**

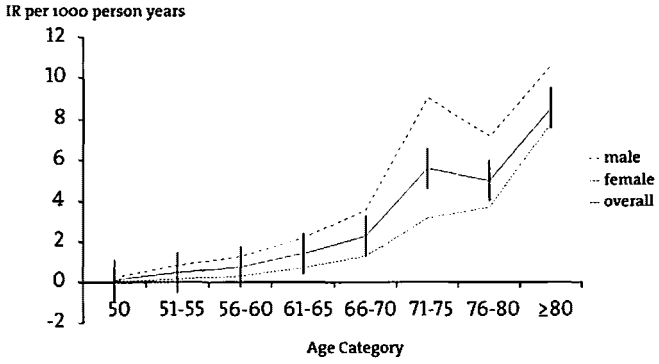
Calendar year	Person years (PY) of follow-up	Cases	Incidence per 1000 PY	95% CI
1996	53223.54	53	1	0.75-1.29
1997	93949.92	101	1.08	0.88-1.3
1998	125417.9	123	0.98	0.82-1.17
1999	173102.9	158	0.91	0.77-1.06
2000	166290.1	131	0.79	0.66-0.93
Overall*	**634314.3**	**582**	**0.92**	**0.84-0.99**

* Sum of cases and person time during the period 1996-2000 does not add up to overall since the sparse data from 1995 and 2001 are not included in this table

The incidence of sudden cardiac death increased with age: from 0.01/1000 person years

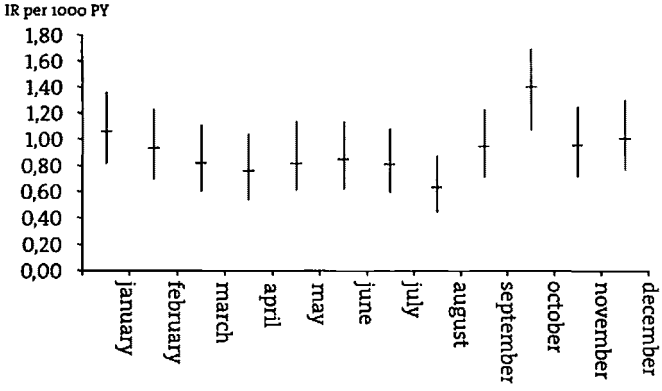
(95% CI: 0.07-0.13) for subjects aged between 18 to 50 years to 7.9/1000 person years (95% CI: 6.79-9.17) for subjects aged above 80 years (FIGURE 1).

FIGURE 1 : **INCIDENCE OF SUDDEN CARDIAC DEATH BY AGE AND GENDER**



The unadjusted incidence of sudden cardiac death in men was significantly higher: 1.1/ 1000 person years (95% CI: 0.99-1.23) than in women 0.73/ 1000 person years (95% CI: 0.65-0.83). After age-standardisation of the female population age to the male population the incidence in women was 0.48 per 1000 person years, leading to a rate ratio of 2.3 for sudden cardiac death in men versus women. The incidence of sudden cardiac death was highest in October (1.36, 95% CI: 1.07-1.69) and lowest in August (0.63, 95% CI: 0.45-0.87 p=0.001 peak low ratio: 1.58) (FIGURE 2).

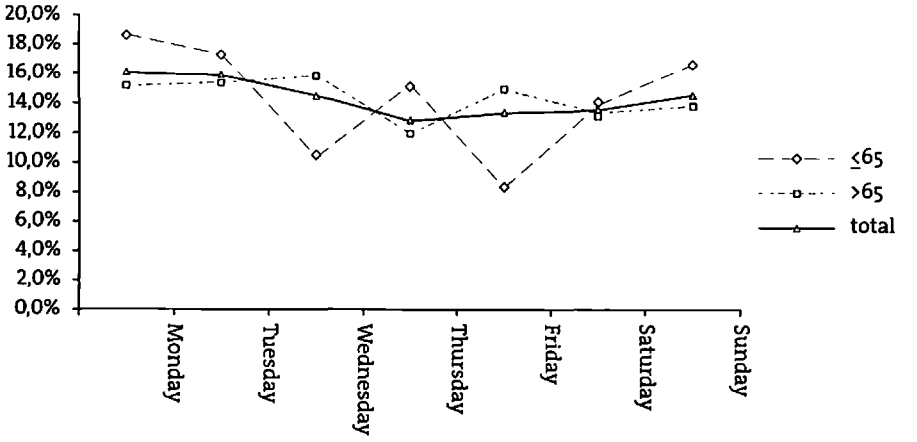
FIGURE 2 : **INCIDENCE OF SUDDEN CARDIAC DEATH BY CALENDAR MONTH**



In our study most cases of sudden cardiac death occurred on Mondays (16%) and Tuesdays (15.8%), but the differences were not statistically significant. In men the incidence was highest on Mondays independent of age (0.59, 95% CI: 0.38-0.87 in men 65 years or younger and 8.14, 95% CI:5.92-10.93 in men elder than 65). In women 65 years of age

or younger the highest incidence occurred on Tuesdays (0.18, 95% CI:0.035-0.25) and in elderly women (above 65) the highest incidence occurred on Wednesdays (5.02, 95% CI: 3.61-6.81) (FIGURE 3).

FIGURE 3 : **PERCENTAGE OF SUDDEN CARDIAC DEATH CASES PER WEEKDAY**



Applying the age specific incidence rates to the Dutch population resulted in incidence rates of 1.07/1000 person years in 1996, 1.15 in 1997, 0.98 in 1998, 0.95 in 1999, and 0.8/1000 person years in 2000.

DISCUSSION

Sudden cardiac death is the most common lethal manifestation of heart disease. This study showed that the incidence of sudden cardiac death in Dutch population is around 1/1000py, the incidence increases with age and varies by gender, calendar month and weekdays.
Our incidence estimate is in line with the incidence in the US, which is estimated to be 1 to 2 per 1000 inhabitants per year.[13 17] The incidence found in other studies varies from 0.19 to 1.9 per 1000 inhabitants, depending on the variations in definition used, differences in study population and area of research.[2 6 10 17] In the British Regional Heart Study, the incidence was relatively high at 1.9 per 1000py since this population comprised only middle aged men, but on the other hand it did not include unwitnessed deaths.[6] In a previous hospital based Dutch study the incidence was estimated at 0.97 per 1000 inhabitants per year (aged 20 to 75).[10] However this study defined sudden cardiac death as an unexpected, non-traumatic loss of vital signs without preceding complaints or within 24 hours after the onset of complaints, unwitnessed deaths were included. A study in healthy workers in Japan showed an incidence of 0.19 per 1000 person-years (cases defined as death occurring within

24 hours of the onset of symptoms or signs without any difficulties in daily working).[11]
The percentage of unwitnessed deaths in our study was similar to other studies. Women suffer more often unwitnessed sudden cardiac death, possibly due to the fact that elderly women more often live alone.[3] [10] The higher incidence in males is consistent with other studies.[9] [18-20]
Seasonal variation of sudden cardiac death has been the subject of previous studies.[21] [22] The peak incidence occurs usually in winter (December and January) with a pronounced reduction in the summer period (from June through September). Our study confirmed that the incidence was lowest in August whereas the incidence peaked in October.
The weekly variation of sudden cardiac death in our western society seems to be related to work stress and most cases occur on Mondays and Tuesdays.[21] [23] In Japan the seasonal peak occurred in April, when the business year starts, and the weekly peak on Sundays, which has been attributed to binge drinking.[11] In our study 16% of the cases occurred on Mondays and 15.8% and Tuesdays. The incidence in men was highest on Mondays, independent of age. In women the highest incidence occurred on Tuesdays in women 65 years or younger and on Wednesdays in women older than 65(FIGURE 3).
Our study has one potential limitation i.e. potential misclassification. Such misclassification might be false positive or false negative. Underestimation of deaths is unlikely as death is mostly registered by the general practitioner in the Netherlands due to the pivotal role of the GP in the Dutch health care system. Some false positive misclassification however may result from the potential inclusion of unwitnessed death of non-cardiac origin. Some of these cases might for instance result from a massive stroke. The percentage unwitnessed death was 39.2% in our study, which is in line with earlier findings.[12] [24] The circumstances surrounding these deaths remain unclear and other causes of death cannot always be excluded. The incidence of unwitnessed death in women is relatively high, possibly due to the fact that elderly women more often live alone.In conclusion we found that incidence of sudden cardiac death was approximately 1 in 1000 person-years, of which the large majority occurred at home.

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❤ 'That depends a good deal on where you want to get to' said the Cat. ❤

(Uit: Alice's adventures in wonderland van Lewis Carroll)

CHAPTER 3

PROLONGED QTc INTERVAL AND RISK OF SUDDEN CARDIAC DEATH IN A POPULATION OF OLDER ADULTS

ABSTRACT

Background: In developed countries, sudden cardiac death is one of the major causes of cardiovascular mortality. Prolongation of the QTc interval has been associated with ventricular arrhythmias but in most population-based studies no consistent association was found between QTc prolongation and total or cardiovascular mortality. Only very few of these studies specifically addressed sudden cardiac death. We investigated whether prolongation of the QTc interval is a risk factor for sudden cardiac death in the general population.

Methods and results: This study was conducted as part of the Rotterdam Study, a prospective population-based cohort study which comprises 3105 men and 4878 women aged 55 years and older. The QTc interval on the ECG was by determined during the baseline visit (1990-1993) and the first follow-up examination (1993-1995). During an average follow-up period of 6.7 years (SD 2.3 years) 125 subjects died from sudden cardiac death. The association between prolonged QTc interval and sudden cardiac death was estimated using Cox's proportional hazards analysis.

An abnormally prolonged QTc interval (> 450 ms in men, > 470 ms in women) was associated with threefold increased risk of sudden cardiac death (RR 3.2, 95% CI: 1.7-5.9), after adjustment for age, sex, body mass index, hypertension, cholesterol/hdl ratio, diabetes mellitus, myocardial infarction and heart failure. In subjects with an age below the median of 68 years, the corresponding relative risk was 7.6 (2.0-29.0). The attributable risk proportion was 0.66, meaning that 66 percent of all cases of sudden cardiac death are associated with an abnormally prolonged QTc interval.

Conclusions: Abnormal QTc prolongation on the ECG should be viewed as an independent risk factor for sudden cardiac death.

INTRODUCTION

In developed countries, sudden cardiac death is one of the major causes of cardiovascular mortality. Sudden cardiac death accounts for almost half of all coronary heart disease

deaths and is often the first and only manifestation of coronary heart disease.[1-3] According to the most recent definition, sudden cardiac death is a natural death due to cardiac causes, heralded by abrupt loss of consciousness, within one hour after the onset of acute symptoms or an unwitnessed, unexpected death of someone seen in a stable medical condition less than 24 hours previously with no evidence of a non-cardiac cause.[2 3] Much of this mortality is assumed to be caused by ventricular tachy-arrhythmias, and evaluation of risk factors is a major challenge when searching for treatments to reduce this risk.[4] In search for non-invasive risk factors to predict mortality, the heart rate corrected QT interval, the QTc interval, has been studied extensively.[4-14] The QT interval on the surface electrocardiogram (ECG) represents the time from onset of ventricular depolarisation to completion of repolarization and prolongation has been associated with ventricular arrhythmias (e.g. Torsade de Pointes) that may trigger ventricular fibrillation and even sudden cardiac death.[15] There is an ongoing debate in the literature on the clinical significance of a prolonged QTc interval.[14 16 17] Several large population-based studies, evaluating the association between the QTc interval and mortality in apparently healthy persons, did not find a consistent association between QTc prolongation and total or cardiovascular mortality.[4 7-9 11 12 18] Only few of these studies specifically addressed sudden cardiac death and when they did the number of cases was often too small to detect significant differences.[5 8 10]
We investigated whether prolongation of the QTc interval is an independent risk factor for sudden cardiac death in a population of older adults.

METHODS

Setting, study population and baseline data collection
The study is embedded in the Rotterdam Study. The Rotterdam Study is a prospective population-based cohort study, which started with a baseline visit between 1990 and 1993. All inhabitants of a suburb in Rotterdam, Ommoord, aged 55 years and over (10,275), were invited to participate. Of these, 7,983 (78%) gave their written informed consent and took part in the baseline examination. Objectives and methods of the Rotterdam Study have been described in detail elsewhere.[19] All participants were visited at home for a standardized questionnaire and 7,151 were subsequently examined at the research center. A second follow up visit took place between 1993 through 1995. For the present study, follow-up started at baseline examination and lasted until January 1, 2000.
Information on smoking was obtained during the home interview of the Rotterdam Study. During the research center visit non-fasting blood samples were obtained and serum total cholesterol was determined by an enzymatic procedure and high density lipoprotein (HDL) was measured similarly after precipitation of the non-HDL fraction.[20] Body mass index (BMI) was computed as weight divided by height squared. Hypertension was defined as

a systolic blood pressure >=160 mm Hg and/or diastolic blood pressure >=100 mm Hg and/or use of antihypertensive medication, encompassing grade 2 and grade 3 hypertension according to World Health Organization (WHO) criteria.[21] Diabetes mellitus was defined as the use of blood glucose–lowering medication and/or a non-fasting or post-load serum glucose level of 11.1 mmol/L or higher according to the WHO.[22] A history of myocardial infarction was assessed by a self report checked with records from the general practitioner or cardiologist and /or electrocardiografic evidence. All reported myocardial infarctions were verified with the medical records and assessment has been described in detail earlier.[23] Assessment of heart failure at baseline and during follow up has also been described in detail earlier. Briefly, prevalent cases were assessed by screening all medical records for the occurrence of at least two signs and symptoms suggestive of heart failure or the use of medication for the indication heart failure and review of all hospital discharge letters. Cases of incident heart failure were obtained by continuously monitoring the participants.[24 25] The ankle arm index (AAI) is the ratio of the systolic blood pressure at the ankle to the systolic blood pressure in the arm. According to the protocol of the Rotterdam Study the AAI was measured at both legs.[26]
The Medical Ethics Committee of the Erasmus Medical Center, Rotterdam, the Netherlands, approved the study.

Outcome assessment
Participants in the Rotterdam Study are continuously monitored for major events that occur during follow up, including incidence of heart failure, myocardial infarction and death. Information on vital status is obtained regularly from municipal health authorities in Rotterdam and from the general practitioners working in the district of Ommoord. In case of a fatal event, general practitioners (GPS) filled in a questionnaire relating to the circumstances of the death, including time since the occurrence of first symptoms until death, most likely cause of death according to the physician, and the time and place of death. Subsequently, research assistants gathered information about these events at the GP offices. All questionnaires and a copy of the medical records were used to assess if the death could be classified as a sudden cardiac death using the most recent definition: a natural death due to cardiac causes, heralded by abrupt loss of consciousness, within one hour after the onset of acute symptoms or an unwitnessed, unexpected death of someone seen in a stable medical condition less than 24 hours previously with no evidence of a non-cardiac cause.[2 3] If death was witnessed and occurred within one hour after the start of symptoms we assumed it to be a sudden cardiac death, without additional review of the medical records for a medical history of cardiovascular disease or the presence of cardiovascular risk factors. In case of an unwitnessed death, evidence of cardiac causes was searched for using all available information. Two research physicians coded all reported events independently

according to the International Classification of Diseases, 10th edition (ICD-10, sudden cardiac death: I.46).[26] In case of disagreement, consensus was sought. Finally, a cardiologist, whose judgment was considered decisive, reviewed all events.

ECG interpretation and measurement

A 10 second 12-lead resting ECG (on average 8-10 beats) was recorded with an ACTA electrocardiograph (ESAOTE, Florence, Italy) at a sampling frequency of 500 Hz and stored digitally. All ECGs were processed by the Modular ECG Analysis System (MEANS) to obtain ECG measurements. The MEANS program has been evaluated extensively.[27-29] MEANS determines common onsets and offsets for all 12 leads together on one representative averaged beat, with the use of template matching techniques.[29] The MEANS program determines the QT interval from the start of the QRS complex until the end of the T wave. To adjust for heart rate, Bazett's formula ($QTc=QT/\sqrt{RR}$) was used.[30]

European regulatory guidelines were used to categorize QTc prolongation into 3 categories, for men and women separately. For women, the cut-off points were less than 450 ms (normal), 450-470 ms (borderline) and more than 470 ms (prolonged), and for men less than 430 ms (normal), 430-450 ms (borderline), and more than 450 ms (prolonged).[31] In addition, we used different QTc thresholds varying from 440 ms to 470 ms, based on the literature, because there is still discussion as to the most relevant cut-off points.[4 5 7-10 12 13 18 32 33]

Digitally stored ECGs of 6134 (86% of the participants who visited the research center) participants who visited the research center were available at the time of the first visit. At the time of the second visit, 4415 (70% of the participants who visited the research center) digitally stored ECGs were available. Missing ECGs were mainly due to temporary technical problems with ECG recording.

Statistical analysis

Differences in baseline characteristics between participants with normal, borderline and abnormal QTc interval prolongation were examined with ANCOVA and adjusted for age. The relative risk (RR) (95% confidence interval) of the association between prolonged QTc interval and sudden cardiac death was estimated using a Cox's proportional hazards analysis. The QTc interval at the time of the first visit was taken as the independent variable. For those participants who also had a second ECG at the follow-up visit, we updated the exposure information at the time of the follow-up visit. All information concerning co-morbidities (hypertension, diabetes, myocardial infarction, heart failure) was also updated at that time. Potential confounders were included in the multivariate model: age, sex, body mass index, hypertension, cholesterol/hdl ratio, diabetes mellitus, myocardial infarction

and heart failure. Since Bazett's formula tends to under-correct for lower heart rates and over-correct for higher heart rates we also included heart rate in the model. Sensitivity analyses were performed using different QTc cut-off points. Because left bundle branch block can cause secondary repolarization changes and atrial fibrillation can cause difficulties in measuring QT interval, analyses were performed also after exclusion of subjects with bundle branch block and atrial fibrillation at baseline. We also assessed the risk of sudden cardiac death in participants with at least one cardiovascular risk factor at baseline. In addition, we added interaction terms of QTc with age, hypertension, smoking, diabetes mellitus, myocardial infarction, and heart failure in the model. Finally, we calculated the attributable risk percent as (RR-1)/RR (x100).[34]

RESULTS

The mean follow-up time was 6.7 years (SD 2.3 years). During follow-up, 1407 (22.8%) participants died and 67 were lost to follow-up. We identified 125 sudden cardiac deaths during this period, yielding an incidence rate of approximately 3 per 1000 person years.

TABLE 1 : **BASELINE CHARACTERISTICS OF THE STUDY POPULATION STRATIFIED BY CATEGORY OF QTC PROLONGATION AT BASELINE***

Characteristic	All (n=6134)	Normal (n=4344)	Borderline (n=1109)	Abnormal (n=681)	P
Age (mean, SD)	69.2 (9)	68.4 (8.9)	70.1 (8.8)	73.5 (9.0)	<0.001
Female sex	59.6%	64.9%	49.4%	42.4%	<0.001
Smoking	22.7%	21.5%	27.1%	22.8%	<0.001
Total/HDL cholesterol ratio	5.2	5.2	5.3	5.4	<0.001
BMI (kg/m2)	26.3 (3.7)				<0.01
Blood pressure					
Systolic (mmHg)	139.4 (22.3)	137.8 (21.9)	142.2 (22.2)	145.1 (23.4)	<0.001
Diastolic (mmHg)	73.5 (11.6)	72.9 (11.3)	75.3 (12.1)	75.0 (12.1)	<0.001
Hypertension	33.6%	30.6%	39%	44.9%	<0.001
Diabetes mellitus	10.5%	8.5%	14%	17.8%	<0.001
Myocardial infarction	6.3%	5.2%	6.6%	12.9%	<0.001
Heart failure	3.2%	2.1%	3.6%	9.5%	<0.001

Values are means (SD) for continuous variables and percentages for dichotomous variables.
Abbreviations RR=relative risk, CI=confidence interval, SD=standard deviation, HDL=high density lipoprotein, BMI=body mass index

* Classification of QTc prolongation:

normal	men	≤430 ms	women	≤450 ms
borderline	men	431-450 ms	women	451-470 ms
abnormal	men	≥451 ms	women	≥471 ms

TABLE 1 shows baseline characteristics of all participants with a normal, borderline and abnormal QTc interval. The prevalence of cardiovascular co-morbidity increased with an increasing QTc

interval. Women had a significantly longer QTc interval (435 ms, SD: 26) than men (426 ms, SD: 28) .The participants who died of sudden cardiac death had a significantly longer mean QTc interval: 441.9 msec (SD: 33.0) as compared to the other participants: 431.3 msec (SD: 27.1). The characteristics of the cases and non-cases are presented in TABLE 2.

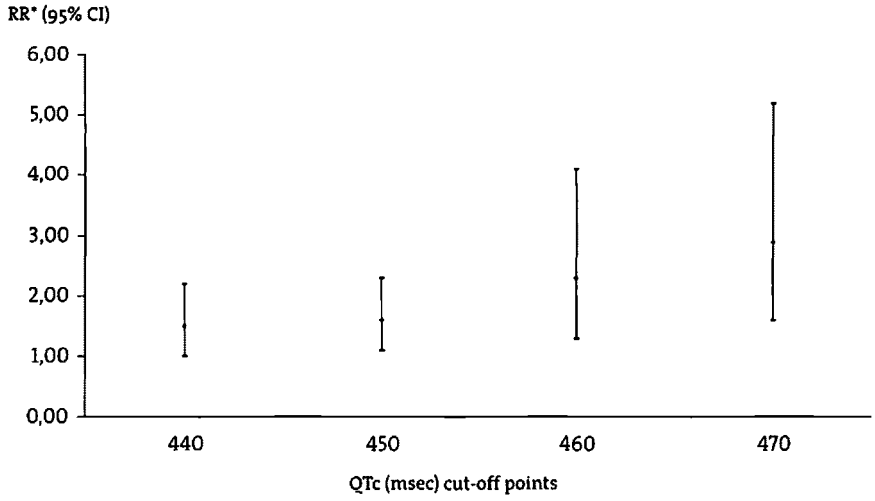
TABLE 2 : **BASE LINE CHARACTERISTICS OF NON-CASES AND CASES OF SUDDEN CARDIAC DEATH**

Characteristics at baseline	Non cases (6009)	SCD case (125)	RR* (95% CI)	P
Age (SD)	69.1 (9)	74.3 (8)	1.1 (1.0-1.1)	<0.000
Female sex	59.9%	44.8%	0.4 (0.3-0.6)	<0.000
Smoking	22.7%	17.6%	1.4 (0.9-2.7)	0.2
Cholesterol/HDL ratio	5.2	5.5	1.1 (1.0-1.2)	0.04
BMI	26.3	26.1	0.9 (0.9-1.0)	0.7
Hypertension	33.2%	56.0%	2.4 (1.7-3.5)	<0.000
Diabetes mellitus	10.3%	23.2%	2.4 (1.6-3.4)	<0.000
Myocardial infarction	5.8%	28%	4.6 (3.1-6.9)	<0.000
Heart failure	2.9%	15.2%	4.5 (2.7-7.5)	<0.000
QTc interval (SD)	431.25 (27.1)	441.9 (33.0)	1.01 (1.00-1.02)	<0.000

Values are means (SD) for continuous variables and percentages for dichotomous variables,
*RR adjusted for age and sex (age: sex adjusted and sex: age adjusted)
Abbreviations RR=relative risk, CI=confidence interval, SD=standard deviation, HDL=high density lipoprotein (mmol/l), BMI=body mass index (kg/m2), age in years, QTc interval in msec.

Borderline QTc prolongation was associated with a twofold increase in the risk of sudden cardiac death and abnormally prolonged QTc intervals with a threefold increased risk of sudden cardiac death as compared to reference QTc values in the fully adjusted model. (TABLE 3 AND FIGURE 1) The relative risk was most pronounced in the lower age group (age 55 to 68 years).

FIGURE 1 : **RISK OF SCD AT DIFFERENT QTc CUT-OFF POINTS**



*adjusted for age, sex, body mass index, cholesterol/HDL ratio, smoking, hypertension, diabetes, myocardial infarction, heart failure.

TABLE 3 : **QTc PROLONGATION AND RISK OF SUDDEN CARDIAC DEATH**

QTc prolongation[1]		RR (95% CI)*	RR (95% CI)**
Normal (n=4344)		1 (reference)	1 (reference)
Borderline (n=1109)		2.3 (1.3-4.2)	1.6 (0.9-3.1)
Abnormal (n=681)		3.7 (2.0-6.9)	2.5 (1.3-4.7)
<median age (55-68 yr)	Normal (n=2314)	1 (reference)	1 (reference)
	Borderline (n=514)	5.0 (1.5-16.8)	3.7 (1.1-14.0)
	Abnormal (n=212)	9.8 (2.7-35.1)	8.0 (2.1-31.3)
≥median age (>68 yr)	Normal (n=2003)	1 (reference)	1 (reference)
	Borderline (n=595)	1.7 (0.9-3.6)	1.3 (0.6-2.7)
	Abnormal (n=469)	2.8 (1.4-5.9)	2.1 (1.0-4.4)
men	Normal (n=1523)	1 (reference)	1 (reference)
	Borderline (n=561)	2.4 (1.0-5.3)	1.8 (0.8-4.1)
	Abnormal (n=392)	3.9 (1.8-8.4)	2.6 (1.1-5.8)
women	Normal (n=2821)	1 (reference)	1 (reference)
	Borderline (n=548)	2.3 (0.9-5.9)	1.3 (0.5-3.7)
	Abnormal (n=289)	3.5 (1.3-9.8)	2.5 (1.0-7.1)

Abbreviations: RR=relative risk, CI=confidence interval, reference=reference value

* adjusted for age in sex-stratified analyses and adjusted for sex in age-stratified analyses

** adjusted for age (only in sex-stratified analyses), sex (only in age-stratified analyses), smoking, cholesterol/HDL ratio, Body Mass Index, hypertension, diabetes mellitus, myocardial infarction, heart failure and heart rate

[1] Classification of QTc prolongation:

cut-off points:	normal	men	≤430 ms	women	≤450 ms
	borderline	men	431-450 ms	women	451-470 ms
	abnormal	men	≥451 ms	women	≥471 msFigure

In persons with at least one cardiovascular risk factor at baseline, abnormal QTc prolongation was associated with a fourfold increase in the risk of sudden cardiac death (RR: 4.3; 2.2-8.6). After exclusion of subjects with left bundle branch block or atrial fibrillation, the risk of sudden cardiac death was significantly increased in both subjects with a borderline prolonged QTc interval (2.2; 95% CI:1.1-4.7) as well as in subjects with an abnormally prolonged QTc interval (RR: 3.4; 95% CI: 1.7-6.7). As many studies used QTc interval classifications into two categories we also analyzed QTc prolongation classified in different categories using cut-off points varying from 440 ms to 470 ms (FIGURE 2). Using 440 ms as a cut-off point of QTc interval prolongation we observed a significant increase in the risk of sudden cardiac death after adjustment for age and sex (2.3: 95% CI:1.4-3.8), and this risk remained increased also after adjustment for risk factors (1.5; 95% CI:1.0-2.2). None of the interactions we assessed with age, smoking, hypertension, diabetes mellitus, myocardial infarction, and heart failure were statistically significant. The increase in the risk of sudden cardiac death corresponded to an attributable risk proportion of 0.66, meaning that in our study 66 percent of all cases of sudden cardiac death were associated with an abnormally prolonged QTc interval.

DISCUSSION

In this population-based study among older adults, an abnormally prolonged QTc interval was associated with a threefold increased risk of sudden cardiac death. In subjects below the median age of 68 years, a prolonged QTc was associated with a nearly eightfold increased risk. The risk estimates were independent of cardiovascular risk factors. In our analyses, we used the most recent regulatory guidelines to classify QTc prolongation in three sex-specific categories.[32] If we classified the QTc interval according to previously used cut-off levels, we also observed a significantly increased risk of sudden cardiac death starting at a cut-off point of 440 ms. The ankle arm index is considered to be a marker of atherosclerosis that is not only influenced by the presence of plaques but also by hemodynamic factors and vascular factors.[36] Since sub-clinical atherosclerotic disease can influence the QTc interval we also analyzed the effect of the ankle arm index as a marker for atherosclerosis on the risk of sudden cardiac death. The adjustment did not change the point estimates. Since Bazett's formula tends to under-correct for lower heart rates and over-correct for higher heart rates we also included heart rate in the model. This did, however, not change the risk estimate substantially.

Results of several epidemiological studies evaluating total mortality and cardiovascular mortality in relation to QTc prolongation have yielded conflicting results[4 7-12 18 37], and only few studies specifically addressed sudden cardiac death.[5 8] In subjects referred for Holter monitoring, a QTc interval of more than 440 ms doubled the risk of sudden cardiac death.[5] In the Zutphen study, QTc prolongation of 420 ms or more was associated with a threefold increased risk of sudden cardiac death (3.0; 95% CI: 1.0-8.9) in elderly men (aged 65-85 years),

but not in men aged 40-60 years.[8] The Framingham study failed to demonstrate an association of baseline QTc prolongation with total mortality, sudden death or coronary mortality.[9] The Cardiovascular Health Study, on the other hand, demonstrated an association between a QTc interval of more than 450 ms and total mortality and in the Strong Heart Study, a QTc interval of 460 ms or more was associated with a twofold increased risk of both cardiac mortality and total mortality.[12] In our study, we found a significantly increased risk of sudden cardiac death in subjects with a prolonged QTc interval after adjustment for other cardiovascular risk factors. In the Rotterdam Study, we previously found that QTc prolongation (>440 ms) was associated with increased risks of total and cardiovascular mortality.[7] In this study, however, a shorter follow-up time and only one baseline ECG were used and we did not specifically examine the relation with sudden cardiac death. The risk of sudden cardiac death in the present study was higher in the population aged 55 to 68 years. This may partly be explained by depletion of susceptible subjects at older age. The proportion of sudden cardiac death attributable to a prolonged QTc interval is larger in the younger age category. It should be emphasized, however, that the absolute risk of sudden cardiac death increases with age.[38 39]

The strength of our study lies in the fact that data were available on large group of subjects. The follow-up period is relatively long and enabled us to take advantage of the fact that a large part of the participants had two ECGs. There was little loss to follow-up and information on cardiovascular risk factors was accurately collected. The conflicting results in earlier studies may partly be explained by the differences in the definition of sudden cardiac death, differences in populations, in the classification of QTc prolongation or the use of general rather than sex-specific QTc cut-off points. We used the most recent European regulatory guidelines to classify QTc prolongation.[32] To our knowledge, this study is the first to use this sex-specific classification in a population-based study. In addition, in all studies QTc prolongation was based on one baseline ECG and related to outcomes that usually occurred many years later.

Nevertheless, also our study has some limitations. First, we cannot exclude that some misclassification of outcome occurred. We were, however, able to take advantage of the fact that in most cases complete information of the facts surrounding death was available for review, including a questionnaire concerning the fatal event and in many cases the time between start of symptoms and death was documented. Second, also in our study misclassification of exposure may have occurred during follow-up since we related sudden cardiac death to QTc prolongation determined on ECGs that were measured before the event and QTc interval could have changed in the period between the last assessment and sudden cardiac death. Finally, our study population consisted of subject aged 55 years and older. Whether our findings also apply to other age groups requires further study.

In conclusion, the results of our study show that abnormal QTc prolongation on the ECG should be viewed as an independent risk factor for sudden cardiac death. Two-third of the cases of sudden cardiac death is associated with an abnormal prolongation of the QTc interval.

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❤ 'I don't much care where-'
said Alice. ❤

(Uit: Alice's adventures in wonderland
van Lewis Carroll)

CHAPTER 4

DRUGS ASSOCIATED WITH QTc PROLONGATION AND TORSADE DE POINTES

ABSTRACT

Background: Current regulatory guidelines, intended to predict whether a new drug carries an increased risk of serious cardiac arrhythmias, place much emphasis on the association of the pharmaceutical with QTc interval prolongation.

In recent years, several lists have been published on drugs implicated in QTc prolongation and cardiac arrhythmias. To our knowledge, no population based ECG data are available on the association of drugs included in these lists and the length of the QTc interval in older adults. Therefore, we examined the association between these drugs and the duration of the QTc interval in a large prospective, community-based follow-up study.

Methods and results: This study was conducted as part of the Rotterdam Study, a prospective population-based cohort study, which comprises 3105 men and 4878 women aged 55 years and older.

The primary endpoint of the study was the length of the QTc interval. The index date was defined as the date of the ECG measurements and current use at the index date was calculated based on prescription information. The associations were examined by means of linear regression analysis.

The current use of antipsychotics, cardiovascular medication, antidepressants and antihistamines was associated with a significantly increased QTc interval. Of the individual drugs, current use of clarithromycin, thioridazine, sotalol, amiodarone, disopyramide, indapamine, amitriptyline and promethazine was associated with a significant QTc interval prolongation.

Conclusions: Drug-associated QTc interval prolongation is common in a population of community-dwelling elderly, even after exclusion of those on cardiovascular medication.

INTRODUCTION

The heart-rate corrected QT (QTc) interval from a 12-lead ECG is the traditional measurement for assessing the duration of the ventricular repolarization.[1] Prolongation of

repolarization may result in early after depolarizations (EAD), which in turn may induce re-entry and provoke Torsade de Pointes, which can develop to fatal ventricular arrhythmias.[2,3] In the past decade, one of the most frequent causes of withdrawal or restriction of marketed drugs has been the prolongation of the QTc interval associated with Torsade de Pointes and fatal cardiac arrhythmias.[4,5] An increasing number of drugs, especially non-cardiac drugs has been recognized to delay cardiac repolarization and to induce Torsade de Pointes.[3] The issue of non-cardiac drugs associated with a pro-arrhythmogenic potential, has been identified as a considerable public-health problem.[3] In recent years, several lists have been published on cardiac and non-cardiac drugs implicated in QTc prolongation and cardiac arrhythmias.[6-9] List 1 of the website of the International Registry for Drug-induced Arrhythmias maintained by the Georgetown University (http://www.qtdrugs.org/medical-pros/drug-lists/drug-lists.htm), provides an up-to-date list of drugs that are reported to cause drug induced arrhythmias.[9] These drugs are classified into 4 categories, varying from drugs that are generally accepted by authorities to have a risk of causing Torsade de Pointes (list 1) to drugs that, in some reports, have been weakly associated with Torsade de Pointes but that, when used in therapeutic dosages, are unlikely to increase the risk (list 4). In addition, De Ponti et al. have published a list of 31 non-anti-arrhythmic drugs with pro-arrhythmogenic effects, based an a structured literature search.[6,7] Although there is considerable overlap between the two lists, there are also some remarkable differences. For example, the anti-arrhythmic drugs are only mentioned in list 1 and not in the list of De Ponti, as the latter focused on non-anti-arrhythmic drugs, while antidepressants, cardiovascular non-anti-arrhythmic drugs and antihistamines are only included in the list of De Ponti et al.
Current guidelines, intended to predict whether a new drug carries an increased risk of serious cardiac arrhythmias, place much emphasis on the association of the pharmaceutical with QTc interval prolongation.[10] To our knowledge, no population-based ECG data are available on the association of drugs included in the existing lists and the length of the QTc interval in older adults. Therefore, we examined the association between drugs on these lists and the duration of the QTc interval in a large prospective, community based follow-up study.

METHODS

Setting, study population and baseline data collection

This study is embedded in the Rotterdam Study. The Rotterdam study is a prospective population-based cohort study, which started with a baseline visit between 1990 and 1993. The Medical Ethics Committee of the Erasmus Medical Center, Rotterdam, the Netherlands, approved the study. All inhabitants of Ommoord, a suburb of Rotterdam, aged 55 years and over, were invited to participate (10,275). Of them, 7983 (78%) gave

their written informed consent and took part in the baseline examination. Objectives and methods of the Rotterdam Study have been described in detail elsewhere.[11] At baseline, all participants were visited at home for a standardized questionnaire, and 7151 were subsequently examined at the research center. Since the start of the study, follow-up visits took place in the period 1993 through 1996 for the second visit and in the period between 1997 through 1999 for the third visit. In addition to follow-up examinations, the total cohort is continuously monitored for major morbidity and mortality through linkage of general practitioner and municipality records. Furthermore, all drug prescriptions dispensed to participants by automated pharmacies are routinely stored in the database since January 1, 1991. For the present study, follow-up started at the baseline examination and lasted until January 1, 2000.

Assessment of QTc interval

The primary endpoint of the study was the length the QTc interval in msec. Hereto, a 10 sec 12-lead resting ECG (on average 8 to 10 beats) was recorded with an ACTA electrocardiograph (ESAOTE, Florence, Italy) at a sampling frequency of 500 Hz and stored digitally. All ECGs were processed by the Modular ECG Analysis System (MEANS) to obtain ECG measurements. The MEANS program has been evaluated extensively.[12-14] MEANS determines common onsets and offsets for all 12 leads together on one representative averaged beat, with the use of template matching techniques.[13] The MEANS program determines the QT interval from the start of the QRS complex until the end of the T wave. To adjust for heart rate, Bazett's formula ($QTc=QT/\sqrt{RR}$) was used.[15] Digitally stored ECGs of 6134 (86%) participants were available at the time of the first visit, of 4415 participants (of 6315 participants visiting the research center, 70%) at the time of the second visit, and of 3806 participants at the time of the third visit (of 4797 participants who visited the research center, 79%). Missing ECGs were mainly due to temporary technical problems with ECG recording.

Exposure

The exposure of interest was the use of QTc prolonging drugs, as specified in the two lists: list 1 from the internet based registry (http://www.qtdrugs.org/medical-pros/drug-lists/drug-lists.htm) and the list from the work of De Ponti et al. [6 7 9 16] Since not all drugs on these lists are licensed or prescribed in the Netherlands, some were not included in our analyses. Our analyses included: gastro-intestinal QTc prolonging medication: cisapride, domperidone; antimicrobial QTc prolonging medication: erythromycin, clarithromycin, co-trimoxazole; chloroquine; antipsychotic QTc prolonging medication: haloperidol, thioridazine; cardiovascular (anti-arrhythmic) QTc prolonging medication: amiodarone, disopyramide, quinidine, sotalol; cardiovascular (non anti-arrhythmic)

QTc prolongation medication: ketanserin, indapamine; antidepressant QTc prolonging medication: clomipramine, amitriptyline, doxepine, sertraline, mianserine; antihistamine QTc prolonging medication: diphenhydramine/dimenhydrinate, astemizole, terfenadine, promethazine.
The index date was defined as the date of the ECG measurements. In order to classify use at the index date, we calculated the duration of each prescription as the total number of units issued per prescription divided by the prescribed daily number of units. Current use was defined as use at the index date.

Co-variates
Clinical measures were obtained during the visits at the Rotterdam Study research center. In 1990-1993 non-fasting blood samples were obtained, while in 1997-2000 blood samples were obtained after an overnight of fasting. Diabetes mellitus was defined as the use of blood glucose–lowering medication and/or a non-fasting serum glucose level of 11.1 mmol/L or higher and/or a serum glucose levels ≥ 7mmol/l (1997-2000).[17] Hypertension was defined as a systolic blood pressure ≥ 160 mm Hg and/or diastolic blood pressure ≥ 100 mm Hg and/or use of antihypertensive medication, encompassing grade 2 and grade 3 hypertension according to World Health Organization (WHO) criteria.[18] Assessment of myocardial infarction at baseline and during follow-up was assessed by hospital discharge diagnosis or in case a patient was not hospitalized, when signs and symptoms, analysis of the standard 12-lead electrocardiogram and cardiac enzyme data were diagnostic of a myocardial infarction, and has been described in detail earlier.[19] [20] Assessment of heart failure at baseline and during follow-up was assessed by the presence of signs and symptoms suggestive of heart failure and the use of medication for the indication heart failure and has also been described in detail earlier.[21] [22]

Statistical analysis
Differences in baseline characteristics were examined with a Chi-square test for dichotomous variables and a t-test or Mann-Whitney test for continuous variables. The association of exposure to QTc prolonging drugs and QTc interval duration was examined by means of linear regression analysis. Analyses were adjusted for age, sex and additionally for diabetes mellitus, hypertension, myocardial infarction and heart failure since these factors may influence the duration of the QTc interval. Because repeated measures for the same subject are correlated, we included all measurements in one model, a repeated measurement analysis, taking into account correlation within persons. All repeated measurements analyses were performed using SAS software, version 8.2 using the MIXED procedure within SAS (PROC MIXED).

RESULTS

Overall 14,013 ECGs were available, 5768 in men and 8245 in women (TABLE 1). The overall median age was 69 years (interquartile range (IQR): 63-74) and women were significantly older than men. The mean QTc interval was significantly longer in women than in men (TABLE 1). Overall, 615 current users of QTc prolonging drugs were identified in our population. Significantly more women used QTc prolonging medication (TABLE 2). This was predominantly related to the more frequent use of several drugs in women, such as antidepressants and domperidone.

TABLE 1 : **CHARACTERISTICS OF THE STUDY POPULATION**

	Overall	Men	Women
Overall number of observations	14,013	5,768 (41.2%)	8,245 (58.8%)
Age in years	69.9 (8.5)	68.9 (7.8)*	70.5 (8.9)*
QTc (mean, SD) in msec	430.0(26.5)	425.0 (27.8)*	433.4 (25.0)*
ECG visit 1 Number of observations	5216	2113	3103
Age (mean, SD) in years	68.9 (9.3)	67.6 (8.3)*	69.8 (9.8)*
QTc (mean, SD) in msec	430.7 (27.3)	425.1 (28.5)*	434.5 (25.9)*
ECG visit 2 Number of observations	4991	2057	2934
Age (mean, SD) in years	69.4 (8.4)	68.4 (7.6)*	70.1 (8.9)*
QTc (mean, SD) in msec	427.9 (26.9)	423.2 (27.3)*	431.2 (24.4)*
ECG visit 3 Number of observations	3806	1598	2208
Age (mean, SD) in years	71.9 (7.0)	71.4 (6.6)*	72.2 (7.2)*
QTc (mean, SD) in msec	431.8 (25.9)	427.3 (27.4)*	435.0 (24.2)*

Values are mean, SD
SD= standard deviation
*P<0.0001

The use of antipsychotics, cardiovascular medication, antidepressants and antihistamines was associated with a significantly increased QTc interval. Of the individual drugs, current use of clarithromycin, thioridazine, sotalol, amiodarone, disopyramide, indapamine, amitriptyline and promethazine was associated with a significant QTc interval prolongation. After exclusion of all current users of cardiovascular QTc prolonging medication (amiodarone, chloroquine disopyramide, quinidine, sotalol, indapamine and ketanserin) the results did not change sunstantially. The current use of clarithromycin, thioridazine, amitriptyline and promethazine remained associated with a significantly prolonged QTc interval. From the drugs listed on both lists, current use of thioridazine and clarithromycin was associated with a significantly increased QTc interval.

TABLE 2 : **MEDICATION AND QTc INTERVAL PROLONGATION**

Medication	Users (n)	Men (%)	Women (%)	Prolongation QTc interval (95% CI)*	Prolongation QTc interval (95% CI)**
All QTc prolonging medication	615	212 (3.7)[A]	403 (4.9)[A]	9.5 (7.6-11.4) [B]	8.8 (6.9-10.7)
Gastrointestinal medication	147			0.4 ([-3.3]-4.2)	0.3 ([-3.4]-4.0)
Cisapride	101	32 (0.6)	69 (0.8)	0.2 ([-4.2]-7.8)	0.2 ([-4.6]-4.2)
Domperidone	46	10 (0.2) [A]	36 (0.4)[¥]	0.9 ([-6.1]-7.8)	1.2 ([-5.7]-8.1)
Antibacterials	18	9 (0.2)	9 (0.1)	2.8 ([-7.0]-12.6)	2.8 ([-6.9]-12.6)
Erythromycin	2	1 (0.0)	1 (0.0)	-5.0 ([-33.0]-22.9)	-5.5 ([-33.5]-22.4)
Clarithromycin	3	0 (0.0)	3 (0.0)	39.7 (44.4-65.0) [B]	37.9 (12.6-62.7) [B]
Co-trimoxazol	7	3 (0.1)	4 (0.0)	-8.8 ([-24.4]-6.8)	-8.3 ([-23.9]-7.3)
Chloroquine	6	5 (0.1)	1 (0.0)	2.9 ([-14.0]-19.7)	3.3 ([-13.5]-20.2)
Antipsychotics	17	6 (0.1)	11 (0.1)	12.2 (0.3-24.0) [B]	12.0 (0.2-23.8) [B]
Thioridazine	6	2 (0.0)	4 (0.0)	25.7 (4.7-46.6) [B]	25.2 (4.4-46.0) [B]
Haloperidol	11	4 (0.1)	7 (0.1)	5.8 ([-8.7]-20.2)	5.7 ([-8.7]-20.0)
Cardiovascular medication	265	110 (1.9)	155 (1.9)	16.8 (14.0-19.7) [B]	15.5 (12.6-18.4) [B]
Anti arrhythmics	223	95 (1.6)	128 (1.6)	17.6 (14.5-20.7) [B]	16.2 (13.1-19.3) [B]
Sotalol	130	34 (0.9)	76 (0.9)	14.4 (10.6-18.3) [B]	13.1 (9.2-16.9) [B]
Amiodarone	66	34 (0.60	32 (0.4)	20.2 (14.3-26.1) [B]	17.7 (11.8-23.6) [B]
Disopyramide	21	6 (0.1)	15 (0.2)	27.1 (16.8-37.5) [B]	26.8 (16.5-37.2) [B]
Quinidine	7	6 (0.1)	15 (0.2)	14.9 ([-4.1]-33.9)	15.6 ([-3.3]-35.6)
Other cardiovascular	44	15 (0.3)	29 (0.4)	11.2 (3.7-18.7) [B]	10.1 (2.6-17.6) [B]
Indapamine	16	11 (0.2)	17 (0.2)	12.7 (3.2-22.1) [B]	13.0 (3.6-22.5) [B]
Ketanserine	28	4 (0.2)	12 (0.1)	8.7([-3.7]-21.0)	5.6 ([-7.2]-17.5)
Antidepressants	154	38 (0.7) [A]	116 (1.4) [A]	6.1 (2.2-10.0) [B]	6.0 (2.2-9.9) [B]
Clomipramine	22	5 (0.1)	17 (0.2)	6.8 ([-3.1]-16.8)	7.0 ([-3.0]-16.9)
Amitriptyline	96	27 (0.5) [A]	69 (0.8) [A]	8.7 (3.8-13.5) [B]	8.6 (3.7-13.4) [B]
Doxepine	6	1 (0.0)	5 (0.1)	-7.8([-27.9]-10.4)	-9.3 ([-28.4[-9.9)
Mianserine	31	5 (0.1) [A]	26 (0.3) [A]	-0.8 ([-9.7]-8.0)	-0.8 ([-9.6]-7.9)
Antihistamines	41	12 (0.2)	29 (0.4)	8.2 (1.6-14.8) [B]	7.9 (1.3-14.5) [B]
Diphenhydramine	2	2 (0.0)	0 (0.0)	-19.7 ([-48.7]-9.4)	-19.4 ([-48.5]-9.6)
Astemizole	3	1 (0.0)	2 (0.0)	3.1 ([-20.1]-26.2)	3.6 ([-19.5]-26.7)
Terfenadine	20	5 (0.1)	15 (0.2)	8.5 ([-0.8]-17.7)	7.5 ([-1.8]-16.7)
Promethazine	16	4 (0.1)	12 (0.1)	13.0 (1.9-24.0) [B]	13.5 (2.5-24.6) [B]

Since some subjects use more than 1 drug, numbers do not add up to the total number of subjects
QTc interval in msec. CI =Confidence Interval
* adjusted for age and sex
** adjusted for age and sex, diabetes mellitus, hypertension, myocardial infarction, and heart failure
[A] P<0.05 Chi square test
[B] P<0.05 linear regression analysis
List 1 includes also: bepridil, sparfloxacine, chlorpromazine, droperidol, mesoridazine, pimozide, halofantrine, arsenic trioxide, levomethadyl, pentamidine.
De Ponti's list includes also: lidoflazine, grepafloxacin, chlorpromazine, droperidol, sultopride, pimozide, protriptyline, zimeldine, pentamidine, tacrolimus and terodiline

DISCUSSION

The results of our study in a population of older adults, showed a significant association between the current use of several, but not all, drugs on two widely used lists which have been associated with QTc interval prolongation and/or Torsade de Pointes. Current use of clarithromycin, thioridazine, sotalol, amiodarone, disopyramide, indapamine, amitriptyline, and promethazine was associated with a significant increase in the length of the QTc interval. Although all listed drugs have been reported to be associated with Torsade de Pointes or cardiac arrhythmias, significant associations were not found for a number of these drugs.[6 7 9] It is possible that avoiding known QTc prolonging drugs in high-risk patients precluded the finding of an association. As a significant number of users, also with known risk factors, were identified in our study population, this seems not to be the explanation. The cross-sectional nature of the study prohibited us to determine if the drugs were the cause of the QTc prolongation or QTc prolongation was already present before the start of the drug. This study design, however, would not have prohibited the finding of an association between a listed drug and QTc prolongation, if present and does not explain the absence of an association for a large number of drugs. The fact that we did not find a significant QTc prolongation could also be explained by a small number of current users of some drugs. For thioridazine, however, we found a significant prolongation of the QTc interval despite a small number of users.

It is known that some drugs associated with QTc prolongation are devoid of torsadogenic effects, whereas others seem not to be associated with a significant QTc prolongation, but are still considered to be associated with cardiac arrhythmias.[5 8 23] Virtually all QTc prolonging drugs act by blocking the rapid component of the delayed rectifier potassium channel (I_{kr}) through blockade of the human ether a go-go related gene (HERG). Unfortunately this finding is not specific, since many drugs that do not seem to cause Torsade de Pointes, also block this current.[5] Amiodarone blocks I_{kr}, is associated with a significant QTc prolongation, yet rarely causes Torsade de Pointes.[3 5 8] Therefore, it is likely that other pharmacological actions are also involved. These actions might prevent Torsade de Pointes, either directly (by blunting early after depolarizations) or indirectly (by blunting the prolongation of the action potential).[5] The problem is that some drugs do not prolong the QTc interval, yet are implicated in the occurrence of cardiac arrhythmias and Torsade de Pointes.[8 23] The antihistamine terfenadine, a potent I_{kr} blocker, did not prolong the QTc interval, not in our study nor in earlier studies. Nevertheless, this drug has been associated with serious cardiac arrhythmias leading to its withdrawal. These are believed to occur mostly when there was concurrent use of inhibitors of cytochrome P450 CYP3A4.[5 8 23 24] Thus, it seems to be difficult to predict whether a drug will cause Torsade de Pointes based on its effect on the length of the QTc interval alone.

Much emphasis has been placed on the potential pro-arrhythmic effects of pharmaceuticals that are associated with QTc interval prolongation in recent guidelines.[10] Recently, collaborating researchers from several pharmaceutical industries published an extensive review of QTc prolonging drugs and their ability to bind to HERG channels in relation to free plasma concentrations.[8] It was shown that, in general, drugs with a small margin (i.e. drugs that bind to the potassium channels in concentrations close to therapeutic plasma concentration) had a high risk of serious cardiac arrhythmias while drugs with a high margin had a lower risk. In this review, cisapride, astemizole and terfenadine were shown to have a very low margin, suggesting a high risk of cardiac arrhythmias, while amiodarone has a very high margin, which is in line with its known low risk of Torsade de Pointes.[8] This margin between HERG binding capacity and free plasma concentration might be a helpful tool in the prediction of the risk of Torsade de Pointes, and might be more important as an indicator of risk for cardiac arrhythmias.

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❤ 'Then it doesn't matter
which way you go' said the Cat. ❤

(Uit: Alice's adventures in wonderland
van Lewis Carroll)

CHAPTER 5

ANTIPSYCHOTICS AND THE RISK OF SUDDEN CARDIAC DEATH

ABSTRACT

Background: Antipsychotics have been associated with QTc prolongation and cases of sudden cardiac death. Only few epidemiologic studies, however, investigated this association. We performed a case-control study to investigate the association between the use of antipsychotics and sudden cardiac death in a well-defined community dwelling population.

Methods and Results: We performed a population-based case-control study in the IPCI project, a longitudinal observational database with complete medical records from 150 general practitioners in the Netherlands. All instances of death between January 1, 1995 and April 1, 2001 were manually reviewed. Potential cases of sudden cardiac death were classified on the basis of the time between onset of cardiovascular symptoms and death. To each case, up to ten random controls were matched on year of birth, gender, date of sudden death and practice. Exposure at the index date was categorised as three mutually exclusive groups of current use, past use and non-use. Furthermore, dose- and duration-effect relationships were studied.

The study population comprised 554 cases of sudden cardiac death and 4463 matched controls. Current use of antipsychotics was associated with a three-fold risk increase of sudden cardiac death (adjusted OR: 3.3; 95% CI: 1.8-6.2). The risk of sudden cardiac death was highest among butyrophenone antipsychotics (OR: 7.3; 95% CI: 2.8-18.8), users of more than 0.5 DDD per day (OR: 9.8; 95% CI: 2.1-44.6) and among short-term (≤ 90 days) users (OR: 5.0; 95% CI: 2.1-12.1). For witnessed cases (n=334), the association with current antipsychotic use was higher (OR 4.7; 95% CI: 2.0-10.8) than for unwitnessed cases (OR: 2.4; 95% CI: 0.9-6.3).

Conclusion: The results of our study indicate that current use of antipsychotics in a general population is associated with an increased risk of sudden cardiac death, even at a low dose and in persons who use antipsychotics for other indications than schizophrenia. The risk of sudden cardiac death seems to be highest among recent starters but remains elevated during long-term use.

INTRODUCTION

In developed countries, sudden cardiac death is one of the major causes of cardiovascular mortality. According to the most recent definition, sudden cardiac death is a natural death due to cardiac causes, heralded by abrupt loss of consciousness within one hour after the onset of acute symptoms or an unwitnessed, unexpected death of someone seen in a stable medical condition less than 24 hours previously with no evidence of a non-cardiac cause.[1 2] Since the early sixties, sudden cardiac death has been reported with antipsychotic use in case reports.[3-5] Although the precise mechanism remains uncertain, several have been suggested including peripheral vasodilatation, leading to cardiovascular collapse, oral laryngeal-pharyngeal dystonia, acute myocarditis or cardiomyopathy.[6] Particular attention has been paid to the ability of antipsychotics to prolong the QTc interval, which may result in torsade de Pointes and other cardiac arrhythmias.[6-8] Only few epidemiological studies have addressed the issue of sudden cardiac death and antipsychotic use. They found an increased risk of sudden cardiac death during the use of antipsychotics, varying from 1.7 to 5.3.[8-10] These studies, however, were either small and performed in hospitalised psychiatric patients or were performed in administrative databases with little information on potential confounders. Moreover, because of the inability to validate the diagnosis of sudden cardiac death in medical records, most of these studies may have suffered from misclassification of the outcome.
We performed a case-control study on the association between the use of antipsychotics and sudden cardiac death in a well-defined community dwelling population with complete coverage of all relevant health care information.

METHODS

Setting

All data were retrieved from the Integrated Primary Care Information (IPCI) project, a longitudinal observational database, containing data from computer-based medical patient records of a group of 150 general practitioners (GPs) in the Netherlands. In the Dutch health care system, the GP has a pivotal role by acting as a gatekeeper for all medical care. Details of the database have been described elsewhere.[11 12] Briefly, the database contains the complete medical records on approximately 500,000 patients. The electronic records contain coded and anonymous data on patient demographics, symptoms (in free text), diagnoses (using the International Classification for Primary Care [13] and free text) from GPs and specialists, referrals, laboratory findings, hospitalisations, and drug prescriptions, including their indications and dosage regimen. To maximise completeness of the data, general practitioners participating in the IPCI project are not allowed to maintain a system of paper-based records besides the electronic medical records. The system complies with

European Union guidelines on the use of medical data for medical research and has been proven valid for pharmaco-epidemiological research in several validation studies that evaluated the quality of the available information.[11] The Scientific and Ethical Advisory Board of the IPCI project approved this study.

Source population

The source population comprised all subjects of 18 years and older, registered with a general practitioner participating in the IPCI project for at least one year. Subjects with a diagnosis of cancer were excluded from the source population, since in these patients the cause of death is often difficult to assess. The study period started on January 1, 1995 and ended on April 1, 2001. All subjects were followed until death, transferral out of practice, last data draw down or end of the study period, whichever came first.

Case and control definition

The computerised medical and demographic data were screened for all deaths, which occurred during the study period. The medical records of all identified cases of death were reviewed manually to assess whether death could be classified as sudden cardiac death. Validation was performed independently by two physicians blinded to exposure (SMJMS, GSB) and in case of discrepancy, a third expert (BHChS) arbitrated. Assessment was based on the most recent definition of sudden cardiac death.[1 2] Cases were classified as (probable) sudden cardiac death if the medical record indicated that death occurred within one hour after the onset of acute symptoms and if the following wording was found in the free text: "sudden cardiac death", "acute cardiac death", "mors subita", "sudden death", "died suddenly", "died unexpectedly", or if this was an unwitnessed, unexpected death of someone seen in a stable medical condition less than 24 hours previously and with no evidence of a non-cardiac cause (e.g. pneumonia, convulsion, choking or stroke). Suicides were excluded. To each case of sudden cardiac death, up to ten controls were randomly drawn from the source population matched on age (year of birth), gender, and practice. The index date was defined as the date on which sudden cardiac death occurred in cases. This date was also the index date for matched controls.

Exposure definition

In order to assess the use of antipsychotics at the index date, we calculated the duration of use for each antipsychotic as the total number of units (capsules/tablets) per prescription divided by the prescribed daily number of these units. Exposure at the index date was categorised into three mutually exclusive groups of current, past and non-use. Use of antipsychotics was defined as current if the index date fell within a period of use or within a maximum of 30 days after the end of the last prescription (to deal with carry-over effects). Past use was defined as discontinuation of an antipsychotic, more than 30 days before the

index date. If patients had no prescription for an antipsychotic prior to the index date they were considered non-exposed. Among current users we evaluated the effect of duration (≤ 90 days; > 90 days continuously), type of antipsychotic (phenothiazines, butyrophenones, thioxanthenes, lithium and other), indication for the antipsychotic prescription and the daily dose in defined daily dose equivalents (DDD), as defined by the World Health Organisation.[14] One DDD-equivalent represents the recommended daily dose for an adult for the indication schizophrenia. In order to evaluate dose response effects the daily dose of antipsychotics was categorised into less than or equal to 0.5 DDD, and more than 0.5 DDD.

Co-variates and risk factors

Known risk factors and other co-variates for sudden cardiac death were gathered from the medical records through computerised searches and manual assessment. The co-variates which were evaluated included cerebro- and cardiovascular ischemia (history of myocardial infarction, stroke, and angina pectoris), heart failure, hypertension, diabetes mellitus, arrhythmia, hypercholesterolemia, smoking and alcohol abuse. Ischemia and heart failure were assessed, based on the diagnoses provided by the general practitioner and by specialists in the medical records. Hypertension was identified through the diagnoses in the medical records, the use of antihypertensive medication and/or the assessment of blood pressure measurements, according to the guidelines of the World Health Organisation (a blood pressure exceeding 140 mm Hg systolic and/or 90 mm Hg diastolic).[15] Diabetes mellitus, arrhythmias and hypercholesterolemia were identified through diagnoses in the medical records from GPs and specialists and/or the use of antidiabetic, anti-arrhythmic or lipid lowering medication. Information on smoking and alcohol abuse was obtained from the medical records. As concomitant medication we considered among others antidepressants, anxiolytics, hypnotics, cardiovascular and known QTc prolonging medication. Current use of these drugs was defined as use at the index date. The indication for the use of antipsychotics, classified according to the DSM IV [16], was obtained from the prescription records. We evaluated the effect of social economic status (SES), by including a variable on health care insurance, which is a proxy for income (all below an income of about 25.000 dollars a year have sick fund insurance, and those above have a private insurance).

Statistical analysis

The relative risk for sudden cardiac death associated with antipsychotics was estimated by calculation of the odds ratios (95% confidence interval) using conditional logistic regression analyses. Co-variates which were univariately associated with sudden cardiac death (at a $p < 0.1$ level) were initially included in the regression analyses. Factors that changed the point estimate of the association between antipsychotic drug use and sudden cardiac death by more than 10% [17] were kept in the final model (diabetes mellitus, arrhythmias,

hypertension, cerebro-and cardiovascular ischemia, use of diuretics, use of ACE-inhibitors, and use of anxiolytic/hypnotic medication). In addition smoking and alcohol abuse were included in the model because these are known risk factors for sudden cardiac death. We investigated potential effect modification by age and gender and performed subanalyses to evaluate potential misclassification of sudden cardiac death by splitting the outcomes between witnessed and unwitnessed death. To evaluate a possible dose-effect relation, a trend test was performed. Furthermore, we evaluated potential confounding by indication by providing risk estimates for current antipsychotic use in patients with the indication schizophrenia and with current antipsychotic use for other indications.

RESULTS

In the source population (n= 250,000), 582 cases of sudden cardiac death were identified, representing an incidence rate of sudden cardiac death of almost 1 per 1000 person-years per year in the source population. No controls could be matched to 28 cases, and these cases were excluded from further analyses. Hence, the study population comprised 554 cases of sudden cardiac death and 4463 matched controls (approximate case:control ratio 1:8). There were 334 witnessed (60.3%) and 220 unwitnessed (39.7%) cases of sudden cardiac death. The median age of the study population was 71 years and approximately 60% were male. Despite matching on year of birth, the median age of cases was higher than the median age of all controls (74 years and 71 years respectively) since more controls were available for younger cases than for elderly cases (TABLE 1). Autopsy had been performed in only seven cases but these were all compatible with a cardiac origin of sudden death. All known potential risk factors for sudden cardiac death were associated with an increased risk, notably ischemic cerebro- and cardiovascular disease, hypertension, arrhythmia, diabetes mellitus, heart failure, hypercholesterolemia, smoking and alcohol abuse (TABLE 1). As expected, use of cardiovascular medication was associated with sudden cardiac death as well. There was no association between socio economic status and sudden cardiac death.
Current use of antipsychotics was associated with a three-foldly increased risk of sudden cardiac death (adjusted OR: 3.3; 95% CI: 1.8-6.2). Past use of antipsychotics was not associated with an increased risk of sudden cardiac death (TABLE 2). The risk of sudden cardiac death was highest among individuals using butyrophenone antipsychotics, predominantly pipamperone and haloperidol. Furthermore, the risk was highest among users of a daily dose higher than 0.5 DDD, and among short-term (≤ 90 days) users. The risk of sudden cardiac death increased significantly with higher doses ($p<0.001$). However, also in persons who used antipsychotics at a daily dose ≤ 0.5 DDD, or continuously for more than 90 days the risk of sudden cardiac death was significantly increased. The majority of current users did not receive antipsychotics for schizophrenia.

TABLE 1 : **DEMOGRAPHICS, DISTRIBUTION OF CO-VARIATES AND USE OF CONCOMITANT MEDICATION IN CASES AND CONTROLS**

Characteristic	Cases (n=554)	Controls (n=4463)	Odds ratio* (95% CI)
Gender			
Male	326 (59%)	2657 (60%)	
Age (median)	74 YR	71 YR	
55 yr	67 (12.1%)	736 (16.4%)	
56-65 yr	77 (13.9%)	792 (17.7%)	
66-75 yr	175 (31.6%)	1551 (34.8%)	
> 75 yr	235 (42.4%)	1390 (31.1%)	
Sudden cardiac death			
Witnessed	334 (60.3%)		
Co-morbidities			
Ischaemic Cerebro-/Cardiovascular Disease	203 (37%)	780 (17%)	2.6 (2.1-3.2)
Hypertension	359 (65%)	2562 (57%)	1.3 (1.0-1.6)
Arrhythmia	114 (21%)	469 (11%)	2.1 (2.1-3.2)
Diabetes mellitus	182 (33%)	871 (20%)	2.0 (1.6-2.5)
Smoking	92 (17%)	469 (11%)	2.2 (1.6-2.9)
Alcohol abuse	32 (6%)	137 (3%)	2.1 (1.4-3.3)
Heart failure	141 (25%)	283 (6%)	5.0 (3.9-6.4)
Hypercholesterolemia	47 (8%)	266 (6%)	1.7 (1.2-2.4)
Concomitant cardiovascular drugs			
ß-blocking agents	71 (13%)	491 (11%)	1.2 (0.9-1.6)
Diuretics	135 (24%)	484 (11%)	2.4 (1.9-3.1)
Ca-blocking agents	63 (11%)	295 (7%)	1.7 (1.3-2.3)
ACE-inhibitors	100 (18%)	378 (8%)	2.4 (1.8-3.0)
ATII-blocking agents	19 (3%)	66 (2%)	2.5 (1.5-4.3)
Lipid lowering agents	31 (6%)	206 (5%)	1.4 (1.0-2.1)
Cardiac glycosides	56 (10%)	125 (3%)	3.4 (2.4-4.9)
Anti-arrhythmics	7 (1%)	32 (1%)	1.6 (0.7-3.9)

* All odds ratios are matched for age, gender, practice and calendar time

Twelve patients (5 cases and 7 controls) met the criteria for diagnoses of schizophrenia or schizo-affective disorders, whereas 44 patients (14 cases and 30 controls) received antipsychotics for other psychiatric diseases such as organic psychosis, dementia, stress, anxiety or bipolar depression. The risk of sudden cardiac death in current users not meeting the criteria for the diagnosis of schizophrenia or schizo-affective disorders was significantly

higher than in non-users (OR: 3.3; 95% CI: 1.6-6.6) and was not significantly different from those with the diagnosis schizophrenia (OR: 3.4; 95% CI: 0.9-12.8).

TABLE 2 : **RISK OF SUDDEN CARDIAC DEATH AND THE USE OF ANTIPSYCHOTIC MEDICATION**

Use of antipsychotic medication	Cases (n=554)	Controls (n=4463)	OR* (95% CI)	OR** (95% CI)
Non-use	520	4352	1.0 (reference)	1.0 (reference)
Past use	15	74	1.4 (0.8-2.4)	1.1 (0.6-2.0)
Current use	19	37	3.7 (2.0-6.7)	3.3 (1.8-6.2)
Type of antipsychotic used [a] [b]				
Non-use	520	4352	1.0 (reference)	1.0 (reference)
Butyrophenones	12	13	6.1 (2.6-14.1)	7.3 (2.8-18.8)
Thioxanthenes	1	3	3.4 (0.5-32.6)	2.9 (0.3-32.9)
Other antipsychotics	2	7	2.6 (0.5-13.1)	1.9 (0.3-11. 8)
Lithium	3	9	2.4 (0.6-9.3)	1.5 (0.3-8.3)
Phenothiazines	3	12	1.7 (0.4-7.7)	0.8 (0.2-3.8)
Daily dose				
Non-use	520	4352	1.0 (reference)	1.0 (reference)
≤ 0.5 DDD	14	33	3.0 (1.6-5.8)	2.8 (1.4-5.6)
> 0.5 DDD***	5	4	8.8 (2.2-34.4)	9.8 (2.1-44.6)
Duration of use				
Non use	520	4352	1.0 (reference)	1.0 (reference)
≤ 90 days	10	15	4.4 (1.9-10.3)	5.0 (2.1-12.1)
> 90 days	9	22	3.2 (1.4-7.1)	2.5 (1.1-6.0)

* Odds ratios matched for age, gender, practice and calendartime

** Odds ratio matched for age, gender, practice and calendartime, adjusted for diabetes mellitus, arrhythmias; use of diuretics, ACE-inhibitors, anxiolytics/hypnotics; hypertension, smoking, alcohol abuse and cerebro/cardiovascular ischemia.

*** trendtest p<0.0001

[a] Antipsychotics included: Butyrophenones: haloperidol, pipamperone, bromberidol, benperidol. Phenothiazines: chloorpromazine, levopromazine, trifluprομazine, perphenazine, prochlorperazine, trifluorazine, perazine,thioridazine, periciazine. Other: pimozide, clozapine, olanzapine, risperidone. Thioxanthenes: flupentixol, zuclopenthixol

[b] Since some patients used > 1 antipsychotic, numbers do not add up

For witnessed cases of death, the association with current antipsychotic use was higher (OR 4.7; 95% CI: 2.0-10.8) than for unwitnessed cases (OR: 2.4; 95% CI: 0.9-6.3). Stratified analyses showed that the risk of sudden cardiac death in users of antipsychotics tended to be higher in male users (OR 4.9; 95% CI: 1.7-13.0) than in female users (OR 2.9; 95% CI: 1.3-6.4) and higher in patients younger than or equal to 65 (OR 5.5; 95% CI: 1.00-31.1) than in patients older than 65 years of age (OR 3.1; 95% CI: 1.6-6.1). None of these interactions, however, were statistically significant.

DISCUSSION

The results of our study indicate that current use of antipsychotics in a community dwelling population is associated with an increased risk of sudden cardiac death, even at a low dose and in persons who use antipsychotics for other indications than schizophrenia. After adjustment for known confounding factors, current use of antipsychotics was associated with a more than tripled risk of sudden cardiac death. The risk was highest among the users of butyrophenone antipsychotics but not significantly different from the other antipsychotics, possibly due to low numbers. Unlike some other studies, we did not find an association with thioridazine but this drug was hardly used in our study population.[9 10] The risk of sudden cardiac death was slightly but not significantly lower after prolonged use of antipsychotics, which might be the result of depletion of susceptibles.

A consistent finding in all studies on the association between antipsychotic use and sudden cardiac death is that there seems to be a positive dose response relationship.[6-10] A potential mechanism by which antipsychotic agents might induce sudden cardiac death relates to their capacity to prolong the QTc interval, which seems to be dose-related.[18] However, the exact role of QTc prolongation in torsade de pointes, ventricular arrhythmias and sudden cardiac death has not been resolved yet.[6 18-20] Antipsychotics seem to share the ability to antagonise the rapid component of the delayed rectifier potassium current, which leads to a variable lengthening of the action-potential. QT prolongation is only a surrogate marker of cardiotoxicity and there is no consensus on the degree of QT prolongation that becomes clinically relevant. In our study, also low doses of antipsychotics were associated with a significantly increased risk of sudden cardiac death. In the Tennessee Medicaid cohort study, the risk of sudden cardiac death was greater in women and in those ≥ 65 years.[8] In contrast, we found that the risk of sudden cardiac death tended to be higher in males and in those younger than 65 years of age. The fact that in our study elderly women predominantly used a low dose (≤ 0.5 DDD), while younger males mostly used a high dose might explain this finding.

Our findings are consistent with earlier studies in which a higher rate of sudden cardiac death was found in patients taking antipsychotic drugs.[8-10] In two retrospective cohort studies among schizophrenic patients the use of anti-psychotics was associated with a significantly increased risk of sudden cardiac death. Reilly et al found that thioridazine use was associated with a 5 fold increased risk of sudden cardiac death in psychiatric in-patients. Most of these studies, however, had limitations. First, patient populations in these studies included only cases with schizophrenia, either hospitalised [9] or in an outpatient setting.[8 10] Therefore, it was impossible to determine whether findings were due to the disease (confounding by indication) or to the antipsychotic drugs taken. Second, two studies used data from Medicaid programs. These data pertain to a skewed population of people from lower socio-economic classes with a high cardiovascular risk profile, and these Medicaid

databases have little or no information on important potential confounders. Third, for exposure assessment these studies used a fixed length of 30 days for a prescription since the exact dosing regimen was unknown. This may have caused exposure misclassification because under real life circumstances dose variation will lead to different prescription lengths, and consequently to varying exposure windows.[21] Finally the outcome can often not be assessed validly in such databases since death and the reason for death are poorly registered and have to be proxied by assuming that not returning for health care consumptions means that the patient died.[10]

In our population, we were able to take advantage of the fact that in the Dutch health care system all medical information (including specialist and hospital care) is collected at practices that cover the general population instead of selected socio-economic groups. As a consequence, there was extensive information available on drug use, potential confounders and the circumstances surrounding death. Moreover, data allowed for subanalysis of different indications which confirmed that sudden cardiac death is associated with antipsychotic use rather than with schizophrenia itself.

Nevertheless, also our study has some limitations. First, we cannot exclude that some misclassification of outcome occurred. We may have missed some deaths although this will be minimal, since death is consistently registered by general practitioners. In contrast to other studies [8 10], we could reduce misclassification by the possibility to differentiate between witnessed and unwitnessed cases. The percentage of unwitnessed deaths in our population was 39.2%, which is in line with earlier findings.[20 22] The risk of witnessed sudden cardiac death alone was more than quadrupled in current antipsychotic users, while the risk in the unwitnessed cases was lower. This is consistent with the fact that misclassification will occur more often in unwitnessed cases. In the latter group, some deaths might have been of non-cardiac origin and this could explain the lower risk estimates. Second, not all acute deaths may have been of cardiac origin. We had pathological autopsy information only for 7 cases, in these instances the cause of death was cardiac. Third, misclassification of exposure may have occurred since we used outpatient prescription data and we had no information as to whether the prescription was actually filled and taken. It is likely, however, that such exposure misclassification will be random and will be evenly distributed among cases and controls. Therefore, the reported estimate is probably a conservative one. Fourth, the number of exposed cases in our study unfortunately prohibited us from comparing individual antipsychotic agents.

In conclusion, the results of our study indicate that current use of antipsychotics in a general population is associated with an increased risk of sudden cardiac death, even at a low dose and in persons who use antipsychotics for other indications than schizophrenia. The risk of sudden cardiac death seems to be highest among recent starters but remained elevated during long-term use.

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❤ '-so long as I get somewhere'
Alice added as an explanation. ❤

(Uit: Alice's adventures in wonderland
van Lewis Carroll)

CHAPTER 6

NON-CARDIAC QTc PROLONGING DRUGS AND THE RISK OF SUDDEN CARDIAC DEATH

ABSTRACT

Background: To assess the association between the use of non-cardiac QTc prolonging drugs and the risk of sudden cardiac death.

Methods and Results: A population-based case-control study was performed in the Integrated Primary Care Information (IPCI) project, a longitudinal observational database with complete medical records from over 500,000 persons. All deaths between January 1, 1995 and September 1, 2003 were reviewed. Sudden cardiac death was classified based on time between onset of cardiovascular symptoms and death. To each case, up to 10 random controls were matched for age, gender, date of sudden death and general practice. The exposure of interest was the use of non-cardiac QTc prolonging drugs. Exposure at the index date was categorized into 3 mutually exclusive groups of current use, past use, and non-use. The study population comprised 775 cases of sudden cardiac death and 6297 matched controls. Current use of any non-cardiac QTc prolonging drug was associated with a significantly increased risk of sudden cardiac death (adjusted OR: 2.7, 95% CI: 1.6-4.7). The risk of death was highest in women, and in recent starters.

Conclusion: The use of non-cardiac QTc prolonging drugs in a general population is associated with an increased risk of sudden cardiac death.

INTRODUCTION

In developed countries, sudden cardiac death is one of the major causes of cardiovascular mortality.[1] According to the most recent definition, sudden cardiac death is a natural death due to cardiac causes, heralded by abrupt loss of consciousness within one hour after the onset of acute symptoms or an unwitnessed, unexpected death of someone seen in a stable medical condition less than 24 hours previously with no evidence of a non-cardiac cause. [1-3] Probably, the large majority of cases of sudden cardiac death is due to ventricular fibrillation.[2 4] The major unanswered question in sudden cardiac death, however, is which precipitating event causes arrhythmia in an otherwise stable patient. Probably

it is a complex interplay between myocardial injury, chronic and acute coronary events, autonomic tone, electrolyte state, drugs and genetic factors that determines the occurrence of a life threatening arrhythmia.[5 6]

In the past decade, one of the most frequent causes of drug restriction or withdrawal has been prolongation of the QTc interval associated with fatal cardiac arrhythmias. Lengthening of QTc interval represents the prolongation of the action potential and is used as a surrogate marker for the prediction of this serious adverse drug effect.[7] The website of the International Registry for Drug-induced Arrhythmias maintained by the Georgetown University (http://www.qtdrugs.org/medical-pros/drug-lists/drug-lists.htm) provides an up-to-date list of drugs that prolong the QTc Interval and/or Induce Torsade de Pointes or Ventricular Arrhythmia.[8] The researchers have classified drugs into 4 categories varying from drugs that are generally considered to confer a risk of Torsade de Pointes (list 1) to drugs that, when used in usual dosages, are unlikely to increase the risk (list 4). This potentially fatal adverse reaction is not only associated with cardiovascular drugs, but also with non-cardiovascular drugs. The risk of arrhythmias and sudden cardiac death during the use of non-cardiac QTc prolonging drugs has attracted considerable clinical and regulatory attention.[7 9]

Therefore, our objective was to assess the risk of sudden cardiac death and the use of non-cardiac QTc prolonging drugs in a case-control study in a well-defined general population with complete coverage of all relevant health care information.

METHODS

Setting

All data were retrieved from the Integrated Primary Care Information (IPCI) project, a longitudinal observational database, containing data from computer-based medical records of a group of 150 general practitioners (GPs) in the Netherlands. In the Dutch health care system, the GP has a pivotal role by acting as a gatekeeper for all medical care. Nearly every citizen is enrolled in the practice of a GP independent of health status.[10] Details of the database have been described elsewhere.[10 11] Briefly, the database contains the complete medical records on approximately 500,000 citizens. The electronic records contain coded and anonymous data on demographics, symptoms (in free text), diagnoses (using the International Classification for Primary Care[12] and free text) from GPs and specialists, referrals, laboratory findings, hospitalizations, and drug prescriptions, including their indications and dosage regimen. To maximize completeness of the data, general practitioners participating in the IPCI project are not allowed to maintain a system of paper-based records besides the electronic medical records. The project complies with European Union guidelines on the use of medical data for medical research and has been proven valid for pharmaco-epidemiological research in several validation studies that

evaluated the quality of the available information.[11] The Scientific and Ethical Advisory Board of the IPCI project approved this study.

Source population

The source population comprised all subjects of 18 years and older, who were registered with a general practitioner participating in the IPCI project for at least 1 year. Subjects with a diagnosis of cancer were excluded from the source population, since in these patients the cause of death is often difficult to assess and usually not unexpected. The study period started on January 1, 1995 and ended on September 1, 2003. All subjects were followed until death, transferal out of practice, date of last data collection or end of the study period, whichever came first.

Case and control definition

The computerized medical and demographic data were screened for deaths that occurred during the study period. The medical records of identified cases of death were reviewed manually to assess whether death could be classified as sudden cardiac death. Validation was performed independently by two physicians who were blinded to exposure (SMJMS, GSB) and in case of discrepancy, a third expert (BHChS) arbitrated. Case assessment was based on the most recent definition of sudden cardiac death: a natural death due to cardiac causes, heralded by abrupt loss of consciousness within one hour after the onset of acute symptoms or an unwitnessed, unexpected death of someone seen in a stable medical condition less than 24 hours previously with no evidence of a non-cardiac cause.[1-3] Cases were classified as (probable) sudden cardiac death if the medical record indicated that death occurred within one hour after the onset of cardiovascular symptoms and if the following wording was found in the free text: "sudden cardiac death", "acute cardiac death", "mors subita", "sudden death", "died suddenly", "died unexpectedly", or if this was an unwitnessed, unexpected death of someone seen in "good health" or in a stable medical condition less than 24 hours previously and without evidence of a non-cardiac cause (e.g. pneumonia, convulsion, choking or stroke). Suicides were excluded. To each case of sudden cardiac death, up to ten controls were randomly drawn from the source population matched on age (year of birth), gender, and practice. If less than 10 controls were available, all of them were included. The index date was defined as the date on which sudden cardiac death occurred in the cases. This date was also the index date for matched controls.

Exposure definition

The exposure of interest was the use of non-cardiac QTc prolonging drugs, as specified in the most recent version of list 1 (Drugs that are generally accepted by authorities to have a risk of causing Torsade de Pointes) from the International Registry for Drug-induced

Arrhythmias maintained by the Georgetown University (http://www.qtdrugs.org/medical-pros/drug-lists/drug-lists.htm)[8] and comprise the following non-cardiac QTc prolonging drugs: chloroquine, chlorpromazine, cisapride, clarithromycin, domperidone, droperidol, erythromycin, halofrantine, haloperidol, levomethadyl, mesoridazine, pentamidine, pimozide, sparfloxacin, and thioridazine. As not all drugs are licensed, marketed or prescribed in the Netherlands, some of these drugs were not included in our analyses. Our analyses included: gastro-intestinal QTc prolonging medication: cisapride, domperidone; antibiotic QTc prolonging medication: erythromycin, clarithromycin, and antipsychotic QTc prolonging medication: chlorpromazine, haloperidol, pimozide and, thioridazine. In order to classify use at the index date, we calculated the duration of each prescription, as the total number of units issued per prescription divided by the prescribed daily number of units. Exposure at the index date was categorized into three mutually exclusive groups of current, past and non-use. To account for the differences in prescription patterns of non-cardiac QTc prolonging drugs, different risk windows were specified. For non-cardiac QTc prolonging drugs normally prescribed for shorter periods of time (gastrointestinal medications and antibiotics), use was defined as current if the index date fell within a period of use or within a maximum of 7 days after the end of the last prescription (to account for carry-over effects). For drugs usually prescribed for longer periods of time (antipsychotics), use was defined as current if the index date fell within a period of use or within a maximum of 30 days after the end of the last prescription. Past use was defined as discontinuation of a non-cardiac QTc prolonging drug more than 7 days (gastrointestinal or antibiotic medication) or 30 days before the index date (antipsychotic medication). If patients had no prescription for any type of non-cardiac QTc prolonging drug prior to the index date they were considered non-exposed. Among current users we evaluated the effect of duration (≤ 90 days and > 90 days continuous use), type of non-cardiac QTc prolonging drug and the current daily dose used in defined daily dose equivalents (DDD), as defined by the World Health Organization.[13] One DDD-equivalent represents the recommended daily dose for an adult for the main indication. To evaluate dose response effects the current daily dose of a non-cardiac QTc prolonging drug was categorized into less than 1 DDD equivalent, and 1 DDD equivalent or more.

Co-variates and risk factors

Known risk factors for sudden cardiac death and other co-variates were gathered from the medical records through computerized searches and manual validation. The co-variates that were evaluated included cerebro-vascular and cardiovascular ischemia (history of myocardial infarction, stroke, and angina pectoris), heart failure, hypertension, diabetes mellitus, arrhythmia, hypercholesterolemia, smoking and alcohol abuse. Cerebro-vascular ischemia, cardiovascular ischemia and heart failure were assessed, based on the diagnoses

provided by the general practitioner and specialists in the medical records. Hypertension was identified through the diagnoses in the medical records, the use of antihypertensive medication and/or the blood pressure measurements, meeting the guidelines of the World Health Organization (a blood pressure exceeding 140 mm Hg systolic and/or 90 mm Hg diastolic).[14] Diabetes mellitus, arrhythmias and hypercholesterolemia were identified through diagnoses in the medical records from GPs and specialists and/or the use of anti-diabetic, anti-arrhythmic or lipid lowering medication. Information on smoking and alcohol abuse was obtained from the free text in the medical records. As concomitant medication we considered amongst others diuretics, ACE inhibitors and other cardiovascular medication. Current use of concomitant medication was defined as use at the index date. We evaluated the effect of social economic status (SES), by including a variable on health care insurance, which is a proxy for income (all below an income of about 25.000 dollars a year have sick fund insurance, and those above have a private insurance).

Statistical analysis

The relative risk for sudden cardiac death during the use of non-cardiac QTc prolonging drugs was estimated by calculation of the odds ratios (95% confidence interval) using conditional logistic regression analyses. We evaluated risk factors and confounders one by one, by including one factor with the exposure variable. Subsequently, we performed a bivariate evaluation for potential multicollinearity of confounders. Thereafter, co-variates that were univariately associated with sudden cardiac death (at a $P<0.1$ level) were included in the regression analyses. After doing this for each factor separately we retained a list of all factors that changed the point estimate of the association between non-cardiac QTc prolonging drugs and sudden cardiac death by more than 5%, which were included in the final model.[15] We investigated potential effect modification by age and gender and performed sub-analyses to evaluate potential misclassification of sudden cardiac death by splitting the outcome between witnessed and unwitnessed death. To evaluate a possible dose-effect relation, a trend test was performed. We calculated the population attributable risk (PAR) percentage.[16]

RESULTS

In the source population, 806 cases of sudden cardiac death were identified, representing an incidence rate of sudden cardiac death of almost 1 per 1000 person-years. As we adhered strictly to the matching criteria to ensure internal validity, the 31 cases (4%) for whom no controls could be found, were excluded from further analyses. Hence, the study population comprised 775 cases of sudden cardiac death and 6297 matched controls (approximate case: control ratio 1:8). The median age of the study population was 72 years and approximately

61% were male. Despite matching for age (year of birth), the median age of cases was higher than the median age of all controls (74 years and 72 years respectively) since more controls were available for younger cases than for elderly cases (TABLE 1). There were 437 witnessed (56.4%) and 338 unwitnessed (43.6%) cases of sudden cardiac death. All known potential risk factors were associated with an increased risk for sudden cardiac death, notably ischemic cerebro-vascular and cardiovascular disease, hypertension, arrhythmia, diabetes mellitus, heart failure, hypercholesterolemia, smoking and alcohol abuse. As expected, use of cardiovascular medication was associated with sudden cardiac death as well (TABLE 1). There was no association between socio economic status and sudden cardiac death.

Current use of non-cardiac QTc prolonging drugs was associated with an almost threefold increased risk of sudden cardiac death (TABLE 2). Past use of non-cardiac QTc prolonging drugs was not associated with an increased risk of sudden cardiac death. The risk was higher among recent starters (≤ 90 days) of non-cardiac QTc prolonging drugs (TABLE 2). The risk was significantly increased in users of gastro intestinal medication and antipsychotics. The risk of sudden cardiac death was not significantly increased in antibiotic users, probably due to the limited number of exposed cases. Antibiotics were only used for less than 90 days and only in a dosage of 1 DDD equivalent or more. Therefore, we could not assess duration and dose response relationships (TABLE 2). The risk of sudden cardiac death was increased to a larger extent in users of a higher daily dose of gastro-intestinal or of antipsychotic medication. The risk was highest in subjects using antipsychotics, predominantly haloperidol. In users of gastrointestinal medication the risk of sudden cardiac death was significantly increased in users of domperidone in contrast to cisapride users, although a threefold higher risk of sudden cardiac death in cisapride users could not be excluded (TABLE 2).

For witnessed cases of death, the association with current use of non-cardiac QTc prolonging drugs was higher (OR 2.9; 95% CI: 1.5-5.9) than for unwitnessed cases (OR: 2.3; 95% CI: 1.0-5.4), but this difference was not statistically significant. Stratified analyses showed that the risk of sudden cardiac death in users of non-cardiac QTc prolonging medications tended to be higher in women (OR 3.1; 95% CI: 1.5-6.4) than in men (OR 2.3; 95% CI: 1.0-5.1) and higher in patients older than 65 years (OR 2.7; 95% CI: 1.5-4.9) than in patients 65 years or younger (OR2.3; 95% CI: 0.6-8.1), but none of these differences were statistically significant. The incidence of sudden cardiac death in our population was almost 1 per 1000 person years.[17] Based on the findings in this study the population attributable risk percentage of non-cardiac QTc prolonging medication could be calculated as 2%.[16]

TABLE 1 : **DEMOGRAPHICS, DISTRIBUTION OF CO-VARIATES AND USE OF CONCOMITANT MEDICATION IN CASES AND CONTROLS**

Characteristic	Cases (n=775)	Controls (n=6297)	Odds ratio* (95% CI)
Gender			
Male	465 (60%)	3842 (61%)	
Female	310 (40%)	2455 (39%)	
Age (mean, SD)	71 YR, 13	69 YR, 13	
≤ 55 yr	95 (12.3%)	1032 (16.4%)	
56-65 yr	108 (13.9%)	1127 (17.9%)	
66-75 yr	224 (28.9%)	2014 (32.0%)	
> 75 yr	348 (44.9%)	2124(33.7%)	
Sudden cardiac death			
Witnessed	437 (56.4%)		
Unwitnessed	338 (43.6%)		
Co-morbidities			
Ischaemic Cerebro-/Cardiovascular Disease	246 (32%)	1022 (16%)	2.3 (1.9-2.7)
Hypertension	444 (57%)	3134 (50%)	1.3 (1.1-1.5)
Arrhythmia	151(19%)	670 (11%)	1.9 (1.6-2.4)
Diabetes mellitus	230 (30%)	1058 (17%)	2.0 (1.7-2.4)
Smoking	98 (12.6%)	495 (8%)	2.2 (1.7-2.9)
Alcohol abuse	87 (11%)	536 (8%)	1.7 (1.3-2.3)
Heart failure	219 (28%)	468 (7%)	4.8 (3.9-5.8)
Hypercholesterolemia	47 (6.1%)	266 (4.2%)	1.7 (1.2-2.4)
Concomitant cardiovascular drugs			
ß-blocking agents	113 (14.6%)	727 (11.5%)	1.3 (1.0-1.6)
Diuretics	190 (24.5%)	677 (10.8%)	2.5 (2.0-3.1)
Calcium channel-blockers	81 (10.5%)	446 (7.1%)	1.5 (1.1-1.9)
ACE-inhibitors	146 (18.8%)	590 (9.4%)	2.2 (1.8-2.8)
ATII-blocking agents	27 (3.5%)	108 (1.7%)	2.1 (1.4-3.3)
Lipid lowering agents	45 (5.8%)	348 (5.5%)	1.2 (0.9-1.7)
Cardiac glycosides	74 (9.5%)	168 (2.7%)	3.3 (2.4-4.5)
Anti-arrhythmics	11 (1.4%)	47 (0.7%)	1.8 (0.9-3.6)

Abbreviations: ACE= angiotensin converting enzyme; Ca=Calcium; ATII= angiotensin II receptor antagonist; CI= confidence interval, SD= standard deviation

* All odds ratios are calculated taking matching for age, gender, practice and calendar time into consideration

TABLE 2 : **RISK OF SUDDEN CARDIAC DEATH AND THE USE OF NON-CARDIAC QTc PROLONGING MEDICATION**

Use of non-cardiac QTc prolonging medication	Cases (n=775)	Controls (n=6297)	OR* (95% CI)	OR** (95% CI)
Overall				
Non use	653	5544	1.0 (reference)	1.0(reference)
Past use	98	696	1.2 (0.9-1.5)	0.9 (0.7-1.2)
Current use	24	57	3.4 (2.0-5.6)	2.7 (1.6-4.7)
Current use of different QTc prolonging medications				
Gastrointestinal drugs[1]	13	43	2.7 (1.4-5.0)	2.1 (1.1-4.2)
Cisapride	4	29	1.2 (0.4-3.5)	1.2 (0.4-3.3)
Domperidone	9	15	5.4 (2.2-12.7)	3.8 (1.5-9.7)
Antipsychotic drugs	7	9	5.1 (1.8-14.4)	5.0 (1.6-15.3)
Chlorpromazine	1		-	-
Haloperidol	6	8	4.7 (1.5-14.4)	5.6 (1.6-18.7)
Pimozide		1	-	-
Antibiotic drugs	4	5	5.4 (1.4-22.1)	3.7 (0.9-15.7)
Erythromycin	1		-	-
Clarithromycin	3	5	3.7 (0.8-17.0)	3.2 (0.7-15.0)
Duration of use in current users				
Non use	653	5544	1.0 (reference)	1.0(reference)
≤ 90 days	17	28	4.5 (2.4-8.6)	3.6 (1.9-7.2)
> 90 days	7	29	2.1 (0.9-7.2)	1.7 (.07-4.2)
DDD				
Gastrointestinal drugs	13	43		
<1DDD	3	12	2.2 (0.6-8.0)	2.0 (0.5-7.4)
≥1DDD	10	31	2.7 (1.3-5.8)	2.2 (1.0-4.8)
Antipsychotic drugs	7	9		
<1DDD	5	8	5.0 (1.5-17.0)	4.8 (1.4-16.1)
≥1DDD[2]	2	1	6.1 (0.3-124)	6.4 (0.3-129.1)
Antibiotic drugs	4	5		
<1DDD	-	-	-	-
≥1DDD	4	5	5.6 (1.4-22.5)	3.8 (0.9-16.0)

Abbreviations: OR=Odds Ratio; CI=Confidence Interval; DDD=Defined Daily Dose equivalent; Ref = reference

* Odds ratios matched for age, gender, practice and calendar time

** Odds ratio matched for age, gender, practice and calendar time, adjusted for diabetes mellitus, arrhythmias, heart failure; hypertension, smoking, alcohol abuse and cerebrovascular and cardiovascular ischaemia, current use of diuretics and cardiac glycosides.

[1] Since one patient used domperidone and cisapride concomitantly, numbers do not add up

[2] Test for trend P<0.005

DISCUSSION

The results of our study indicate that current use of non-cardiac QTc prolonging drugs in a general population is associated with a significantly increased risk of sudden cardiac death. After adjustment for known confounding factors, current use of non-cardiac QTc prolonging drugs was associated with an almost threefold increased risk of sudden cardiac death. The risk was higher in women than in men. This is in line with earlier findings that women seem to be more susceptible to drug induced cardiac arrhythmias than men.[7 18]

Drug induced Torsade de Pointes are a significant cause of morbidity and mortality and non-cardiac drugs have been implicated in an increasing number of cases.[7 19-21] Prolongation of the QTc interval, ventricular arrhythmias and Torsade de Pointes have been associated with cisapride use in anecdotal reports. These case reports raised concern, but could not be confirmed in cohort- and case control analyses in the UK and Canada and in some studies no substantial increase in the QTc interval could be identified.[7] Our results are in line with these findings.[22] This is not surprising, since life-threatening arrhythmias during cisapride use in adults are believed to occur predominantly when there is concurrent use of inhibitors of cytochrome P450 CYP3A4, such as itraconazole, ketoconazole or macrolides. This was not the case in our population. Domperidone seemed an attractive, safer alternative to cisapride. Our findings of a significantly increased risk of sudden cardiac death in domperidone users, however, suggest that domperidone should not be viewed as a low risk alternative to cisapride and are in line with earlier results.[23] Unfortunately the number of exposed cases in our study prohibited us from analyzing the macrolides individually. At a FDA advisory committee meeting the relative reporting rate of Torsade de Pointes was increased in clarithromycin users and the risk was highest shortly after initiating therapy, as was also the case in our data.[24] Case reports have since long suggested that erythromycin is associated with an increased risk of Torsades the Pointes and recent research has shown a twofold increase in the rate of sudden cardiac death in current erythromycin users.[25] Since the early sixties, sudden cardiac death has been reported with antipsychotic use in case reports and epidemiological studies.[26-28] Also in our study the use of antipsychotics, particularly haloperidol is associated with a significant increase in the risk of sudden cardiac death.

Many drugs can prolong the QTc interval.[19 21 29 30] QT prolongation however, is a surrogate marker with an imperfect predictive value for fatal cardiac arrhythmias and sudden cardiac death and it is difficult to predict whether a drug will cause Torsade de Pointes.[21] For the vast majority of drugs known to induce QTc prolongation, it has been demonstrated that the slowing of the action potential is a consequence of the blockage of the rapid component of the delayed rectifier potassium channel (I_{kr}) through blockade of the human ether a go-go related gene (HERG).[21 31-33] The extent to which blocking of this channel results in Torsade de Pointes or sudden cardiac death, however, is highly variable among subjects.[7 20 22 34-36]

A unifying concept "reduced repolarization reserve" has been used to explain this variable risk.[36] Current evidence also suggests that 5 to 10% of persons in whom cardiac arrhythmias occur carry a (silent) mutation in one of the genes responsible for the congenital long QT syndrome.[37 38]

In our population, we were able to take advantage of the fact that in the Dutch health care system all medical information (including specialist and hospital care) is collected at practices that cover the general population instead of selected socio-economic groups. As a consequence, there was extensive information available on drug use, potential confounders and all the circumstances surrounding death. Nevertheless, our study has some potential limitations. First, we cannot exclude that some misclassification of outcome occurred. We may have missed some deaths although this will be minimal, since death is consistently registered by general practitioners. Second, not all acute deaths may have been of cardiac origin. We determined sudden cardiac death, however, on the basis of the full medical records and all circumstances surrounding the death were available. Recently, an evaluation comparing different methods to determine the incidence of sudden cardiac death, suggested that this method provides a very reliable way of determining sudden cardiac death cases.[3] In addition, we could reduce misclassification by differentiating between witnessed and unwitnessed cases of sudden cardiac death. The percentage of unwitnessed deaths in our population was 43.6% which is in line with earlier findings.[3 39] The risk of witnessed sudden cardiac death associated with the use of non-cardiac QTc prolonging drugs was higher than the risk of unwitnessed sudden cardiac death. This may be consistent with the fact that misclassification will occur more often in unwitnessed cases. In addition, slight misclassification of exposure may have occurred since we used outpatient prescription data and we had no information as to whether the prescription was actually filled and taken. It is likely however, that such exposure misclassification will be random and will be evenly distributed among cases and controls. Although we adjusted for all known confounders residual confounding may exist, but is unlikely to explain the strong association we have observed.

In conclusion, our findings suggest that the current use of non-cardiac QTc prolonging drugs in a general population is associated with an increased risk of sudden cardiac death. Although prolongation of the QTc interval by non-cardiac drugs is not an unusual finding, potentially fatal arrhythmias and sudden cardiac death are relatively uncommon. Our results suggest that 320 cases of sudden cardiac death can be attributed to the use of non-cardiac QTc prolonging medication in the Netherlands on a yearly basis.[16 17] This is important, because regulatory authorities have to evaluate the clinical significance of QTc prolongation observed in relatively small clinical trials without cases of sudden cardiac death.

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❤ 'Oh, you're sure to do that' said the Cat. ❤

(Uit: Alice's adventures in wonderland van Lewis Carroll)

CHAPTER 7

INHALED ß-AGONISTS AND THE RISK OF SUDDEN CARDIAC DEATH

ABSTRACT

Background: Several studies have evaluated the association between use of inhaled ß-2 adrenergic receptor agonists and sudden cardiac death, but with contradictory results. Therefore we set out to assess the association between use of inhaled ß-agonists and the risk of sudden cardiac death in a general population and in patients with Chronic Obstructive Pulmonary Disease.

Methods and results: A population-based case-control study in the Integrated Primary Care Information (IPCI) project, a longitudinal medical record database and a nested case cross-over study to further analyze current use of ß-agonists and the risk of sudden cardiac death in patients with COPD were performed. All deaths between January 1, 1995 and September 1, 2003 were reviewed. Sudden cardiac death was classified based on time between onset of cardiovascular symptoms and death. To each case, up to 10 controls were matched. The exposure of primary interest was use of inhaled ß-agonists. The relative risk of sudden cardiac death was estimated by calculation of odds ratios (95% confidence interval) using conditional logistic regression analyses. The study population comprised 775 cases and 6297 matched controls. In the case-control study in the general population as well as in the case-crossover analysis restricted to COPD patients, current use of inhaled ß-agonists was associated with a significantly increased risk of sudden cardiac death (OR: 1.5; 95% CI: 1.1-2.1 and OR: 4.8; 95% CI: 1.5-15.1 respectively).

Conclusion: Inhaled ß-agonists may increase the risk of sudden cardiac death although a causative role of COPD itself cannot be excluded

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a major public health problem and one of the leading causes of morbidity and mortality.[1 2] Bronchodilation therapy is central to the symptomatic management of COPD.[2]

Due to their effects on the sympathetic nerve system, bronchodilators are known to have a variety of cardiac adverse effects. Evidence that bronchodilator therapy may increase cardiovascular morbidity and mortality has been accumulating over the years, especially

for inhaled ß-agonists.[4-10] A recent meta-analysis of randomized placebo-controlled trials showed an increased risk for adverse cardiovascular events in patients with obstructive airway disease using ß-agonists.[11]

Inhaled ß-2 adrenergic receptor agonists (ß-agonists) increase heart rate, prolong the duration of the action potential, and may cause hypokalemia, compared to placebo. These factors may all increase the risk of cardiovascular adverse events, including sudden cardiac death.[11] Several case-control studies have evaluated the association between inhaled ß-agonists and cardiac arrest or sudden cardiac death, but not all found a significant increase in risk in patients with COPD.[4 5 9 10 12]

Therefore, we assessed the association between use of bronchodilators, specifically ß-agonists, and the risk of sudden cardiac death in a case-control analysis in a well-defined general population with complete coverage of all relevant health care information. In addition, we used a nested case-crossover design to further analyze the association between use of ß-agonists and the risk of sudden cardiac death in patients with COPD.

METHODS

Setting

All data were retrieved from the Integrated Primary Care Information (IPCI) project, a general practice research database with data from computer-based patient records from a group of 150 general practitioners (GPs) in the Netherlands. In the Dutch health care system, the GP has a pivotal role by acting as a gatekeeper for all medical care.[13] Details of the database have been described elsewhere.[14 15] Briefly, the database contains the complete medical records on approximately 500,000 patients. The electronic records contain coded and anonymous data on patient demographics, symptoms (in free text), diagnoses (using the International Classification for Primary Care[16] and free text) from GPs and specialists, referrals, laboratory findings, hospitalizations, and drug prescriptions, including their indications and dosage regimen. To maximize completeness of the data, general practitioners participating in the IPCI project are not allowed to maintain a system of paper-based records besides the electronic medical records. The system complies with European Union guidelines on the use of medical data for medical research and has been proven valid for pharmaco-epidemiological research in several validation studies that evaluated the quality of the available information.[14 15] The Scientific and Ethical Advisory Board of the IPCI project approved this study.

Source population

The source population comprised all subjects of 18 years and older, who were registered with a general practitioner participating in the IPCI project for at least 1 year. Subjects with

a diagnosis of cancer were excluded from the source population, since in these patients the cause of death is often difficult to assess. The study period started January 1, 1995 and ended September 1, 2003. All subjects were followed until death, transferral out of practice, date of last data collection or end of study period, whichever came first.

Case and control definition

The computerized medical and demographic data were screened for all deaths that occurred during the study period. The full medical records of identified cases of death were reviewed manually to assess whether death could be classified as sudden cardiac death. Validation was performed independently by two physicians blinded to exposure (SMJMS, GSB) and in case of discrepancy, a third expert (BHChS) arbitrated. Assessment was based on the most recent definition of sudden cardiac death[16 17]: sudden unexpected death within 1 hour of symptom onset (witnessed) or within 24 hours of having been observed alive and symptom free (unwitnessed). All patients with an identifiable non-cardiac cause and all patients with cancer were excluded. Cases of sudden cardiac arrest associated with trauma, violent death, drowning, overdose and suicide were also excluded. For each case of sudden cardiac death, up to ten controls were randomly drawn from the source population matched on age (year of birth), gender, and practice. The index date was defined as the date on which sudden cardiac death occurred in cases. This date was also the index date for matched controls.

To limit confounding by indication we conducted a nested case-crossover analysis restricted to patients with COPD. In this analysis, each case of sudden cardiac death served four times as its own control period with index dates 3, 6, 9 and 12 months preceding death. In the case-crossover design the occurrence of an acute event (in this study sudden cardiac death) following a transient exposure is compared with exposure in the same person prior to disease onset. This design eliminates many, although not all, of the confounding factors. [19-23]

Exposure definition

To classify exposure to each type of bronchodilator (inhaled or oral ß-agonists, anticholinergics and xanthines) at the index date, we calculated the duration of use for each prescription as the total number of units per prescription divided by the prescribed daily number of these units. Exposure at the index date was subsequently categorized into three mutually exclusive groups of current, past and non-use. Use of bronchodilator medication was defined as current if the prescription duration covered the index date or if it stopped less than 30 days before (to account for carry-over effects). Past use was defined as discontinuation of the bronchodilator more than 30 days before the index date. If patients had no prescription during the study period prior to the index date they were considered non-exposed.

Among current users of inhaled ß-agonists, we evaluated the effect of duration of use in two groups (≤ 90 days: short term users; > 90 days: long term users), the type (long acting or short acting inhaled ß-agonists), and the effect of concomitant use of inhaled corticosteroids.
In the nested case-crossover design, exposure was determined in the three months-periods preceding the index date. Exposure status at the index date was also categorized into three mutually exclusive groups of current, past and non-use. Use of bronchodilator medication was defined as current if the prescription duration covered the index date or if it stopped less than 30 days before (to account for carry-over effects). Past use was defined as discontinuation of the bronchodilator between 90 and 30 days before the index date. If patients had no prescription for the specific class of bronchodilator medication in the three months prior to the index date they were considered non-exposed.

Co-variates and risk factors

Risk factors for sudden cardiac death and co-variates were gathered from the medical records through computerized searches and manual validation. Co-variates evaluated included: cerebro- and cardiovascular ischemia (history of myocardial infarction, stroke, and angina pectoris), heart failure, hypertension, diabetes mellitus, arrhythmia, hypercholesterolemia, smoking and alcohol abuse. COPD, ischemia and heart failure were assessed, based on the diagnoses provided by the general practitioner and specialists in the medical records.
Hypertension was identified through the diagnoses in the medical records, the use of antihypertensive medication and/or the assessment of blood pressure measurements, according to the guidelines of the World Health Organization (blood pressure exceeding 140 mm Hg systolic and/or 90 mm Hg diastolic).[24] Diabetes mellitus, arrhythmias and hypercholesterolemia were identified through diagnoses in the medical records from GPs and specialists and/or the use of antidiabetic, anti-arrhythmic or lipid lowering medication. Information on smoking and alcohol abuse was obtained from the medical records.
As concomitant medication we considered antibiotics, inhaled and oral corticosteroids, mucolytics, hypnotics, anxiolytics, antipsychotics, non-cardiac QTc prolonging drugs and cardiovascular medication. Current use of these drugs was defined as use at the index date, except for inhaled steroids and mucolytics for which we applied the same exposure classification as for bronchodilators.
In the case-crossover study, which by design adjusts for stable intra-individual confounders we assessed time-varying co-morbidity, concomitant drug use and severity of COPD in each 3 month period before the index date. Severity of COPD was assessed based on the use of antibiotics for respiratory tract infections, the use of oral steroids for COPD, the occurrence of exacerbations, the use of oxygen, and hospitalizations for respiratory tract disease. Patients with use of oxygen, oral steroid for COPD, occurrence of exacerbation or hospitalization were defined as more severely diseased patients. [25]

The severity was assessed at each index date and could vary over time.

Statistical analysis

The relative risk of sudden cardiac death associated with each class of bronchodilator medication was estimated by calculation of the odds ratios (95% confidence interval) using conditional logistic regression analyses. Co-variates univariately associated with sudden cardiac death (at a $p < 0.1$ level) were initially included in the regression analyses. Factors that changed the point estimate of the association between current use of inhaled ß-agonists and sudden cardiac death by more than 10%[25] were kept in the final model (heart failure and smoking). We investigated potential effect modification by age and gender with interaction terms, and performed sub-analyses in patients using beta-blockers and patients with a cardiovascular history. In the case-crossover study, the relative risk of sudden cardiac death associated with the use of inhaled ß-agonists was estimated by calculation of the odds ratios (95% confidence interval) using conditional logistic regression analyses. Also in this analysis, co-variates that changed the point estimate of the association between current use of inhaled ß-agonists and sudden cardiac death by more than 10% were kept in the final model (use of anticholinergics, season of the sudden cardiac death, use of inhaled steroids, and use of antibiotic medication for respiratory tract infections). Each case served as its own control period in 4 periods of 3 months preceding the occurrence of sudden cardiac death. As in this analysis each case could differ up to one year in age with the control period we did an additional analysis to explore the effect of residual confounding by age. A sub-analysis was conducted in which the control periods were restricted to those with an index date 3 months prior to the date of death. In this way each case had one control period with an age difference of 3 months.

RESULTS

In the source population 806 cases of sudden cardiac death were identified, yielding an incidence rate of sudden cardiac death of almost 1 per 1000 persons per year.[27] No controls could be matched to 31 cases, and these cases were excluded from further analyses. Hence, the study population comprised 775 cases of sudden cardiac death and 6297 matched controls (approximate case:control ratio 1:8). The median age of the study population was 72 years and approximately 60% was male. There were 437 witnessed (56.4%) and 338 unwitnessed (43.6%) cases of sudden cardiac death. All known potential risk factors for sudden cardiac death were associated with an increased risk, notably ischemic cerebro-vascular and cardiovascular disease, hypertension, arrhythmia, diabetes mellitus, heart failure, hypercholesterolemia, COPD, smoking and alcohol abuse. Current use of antipsychotics, non-cardiac QTc prolonging medication, as well as cardiovascular medication was associated with sudden cardiac death (TABLE 1). [28 29]

TABLE 1 : **DEMOGRAPHICS, DISTRIBUTION OF CO-VARIATES AND USE OF CONCOMITANT MEDICATION IN CASES AND CONTROLS**

Characteristic	Cases (n=775)	Controls (n=6297)	Odds ratio* (95% CI)
Gender			
Male	465 (60%)	3842 (61%)	
Female	310 (40%)	2455 (39%)	
Age (median)	74 YR	71 YR	
≤55 yr	95 (12.3%)	1032 (16.4%)	
55-65 yr	108 (13.9%)	1127 (17.9%)	
66-75 yr	224 (28.9%)	2014 (32.0%)	
>75 yr	348 (44.9%)	2124(33.7%)	
Sudden cardiac death			
Witnessed	437 (56.4%)		
Unwitnessed	338 (43.6%)		
Co-morbidities and other cofactors			
Ischaemic Cerebro-/Cardiovascular Disease	246 (32%)	1022 (16%)	2.3 (1.9-2.7)
Hypertension	444 (57%)	3134 (50%)	1.3 (1.1-1.5)
Arrhythmia	151 (19%)	670 (11%)	1.9 (1.6-2.4)
Diabetes mellitus	230 (30%)	1058 (17%)	2.0 (1.7-2.4)
Heart failure	219 (28%)	468 (7%)	4.8 (3.9-5.8)
Hypercholesterolemia	47 (6.1%)	266 (4.2%)	1.7 (1.2-2.4)
COPD	65 (8.4%)	387 (6.1%)	1.3 (1.0-1.8)
Alcohol abuse	87 (11%)	536 (8%)	1.7 (1.3-2.3)
Smoking	98(12.6%)	495 (8%)	2.2 (1.7-2.9)
Concomitant drugs			
ß-blocking agents	113 (14.6%)	727 (11.5%)	1.3 (1.0-1.6)
Diuretics	190 (24.5%)	677 (10.8%)	2.5 (2.0-3.1)
Ca-blocking agents	81 (10.5%)	446 (7.1%)	1.5 (1.1-1.9)
ACE-inhibitors	146 (18.8%)	590 (9.4%)	2.2 (1.8-2.8)
ATII-blocking agents	27 (3.5%)	108 (1.7%)	2.1 (1.4-3.3)
Lipid lowering agents	45 (5.8%)	348 (5.5%)	1.2 (0.9-1.7)
Cardiac glycosides	74 (9.5%)	168 (2.7%)	3.3 (2.4-4.5)
Anti-arrhythmics	11 (1.4%)	47 (0.7%)	1.8 (0.9-3.6)
Antibiotics	12 (1.5%)	60 (1%)	1.5 (0.8-7.8)
Antipsychotics	17 (2.2%)	40 (0.6%)	3.4 (1.9-6.1)
Non-cardiac QTc prolonging drugs	16 (2.1%)	47 (0.7%)	2.8 (1.5-5.0)
Inhaled Corticosteroids	49 (6.3%)	195 (3.1%)	2.1 (1.5-2.9)
Oral corticosteroids	15 (1.9%)	70 (1.1%)	1.6 (0.9-2.9)

Abbreviations: CI=confidence interval; COPD= Chronic Obstructive Pulmonary Disease; Ca=Calcium; ACE= angiotensin converting enzyme; ATII= angiotensin II receptor antagonist

* All odds ratios are matched for age, gender, practice and calendar time

Current use of anticholinergics, and xanthines was also associated with an increased risk of acute sudden cardiac death, the strongest association was observed with xanthines (TABLE 2). Current use of inhaled ß-agonists was associated with a 50% increased risk of acute sudden cardiac death (TABLE 2).

TABLE 2 : **RISK OF SUDDEN CARDIAC DEATH AND THE USE OF BRONCHODILATOR MEDICATION**

Use of bronchodilator medication[1]	Cases (n=775)	Controls (n=6297)	OR* (95% CI)	OR** (95% CI)
Oral or inhaled ß agonists				
Current oral ß agonists	2	3	4.6 (0.7-30.5)	2.6 (0.3-23.5)
Past oral ß agonists	1	17	0.5 (0.07-4.0)	0.3 (0.03-2.2)
Current inhaled ß agonists	63	234	2.3 (1.7-3.1)	1.5 (1.1-2.1)
Long-acting[1]	23	92	2.1 (1.3-3.4)	1.6 (1.0-2.6)
Short-acting[1]	46	160	2.3 (1.6-3.3)	1.5 (1.0-2.2)
≤ 90 days	35	107	2.6 (1.7-3.9)	1.7 (1.1-2.6)
> 90 days	28	127	2.0 (1.3-3.1)	1.4 (0.9-2.2)
With inhaled corticosteroids	38	149	0.8 (0.6-1.0)	1.0 (0.8-1.4)
without inhaled corticosteroids	25	85	1.7 (1.0-2.7)	1.6 (1.0-2.6)
Past inhaled ß agonists	55	381	1.3 (1.0-1.8)	1.0 (0.7-1.3
Long-acting	23	105	1.9 (1.2-3.0)	1.2 (0.7-2.0)
Short-acting	57	376	1.4 (1.0-1.9)	1.0 (0.8-1.4)
Other bronchodilators				
Anticholinergics				
Current	42	137	2.5 (1.7-3.6)	1.7 (1.1-2.5)
Past	45	224	1.6 (1.1-2.3)	1.1 (0.8-1.6)
Xanthines				
Current	9	17	4.6 (1.9-11.0)	3.3 (1.3-8.4)
Past	10	17	5.4 (2.4-12.1)	4.2 (1.8-9.9)

* All odds ratios are matched for age, gender, practice and calendar time

** All odds ratio matched for age, gender, practice and calendar time, adjusted for heart failure and smoking. Reference category: non-use

[1] Since some patients used >1 bronchodilator, numbers do not add up. ß-agonists include: salbutamol, terbutaline, fenoterol, salmeterol, formoterol. Long acting inhaled ß-agonists salmeterol, formoterol. Short acting inhaled ß-agonists salbutamol, terbutaline, fenoterol. Inhaled corticosteroids include: beclomethasone, budesonide, flunisolide, betamethasone, fluticasone. Anticholinergics: ipratropium. Xanthines: theophylline

TABLE 3 : **ASSOCIATION BETWEEN USE OF INHALED ß-AGONISTS AND SUDDEN CARDIAC DEATHS IN COPD PATIENTS (CASE-CROSSOVER ANALYSIS)**

Use of inhaled ß- agonists[1]		Cases (n=65)	Controls (n=260)	OR* (95% CI)	OR** (95% CI)
Overall					
Inhaled ß agonists					
	Non-use	38	186	1.0(reference)	1.0 (reference)
	Past use	5	21	2.4 (0.7-8.4)	1.6 (0.4-6.0)
	Current use	22	53	5.6 (2.0-15.6)	4.8 (1.5-15.1)
	Long-acting	8	28	1.6 (0.6-6.7)	1.4 (0.3-6.8)
	Short-acting	14	31	3.3 (1.3-8.6)	2.6 (0.9-7.7)
with ICS		9	24	8.1 (1.4-47.9)	7.3 (1.2-46.0)[§]
without ICS		13	29	5.0 (1.6-15.1)	3.6 (1.1-12.3)[§]
	Anticholinergics	17	48	1.9 (0.9-4.3)	1.8 (0.8-4.1)
	Xanthines	4	9	5.8 (0.5-65.6)	7.8 (0.6-00.6)
	Oral ß agonists	1	0		
Restriction of controls 3 months before					
Inhaled ß-agonists					
	Non-use	38	44	1.0 (reference)	1.0 (reference)
	Past use	5	7	1.5 (0.3-7.0)	1.5 (0.2-9.8)
	Current use	22	14	6.0 (1.1-2.7)	8.8 (1.1-71.4)

* Odds ratios matched for age, gender, practice and calendar time
** Odds ratio matched for age, gender, practice and calendar time, adjusted for the use of anticholinergics (for the inhaled ß-agonists only), inhaled corticosteroids, severity of disease, season and the use of antibiotics for airway infections
§ Odds ratio matched for age, gender, practice and calendar time, adjusted for the use of anticholinergics, severity of disease, season and the use of antibiotics for airway infections
[1] Since some patients used > 1 bronchodilator, numbers do not add up

Inhaled ß-agonists include: salbutamol, terbutaline, fenoterol, salmeterol, formoterol.
Long acting inhaled ß-agonists salmeterol, formoterol
Short acting inhaled ß-agonists salbutamol, terbutaline, fenoterol
Inhaled corticosteroids include: beclomethasone, budesonide, flunisolide, betamethasone, fluticasone
Anticholinergics: ipratropium
Xanthines: theophylline
Mucolytics : acetylcysteine

The risk was higher in short-term users of ß-agonists (recently started): OR: 1.7 (95% CI: 1.1-2.6) than in longer-term users: OR: 1.4 (95% CI: 0.9-2.2). The risk was also slightly higher during current use of short-acting inhaled ß-agonists than in during use of long acting inhaled ß-agonists. However, the risk of sudden cardiac death was elevated only in patients using inhaled ß-agonists but without inhaled corticosteroids. In order to further evaluate our findings we analyzed the risk of sudden cardiac death in patients without the

diagnosis of COPD. The risk in those without the diagnosis of COPD was also significantly increased: OR: 1.7 (95% CI: 1.1-2.7).
Stratified analyses showed differences in ß-agonists associated risks however, none of the tests for effect-modification were significant. The relative risk associated with current use of inhaled ß-agonists was 1.7 (95% CI: 1.2-2.4) in subjects older than 65 and 1.0 (95% CI: 0.5-2.2) in those 65 years and younger. It was also slightly higher in women (OR: 2.0; 95% CI: 1.2-3.5) than in men (OR: 1.3; 95% CI: 0.9-2.0). For witnessed cases, the risk of sudden cardiac death was somewhat higher in patients using inhaled ß-agonists (OR: 1.6; 95% CI: 1.0-2.4), than for unwitnessed cases (OR: 1.5; 95% CI: 0.9-2.5). The antagonistic effect of ß-blockers may neutralise the effects of inhaled ß-agonists. Indeed in patients using ß-blockers the risk associated with inhaled ß-agonists was lower: OR: 0.4 (95% CI: 0.04-4.0) than in patients not using ß blockers OR: 1.6 (95% CI: 0.9-2.6). In patients with a cardiovascular disease history, current use of inhaled ß-agonists was associated with a significant increase in the risk of sudden cardiac death: OR: 1.8 (95% CI: 1.1-3.1).
In the case-crossover analysis that was restricted to acute sudden death cases with COPD, current use of inhaled ß-agonists was associated with a significantly increased risk of sudden cardiac death: OR: 4.8 (95% CI: 1.5-15.1) (TABLE 3). The risk of sudden cardiac death was higher in patients using inhaled ß-agonists in combination with inhaled corticosteroids than in patients using inhaled ß-agonists without inhaled corticosteroids but this difference was not statistically significant. The risk of sudden cardiac death associated with use of inhaled ß-agonists remained after restriction of the controls to those with an index date 3 months before the date of death. In the case-crossover analysis, there was also an increased risk with anticholinergics and xanthines but this increase was not significant.

DISCUSSION

The results of our study indicate that current use of long-acting and short-acting ß-agonists is associated with an increased risk of sudden cardiac death, both in the general population as well as in COPD patients. However, also xanthines and anticholinergics were associated with an increased risk of sudden cardiac death, but the association with anticholinergics was only observed in the general population.
Nevertheless also in the Lung Health Study an unexpected, small and non significant increase in death from cardiovascular causes was reported in COPD patients treated regularly with ipatropium.[30] Xanthine derivatives have been associated with cardiac arrhythmias previously. Due to their toxicity their use is restricted to the most severely affected patients. The increased risk of sudden cardiac death we found is therefore not unexpected.[8 31 32]
Inhaled ß-agonists have been associated with an increased risk of cardiovascular events previously.[3 4 8 9 33] However, the currently available studies have yielded conflicting results.

In a case-control study, the use of inhaled ß-agonists was not associated with a significantly increased risk of primary cardiac arrest in COPD patients, but it was in asthma patients.[9] An earlier case-control study suggested that the use of theophylline and ß-agonists was associated with an increased risk of cardiac arrest in patients with heart disease.[8] In a nested case-control study, evaluating the entire population, the risk of myocardial infarction (fatal and non fatal) was increased in patients using ß-agonists, whereas another case-control study, restricted to patients with COPD, showed no increase in risk.[4 11] Attribution of mortality to COPD or to therapy is difficult, since COPD is a risk factor for sudden cardiac death. COPD patients are known to have an increased risk of cardiac arrhythmia. Several factors, such as hypoxia and hypokaliemia may contribute to the development of arrhythmias and sudden cardiac death.[34]

As our study examined the use of ß-agonists in the entire population, a large part of the population did not have obstructive lung disease. Since COPD is a known risk factor for sudden cardiac death, we adjusted in the analyses for this confounder. In addition we assessed the risk of sudden cardiac death in a nested case cross-over design, restricted to COPD patients. In this analysis the current use of inhaled ß-agonists was associated with a more than fourfold increase in risk of sudden cardiac death. Due to the design we could not completely adjust for age since the patients in the control period were always younger (up to one year) than the cases. However, the association remained if we restricted the analysis to the control period in the three months before the index date. In contrast to the findings in the total population, the use of inhaled corticosteroids in the case-crossover analysis in COPD patients was associated with a higher risk of sudden cardiac death. We have tried to adjust for severity, but as the FEV1 (Forced Expiratory Volume in one second) is not available in many patients we classified severity of COPD based on the need to seek medical help, which is helpful to classify the most severely ill patients.[25] Nevertheless there still might be residual confounding by severity.

In our population, we were able to take advantage of the fact that in the Dutch health care system all medical information (including specialist and hospital care) is collected at practices that cover the general population instead of selected socio-economic groups. As a consequence, there was extensive information available on drug use, potential confounders and the circumstances surrounding death. Nevertheless, also our study has limitations. First, we cannot exclude that some misclassification of outcome occurred. We may have missed some deaths although this will be minimal, since general practitioners have pivotal role in the Dutch health care system and they register death consistently. Second, not all acute deaths may have been of cardiac origin, especially in patients with COPD. Primary ventilatory death is, however, usually not unexpected and mostly not sudden.[35] Moreover, the complete medical records of all patients are available and we had information concerning all circumstances surrounding death, including the full medical history. Recently, an evaluation comparing

different methods to determine the incidence of sudden cardiac death, suggested this method provides probably the most reliable way of determining sudden cardiac death.[18] We could in addition reduce misclassification by differentiating between witnessed and unwitnessed cases. The percentage of unwitnessed deaths in our population was 43.6% which is in line with earlier findings.[36] The risk associated with use of inhaled ß-agonists was significantly increased in witnessed sudden cardiac death, while it was lower for unwitnessed deaths. This is consistent with the fact that misclassification will occur more often in unwitnessed cases. In the latter group, some deaths might have been primarily of ventilatory origin instead of cardiac origin. Third, in COPD the effects of drugs studied are susceptible to confounding by disease severity (confounding by indication). Severity of disease and presence of co-morbidities may play an important role in therapy choice. We tried to reduce confounding by indication by conducting a case cross-over study, where each case acts as its own control, thereby minimizing the confounding by severity and co-morbidities.[19 21] However, residual confounding by intra-individual time-varying factors cannot be excluded. In addition, misclassification of exposure may have occurred since we used outpatient prescription data and had no information as to whether the prescription was filled and was actually taken. However, as COPD is a disease that requires significant assistance with bronchodilation, we can expect that most were taken.[11] In addition, it is likely that such exposure misclassification will be random and will be evenly distributed among cases and controls. As in earlier research, also in our study protopathic bias might have occurred, meaning the prescription of a ß-agonist has been driven by the symptoms that may herald serious cardiovascular problems.[3 4] To address this bias we performed additional analysis after the exclusion of all patients who received the first prescription for a short acting ß-agonist within 3 days before the index date. This did, however, not change the findings substantially, (OR adjusted for inhaled ß-agonists: 1.5; 95% CI:1.1-2.1) in the case control study nor in the case cross over study(OR adjusted: 4.0; 95% CI: 1.3-13.1). Protopathic bias alone can therefore not the explain our findings.

Inhaled ß-agonists have been the mainstay of therapy for asthma and COPD since the 1960s, with significant improvement in peak flow and respiratory symptoms.[1 10 37] Evidence that their use is associated with an increase in morbidity and mortality has been accumulating over past decades. Many elderly patients with underlying cardiovascular diseases have concomitant COPD and many patients with COPD have underlying cardiovascular disease. At the end stage of the disease it is often difficult to discriminate between these two diseases and confounding can easily occur. In our study we have tried to address this issue by several different methods. The results of our study suggest that inhaled ß-agonists may increase the risk of sudden cardiac death although a causative role of COPD itself cannot be excluded.

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❤ 'If you only walk long enough.' ❤

(Uit: Alice's adventures in wonderland van Lewis Carroll)

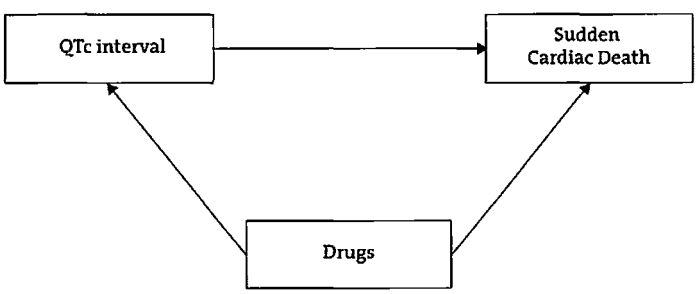
CHAPTER 8

DISCUSSION

Sudden cardiac death is a major health problem. Many causes of sudden cardiac death are known, yet seldom is one single cause sufficient to provoke a life-threatening arrhythmia. Sudden cardiac death is a multifactorial process and probably represents a probabilistic event in which each of the risk factors comprises only a small fraction of the process. In this chapter, the main findings of this research and the main methodological limitations of pharmaco-epidemiological studies are discussed to facilitate a proper interpretation of the results described in this thesis.

MAIN FINDINGS

In the first part of this thesis, we estimated the incidence of sudden cardiac death, evaluated the QTc interval as a non invasive predictor of sudden cardiac death and the effect of drugs on the length of the QTc interval. In the second part, we assessed the association between the use of drugs and sudden cardiac death.



The incidence of sudden cardiac death

The incidence rate of sudden cardiac death varies between 0.5-2 per 1000 persons annually, depending on populations studied and the definitions and the methods used to study the incidence.[1-3] Death certificate-based retrospective surveillance that uses out of hospital death as a proxy for sudden cardiac death results in an overestimation of the incidence of sudden cardiac death. [1 4] We used the IPCI database to assess the incidence of sudden cardiac death in a well-defined general population according to the most recent definition of sudden cardiac death: sudden unexpected death within 1 hour of symptom onset (witnessed) or within 24 hours of having been observed alive and without symptoms (unwitnessed). All patients with an identifiable non-cardiac cause were excluded and all patients with cancer

were excluded. Cases of sudden death associated with trauma, violent death, drowning, overdose and suicide were also excluded. This population-based database with data from general practice has many advantages. Thanks to the pivotal role of the general practitioner in the Dutch health care system, all relevant medical data are usually available at the general practice level. The presence of both disease data and prescription data facilitates studies on the association between drugs and disease. Moreover, the complete medical records of all patients are available. Therefore, we had information concerning all circumstances surrounding death, including the full medical history. Recently, an evaluation comparing different methods to determine the incidence of sudden cardiac death, suggested that this method provides a very reliable way of determining sudden cardiac death.[4]

QTc interval

In search for non-invasive risk factors to predict mortality the heart rate corrected QT interval, the QTc interval, has been studied extensively.[5-17] Prolongation of the QTc interval has been associated with ventricular arrhythmias (e.g. Torsade de Pointes) that may trigger ventricular fibrillation and sudden cardiac death. We evaluated whether prolongation of the QTc interval was an independent risk factor for sudden cardiac death in a population of older adults in the Rotterdam study. In the Rotterdam study, a prospective population-based cohort study, data are available on a large group of older adults and the follow-up period is relatively long. This enabled us to take advantage of the fact that the majority of participants had two ECGs, in contrast to many other studies evaluating the QTc interval. In addition, in almost all cases extensive information of the facts surrounding death was available for review, including a questionnaire concerning the fatal event and in many cases the time between start of symptoms and death was documented.

The QT interval and its correction formulas gained clinical importance already in 1957, with the description of the Long QT syndrome and its association with sudden cardiac death.[18 19] Although the degree of QTc prolongation in itself does not seem to be directly predictive of pro-arrhythmia, it has been shown that it is associated with early after depolarizations, that can lead to Torsade de Pointes and sudden cardiac death. QTc prolongation in itself may not be enough to cause fatal arrhythmias and may require the presence of other risk factors. Nevertheless, the QTc interval has become a surrogate marker for the risk of Torsade de Pointes and sudden cardiac death.[20] The QTc interval represents a surface ECG measurement of the action potential duration. Many factors affect the QTc interval, including heart rate, autonomic system activity, cardiac diseases and congenital long QT syndromes.[18 19] In 1920, Bazett examined the mathematical relationship of QT to RR interval and found that the QT interval divided by the square root of the RR interval was a constant: QTc, the corrected QT interval.[21] Although the shortcomings of this correction have long been recognized, it has gained a widespread use. Many alternative methods have

been proposed since Bazett's original article in 1920, but all had their own shortcomings and limitations, and none proved to be superior to the Bazett's formula for the QTc interval.[19] Another important reason for us to use Bazett's formula was that the major part of the existing literature employs the same correction and Bazett's formula is used in the definition of the long QT Syndrome. We used the European regulatory guidelines to categorise QTc prolongation into 3 sex specific categories for the first time in a population-based study.[22]

In the past decade, one of the most frequent causes of withdrawal or restriction of marketed drugs has been the prolongation of the QTc interval associated with Torsade de Pointes and fatal cardiac arrhythmias.[20 23] In the area of drug development and drug testing the QTc interval prolongation has become an accepted surrogate marker for the risk of cardiac arrhythmia.[19] The recent European guidelines, intended to predict whether a new drug carries an increased risk of serious cardiac arrhythmias, also place much emphasis on the association of the pharmaceutical with QTc prolongation.[22] Although an increasing number of drugs, especially non-cardiac drugs has been recognized to delay cardiac repolarization and to induce Torsade de Pointes[24], no population based ECG data are available on the association of these drugs and the length of the QTc interval in older adults. In our study, we did not find an association between the prolongation of the QTc interval and the use of all drugs, known to be implicated in the occurrence of fatal cardiac arrhythmias. [25 26]

Although QTc prolongation has become an established surrogate marker for pro-arrhythmia, there is no clear understanding of what is "good" and what is "bad" QTc prolongation.[19] Virtually all QTc prolonging drugs act by blocking the rapid component of the delayed rectifier potassium channel (I_{kr}) through blockade of the human ether a go-go related gene (HERG). Clinical and experimental studies of drugs that inhibit HERG currents showed that HERG channel inhibition does not necessarily lead to acquired long QTc syndrome and severe cardiac arrhythmias with the risk of sudden cardiac death.[27 28] With the increased knowledge of the molecular action of drugs on HERG channels, it becomes apparent that multiple molecular actions are involved. Moreover the broad diversity in response to pharmacological treatment among individuals could be explained by a combination of factors rather than by inhibition of HERG channels alone, combining factors such as underlying pathology, physiology and genetic susceptibility.

The lists of drugs that prolong the QTc interval are long, and comprise several different classes. There is no reliable threshold below which prolongation of the QTc interval is considered to be free of risk.[19] Although the use of QTc prolonging medication can predispose to Torsade de Pointes, there is still a paucity of information that can help clinicians to make optimal informed decisions on how to best minimise the risk for this serious complication, as is also illustrated by our findings. Although all drugs evaluated have been implicated in the occurrence of serious cardiac arrhythmias, we could nevertheless not identify significant QTc prolongation in all drugs.[25 26]

Drugs as a potential risk factor for sudden cardiac death

Some drugs are associated with QTc prolongation but devoid of torsadogenic effects, whereas others seem not to be associated with QTc prolongation, but are still considered to be associated with cardiac arrhythmias.[27] Despite its clinical and regulatory importance the potentially pro-arrhythmogenic effect of drugs on the QTc interval is not well understood.[29] QTc interval prolongation per se does not always seem to be pro-arrhythmogenic. Amiodarone, for example significantly prolongs the QTc interval, but rarely causes Torsade de Pointes.[20] Terfenadine, a potent I_{kr} blocker on the other hand has been withdrawn from the market because of its potential to induce Torsade de Pointes. The prolongation of the QTc interval caused by terfenadine however, is only minimal.[20]

Thus, it seems to be difficult to predict whether a drug will cause Torsade de Pointes based on its effect on the length of the QTc interval or on its potency to block the I_{kr} channel. The pro-arrhythmogenic threshold is not a sharp one and Torsade de Pointes can occur after only a minimal prolongation of the QTc interval. The clinical manifestations of Torsade de Pointes vary from transient palpitations, dizziness and syncope, but can also degenerate into ventricular fibrillation and sudden cardiac death, in approximately 20% of the cases.[20 29]

Therefore, we have assessed in the second part of this thesis the association between the risk of sudden cardiac death and the current use of certain drugs known to prolong the QTc interval.

Spontaneous reporting of adverse drug reactions has been the mainstay of pharmacovigilance for many years. The signal provided by spontaneous reporting systems and also by case reports may be the start of subsequent clinical and pharmaco-epidemiological research. At first thought, a prospective randomised controlled trial might seem the most ideal method for quantifying a potential adverse event. Although the importance of randomisation cannot be overestimated, there are many situations where a randomized clinical trial is not suitable. For example, a clinical trial can only detect the more frequent adverse drug effects. To detect a relative risk of 2 (with an α of 0.05 and a ß of 0.1) of a disease with a background incidence of 0.1%, a study would need to include at least 21,000 patients, making such studies extremely expensive and time consuming.[30] In these situations, observational methods of pharmacovigilance can be used instead. Carefully designed and conducted pharmaco-epidemiological studies, specifically observational (non-interventional, non-experimental) studies, are important tools in pharmacovigilance for assessing the risk of rare adverse events such as sudden cardiac death. In order to study the possible association between drugs and sudden cardiac death, we performed several case-control studies in the IPCI database. We evaluated the association between the use of antipsychotics and the risk of sudden cardiac death. In our study, the current use of antipsychotics was associated with an increased risk even at a low dose and also in persons who used antipsychotics for other indications than schizophrenia. Antipsychotics seem to share the ability to antagonise the

rapid component of the delayed rectifier potassium channel (I_{kr}) through blockade of the HERG gene. This in turn can lead to variable action potential prolongation and cardiac arrhythmias. Also the current use of non-cardiac QTc prolonging drugs, as specified on the website from the International Registry for Drug-induced Arrhythmias (http://www.qtdrugs.org/medical-pros/drug-lists/drug-lists.htm) was associated with an increased risk of sudden cardiac death. The extent to which blocking of the rapid component of the delayed rectifier potassium channel (I_{kr}) results in Torsade de Pointes or sudden cardiac death, is highly variable among subjects. A unifying concept "reduced repolarization reserve" has been used to explain this variable risk. Current evidence also suggests that 5 to 10% of persons in whom cardiac arrhythmias occur carry a (silent) mutation in one of the genes responsible for the congenital long QT syndrome.[20] The last study addressed the risk of sudden cardiac death associated with the use of inhaled ß-2 adrenergic receptor agonists. Here the blockade of the HERG channel does not seem to play a major role to explain the effects of the ß-agonists. Inhaled ß-2 adrenergic receptor agonists increase heart rate, prolong the duration of the action potential, and may cause hypokalemia. These factors may all increase the risk of cardiovascular adverse events, including sudden cardiac death. A complicating factor is that Chronic Obstructive Pulmonary Disease itself is a known risk factor for sudden cardiac death. The results of our study suggested that inhaled ß agonists may increase the risk of sudden cardiac death although a causative role of COPD itself cannot be excluded.

METHODOLOGICAL CONSIDERATIONS

Non-experimental, observational, pharmaco-epidemiological studies have an important role in assessing the risk of rare adverse reactions such as drug-induced cardiac arrhythmias. The validity of observational studies is frequently questioned because of potential bias and confounding, but careful design and analysis may deal with most of these problems. The two main observational approaches in pharmaco-epidemiology are cohort and case-control designs. [30] In the cohort design, the frequency of the adverse events is compared between patients with and without the exposure of interest. Our studies that evaluated the QTc interval were embedded in the Rotterdam study, a prospective population-based cohort study, which started with a baseline visit between 1990 and 1993. All inhabitants of a suburb in Rotterdam, Ommoord, aged 55 years and over (10,275) were invited to participate.

In this study a large population of older adults is included in a follow-up. The advantages are that the follow-up duration is relatively long and extensive information is available on all participants. In addition to follow-up surveys, the total cohort is continuously being monitored for major morbidity and mortality through linkage of general practitioner and

municipality records. Furthermore, all drug prescriptions dispensed to participants by automated pharmacies are routinely stored in the database since January 1, 1991.
All information is gathered before, and irrespective of, the outcome under study from the large majority of the study participants. This limits the chance of selection and information bias. Confounding by indication or contra indication may bias the study results. In non-experimental studies the allocation of treatment is by definition not random. Therefore, if we assume that prescribing is rational, the prognosis of patients receiving treatment will obviously differ from those not being treated. The untreated patients will generally not have an indication for the treatment under study. Therefore, the treated patients will probably have a higher rate of any disease that the drug is intended to treat (or cure). Consequently, a drug that is intended to treat a patient may seem to enhance the risk rather than to decrease it. If the treatment under study is contra-indicated in high-risk patients with underlying diseases, confounding by contra-indication may occur. It is possible that in our cross sectional study, QTc prolonging drugs were not prescribed to patients at high risk. As a significant number of users, also with known risk factors, were identified in our study population this seems, however, not likely.
Other major issues in pharmaco-epidemiology pertain to the definition of drug exposure. Accurate and complete information on drug exposure is essential to avoid information bias. The use of pharmacy records in the Rotterdam study bypasses the potential for recall bias, as these data are gathered continuously and independently of outcome. However, even with the use of pharmacy records, misclassification of exposure may occur, since patients might not have taken the medication as prescribed. This bias will often be non-differential and will then lead to an underestimation of the true effect. A cohort study is not a very efficient way to study the association between drugs and sudden cardiac death since this adverse drug reaction has a low frequency. Therefore if the outcome of interest is uncommon, a case-control design is mostly followed. In case-control studies, drug exposure is compared between patients with and without the outcome of interest. The case-control design is an efficient way to study rare outcomes since exposure is only measured in patients with the outcome and in a sample of the source population. An important limitation of case-control studies is their vulnerability to bias. Inclusion of cases and controls may depend on their exposure status (selection bias) and patients with the disease may recollect former drug exposure more accurately (information- or recall bias).
These arguments apply, however, to *de novo* initiated case-control studies and not to already existing databases, where data are gathered prospectively, without knowledge of later formulated research questions and before the adverse event has occurred. The Integrated Primary Care Information (IPCI) project is a large database, which contains the computer-based full medical patient records from a group of 150 general practitioners (GPs) in the Netherlands. We used the IPCI database to assess the incidence of sudden cardiac death

and to perform the case-control studies described in this thesis. Another advantage of data being collected prospectively during general practitioner visits and recorded in the database is the relatively short period of time in which studies can be performed. This is especially important in pharmacovigilance, as safety issues often require fast but valid reactions. A potential problem with database studies concerns the limited possibility for adjustment for other risk factors. Automated databases often tend to have little or no information on important potential confounders. In addition, they sometimes include data from a skewed population of people from lower socio-economic classes, such as in de Medicare databases in the U.S.A. Since the exact dosing regimen in many databases is unknown a fixed length of 30 days for a prescription is often used for exposure assessment, causing misclassification of exposure. These disadvantages do not apply to the IPCI database since it contains the complete medical records of all patients irrespective of economic status. Moreover, extensive information is available on drug use and potential confounders. The use of prescription data bypasses the potential for information bias from doctor or patient (recall bias), as these data are gathered before and irrespective of the outcome/adverse event under study. Prescription data form a reliable and precise source of information. Misclassification of exposure may, however, still have occurred in our studies since we used outpatient prescription data and had no information as to whether the prescription was actually filled and taken. It is likely, however, that such exposure misclassification will be random, evenly distributed among cases and controls and will therefore lead to an underestimation of the true effect.

Also case-control studies are susceptible to confounding by indication. Confounding by indication was an issue in the case-control study evaluating the association between antipsychotics and sudden cardiac death. Schizophrenia, one of the indications for antipsychotic drugs, is also a risk factor for sudden cardiac death and may therefore act as a confounder. However, we found that the risk for sudden cardiac death was similarly increased in patients using antipsychotics for schizophrenia as in patients taking these drugs for other indications. In the case-control study of non-cardiac QTc prolonging drugs, we restricted our evaluation to the non-cardiac drugs thereby minimizing confounding by indication that might have been occurred in cardiac QTc prolonging drugs that are used in the treatment of arrhythmias.

A special form of confounding by indication is confounding by severity, in which the severity of the disease that forms the indication for treatment rather than the disease itself constitutes an important factor in the choice of therapy. In Chronic Obstructive Pulmonary Disease (COPD) the severity of the disease and presence of co-morbidities may play an important role in therapy choice. The effects of drugs studied in this disease are therefore susceptible to confounding by severity. We tried to reduce this confounding by conducting a case-crossover study, nested in our case-control study. The case-crossover design is a special type of matched case-control study. [31-33] In this

design, each case acts as its own control, thereby minimizing confounding by severity and co-morbidities. The underlying assumption is that the cases themselves are the best representatives of the study base from which the case emerged. An advantage of this design is that the controls inherently fully adjust for stable intra-individual confounders and risk factors. However, residual confounding cannot be excluded in our last study, especially not by time-varying confounders.

FUTURE DIRECTIONS

Sudden cardiac death is by its nature unpredictable. Studying sudden cardiac death is complex as there are many different fields of research involved. In this thesis, the objective was to increase our knowledge of drugs as a potential cause of sudden cardiac death, the role of the QTc interval in sudden cardiac death and the effects of drugs on the QTc interval. Although some pieces of the puzzle have been identified, increased knowledge has at the same time further illuminated the fact that there are still many more questions and issues that need to be addressed

Research has shown that QTc interval prolongation as a predictor of this serious adverse event might be imperfect both for individual patients and for populations. The link between drugs, HERG blockade, the prolongation of QTc interval, Torsade de Pointes, and sudden cardiac death is unclear, and reliable identification of the pro-arrhythmic potential of drugs remains a challenge. None of the predictors currently known seems to be able to reliably predict the risk of Torsade de Pointes. Recent work showed that, in general, drugs with a small HERG/free plasma concentration margin (i.e. drugs, which bind to the potassium channels in concentrations close to therapeutic plasma concentration) had a high risk of serious cardiac arrhythmias while drugs with a high margin had a lower risk.[27] Other recent work corroborated these findings. De Bruin et al showed that drugs that bind to HERG channels in concentrations close to or lower than plasma concentrations have a high risk of adverse reports of serious ventricular arrhythmia and sudden cardiac death in the WHO-UMC databases, indicating a higher pro-arrhythmic risk.[34] This margin between HERG binding capacity and free plasma concentration might be a helpful tool in the prediction of the risk of Torsade de Pointes in future drug development.

This highlights the importance of also understanding the molecular mechanisms that underlie HERG channel blockade. Despite recent advances, the knowledge of the molecular action of drugs on HERG channels is still immature. The individual molecular mechanisms of a drug action on the HERG channel may play an important role since it determines the pro-arrhythmogenic potential of a drug. Although blockade of HERG channels requires channel opening for most compounds, inhibition of HERG channels by amiodarone and chlorpromazine involves inhibition of closed channels. It has also been hypothetized that

additional drug action on different ion channels and/or receptors may reduce the pro-arrhythmic potential of HERG blockers. In particular, additional inhibition of calcium currents and/or additional beta adrenoceptor blockade have been suggested to play a role in limiting the pro-arrhythmic effects of HERG channel blockers.[20 27 29]

Finally, the clinical presentation of adverse events in an individual patient is also determined by genetic background. In the future, screening of patients at high risk for sudden cardiac death may include genetic screening. Risk prediction based on familial and genetic characteristics are in their infancy, but offer promise of better prediction.[35] Recent work supports the possibility that silent mutations can contribute to increased susceptibility to sudden cardiac death.[36] Studies suggest that polymorphisms coding for ion channels genes are surprisingly common. Spontaneous and inherited variations in the genes coding for rare inherited arrhythmia syndromes are being found on an almost daily basis. There is now good evidence for the existence of at least [10] such variations with overall populations frequencies of at least 5% and the discovery has only just begun.[20] These estimates do not include variations in possible "modifying" genes. These seem to include alterations in the genes for cholinergic and adrenergic pathways and other regulatory molecules that control regional expression of different electrogenic proteins in various cardiac tissues.[37]

Heterogeneity in the individual response to drugs is a major problem in clinical practice and in drug development. When several patients are prescribed the same recommended dose of a certain drug, the drug can be efficacious in most, have little or no effect in other and/or result in adverse drug reactions, sometimes fatal, in a small group of patients.[38 39] Besides the importance of clinical factors that determine the variability in drug response, including age, gender, concomitant therapy and co-morbidities, it is clear that genetic factors have a large impact on efficacy and toxicity of drugs.

The quest for effective and safe drugs continues and pharmaco-epidemiological research will remain an important tool in the assessment of risk benefit profile and safety of drugs in the population at large. Pharmacogenetic studies assessing the variability in drug responses attributed to hereditary factors, such as genetic polymorphism will become more and more important. As a result of further research maybe individual genetic tailored therapy will become reality and prevent serious adverse events.

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❤ 'But I don't want to go among mad people,' Alice remarked.
'Oh, you can't help that,'
said the Cat: 'we're all mad here.
I'm mad. You're mad.'
'How do you know I'm mad?'
said Alice.
'You must be,' said the Cat, 'or you wouldn't have come here.' ❤

(Uit: Alice's adventures in wonderland
van Lewis Carroll)

CHAPTER 9

SUMMARY/SAMENVATTING

Sudden cardiac death is a major health problem. Many causes of sudden cardiac death are known, yet seldom is one single cause sufficient to provoke a life-threatening arrhythmia. Sudden cardiac death is a multifactorial process and probably represents a probabilistic event in which each of the risk factors comprises only a small fraction of the process.

In **Chapter 1**, a general introduction of sudden cardiac death is given. The term sudden cardiac death pertains to an unexpected death from cardiac causes within a short time period and has been described throughout history. Ventricular tachy-arrhythmia is the final fatal mechanism in approximately 85% of all cases of sudden cardiac death. Brady-arrhythmias and pulse-less electrical activity occur less frequently and generally in hearts with more advanced disease. Despite progress in clinical profiling and interventions, sudden cardiac death remains an important clinical problem.

Chapter 2 focuses on the magnitude of sudden cardiac death in the general population. The commonly used estimate of 300,000 sudden cardiac deaths in the United States has not been based on formal epidemiological studies, but has rather been derived from the estimation that there were 600,000 cardiovascular deaths annually, of which 50% were assumed to be sudden. We used the IPCI database to assess the incidence of sudden cardiac death in a well-defined general population according to the most recent definition of sudden cardiac death: sudden unexpected death within 1 hour of symptom onset (witnessed) or within 24 hours of having been observed alive and symptom free (unwitnessed). This study showed that the incidence of sudden cardiac death in the Dutch population is around 1/1000 per year, and that the incidence increases with age and varies by gender, calendar month and week days.

Chapter 3 evaluates the heart rate corrected QT interval, the QTc interval, as a non-invasive risk factor to predict sudden cardiac death. The QT interval on the surface electrocardiogram (ECG) represents the time from onset of ventricular depolarization to completion of repolarization. Prolongation of repolarization has been associated with ventricular arrhythmias (e.g. Torsade de Pointes) that may trigger ventricular fibrillation and even sudden cardiac death. This study was conducted as part of the Rotterdam Study, a prospective population-based cohort study, which comprises 3105 men and 4878 women aged 55 years and older. The QTc interval on the ECG was determined during the baseline visit (1990-1993) and the first follow-up examination (1993-1995). During an average follow-up period of 6.7 years, 125 subjects died from sudden cardiac death. European

regulatory guidelines were used to categorize QTc prolongation into 3 sex specific categories. In addition, we used different QTc thresholds varying from 440 ms to 470 ms, based on the literature, because there is still discussion as to the most relevant cut-off points. An abnormally prolonged QTc interval (> 450 ms in men, > 470 ms in women) was associated with a threefold increased risk of sudden cardiac death, after adjustment for age, sex, body mass index, hypertension, cholesterol/hdl ratio, diabetes mellitus, myocardial infarction and heart failure. In subjects with an age below the median of 68 years, the corresponding relative risk was almost 8. The results of our study show that abnormal QTc prolongation on the ECG should be viewed as an independent risk factor for sudden cardiac death. Two-third of the cases of sudden cardiac death is associated with an abnormal prolongation of the QTc interval.

In **Chapter 4,** we examined the association between drugs, listed as QTc prolonging and the duration of the QTc interval in a large prospective, community-based follow-up study. This study is embedded in the Rotterdam Study. In recent years, several lists have been published on drugs implicated in QTc prolongation and cardiac arrhythmias. In list 1 of the web site of the International Registry for Drug-induced Arrhythmias maintained by the Georgetown University, an up-to-date list is published. In this list, the QTc prolonging drugs are classified into 4 categories, varying from drugs that are generally accepted by authorities to have a risk of causing Torsade de Pointes (list 1) to drugs that, in some reports, have been weakly associated with Torsade de Pointes but that, when used in usual dosages, are unlikely to increase the risk (list 4). In addition, De Ponti et al have published a list of 31 non-anti-arrhythmic drugs with pro-arrhythmogenic effects, based on a structured literature search. Overall, 14,013 ECGs were available, 5768 in men and 8245 in women. In this population, 615 current users of QTc prolonging drugs were identified. Significantly more women used QTc prolonging medication than men. This was predominantly related to the more frequent use of antidepressants and domperidone in women. The results of our study showed an association between the current use of several, but not all, drugs listed on the two lists and prolongation of the QTc interval in a population of older adults. Virtually all QTc prolonging drugs act by blocking the rapid component of the delayed rectifier potassium channel (I_{kr}) encoded by the human ether a go-go related gene (HERG). Unfortunately, this finding is not specific since many drugs that do not seem to cause Torsade de Pointes, also block this current. Therefore, it is likely that other pharmacological actions are also involved. These actions might prevent Torsade de Pointes, either directly (by blunting early after depolarizations) or indirectly (by blunting the prolongation of the action potential). Much emphasis has been placed on the potential pro-arrhythmic effects of pharmaceuticals that are associated with QTc interval prolongation in recent guidelines. Paradoxically, however, increased knowledge has illuminated the fact that the current predictors of this serious adverse event might be imperfect both for individual patients and

for populations. Post-marketing surveillance seems to remain an important tool in assessing the torsadogenic effects in newly marketed drugs in the general population.

In **Chapter 5** the risk of sudden cardiac death in current users of antipsychotics was assessed. This study used data from the Integrated Primary Care Information (IPCI) project in the Netherlands. The IPCI project is a general practice research database, containing the complete medical records on approximately 500,000 patients. The electronic records contain coded and anonymous data on patient demographics, symptoms, diagnoses from GPs and specialists, referrals, laboratory findings, hospitalizations, and drug prescriptions, including their indications and dosage regimen. To maximize completeness of the data, general practitioners participating in the IPCI project are not allowed to maintain a system of paper-based records besides the electronic medical records. The study period started on January 1, 1995 and ended on September 1, 2001. All subjects were followed until death, transferal out of practice, date of last data collection or end of the study period, whichever came first. In the source population, 582 cases of sudden cardiac death were identified, representing an incidence rate of sudden cardiac death of almost 1 per 1000 person-years in the source population. No controls could be matched to 28 cases, and these cases were excluded from further analyses. Hence, the study population comprised 554 cases of sudden cardiac death and 4463 matched controls. The results of our study indicate that current use of antipsychotics in a community dwelling population is associated with an increased risk of sudden cardiac death, even at a low dose and in persons who use antipsychotics for other indications than schizophrenia. After adjustment for known confounding factors, current use of antipsychotics was associated with a more than tripled risk of sudden cardiac death. The risk was highest among the users of butyrophenone antipsychotics but not significantly different from the other antipsychotics, possibly due to low numbers. Unlike some other studies, we did not find an association with thioridazine but this drug was hardly used in our study population.

In **Chapter 6**, we evaluated the risk of sudden cardiac death in current users of non-cardiac QTc prolonging medication. In this study, we also used the IPCI database. The study period started on January 1, 1995 and ended on September 1, 2003. All subjects were followed until death, transferal out of practice, date of last data collection or end of the study period, whichever came first. The exposure of interest was the use of non-cardiac QTc prolonging drugs, as specified in the most recent version of list 1 (Drugs that are generally accepted by authorities to have a risk of causing Torsade de Pointes) from the International Registry for Drug-induced Arrhythmias maintained by the Georgetown University (http://www.qtdrugs.org/medical-pros/drug-lists/drug-lists.htm). In the source population, 806 cases of sudden cardiac death were identified, representing an incidence rate of sudden cardiac death of almost 1 per 1000 person-years. No controls could be matched to 31 cases, and these cases were excluded from further analyses. Hence, the study population comprised 775

cases of sudden cardiac death and 6297 matched controls. The results of our study indicate that current use of non-cardiac QTc prolonging drugs in a general population is associated with a significantly increased risk of sudden cardiac death. After adjustment for known confounding factors, current use of non-cardiac QTc prolonging drugs was associated with an almost threefold increased risk of sudden cardiac death. The risk was higher in women than in men. This is in line with earlier findings that women seem to be more susceptible to drug induced cardiac arrhythmias than men. Our results suggest that 320 cases of sudden cardiac death can be attributed to the use of non-cardiac QTc prolonging medication in the Netherlands on a yearly basis.

The association between use of bronchodilators, specifically ß-agonists, and the risk of sudden cardiac death in a case-control analysis in a well-defined general population, the IPCI database, is presented in **Chapter 7**. In addition, we used a nested case-crossover design to further analyze the association between use of ß-agonists and the risk of sudden cardiac death in patients with COPD. The study period started on January 1, 1995 and ended on September 1, 2003 and the study population comprised 775 cases of sudden cardiac death and 6297 matched controls. In the case-crossover study, which by design adjusts for stable intra-individual confounders, we assessed time-varying co-morbidity, concomitant drug use and severity of COPD in each 3 month period before the index date. Severity of COPD was assessed based on the use of antibiotics for respiratory tract infections, the use of oral steroids for COPD, the occurrence of exacerbations, the use of oxygen, and hospitalizations for respiratory tract disease. Patients with use of oxygen, oral steroid for COPD, occurrence of exacerbation or hospitalization were defined as more severely diseased patients. The results of our study indicate that current use of long-acting and short-acting ß-agonists is associated with an increased risk of sudden cardiac death, both in the general population as well as in COPD patients. However, also xanthines and anticholinergics were associated with an increased risk of sudden cardiac death, but the association with anticholinergics was only observed in the general population. Attribution of mortality to COPD or to therapy is difficult, since COPD is a risk factor for sudden cardiac death. COPD patients are known to have an increased risk of cardiac arrhythmia. Although the results of our study suggest that inhaled ß-agonists may increase the risk of sudden cardiac death a causative role of COPD itself cannot be excluded.

In the general discussion in **Chapter 8** the main findings of the studies presented in this thesis are discussed and the methodological issues are addressed. In addition suggestions for future research are considered.

Acute hartdood vormt een aanzienlijk gezondheidsprobleem. Er zijn vele oorzaken van acute hartdood bekend. Er is echter maar zelden slechts één duidelijke oorzaak aan te wijzen voor het ontstaan van een levensbedreigende ventriculaire ritmestoornis.

Acute hartdood is een complex probleem, waarbij elke afzonderlijke (risico) factor slechts een kleine rol speelt in het hele proces.

Hoofdstuk 1 bevat een algemene inleiding over acute hartdood. De term 'acute hartdood' wordt gebruikt voor een niet verwachte dood als gevolg van cardiale oorzaken binnen een korte tijd na het ontstaan van de eerste symptomen. De term acute hartdood wordt al vroeg in de geschiedenis gebruikt. Ventriculaire tachycardie is het uiteindelijke fatale mechanisme in ongeveer 85% van de gevallen van acute hartdood. Bradycardie en elektromechanische dissociatie komen veel minder frequent voor. Ondanks de vooruitgang in het opsporen van risicofactoren en de verbeterde mogelijkheden tot interventie blijft acute hartdood een belangrijk klinisch probleem.

Het vóórkomen, de incidentie, van acute hartdood in een algemene populatie is onderwerp van **hoofdstuk 2**. De veel gebruikte schatting van 300.000 acute hartdoden in de Verenigde Staten is niet gebaseerd op onderzoek, maar is afgeleid van de veronderstelling dat ongeveer 50% van het totale aantal cardiovasculaire doden, acute hartdood betreft. Wij hebben gebruik gemaakt van de IPCI gegevens om de incidentie van acute hartdood te bepalen in een goed gedefinieerde populatie. We hebben hierbij gebruik gemaakt van de meest recente definitie van acute hartdood. Acute hartdood is een plotseling, onverwacht overlijden binnen 1 uur na het begin van de symptomen (als er getuigen aanwezig zijn) of binnen 24 uur nadat iemand voor het laatst gezien is en symptoomvrij was (indien er geen getuigen zijn). De incidentie van acute hartdood is in ons onderzoek 1 per 1000 personen per jaar. De incidentie van acute hartdood neemt toe met het stijgen van de leeftijd, verschilt tussen mannen en vrouwen en varieert per maand en per dag van de week.

De vraagstelling in **hoofdstuk 3** betreft de voorspellende waarde van de lengte van het QTc interval, als niet invasieve factor voor het optreden van acute hartdood. Het QTc interval op het elektrocardiogram (ECG) weerspiegelt het begin van de ventrikeldepolarisarie tot de voltooiing van de repolarisatie. Verlenging van het QTc interval kan aanleiding geven tot het optreden van hartritmestoornissen, zoals Torsade de Pointes, die ventrikelfibrilleren kunnen uitlokken en kunnen leiden tot acute hartdood. Dit onderzoek maakte gebruik van de data van de Rotterdam Studie, een grootschalig, prospectief bevolkingsonderzoek van 7983 personen van 55 jaar en ouder. Het QTc interval op het ECG werd bepaald bij het eerste bezoek (1990-1993) en het tweede vervolgbezoek (1993-1995). In deze tijd (met een gemiddelde vervolgduur van 6,7 jaar) stierven 125 personen een acute hartdood. Wij hebben de Europese richtlijnen van de EMEA (European Medicines Agency) gebruikt om de lengte van het QTc interval in 3 geslachtsspecifieke categorieën in te delen. Bovendien hebben we verschillende grenzen van het QTc interval, variërend van 440 msec tot 470 msec onderzocht, gebaseerd op eerdere studies. Een abnormaal verlengd QTc interval (meer dan 470 msec voor vrouwen en meer dan 450 msec voor mannen) was geassocieerd met een drie maal hogere kans op acute hartdood, na correctie voor andere risicofactoren,

zoals leeftijd, geslacht, BMI (body mass index), hypertensie, cholesterol/hdl ratio, diabetes mellitus, myocard infarct en hartfalen.
Bij mensen onder de 68 jaar was het risico zelfs 8 keer verhoogd. Uit onze studie blijkt dat verlenging van het QTc interval een onafhankelijke risicofactor is voor het optreden van acute hartdood. Twee derde van de gevallen van acute hartdood is geassocieerd met een abnormale verlenging van het QTc interval.
In **hoofdstuk 4** bestudeerden we het verband tussen gebruik van geneesmiddelen, waarvan bekend is dat ze hartritmestoornissen en QTc verlenging kunnen veroorzaken, en de lengte van het QTc interval op het ECG. Dit onderzoek maakt, evenals het voorgaande, gebruik van de gegevens van de Rotterdam Studie. De laatste tijd is er veel gepubliceerd over geneesmiddelen die QTc verlenging kunnen veroorzaken. Lijst 1 van de website van de International Registry for Drug-induced Arrhythmias (http://www.qtdrugs.org/medical-pros/drug-lists/drug-lists.htm) bevat een recente lijst, die regelmatig wordt bijgewerkt. Deze bestaat uit 4 categorieën geneesmiddelen, variërend van geneesmiddelen waarvan het algemeen geaccepteerd is dat ze ernstige hartritmestoornissen kunnen veroorzaken (lijst 1) tot geneesmiddelen waarvan weliswaar gevallen van QTc verlenging beschreven zijn maar die bij normaal verantwoord gebruik niet geassocieerd lijken met ernstige hartritmestoornissen (lijst 4). Daarnaast hebben de Ponti en collegae een lijst samengesteld van 31 QTc verlengende geneesmiddelen met pro aritmogene effecten (hierop staan geen geneesmiddelen, die bedoeld zijn om ritmestoornissen te behandelen) gebaseerd op literatuuronderzoek. Er waren in de Rotterdam Studie 14.013 ECGs beschikbaar voor dit onderzoek, 5768 bij mannen en 8245 bij vrouwen. In deze populatie gebruikten 615 personen een QTc verlengend middel op het moment van de registratie van het ECG. Significant meer vrouwen dan mannen gebruikten QTc verlengende middelen. Dit verschil werd vooral veroorzaakt doordat vrouwen vaker antidepressiva en vaker domperidone gebruikten dan mannen in onze populatie. Uit deze studie blijkt een verband tussen een aantal, maar niet alle, geneesmiddelen van de beide lijsten en QTc verlenging in een groep van oudere volwassenen. Bijna alle middelen die QTc verlenging veroorzaken doen dat door beïnvloeding van de snelle kaliumstroom (I_{kr}) via het vertraagde kalium kanaal, dat gecodeerd wordt door het HERG (humane ether-a-go-go) gen. Helaas is dit geen specifieke bevinding, want een groot aantal middelen blokkeert dit kanaal maar veroorzaakt geen Torsade de Pointes. Het is daarom waarschijnlijk dat andere electrofysiologische eigenschappen ook een rol spelen. Deze effecten kunnen Torsade de Pointes voorkomen of door directe effecten (door "early after depolarisations" te dempen) of door indirecte effecten (door de verlenging van de actiepotentiaal te verminderen). In de recente richtlijnen is veel nadruk gelegd op het feit dat geneesmiddelen, die geassocieerd zijn met ernstige hartritmestoornissen, ook een verlenging van het QTc interval veroorzaken. Paradoxaal genoeg lijkt met de toename in kennis de voorspelbaarheid van deze ernstige bijwerking

niet groter te worden. Het zorgvuldig volgen van geneesmiddelen nadat ze op de markt zijn gekomen (postmarketing surveillance) blijft een heel belangrijk middel om torsadogene effecten in nieuwe geneesmiddelen op te sporen.

Onderzoek naar het risico op acute hartdood bij personen, die antipsychotica gebruiken, is onderzocht in **hoofdstuk 5**. In dit onderzoek gebruikten we de gegevens van de Integrated Primary Care Information (IPCI) project, een database met de complete medische gegevens van ongeveer 500.000 personen. De elektronische gegevens bevatten de gecodeerde en geanonimiseerde gegevens over demografie, symptomen, diagnoses van huisartsen en specialisten, verwijzingen, laboratorium gegevens, ziekenhuisopnames en geneesmiddelenrecepten met hun indicatie en dosering. Om te zorgen dat de data zo compleet mogelijk zijn, gebruiken de huisartsen die deelnemen aan het IPCI project, uitsluitend elektronische medische dossiers en geen papieren dossiers. Het onderzoek betreft de periode van 1 januari 1995 tot 1 september 2001. Alle personen werden gevolgd tot overlijden, verhuizen of het einde van het onderzoek. In onze bron populatie hebben wij 582 gevallen van acute hartdood gevonden. Dit komt overeen met een incidentie van acute hartdood van 1 per 1000 personen per jaar. Bij 28 gevallen van acute hartdood zijn geen controles gevonden en deze zijn van de verdere studie uitgesloten. Onze studiepopulatie bestond uit 554 gevallen van acute hartdood en 4463 controles, gematched op leeftijd (geboortejaar), geslacht en praktijk. Uit de resultaten van deze studie blijkt dat het gebruik van antipsychotica geassocieerd is met een verhoogd risico op acute hartdood, ook in lage doses en bij mensen die antipsychotica gebruiken voor andere indicaties dan schizofrenie. Na correctie voor andere risicofactoren was het gebruik van antipsychotica geassocieerd met een drievoudig hoger risico op acute hartdood. Het risico was het hoogste in de gebruikers van butyrophenonen, maar niet significant anders dan bij gebruikers van andere middelen, misschien door de lage aantallen. In tegenstelling tot andere studies, vonden wij geen verhoogd risico bij gebruikers van thioridazine maar dit geneesmiddel werd nauwelijks gebruikt in onze studiepopulatie.

In **hoofdstuk 6** evalueren we het risico op acute hartdood bij gebruikers van niet cardiale QTc verlengende middelen. Ook hier hebben we gebruik gemaakt van de gegevens van de IPCI database. De studieperiode loopt van 1 januari 1995 tot 1 april 2003. Alle personen werden ook voor dit onderzoek gevolgd tot overlijden, verhuizen of het einde van het onderzoek. De geneesmiddelen, die we hebben bestudeerd, staan vermeld op de meest recente versie van lijst 1 van het internationale register van geneesmiddelen geïnduceerde ritmestoornissen (International Registry for Drug-induced Arrhythmias maintained by the Georgetown University, http://www.qtdrugs.org/medical-pros/drug-lists/drug-lists.htm). In de bronpopulatie hebben we 806 gevallen van acute hartdood gevonden. Bij 31 gevallen waren geen controles beschikbaar en deze werden van het verdere onderzoek uitgesloten. De studie populatie bestond uit 775 gevallen van acute hartdood en 6297

controles, gematched op leeftijd (geboortejaar), geslacht en prakrijk. Uit de resultaten van deze studie blijkt dat het gebruik van niet cardiale QTc verlengende middelen de kans op acute hartdood significant verhoogt. Na correctie voor andere risicofactoren is het risico bij gebruikers van niet cardiale QTc verlengende middelen bijna driemaal hoger. Het risico was groter voor vrouwen dan voor mannen. Dit past bij eerdere bevindingen dat vrouwen gevoeliger zijn voor geneesmiddel geïnduceerde hartritmestoornissen dan mannen. Onze studie laat zien dat 320 gevallen van acute hartdood per jaar in Nederland het gevolg kunnen zijn van niet cardiale QTc verlengende middelen.

De associatie tussen het gebruik van bronchodilatoren, in het bijzonder ß agonisten, en de kans op acute hartdood in een case controle studie in een algemene populatie wordt besproken in **hoofdstuk 7**. Naast de case controle opzet hebben we ook een "nested case crossover" onderzoek gedaan om de mogelijke associatie verder te onderzoeken. De studie periode liep van 1 januari 1995 tot 1 april 2003. In de case crossover studie, hebben we co-morbiditeit en gelijktijdig medicatie gebruik en ernst van de chronische obstructieve longziekte onderzocht als tijdsafhankelijke variabelen in iedere 3 maandelijkse periodes in het jaar voorafgaande aan de indexdatum. De ernst van de chronische obstructieve longziekte hebben we vastgesteld aan de hand van antibiotica gebruik voor luchtweginfecties, het gebruik van orale steroïden voor longaandoeningen, het optreden van exacerbaties, het gebruik van zuurstof en ziekenhuisopname voor luchtwegaandoeningen. Patiënten met zuurstofgebruik, orale steroïden, exacerbaties of ziekenhuisopname werden beschouwd als ernstiger ziek. De resultaten van dit onderzoek wijzen in de richting van een associatie tussen het gebruik van langwerkende en kortwerkende ß-agonisten en de kans op acute hartdood, zowel in de hele populatie als in patiënten met chronische obstructieve longziekte. Ook xanthines en anticholinergica lijken de kans op acute hartdood te verhogen. De associatie met anticholinergica werd alleen in de gehele populatie gezien. Het is vaak moeilijk om vast te stellen of het overlijden veroorzaakt is door de therapie of door de chronische obstructieve longziekte, omdat chronisch obstructieve longziekte zelf een risico is voor het optreden van acute hartdood. In de algemene discussie, **hoofdstuk 8**, worden de belangrijkste resultaten en methodologische aspecten van het onderzoek besproken. Tot slot worden suggesties gegeven voor mogelijk toekomstig onderzoek.

❤ On ne voit bien qu'avec le coeur. L'essentiel est invisible pour les yeux. ❤

(uit: Le Petit Prince
van Antoine de Saint-Exupéry)

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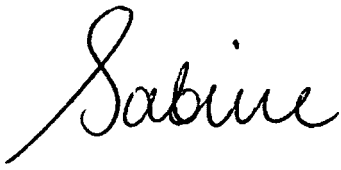

*(met dank aan Tom, Keith en Lou).

CURRICULUM VITAE

Sabine Straus was born on April 9 in Heerlen, the Netherlands. She completed Gymnasium ß in 1977 at the Bernardinus College in Heerlen (cum laude). In the same year she started to study Dentistry at the University of Utrecht. After one year she switched to Medicine at the same university. She obtained her doctoral in 1983 (cum laude) and her Medical Degree in 1985. Subsequently she held several positions in the pharmaceutical industry, the last one as medical director at Searle Monsanto. In 1997 she started working for the Medicines Evaluation Board in The Hague as clinical assessor pharmacovigilance. In February 2001 she began the work described in this thesis at the Department of Epidemiology and Biostatistics and the Department of Medical Informatics at the Erasmus Medical Center in Rotterdam, in combination with her work in The Hague. She obtained her Master of Science degree in Clinical Epidemiology at the Netherlands Institute for Health Sciences in 2004.