Disease and drug-induced arrhythmias

The example of obstructive pulmonary disease

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Voor Tijn

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Ziekte- en geneesmiddel-geïnduceerde hartritmestoornissen
Het voorbeeld van obstructieve longziekten
(met een samenvatting in het Nederlands)

Proefschrift

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CONTENT

1

INTRODUCTION

A 70 year old man with chronic obstructive pulmonary disease (COPD) and hypertension was admitted to hospital with a two month history of worsening dyspnoea on exertion and ankle swelling. On examination, the patient was in atrial fibrillation with an apical ventricular rate of 136 beats per minute. The jugular venous pressure was not visible, but there was bilateral pitting oedema to the knees. Auscultation of the chest revealed polyphonic wheeze and poor air entry but no crepitations. An electrocardiogram (ECG) confirmed atrial fibrillation. The patient was treated with oral digoxin, intravenous furosemide, and nebulised salbutamol. Within 24 hours of admission, the patient had a cardiac arrest and was successfully resuscitated. Three further cardiac arrests involving a similar rhythm disturbance occurred during the second day. ECGs showed a prolonged QT interval (corrected QT 520 milliseconds), macroscopic T wave alternans, and recurrent torsade de pointes.[1]

This case report exemplifies the complex interaction between lung disease, heart disease, and drug treatment. Several questions arise, including 'How often do cardiac arrhythmias, including sudden cardiac arrest, occur in patients suffering from COPD?', 'What are the underlying mechanisms of cardiac arrhythmias in patients with obstructive pulmonary disease, and what is the impact of drug treatment?', 'How can cardiac arrhythmias be prevented in lung patients?'.

The purpose of this thesis is to gain more insight in the risks and mechanisms of underlying cardiac arrhythmias in patients suffering from obstructive pulmonary disease, and the role of drug treatment. Furthermore, we aim to evaluate how arrhythmias in patients with obstructive pulmonary disease could be prevented.

Obstructive pulmonary disease

Obstructive pulmonary disease, including chronic obstructive pulmonary disease (COPD) and asthma, are characterised by inflammation of the bronchi causing reversible (asthma) or irreversible (COPD) airway obstruction.[2]

COPD is primarily caused by smoking[3] and carries a poor prognosis, as it is a chronic and progressive disease. Symptoms include dyspnoea, chronic cough and sputum production,[4] and episodes of acute worsening of these symptoms, exacerbations, often occur.[4] Unfortunately, despite improved understanding of the pathophysiology of COPD, no curative treatment is available.[5] Treatment with bronchodilator drugs (e.g. anticholinergics and β_2-agonists) and inhaled corticosteroids is mainly symptomatic, as smoking cessation is the only intervention that substantially improves survival of patients with COPD.[6] As a result, COPD remains a leading cause of morbidity and mortality worldwide,[7] and it is one of the few diseases that still shows a rising mortality rate. The World Health Organization estimates that by 2020, COPD will be the third most common cause of death in the world.[4,8]

Asthma, also an obstructive pulmonary disease, is characterised by inflammation of the bronchi, causing reversible airway obstruction and bronchospasm.[2] Symptoms include recurrent episodes of wheezing, often accompanied by breathlessness, chest tightness and coughing, particularly at night or in the early morning, caused by airway hyper responsiveness or inhalation allergy.[9] Asthma occurs worldwide, but the prevalence varies widely between countries, ranging from 2% in Vietnam to 27% in Australia.[10] In the Netherlands, the prevalence of adults with asthma is approximately 2.8%.[11] Unlike COPD, asthma is not caused by cigarette smoking, but by a genetic predisposition to atopy and airway hyperresponsiveness.[12] The natural history of asthma varies with sex, age at onset of symptoms, and severity of the disease. Asthma typically is a childhood disease, but the majority of patients, about 80%, has mild, persistent asthma in adulthood.[13]

Obstructive pulmonary disease and cardiac arrhythmias

During the last decade it became increasingly clear that patients suffering from COPD are at increased risk of cardiovascular morbidity and mortality.[14-19] Compared with people without COPD, they are more prone to ischaemic heart disease, cardiac arrhythmias and heart failure.[14,16] More than 20% of the patients with COPD, aged 65 year or older, concomitantly have heart failure.[20] A cohort study by Sidney *et al*. showed that patients with COPD experienced an almost three-fold increased risk of hospitalisation for cardiac arrest or ventricular tachycardia, as compared to sex and age comparable controls without COPD.[21] Actually, more hospitalisations and deaths are caused by cardiovascular events than by respiratory failure in COPD patients.[8]

In patients with asthma the relation with cardiovascular disease is less unequivocal, although asthma patients appear to have an increased risk of arrhythmia as well.[22] When patients have severe acute asthma, they have an increased risk of potentially fatal arrhythmias and death due to ischaemic heart disease.[23-25] However, with stable disease, there is conflicting evidence whether asthma is associated with cardiovascular disease. Appleton *et al*. showed that asthma was associated with an increased risk of cardiac disease,[26] while Schanen *et al*. reported that asthma was associated with an increased risk of stroke, but not of coronary heart disease.[27] Other studies showed only an increased risk of coronary heart disease in asthmatic women, but not in men,[28, 29] whereas the study of Enright *et al*. failed to find an association between asthma and cardiovascular disease.[30] Hence, further research is needed to determine the actual risk of cardiac arrhythmias in asthma.

Cardiac arrhythmias in obstructive pulmonary disease: possible mechanisms

Smoking

Several different mechanisms have been proposed to explain why an increased risk of cardiac arrhythmias has been observed in patients with asthma and COPD.[31] Smoking is the most important risk factor for COPD as well as for coronary artery disease. Patients with coronary artery disease are at an increased risk of cardiac arrhythmias,[32] but in addition, smoking as such may also induce cardiac arrhythmias.[33] Current smokers are at increased risk of sudden cardiac death, while after smoking cessation the risk of sudden cardiac death immediately declines to the risk of those who never smoked.[34] Nicotine, carbon monoxide, and oxidative stress induce fibrosis of the cardiac tissue, generating structural remodelling that may predispose to arrhythmia. Moreover, nicotine is suggested to be arrhythmogenic in animal models, causing mainly supraventricular arrhythmias.[33] In humans some case reports have been published on nicotine replacement therapy used for smoking cessation causing atrial fibrillation, but confirming evidence from pharmacological or epidemiological studies is lacking.[33]

Systemic inflammation and autonomic dysfunction

Systemic inflammation is an important pathophysiologic mechanism in systemic diseases characterised by chronic inflammation, such as obstructive pulmonary disease,[35,36] but it also plays an important role in the development of atherosclerosis and ischaemic heart disease.[17,19] In addition, functional and structural changes of the respiratory system in COPD influence cardiovascular function.[37] Obstructive pulmonary disease may result in autonomic dysfunction, most likely caused by chronic hypoxemia. Hypoxemia, together with dyspnoea and increased respiratory drive, is associated with elevated sympathetic activity in obstructive pulmonary disease, which may contribute to the development of cardiac arrhythmias by increasing the resting heart rate. Increased heart rate is associated with an increased risk of cardiac mortality in the population at large.

QT interval prolongation

QT interval prolongation is a marker for prolongation of cardiac repolarisation.[42,43] Drugs are an important cause of QT prolongation. Although the occurrence of QT interval prolongation is generally rare, it may result in ventricular arrhythmias such as torsade de pointes, ventricular fibrillation, and sudden cardiac arrest.[43] Especially in patients with other risk factors for QT prolongation, including structural heart disease such as myocardial infarction and heart failure, concomitant use of other arrhythmogenic drugs, and a history of congenital long QT syndrome: use of QT prolonging drugs may cause arrhythmias.[42-44] Patients with asthma are more prone to developing cardiac arrhythmia when using QT interval prolonging drugs, than those without this condition using QT prolonging drugs,[45] and asthma may be associated with the congenital long QT syndrome.[46] However, information on QT interval duration in patients with obstructive pulmonary disease, a possible explanatory mechanism for the increased risk of cardiac arrhythmia, is lacking.

Drug therapy

Finally, there is a growing concern that pulmonary medication, most notably β_2-agonists and anticholinergics - cornerstones in asthma and COPD therapy - increase resting heart rates and may promote cardiac arrhythmias.[47-53] Evidence, however, is conflicting and much uncertainty remains. In addition, patients with obstructive lung disease are often treated with QT interval prolonging drugs, which may add to the risk of cardiac arrhythmias in patients with obstructive pulmonary disease. Further study is needed to evaluate if respiratory drugs indeed are associated with an increased cardiovascular risk.

In conclusion, important information is lacking regarding the baseline risk of cardiac arrhythmias in patients with obstructive pulmonary disease and the exact underlying mechanisms. Moreover, the role of respiratory drugs remains to be further elucidated. New evidence on these issues may create new opportunities to prevent of cardiac arrhythmias in patients with obstructive pulmonary disease.

Objective and outline of the thesis

The overall aim of this thesis is to gain more insight in the risks for cardiac arrhythmias in patients with obstructive pulmonary disease. Focus will be on the following aims:

- To quantify the background risk of cardiac arrhythmias in patients with obstructive pulmonary disease.
- To elucidate the underlying mechanisms of cardiac arrhythmias in patients with obstructive pulmonary disease.
- To determine if drug therapy is associated with the occurrence of cardiac arrhythmias in patients with obstructive pulmonary disease.
- To evaluate how arrhythmias in patients suffering from obstructive pulmonary disease can be prevented.

In chapter 2 the association between obstructive pulmonary disease and the risk of electrocardiographic abnormalities is determined. Chapter 2.1 reports on the prevalence of various ECG characteristics in COPD patients and those without COPD. Chapter 2.2 handles the association between asthma and the risk of cardiac arrhythmias and ECG characteristics of arrhythmogenicity. Chapter 2.3 focuses on the association between resting heart rate and mortality and non-fatal pulmonary endpoints in patients with COPD.

Chapter 3 provides new insights into sudden cardiac arrest in patients with obstructive pulmonary disease. Chapter 3.1 focuses on the risk of sudden cardiac arrest in patients with obstructive pulmonary disease. Chapter 3.2 reports on survival rates after out of hospital cardiac arrest in patients with obstructive pulmonary disease.

Chapter 4 focuses on the prevention of cardiac arrhythmias in patients with obstructive pulmonary disease. Since smoking is an important risk factor for arrhythmias, chapter 4.1 presents a review of smoking cessation strategies in patients with chronic obstructive pulmonary disease. Chapter 4.2 reports on ECG monitoring as a risk minimisation strategy to prevent drug-induced arrhythmias in patients treated with haloperidol and assessed the compliance of general practitioners to these recommendations.

In chapter 5 the focus is on the quality and variation of information on QT prolongation in the drug label, using the label as a tool to minimise the risk of drug-induced arrhythmias. Chapter 5.1 reports on the variation of extensiveness and content of information on QT prolongation in the European product label. Chapter 5.2 handles the concordance in safety information on QT prolongation between the European and American drug labelling.

Chapter 6 provides a general discussion of the manuscripts presented in this thesis with special emphasis on the role of drug therapy in cardiac arrhythmias in patients with obstructive pulmonary disease.

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2

ELECTROCARDIOGRAPHIC ABNORMALITIES IN PATIENTS WITH OBSTRUCTIVE PULMONARY DISEASE

2.1

ELECTROCARDIOGRAPHIC CHARACTERISTICS OF PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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Abstract

Background

Patients with chronic obstructive pulmonary disease (COPD) are at increased risk of cardiovascular disease. Electrocardiography (ECG) carries information about cardiac disease and prognosis, but studies comparing ECG characteristics between patients with and without COPD are lacking. We related ECG characteristics of patients with COPD, to ECG characteristics of patients without COPD, and determined whether ECG abnormalities are related to COPD severity.

Methods

A cross-sectional study was conducted within a cohort of 243 COPD patients, aged 65 years or older. All patients underwent extensive examinations, including resting 12-lead ECG and pulmonary function tests. The reference group ($n = 293$) was a sample from the general population, also aged 65 or older, without COPD.

Results

Abnormal ECGs were more prevalent in COPD patients (50%) than in patients without COPD (36%, $p = 0.054$). Conduction abnormalities were the most common ECG abnormality in COPD patients (28%) being significantly more prevalent than in patients without COPD (11%, $p < 0.001$). The mean heart rate was higher in COPD patients (72 beats per minute [bpm, 14]) compared to controls (65 bpm [13], $p < 0.001$), and QTc prolongation was less frequent in COPD patients (9% versus 14%, $p = 0.01$). The prevalence of ECG abnormalities increased with severity of pulmonary obstruction.

Conclusions

ECG abnormalities, especially conduction abnormalities are common in COPD patients, and the prevalence of ECG abnormalities increases with severity of COPD. This underlines the importance of an integrated-care approach for COPD patients, paying attention to early detection of unrecognised coexisting cardiac disorders.

Introduction

Patients suffering from chronic obstructive pulmonary disease (COPD) are at increased risk of cardiovascular morbidity and mortality.[1-3] Compared to people without COPD, they are more prone to develop ischaemic heart disease, cardiac arrhythmias, and heart failure.[2] Moreover, most hospitalisations and deaths in COPD patients are caused by cardiovascular disease.[3] High co-existence of COPD and cardiovascular diseases (CVD) is partly attributable to high prevalence of both diseases. In addition, they share important risk factors: cigarette smoking, advanced age, inactive lifestyle, and low socioeconomic status.[2,4,5] Importantly, however, after adjusting for risk factors for CVD, including the aforementioned, COPD remains a strong independent predictor for cardiovascular events and death.[2,6,7] Large population-based studies also showed a strong association between lung function impairment and cardiovascular morbidity and mortality, independent of age and smoking habits.[7-9]

Schneider *et al*. recently showed that the relative risk of developing arrhythmia was comparable for patients with and without COPD, and independent of COPD severity.[10] In contrast, Finkelstein *et al*. demonstrated that COPD patients had a higher risk of myocardial infarction (OR 2.0 [1.5-2.5]) and arrhythmia (OR 2.4 [2.0-2.8]) than non-COPD controls.[2] Many previous studies also reported that COPD patients are at increased risk of cardiac arrhythmias.[3,6]

Although an increasing body of evidence is available on the elevated risk of cardiovascular events in COPD patients, information on ECG characteristics of these patients is scarce and comparisons with patients without COPD are lacking. In addition, studies of ECG characteristics in COPD patients focus on ECG abnormalities related to pulmonary hypertension and cor pulmonale, i.e. right atrial enlargement, right ventricular hypertrophy, P-pulmonale, right axis deviation, and right bundle branch block, while less than 1% of the COPD patients develop pulmonary hypertension.[11] Electrocardiography is the standard method for diagnosing cardiac arrhythmias.[12]

In addition, it can provide useful information about cardiac disease or end-organ damage, e.g. detection of prior myocardial infarction, ischemia, chamber enlargements, conduction abnormalities, left ventricular hypertrophy, etc., and it is helpful for indicating which additional cardiac investigations should be considered.[12] Finally, the ECG carries prognostic information, and it can offer clues for targeted preventive therapy. We determined the prevalence of various ECG characteristics among COPD patients and focused on abnormalities related to cardiac disease, classified according to the Minnesota coding criteria.[13] Secondary objectives were to determine whether COPD patients are at higher risk for ECG abnormalities than patients without COPD, and to assess if the prevalence of various ECG characteristics is related to severity of pulmonary obstruction.

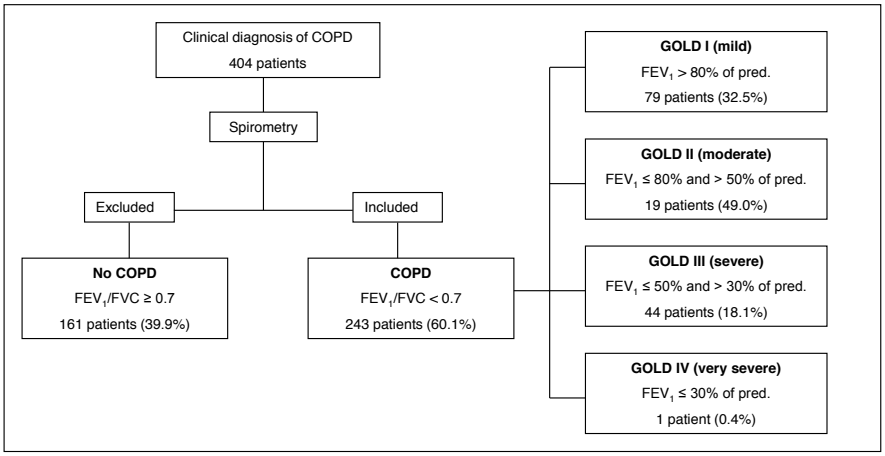
Methods

Setting and study design

We performed a cross-sectional study within a cohort of 404 COPD patients from the vicinity of Utrecht, the Netherlands, aged 65 years or older, with a general practitioners diagnosis of COPD (International Classification of Primary Care [ICPC] code R91 [chronic bronchitis] or R95 [COPD or emphysema]). Patients were investigated between April 2001 and June 2003. The cohort is described in detail elsewhere.[14] In short, all patients underwent extensive examinations in an outpatient clinic, including history taking, physical examination, ECG, chest radiography, blood tests, pulmonary function tests, and echocardiography. All patients with COPD were included, including those (co-)treated by a pulmonologist, because in the Netherlands all individuals, except nursing residents, are registered with one general practice.

Patients with a cardiologist-confirmed diagnosis of heart failure were excluded, because the aim of the original study was to assess the prevalence of unrecognised heart failure. This cohort is a representative sample of the COPD patients in the general practice population. From this cohort we selected all patients

Figure 1. Inclusion of participants and severity of COPD according to the GOLD criteria in the study population.[15]



($n = 243$) that fulfilled the GOLD criteria for COPD diagnosis: i.e. post-dilatory FEV_1/FVC was $< 70\%$, either with or without complaints.[15] GOLD stages were defined according to current guidelines: stage I (mild): $FEV_1 > 80\%$ of predicted; stage II (moderate): $FEV_1 \leq 80\%$ of predicted and $FEV_1 > 50\%$ of predicted; stage III and IV ([very] severe): $FEV_1 \leq 50\%$ of predicted (Figure 1). The Medical Ethics Committee of the University Medical Center Utrecht, the Netherlands, approved the study and all participants gave written informed consent.

Electrocardiography

A standard resting 12-lead ECG was recorded at a paper speed of 25 mm per second (GE electronics, San Diego, California). ECG characteristics and abnormalities studied included heart rate, arrhythmias (pacemaker rhythm, sinus tachycardia, bradycardia (sinus bradycardia or bradyarrhythmia), premature ventricular contractions (PVC), atrial fibrillation), conduction abnormalities (left bundle branch block (complete left bundle branch block, left anterior fascicular block, or

left posterior fascicular block) right bundle branch block (complete or incomplete right bundle branch block), atrioventricular (AV) block, right atrial and left ventricular enlargement, left and right ventricular hypertrophy, ischaemic heart disease ([prior] myocardial infarction [inferior or anterior Q-wave myocardial infarction], ST and/or T-wave abnormalities [ST segment elevation or depression, other repolarisation abnormalities or T-wave abnormalities]), and characteristics of arrhythmogenecity, that is, ventricular repolarisation abnormalities (QTc, QTc dispersion) and autonomic activity (heart rate variability [HRV]).

Each ECG was visually analysed for recording errors and classified according to the Minnesota coding criteria by a single cardiologist to detect arrhythmias, conduction abnormalities and ischaemic heart diseases.[13] The hard-copy ECGs were also scanned and converted to digital ECG files (ECGScan Version 3.0, AMPSLLC, New York).[16] Subsequently, the ECGs were processed by a digital calliper software system (CalECG, Version 1.0, AMPSLLC, New York) to obtain the following ECG measurements: mean corrected QT (QTc) interval, QTc dispersion, mean RR interval and standard deviation of the RR interval.[17]

The QT interval was corrected for heart rate according to Bazett's formula: $\text{QTc} = \text{QT}/\sqrt{\text{RR}}$.[18] A normal QTc interval was defined as < 430 ms for males and < 450 ms for females, a borderline QTc interval as 430-450 ms for males and 450-470 for females, and a prolonged QTc interval as > 450 ms for males and > 470 ms for females.[19] QTc dispersion was defined as the difference between the maximum and minimum QT across the 12-lead ECG, and was calculated in ECGs in which at least 5 leads were measurable and corrected for heart rate according to Bazett's formula.[18] To compute mean RR interval and HRV, only intervals between two adjacent 'normal' dominant beats were used (both premature atrial and ventricular complexes were considered abnormal). HRV was defined as the standard deviation of the RR intervals (SDNN).

Reference group without COPD

Participants aged 65 or older from the population-based Utrecht Health Project (UHP) and without COPD or an established diagnosis of heart failure, were included in the reference group. The UHP is an on-going longitudinal primary care based study among all inhabitants of 'Leidsche Rijn', a newly developed residential area of Utrecht, the Netherlands. The UHP started recruitment in 2000 and for this study data were available of 6542 unselected adult participants. The cohort is described in detail elsewhere.[20] In short, baseline assessments included physical examination, ECG, blood tests, pulmonary function tests, and an interview assisted questionnaire, including information about smoking habits, demographic factors and current health status. More than 50% of the invited residents of 'Leidsche Rijn' participated in the UHP cohort and gave informed consent.

Standard 12-lead resting ECGs were obtained from all participants of the UHP older than 18 years old recruited from April 2000 to January 2007, and stored digitally. Each ECG was manually classified according to the Minnesota coding criteria, and analysed by the Modular ECG Analysis System (MEANS) as described previously in detail.[13,21] ECG characteristics and abnormalities studied included heart rate, arrhythmias (sinus tachycardia, bradycardia, PVC, atrial fibrillation), conduction abnormalities (left bundle branch block, right bundle branch block, AV block), ischaemic heart disease ([prior] myocardial infarction, ST and/or T-wave abnormalities), QTc, QTc dispersion and heart rate variability). Pharmacy records were used to obtain medication use at baseline.

Only patients 65 or older of age, with an available ECG and a spirometry result not compatible with COPD (predilatory $FEV_1/FVC > 70$), and without an ICPC code R91 (chronic bronchitis) or R95 (COPD or emphysema) were included in the reference group. Of the 824 patients with a pre-dilatory $FEV_1/FVC > 70$, 306 patients were 65 years or older. Eleven patients were excluded because they had an ICPC code R95 and 2 patients were excluded because of an ICPC code R91.

In total, 293 participants of the UHP were included in the present study. The Medical Ethics Committee of the University Medical Center Utrecht, the Netherlands, approved the UHP.

Data analysis

Continuous variables were described as means and standard deviations and categorical variables as absolute numbers and percentages. Differences in baseline characteristics were examined with chi-square tests or t-tests, when appropriate. Dichotomous outcome variables were analysed with multivariate logistic regression to compute odds ratios (OR). Linear regression analysis was used for analysing continuous outcome variables. We corrected for differences in age and sex distribution between the COPD group and the control group using multivariate analysis. As this is a non-etiological prevalence study, we do not correct for confounding factors. To test the robustness of the association, several sensitivity analyses were performed. All data were analysed using the statistical software package of SPSS (SPSS for Windows, version 16.0, SPSS Inc.).

Results

The characteristics of the participants with and without COPD are presented in Table 1. The mean age of the 243 COPD patients was 73 years, and 69% were male (reference group: 71 years and 51% male, respectively). Of the COPD patients, 33% had stage GOLD I, 49% stage GOLD II and 18% stage GOLD III (Figure 1). Only one patient (0.4%) had stage GOLD IV COPD and was included in the GOLD III COPD group. Patients with GOLD III COPD were more often male and current or previous smokers compared to GOLD I and II patients. Table 2 presents the occurrence of all possible ECG diagnosis in the COPD patient population. Left anterior fascicular block (14%), premature ventricular contraction (11%), ST segment depression (10%), and intraventricular block (10%) were most present.

Table 1. Baseline characteristics of the study population stratified by severity of COPD according to the GOLD criteria.

	Participants without COPD	Participants with COPD				p-value[1]
		All	GOLD I	GOLD II	GOLD III	
Total	293	243	79 (33%)	119 (49%)	45 (19%)	-
Male	148 (51%)	167 (69%)	44 (56%)	82 (69%)	41 (91%)	<0.001
Age (years)	71 (5)	73 (5)	73 (5)	74 (5)	73 (5)	<0.001
Current or past smoker	191 (65%)	206 (85%)	64 (81%)	99 (83%)	43 (96%)	<0.001
Signs and symptoms						
FEV_1 (% of predicted)	-	71 (20)	94 (10)	66 (8)	42 (6)	-
FEV_1/FVC	0.85 (0.08)	0.55 (0.11)	0.63 (0.05)	0.56 (0.09)	0.42 (0.09)	<0.001
History of						
Cardiac arrhythmias[2]	7 (2%)	24 (10%)	8 (10%)	12 (10%)	4 (9%)	<0.001
Ischemic heart disease[3]	22 (8%)	82 (34%)	25 (32%)	41 (35%)	16 (36%)	<0.001
Medication use at baseline						
Cardiovascular drugs[4]	145 (50%)	145 (60%)	38 (48%)	76 (64%)	31 (69%)	0.02
QT prolonging drugs[5]	4 (1%)	12 (5%)	4 (5%)	7 (6%)	1 (2%)	0.02
β-blockers	70 (24%)	25 (10 %)	12 (15%)	12 (10%)	1 (2%)	<0.001
Respiratory drugs use[6]	22 (8%)	215 (89%)	64 (81%)	106 (89%)	45 (100%)	<0.001
Inhaled corticosteroids	17 (6%)	160 (66%)	47 (60%)	79 (66%)	34 (76%)	<0.001
Inhaled anticholinergics	4 (1%)	134 (55%)	34 (43%)	64 (54%)	36 (80%)	<0.001
Inhaled β_2-agonists	13 (4%)	170 (70%)	48 (61%)	81 (68%)	41 (91%)	<0.001

Values are means (SD) for continuous variables and absolute numbers (percentages) for dichotomous variables. COPD: chronic obstructive pulmonary disease, GOLD: global initiative for chronic obstructive lung disease, FEV_1: forced expiratory volume in 1 second, FVC: forced vital capacity, SD: standard deviation, n: number.

1. p-value: COPD vs. no COPD.
2. Including atrial fibrillation, supra ventricular tachycardia, ventricle fibrillation, ventricular tachycardia, and other cardiac arrhythmias.
3. Including prior myocardial infarction, angina pectoris, coronary artery bypass grafting, and percutaneous coronary intervention.
4. Including diuretics, β-blockers, dioxin, calcium-antagonists, anti-arrhythmics, platelet aggregation inhibitors, ACE-inhibitors, ATII receptor blockers, nitrates, and statins.
5. Drug with (possible) risk of QT prolongation according to the internet based registry of QT prolonging drugs (Appendix 1)
6. Including β_2-agonists, anticholinergics, and inhaled corticosteroids.

ECG characteristics of patients with and without COPD

COPD patients, had significantly more abnormal ECGs compared to patients without COPD (50% vs. 36%, adjusted OR 1.5 [1.0-2.1], Table 3). In COPD patients, conduction abnormalities were most frequently observed (28%); and conduction abnormalities, especially left bundle branch block, were significantly more common in COPD patients (28% and 16%, respectively) than in patients without COPD (11%, $p < 0.001$ and 2%, $p < 0.001$, respectively). Sensitivity analyses showed that even after excluding all patients with known heart disease ($n = 98$ patients with COPD, 27 people without COPD), conduction abnormalities, especially left bundle branch block, were significantly more common in COPD patients (27% and 15%, respectively) than in patients without COPD (9%, $p < 0.001$ and 2%, $p < 0.001$, respectively).

In patients without COPD signs of ischaemic heart disease was the most common ECG abnormality (22%). The mean heart rate was significantly higher in COPD patients (72 bpm [SD 14]) compared to controls (65 bpm [SD 13], $p < 0.001$). Bradycardia was significantly less frequently observed in patients with COPD (1%) than in patients without COPD (5%, adjusted OR 0.2 [0.1-0.7], $p = 0.01$). Overall, 9% of the COPD patients and 14% of the participants without COPD had a prolonged QTc interval (adjusted OR 0.5 [0.3-0.8]). In addition, the mean QTc length was lower in COPD patients (421 ms [SD 25]) compared to controls (427 ms [SD 29], $p = 0.06$).

ECG characteristics in COPD patients according to disease severity

The prevalence of ECG abnormalities increased, although not statistically significantly, with increasing severity of obstruction (GOLD I: 46%, GOLD II: 50%, GOLD III: 58%, adjusted OR III vs. I: 1.5 [0.7-3.3], Table 4). The prevalence of conduction abnormalities, ECG changes suggestive of ischaemic heart disease, and QTc prolongation increased with increasing GOLD stage. Heart rate significantly increased from 69 bpm (SD 11) in stage GOLD I to 76 bpm (SD 14) in GOLD III ($p = 0.002$, Table 4).

Table 2. Frequency of all ECG abnormalities, classified according to the Minnesota coding criteria, in 243 patients with COPD.

Electrocardiographic abnormality	n	%
Pacemaker rhythm	0	0%
Sinus tachycardia (>100 bpm)	4	2%
Sinus bradycardia (<50 bpm)	2	1%
Bradyarrhythmia	1	0.4%
Premature ventricular contraction	27	11%
Premature atrial contraction	10	4%
Atrial fibrillation	16	7%
Complete left bundle branch block	5	2%
Left anterior fascicular block	34	14%
Left posterior fascicular block	1	0.4%
Complete right bundle branch block	17	7%
Incomplete right bundle branch block	9	4%
Intra-ventricular block	23	10%
Atrio-ventricular block	19	8%
Right atrial enlargement	3	1%
Left ventricular enlargement	15	6%
Left ventricular hypertrophy	17	7%
Right ventricular hypertrophy	3	1%
Inferior Q-wave myocardial infarction	18	7%
Anterior Q-wave myocardial infarction	9	4%
ST segment elevation	3	1%
ST segment depression	25	10%
Other repolarization abnormalities	31	13%
T-wave abnormalities	0	0%
Prolonged QTc interval	21	9%

More than one electrocardiographic diagnosis per patient is possible.
Values are numbers and percentages.

QTc dispersion increased with increasing disease severity from 42 ms in GOLD I to 48 ms in GOLD III ($p = 0.50$). With the exception of heart rate ($p = 0.05$) none of the differences in ECG characteristics between stage GOLD II and I were statistically significant.

Discussion

To our knowledge, this is the first study that compares differences in cardiac-disease-related ECG characteristics of COPD patients with persons without COPD. In our study among 243 COPD patients and 295 men and women without COPD, ECG abnormalities known to be related to cardiovascular disease, were more prevalent in COPD patients (the majority being conduction abnormalities) than in those without COPD. Heart rate was higher and QTc prolongation less common in COPD patients.

The prevalence of ECG abnormalities, in general, increased with GOLD stage. Recently, Holtzman *et al*. reported the prevalences of some ECG abnormalities associated with COPD in patients with mild or moderate COPD versus severe COPD. In concordance with our results, they reported high prevalences of ECG abnormalities in COPD patients, which increased with severity of the disease.[22]

Consistent with large population-based studies, we demonstrated that COPD is associated with an excess of cardiac arrhythmias, particularly atrial fibrillation.[2,3,8] As arrhythmias are often intermittently present and ECGs are a snap-shot of the cardiac situation, our results could underestimate the actual prevalence of arrhythmias. Nevertheless, bradycardia (heart rate $<$ 50 bpm) was significantly less prevalent in our patients with COPD than in patients without COPD. This could be partly attributable to the higher prevalence of β-blocking agent use in patients without COPD (24%) compared to COPD patients (10%, p $<$ 0.001). However, exclusion of patients receiving β-blockers revealed similar results (bradycardia: COPD: 1.4%, no COPD: 4.0%, OR adjusted for age and sex: 0.2 [0.1-0.9], p $=$ 0.04). In analogy with other studies, we showed that patients with COPD had a relatively high heart rate and that heart rate significantly increased with increasing GOLD stage.[23,24] Exclusion of patients receiving β-blocking agents did not change these findings (e.g. mean heart rate: COPD 72 bpm, no COPD: 66 bpm, p-value adjusted for age and sex: $<$ 0.001). An elevated heart rate is associated with an increased risk of cardiac mortality in population based studies,[25] and a

Table 3. ECG characteristics of participants with or without COPD.

	COPD n = 243	No COPD n = 293	Crude OR (95%CI)	p-value	Adjusted[1] OR (95%CI)	p-value
Abnormal ECG[2]	122 (50%)	104 (36%)	1.8 (1.3-2.6)	<0.001	1.5 (1.0-2.1)	0.04
Arrhythmias	47 (19%)	41 (14%)	1.5 (0.9-2.3)	0.10	1.2 (0.8-2.0)	0.39
Tachycardia (>100 bpm)	4 (2%)	5 (2%)	1.0 (0.3-3.6)	0.96	1.1 (0.3-4.3)	0.94
Bradycardia (<50 bpm)	3 (1%)	15 (5%)	0.2 (0.1-0.8)	0.02	0.2 (0.1-0.7)	0.01
PVC	27 (11%)	18 (6%)	1.9 (1.0-3.6)	0.04	1.7 (0.9-3.3)	0.10
Atrial fibrillation	16 (7%)	7 (2%)	3.4 (1.3-8.8)	0.01	2.7 (1.0-7.2)	0.05
Conduction abnormalities	67 (28%)	31 (11%)	3.2 (2.0-5.1)	<0.001	2.8 (1.7-4.5)	<0.001
LBBB	38 (16%)	6 (2%)	8.9 (3.7-21.4)	<0.001	7.7 (3.1-18.9)	<0.001
RBBB	26 (11%)	6 (2%)	5.7 (2.3-14.2)	<0.001	4.6 (1.8-11.5)	0.001
AV block	19 (8%)	19 (7%)	1.2 (0.6-2.4)	0.55	1.1 (0.5-2.1)	0.89
Ischaemic heart disease	45 (19%)	63 (22%)	0.8 (0.5-1.3)	0.39	0.7 (0.4-1.1)	0.09
Myocardial infarction	25 (10%)	30 (10%)	1.0 (0.6-1.8)	0.99	0.8 (0.5-1.5)	0.52
ST/T-wave changes	27 (11%)	41 (14%)	0.8 (0.5-1.3)	0.32	0.6 (0.4-1.1)	0.11
Heart rate (bpm, SD)	72 (14)	65 (13)	-	<0.001	-	<0.001
Mean QRS length (ms, SD)	100 (20)	102 (18)	-	0.37	-	0.04
Mean RR (ms, SD)[3]	863 (161)	952 (164)	-	<0.001	-	<0.001
Median SDNN (ms, Q1-Q3)[3]	24 (14-49)	20 (12-33)	-	0.04	-	0.15
Mean QTc length (ms, SD)[3,4]	421 (25)	427 (29)	-	0.02	-	0.06
Normal	184 (76%)	211 (72%)				
Borderline	38 (16%)	42 (14%)				
Prolonged	21 (9%)	40 (14%)	0.6 (0.3-1.0)	0.07	0.5 (0.3-0.8)	0.01

Differences in ECG abnormalities between participants with or without COPD were determined by multivariate logistic regression or linear regression analysis.
AV block: atrioventricular block, CI: confidence interval, COPD: chronic obstructive pulmonary disease, LBBB: left bundle branch block, PVC: premature ventricular contraction, OR: odds ratio, QTc: corrected QT time, RBBB: right bundle branch block, SDNN: standard deviation of all normal to normal RR-intervals.

1. Adjusted for age and sex.
2. Including arrhythmia, conduction abnormality, and ischaemic heart disease. More than one electrocardiographic diagnosis per patient is possible.
3. Mean RR, median SDNN: 292 participants without COPD, 239 COPD patients; heart rate, mean QTc length: 242 COPD patients; mean QRS length: 240 COPD patients.
4. Normal QTc interval: QTc <430 ms for males, QTc <450 ms for females. Borderline QTc interval: QTc = 430-450 ms for males, QTc = 450-470 ms for females. Prolonged QTc interval: QTc > 450 ms for males, QTc > 470 ms for females.

recent observational study from our group suggested that β-blocking agents may improve prognosis in COPD patients.[26] Next, tachyarrhythmia is a well-recognised side effect of β_2-agonist and anticholinergic agents. As inhaled β_2-agonist as well as anticholinergic agents are central to symptom management in COPD, this could be another explanation of the increased heart rate of COPD patients. However, as 84% of the COPD patients used at least one of these medications (41% of the COPD patients used both) we were not able to determine the effect of these drugs on heart rate. Finally, another potential cause of the increased heart rate could be lung hyperinflation. Hyperinflation in COPD may lead to decrease of the ventricular size and function, with decreased stroke volume and cardiac output. As a result, this may cause an increase in heart rate and tachycardia.[27]

Although COPD patients are prone to cardiac arrhythmias, this seems not to be related to QTc prolongation, because the mean corrected QT interval was lower in COPD patients than in controls. This, although patients with COPD more often received QT prolonging medication (according to the internet based registry of QTc prolonging drugs, Appendix 1)[28] than patients without COPD. The QT interval in both groups was corrected for heart rate according to Bazett's formula. This correction is necessary as the QT interval varies with RR interval: the shorter the RR interval (or the faster the heart rate), the shorter the QT interval. However, QT corrections are prone to under- or overestimation of the true QT interval.[29] As the mean RR interval is significantly shorter in COPD patients than in controls, it is questionable if heart rate correction was optimal. The QTc interval of the COPD patients could be underestimated due to the shorter RR interval. However, different techniques were used to determine the QT interval in COPD patients and controls, and the effect of this is difficult to predict, but may partly account for the differences in QTc length between both groups.

Table 4. ECG characteristics of COPD patients, stratified by disease severity according to the GOLD criteria.[15]

	GOLD I	GOLD II	GOLD III	GOLD III vs. I	
	79 (33%)	119 (49%)	45 (19%)	Adjusted OR[1] (95%CI)	p-value
Abnormal ECG[2]	36 (46%)	60 (50%)	26 (58%)	1.5 (0.7-3.3)	0.30
Arrhythmias	12 (15%)	26 (22%)	9 (20%)	1.3 (0.5-3.5)	0.63
Tachycardia (>100 bpm)	1 (1%)	1 (1%)	2 (4%)	3.8 (0.3-50.6)	0.32
Bradycardia (<50 bpm)	1 (1%)	2 (2%)	0 (0%)	-	-
PVC	8 (10%)	14 (12%)	5 (11%)	1.0 (0.3-3.4)	0.99
Atrial fibrillation	3 (4%)	11 (9%)	2 (4%)	1.3 (0.2-9.5)	0.77
Conduction abnormalities	20 (25%)	31 (26%)	16 (36%)	1.4 (0.6-3.2)	0.44
LBBB	6 (8%)	17 (14%)	15 (33%)	4.7 (1.6-13.5)	0.005
RBBB	10 (13%)	12 (10%)	4 (9%)	0.6 (0.2-2.1)	0.41
AV block	7 (9%)	8 (7%)	4 (9%)	0.8 (0.2-3.0)	0.72
Ischaemic heart disease	12 (15%)	21 (18%)	12 (27%)	1.9 (0.7-4.9)	0.18
Myocardial infarction	7 (9%)	11 (9%)	7 (16%)	1.3 (0.4-4.2)	0.62
ST/T-wave changes	7 (9%)	12 (10%)	8 (18%)	2.7 (0.8-8.8)	0.09
Heart rate	69 (12)	72 (14)	76 (14)	-	0.002
Mean QRS length	98 (19)	101 (22)	103 (18)	-	0.63
Mean RR (ms)[3]	897 (151)	857 (168)	819 (150)	-	0.003
Median SDNN (ms, Q1-Q3)[3]	22 (12-47)	24 (15-52)	24 (14-47)	-	0.57
Mean QTc length (ms)[3,4]	422 (21)	421 (27)	419 (26)	-	0.93
Normal	61 (77%)	88 (75%)	34 (76%)		
Borderline	13 (17%)	20 (17%)	5 (11%)		
Prolonged	5 (6%)	10 (8%)	6 (13%)	1.7 (0.5-6.2)	0.41
QTc dispersion (ms)	42 (33)	46 (42)	48 (34)	-	0.50

Values are absolute numbers (percentages) for dichotomous variables and means (SD) for continuous variables. Odds ratios (OR) and p-values were calculated by multivariate logistic regression (dichotomous variables) or linear regression analysis (continuous variables) and adjusted for age and sex.
AV block: atrioventricular block, CI: confidence interval, COPD: chronic obstructive pulmonary disease, GOLD: global initiative for chronic obstructive lung disease, LBBB: left bundle branch block, PVC: premature ventricular contraction, OR: odds ratio, QTc: corrected QT time, RBBB: right bundle branch block, SDNN: standard deviation of all normal to normal RR-intervals.

1. Adjusted for age and sex.
2. Including arrhythmia, conduction abnormality, and ischaemic heart disease. More than one electrocardiographic diagnosis per patient is possible.
3. Mean RR, median SDNN: n = 239 COPD patients; heart rate, mean QTc length, mean QTc dispersion: n = 242 COPD patients; mean QRS length: n = 240 COPD patients.
4. Normal QTc interval: QTc <430 ms for males, QTc <450 ms for females.
   Borderline QTc interval: QTc = 430-450 ms for males, QTc = 450-470 ms for females.
   Prolonged QTc interval: QTc > 450 ms for males, QTc > 470 ms for females.

In agreement with our results, Lange *et al.* found that COPD patients, particularly with stage GOLD III and IV, frequently have conduction defects (36%).[8] COPD is one of the main causes of right bundle branch block, due to chronically increased right ventricular pressure, and 11% of the COPD patients in this study showed right bundle branch block. However, left bundle branch block, which usually indicates underlying cardiac pathology, is even more common in our COPD patients. This further underlines that COPD is an important risk factor of cardiac disease.[1]

Several limitations of the current study should be discussed: the number of COPD patients was limited, and consequently, because of limited power, none of the trends in the association of cardiovascular disease with COPD severity were statistically significant, although some interesting trends of increased prevalences with increasing COPD severity were observed. Many trends shown are not statistically significant. However, although not statistically significant, we think we should mention that ECG abnormalities have a trend to increase with GOLD class, and thus severity of pulmonary obstruction, which may be clinically relevant. Furthermore, in the reference group only pre-dilatory measurements of the pulmonary function were available. For establishing a diagnosis of COPD according to GOLD criteria, post-dilatory measurements should be used. However, for excluding COPD, predilatory measurements are sufficient. Next, we measured heart rate variability for periods shorter than 10 seconds. Heart rate variability, when measured on continuous ECG registrations, is an indication of autonomic nervous system functioning. Short-term variability mainly reflects sinus arrhythmia, and autonomic nerve system functioning is less represented.[30]

Previous studies showed that COPD, as well as a decreased FEV_1 value, are independently associated with cardiovascular events and death;[2,6,7] an association that persists after adjusting for multiple risk factors of cardiovascular disease, including cigarette smoking, age, inactive lifestyle, and low socioeconomic status.[2,4,5] However, residual confounding cannot be completely excluded in these studies, and thus, could explain part of the observed association. Importantly, this finding does not preclude that both diseases have important common pathophys-

iological pathways, including cigarette smoking and systemic inflammation.

Different mechanisms have been proposed to explain why COPD patients have a higher risk of cardiovascular events. One potential mechanism may relate to systemic inflammation. The increased cardiovascular risk is not only shown in COPD, but also in other systemic diseases characterised by chronic inflammation, such as rheumatic arthritis or chronic renal impairment. Epidemiologic data strongly associate systemic inflammation to atherosclerosis and ischaemic heart disease.[7]

Furthermore, there is evidence that COPD patients have autonomic dysfunction, most likely due to chronic hypoxemia, which contributes to the development of CVD: increased resting heart rate, as well as an increased risk of arrhythmias, abnormal conduction, and ectopic beats.[31] Heart rate variability, being the beat-to-beat alteration in heart rate, is an indication of autonomic nervous system functioning, and when reduced, this indicates autonomic dysfunction. In contrast with our results, several studies showed that heart rate variability is reduced in COPD patients,[23,24] and heart rate invariability is associated with a higher risk of cardiovascular mortality the elderly.[32] However, the fact that we did not find a reduced HRV could be due to the fact that we measured heart rate variability for periods shorter than 10 seconds, while in the former studies, which did show a reduced HRV in COPD patients, was measured for longer periods.

Finally, there is a growing concern that the pulmonary medications used for COPD increases morbidity and mortality, although the currently available studies and meta-analysis yield conflicting results.[33-35] Lee *et al.* as well as the Lung Health Study showed that the use of ipratropium was associated with an increased risk of cardiovascular death,[33,35] and a meta-analysis of Salpeter *et al.* showed that use of β_2-agonists in COPD patients increases the risk of cardiovascular events.[34] In contrast with these trials, the Understanding Potential Long-Term Impacts on Function with Tiotropium (UPLIFT) trial did not show an increased risk of cardiovascular morbidity and mortality in COPD patients using tiotropium[36] and a review

of Wood-Baker *et al*. concludes that there is no evidence of increased mortality associated with the use of β_2-agonists in patients with COPD.[37] Currently, much uncertainty remains about the association of pulmonary medication with mortality.

Although the available evidence strongly suggests that COPD patients are at increased risk of cardiovascular morbidity and mortality, the care provided seems to be focused mainly on the lungs. The NICE guideline on COPD does not point out the high risk of cardiovascular morbidity and mortality at all,[38] and the GOLD guideline only mentions it briefly.[15] An integrated-care approach for COPD patients with special attention for investigating of previously unrecognised cardiovascular disease is desirable, as is a more integrated pulmonary and cardiovascular care.

Conclusion

We conclude that electrocardiographic abnormalities, particularly conduction abnormalities, are common in patients with chronic obstructive pulmonary disease, and more prevalent than in patients without COPD. The prevalence of ECG abnormalities related to cardiac diseases, in general, is higher in those with more severe pulmonary obstruction. Previous studies suggest that COPD is related with cardiovascular morbidity and mortality. Our results show that COPD patients more often have ECG abnormalities, including abnormalities that have been shown to increase the risk of future cardiovascular events and mortality.[39-41] Therefore, special attention in the diagnostic work-up of these patients is needed, including ECG and in selected cases echocardiography, coming to a more integrated pulmonary and cardiovascular care.

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Appendix 1. Drug with (possible) risk of QTc prolongation according to the internet based registry of QTc prolonging drugs (http://www.azcert.org/medical-pros/drug-lists/bycategory.cfm, accessed August 25, 2010).

Class 1 QT prolonging drugs[1]	Class 2 QT prolonging drugs[2]	
Amiodarone	Alfuzosin	Paliperidone
Arsenic trioxide	Amantadine	Quetiapine
Astemizole	Atazanavir	Ranolazine
Bepridil	Azithromycin	Risperidone
Chloroquine	Chloral hydrate	Roxithromycin
Chlorpromazine	Clozapine	Sertindole
Cisapride	Dolasetron	Sunitinib
Clarithromycin	Dronedaron	Tacrolimus
Disopyramide	Felbamate	Tamoxifem
Dofetilide	Flecinide	Telithromycin
Domperidone	Foscarnet	Tizanidine
Droperidol	Fosphenytoin	Vardenafaxine
Erythromycin	Gatifloxacin	Voriconazole
Halofantrine	Gemifloxacin	Ziprasidone
Haloperidol	Granisetron	
Ibutilide	Indapamide	
Levomethadyl	Isradipine	
Mesoridazine	Lapatinib	
Methadone	Levofloxacin	
Pentamidine	Lithium	
Pimozide	Moexipril/Hydrochlorothiazide	
Probucol	Moxifloxacin	
Procainamide	Nicardipine	
Quinide	Nilotinib	
Sotalol	Octreotide	
Sparfloxacin	Ofloxacin	
Terfenadine	Ondansetron	
Thioridazine	Oxytocin	

1. Drugs with Risk of torsade de pointes and QT prolongation
2. Drugs with Possible Risk of torsade de pointes and QT prolongation

2.2

CARDIAC ARRHYTHMIAS IN ADULT PATIENTS WITH ASTHMA

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Abstract

Background

The pathogenesis of cardiac arrhythmias in asthma patients has not been fully elucidated. Adverse drug effects, particularly those of β_2-agonists, may play a role. The aim of this study was to determine whether asthma is associated with the risk of cardiac arrhythmias and electrocardiographic (ECG) characteristics of arrhythmogenicity and to explore the role of β_2-agonists.

Methods

A cross-sectional study was conducted among 158 adult patients with a diagnosis of asthma and 6303 participants without asthma from the cohort of the Utrecht Health Project - an on-going, longitudinal, primary care-based study. All patients underwent extensive examinations, including resting 12-lead electrocardiogram and pulmonary function tests. The primary outcome was 'any arrhythmia on the ECG' (including tachycardia, bradycardia, premature ventricular contraction (PVC), and atrial fibrillation or flutter). Secondary outcomes were tachycardia, bradycardia, PVC, atrial fibrillation or flutter, mean heart rate, mean corrected QT (QTc) interval length, and prolonged QTc interval.

Results

Tachycardia and PVCs were more prevalent in patients with asthma (3% and 4%, respectively) than those without asthma (0.6%, $p < 0.001$; 2%, $p = 0.03$, respectively). The prevalence of QTc interval prolongation was similar in participants with (2%) and without asthma (3%, odds ratio [OR] 0.6 [0.2-2.0]). In 74 asthma patients, who received β_2-agonists, tachycardia and PVCs were more common (OR: 12.4 [4.7-32.8] and 3.7 [1.3-10.5], respectively).

Conclusions

The adult patients with asthma more commonly show tachycardia and PVCs on the ECG than those without asthma. In the patients with asthma who received β_2-agonists, the risk of tachycardia and PVCs is even more pronounced.

Introduction

Asthma is a chronic condition, characterised by inflammation of the bronchi, causing reversible airway obstruction, and bronchospasm.[1] Asthma patients have an increased risk of arrhythmia when using corrected QT (QTc) interval prolonging drugs.[2] Moreover, asthma may be associated with the long QT syndrome,[3] a disorder causing an increased risk of ventricular tachycardia and sudden cardiac death from arrhythmia.[4] The pathogenesis of cardiac arrhythmia and sudden cardiac death in asthma patients has not been fully elucidated, although adverse effects of medications used to treat the disease, mainly β_2-agonists, may play a role.[5,6]

Studies that evaluated the risk of cardiac arrhythmias in adult asthma patients, and compared this risk with those without asthma, however, are scarce and lacking a representative sample of all asthmatics, including those with mild symptoms.[7] Electrocardiography can provide useful information about cardiac disease and carries prognostic information, offering clues for targeted preventive measures. Therefore, the aim of this study was to determine whether asthma is associated with an increased risk of cardiac arrhythmias and electrocardiographic characteristics of arrhythmogenicity, and to determine the role of respiratory inhalation medication, especially β_2-agonists, in this association.

Methods

We performed a cross-sectional population study within the Utrecht Health Project (UHP) cohort. The UHP is an on-going, longitudinal, primary care-based study. The cohort is described in detail elsewhere.[8] In short, baseline assessments included physical examination, 12-lead electrocardiogram (ECG), blood tests, pulmonary function tests (predilatory measurements only), and questionnaires. Pharmacy records were used to obtain information on drug prescriptions during a time period of 3 months before to until 3 months after the baseline assessment; for

the sensitivity analyses, this period was extended up to 2 years after the baseline assessments. The Medical Ethics Committee of the University Medical Center Utrecht, the Netherlands approved the UHP.

In this study, all patients aged 18 years or older, assessed between April 2000 and January 2007, were included (n = 6492). Patients with missing gender (n = 21) or missing ECG data (n = 10) were excluded from the analyses. Patients labelled with the International Classification of Primary Care (ICPC) code R96 (asthma) in the electronic medical record of the general practitioner were considered to have asthma (n = 158). These community-dwelling patients with asthma in general have mild disease; in the 2 years after the baseline assessments, only one single patient required hospital admission for an asthma exacerbation and 35% of the patients visited a pulmonologist at least once. The reference group consisted of all the remaining participants in the UHP (n = 6303), who were aged 18 years or over and had no diagnosis of asthma.

The primary outcome "any arrhythmia on the ECG" included tachycardia, bradycardia, premature ventricular contraction (PVC), and atrial fibrillation or flutter; more than one electrocardiographic abnormality per patient was possible. Standard 12-lead ECGs were obtained and stored digitally. Each ECG was visually analysed for recording errors and manually classified according to the Minnesota coding criteria by an experienced cardiologist.[9] Then, the ECGs were digitally analysed by the Modular ECG Analysis System (MEANS) as described previously in detail.[10] The following ECG characteristics were determined: any arrhythmia, heart rate, sinus tachycardia (heart rate $>$ 100 beats per minute [bpm]), bradycardia (heart rate $<$ 50 bpm), PVCs, atrial fibrillation, QTc interval, and QTc interval prolongation. The QT interval was corrected for heart rate according to Bazett's formula: $QTc = QT/\sqrt{RR}$.[11] A prolonged QTc interval was defined as $>$ 450 milliseconds (ms) for males and $>$ 470 ms for females.[12] Spirometry was performed in order to obtain predilatory forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) values.

We adjusted for differences in age and sex distribution between the asthma group and the reference group using multivariate analysis. Dichotomous outcome variables were analysed with multivariate logistic regression to compute odds ratios (ORs). Linear regression analysis was used for analysing continuous outcome variables. A subgroup analysis was performed to determine whether there was a modifying effect of respiratory medication on the association of asthma with arrhythmia, using multivariate analysis adjusting for age and gender. Sensitivity analyses were conducted to investigate whether the effect of misclassification of asthma or status of β_2-agonist use influenced the results. Data on respiratory medication use were obtained for an extended period, running from 3 months to 2 years after the baseline assessments. We identified 28 patients labelled with the ICPC code R96 (asthma), who did not receive any β_2-agonists in this 2.25 year period, and repeated the multivariable analyses after excluding these 28 patients. Next, we identified 18 patients labelled with the ICPC code R96 (asthma), who did not use any respiratory medications (β_2-agonists, anticholinergics, or inhaled corticosteroids) in the 2.25-year period, and again repeated the analyses after excluding these 18 patients from the analyses. All data were analysed using the statistical software package of SPSS (SPSS for Windows, version 16.0, SPSS Inc., 233 South Wacker Drive, 11th Floor, Chicago, IL 60606-6412, USA).

Table 1. Baseline characteristics of the study population.

	Participants without asthma n = 6303	Participants with asthma n = 158	Participants with asthma	
			Receiving β_2-agonists[1] n = 73	Not receiving β_2-agonists[1] n = 85
Age (years)	39 (12)	39 (12)	39 (13)	39 (12)
Male gender	2818 (45%)	70 (44%)	30 (41%)	40 (47%)
Smoking				
Current	1400 (22%)	31 (20%)	14 (19%)	17 (20%)
Past	1848 (29%)	45 (29%)	21 (29%)	24 (28%)
Never	2844 (45%)	71 (45%)	36 (49%)	35 (41%)
Smoking status missing	211 (3%)	11 (7%)	2 (3%)	9 (11%)
History of				
COPD	33 (0.5%)	7 (4%)	3 (4%)	4 (5%)
Cardiac arrhythmia	32 (0.5%)	1 (0.6%)	1 (1%)	0
Use of cardiovascular drugs[2]	620 (10%)	17 (11%)	6 (8%)	11 (13%)
Use of respiratory drugs[3]	232 (4%)	88 (56%)	73 (100%)	15 (18%)
β_2-agonists	177 (3%)	73 (46%)	73 (100%)	0
Anticholinergics	20 (0.3%)	5 (3%)	4 (6%)	1 (1%)
Inhaled corticosteroids	152 (2%)	72 (46%)	57 (78%)	15 (18%)
FEV_1/FVC[4]	0.85 (0.09)	0.81 (0.09)	0.80 (0.10)	0.83 (0.08)
$FEV_1/FVC < 0.70$[4]	237 (4%)	16 (10%)	12 (16%)	4 (5%)
FEV_1 (% of predicted)[4]	0.96 (0.15)	0.89 (0.18)	0.86 (0.20)	0.92 (0.15)

Values are means (SD) for continuous variables and absolute numbers (percentages) for dichotomous variables. COPD: chronic obstructive pulmonary disease, ICS: inhaled corticosteroids, FEV_1: forced expiratory volume in 1 second, FVC: forced vital capacity.

1. β_2-agonists received during a time period of 3 months until 3 months after the baseline assessments.
2. Including diuretics, β-blockers, dioxin, calcium-antagonists, anti-arrhythmics, platelet aggregation inhibitors, ACE-inhibitors, ATII receptor blockers, nitrates, and statins.
3. Including β_2-agonists, anticholinergics, or inhaled corticosteroids. Patients may be treated with multiple drugs, numbers do not add up.
4. Pre-dilatory values of spirometry are presented, missing n = 5.

Results

The characteristics of the participants are presented in Table 1. The mean age of 158 patients with asthma was 39 (SD 12) years and 44% were males; in the reference group, the mean age was 39 (SD 12) years and 45% were males.

The overall prevalence of arrhythmias was comparable in patients with asthma (10%) and in those without asthma (8%, adjusted OR: 1.4 [0.8-2.4]). Tachycardia and PVCs were significantly more common in asthma patients (age- and sex adjusted ORs: 5.5 [2.1-14.3] and 2.5 [1.1-6.0], respectively; Table 2). The mean heart rate was nonsignificantly higher in patients with asthma (66 bpm) than those without asthma (65 bpm, adjusted $p = 0.26$).

The prevalence of QTc interval prolongation was similar in patients with asthma (2%) and without asthma (3%) (adjusted OR: 0.6 [0.2-2.0]) and the mean QTc interval length was comparable between both the groups (adjusted $p = 0.94$).

In 73 patients with asthma, who received β_2-agonists, tachycardia was more common (7%) than those who did not receive β_2-agonists (0%) and the group without asthma (0.6%; adjusted OR β_2-agonist users with asthma vs. no asthma 12.4 [4.7-32.8]; Table 3). In addition, β_2-agonists-receiving asthma patients more often showed PVCs on the ECG (6%) than those not prescribed with β_2-agonists (2%) and than those without asthma (2%, adjusted OR β_2-agonist users with asthma vs. no asthma 3.7 [1.3-10.5])..

With respect to possible misclassification of asthma, first, we performed sensitivity analyses by repeating the multivariable analyses after excluding the 28 asthmatics (18%) who did not receive β_2-agonists in the period from 3 months to 2 years after the baseline assessments and, second, excluding 18 asthmatics (11%) who did not receive any respiratory medication in this 2.25-year period. Exclusion of these two groups did not reveal any different results; the shown effects were only marginally larger when comparing asthma patients with participants without

asthma (Table 4). The exclusion of the two groups did not change the association of tachycardia and PVCs in asthma patients who did or did not receive β_2-agonists in the 6-month period around the ECG measurements (data not shown).

Discussion

In this study, among the 158 asthma patients and 6303 participants without asthma, tachycardia and PVCs were more prevalent in asthma patients (3% and 4%, respectively) than those without asthma (0.6%; adjusted $p < 0.001$ and 2%; adjusted $p = 0.03$, respectively). In 73 patients with asthma, who received β_2-agonists in the 6-month period around the ECG measurements, tachycardia (7%) and PVCs (6%) were more common (adjusted ORs vs. no asthma: 12.4 [4.7-32.8] and 3.7 [1.3-10.5], respectively).

When patients have severe acute asthma, they have an increased risk of potentially fatal arrhythmias and death due to ischaemic heart disease, caused by the effects of medications (predominantly high dosages of [oral] β_2-agonists), but also by hypoxemia, acidosis, coronary vasospasm, and hypercatecholaminemia (including Takotsubo-type cardiomyopathies).[13-15] However, with stable disease, there is conflicting evidence whether adult patients with asthma are at increased risk of cardiovascular disease. Appleton *et al.* showed that asthma was associated with cardiac and cerebrovascular diseases in the general population,[16] while Schanen *et al.* reported that asthma was associated with an increased risk of stroke, but not of coronary heart disease.[17] Other studies showed only an increased risk of coronary heart disease in women, but not in men,[18,19] and finally the study of Enright *et al.* did not find an association between asthma and cardiovascular disease.[20] ECG abnormalities, such as tachycardia, QTc interval prolongation, and PVC, may be the (early) indicators of increased cardiovascular risk.[4,21,22]

Table 2. ECG characteristics of participants with and without asthma.

	No Asthma n = 6303	Asthma n = 158	Adjusted OR[1] (95%CI)	p-value
Tachycardia (>100 bpm)	37 (0.6%)	5 (3%)	5.5 (2.1-14.3)	<0.001
Bradycardia (<50 bpm)	320 (5%)	5 (3%)	0.6 (0.2-1.5)	0.28
Premature ventricular contraction	97 (2%)	6 (4%)	2.5 (1.1-6.0)	0.03
Atrial fibrillation or flutter	34 (0.5%)	1 (0.6%)	1.2 (0.2-8.6)	0.89
Any arrhythmia[2]	473 (8%)	16 (10%)	1.4 (0.8-2.4)	0.21
Mean heart rate (bpm)	65 (11)	66 (11)	-	0.26
Mean QTc length (ms)	415 (23)	415 (23)	-	0.94
Prolonged QTc interval[3]	194 (3%)	3 (2%)	0.6 (0.2-2.0)	0.42

Values are means (SD) for continuous variables and absolute numbers (percentages) for dichotomous variables.
Bpm: beats per minute, ms: milliseconds, CI: confidence interval, QTc: corrected QT interval.
1. Adjusted for age and sex.
2. Including tachycardia, bradycardia, premature ventricular contraction, atrial fibrillation or flutter. Patients may experience more than one electrocardiographic abnormality, numbers do not add up.
3. Prolonged QTc interval: QTc > 450 ms for males, QTc > 470 ms for females.

We demonstrated that the asthma patients had an increased risk of PVCs (adjusted OR: 2.5; 95% CI: 1.1 to 6.0) and that this risk is even more pronounced in asthma patients who received β_2-agonists in the 6 month period around the ECG measurements. Although PVCs are usually asymptomatic, the ECG appearance is related to increased mortality risk in patients with no apparent cardiac disease.[23,24] In patients with reduced pulmonary function, this relation may be even more pronounced.[21]

Large epidemiological studies showed that increased heart rate is related to increased mortality.[22] β_2-agonists, a cornerstone in asthma therapy, enhance the sympathetic system and, thus, may cause increased heart rates and arrhythmias. We demonstrated that asthma patients have an increased risk of tachycardia compared with those without asthma and that this risk is even higher in asthma patients receiving β_2-agonists. Importantly, several studies and meta-analyses showed that adult asthma patients using β_2-agonists are at increased risk of death[25,26] and cardiovascular complications.[5,27]

This study has some limitations. Misclassification in the diagnosis of asthma could have occurred, because not all general practitioners performed spirometry with post-dilatory measurements and histamine provocation tests to establish the diagnosis of asthma. Such a misclassification, however, would result in an underestimation of the true association between asthma and cardiac arrhythmias.

Table 3. Tachycardia and premature ventricular contraction of participants with and without asthma receiving β_2-agonists or not during a time period of 3 months until 3 months after the baseline assessments.

	Total number	Number of events (%)	Adjusted OR[1] (95%CI)
Tachycardia			
No asthma	6303	37 (0.6%)	Reference
Asthma, no β_2-agonists	85	0 (0%)	-
Asthma, β_2-agonists	73	5 (7%)	12.4 (4.7-32.8)
Premature ventricular contraction			
No asthma	6303	97 (2%)	Reference
Asthma, no β_2-agonists	85	2 (2%)	1.6 (0.4-6.5)
Asthma, β_2-agonists	73	4 (6%)	3.7 (1.3-10.5)

1. Adjusted for age and sex.

Sensitivity analyses addressing the misclassification of asthma did not reveal different results, only a tendency to a larger effect of the association between asthma (with β_2-agonists use) and arrhythmogenic effects. Next, there may be some misclassification on drug exposure as it is uncertain whether the participants, who received a prescription for inhalation medications, actually used these drugs on the day that the ECG was recorded, especially β_2-agonists, as these are generally used intermittently as symptomatic treatment.

Subsequently, as we were not able to differentiate between chronic use and “as needed” use of β_2-agonists, the results shown are most likely an underestimation of the actual association between β_2-agonists use and tachycardia and PVCs. With respect to the outcome definition, arrhythmias are often intermittently present and ECGs are a snapshot of the cardiac situation, this too could result in underestimation of the actual prevalence of arrhythmias. Finally, we were not able to fully

distinguish between the effect of β_2-agonist use and disease severity. However, after the correction of the underlying disease severity, by adjusting the predilator values of FEV_1/FVC ratio and FEV_1 (% of predicted), and (co)treatment by a pulmonologist, the results remained similar (data not shown).

Conclusion

Adult patients with a clinical diagnosis of asthma more commonly show tachycardia and PVCs on the ECG than those without asthma. In patients with asthma, who receive β_2-agonists, the risk of tachycardia and PVCs is even more pronounced. Elevated heart rate is associated with an increased risk of cardiac mortality in epidemiological studies in the population at large.[22,28-30] Our study shows that adult patients with asthma have increased heart rates when compared with the population at large. Future research should evaluate whether the increased heart rate is related to the disease itself or the use of inhalers, notably β_2-agonists.

Table 4. Sensitivity analyses. Risk of various ECG abnormalities in asthma patients (n = 158, see Table 1), in asthma patients with exclusion of asthmatics who did not receive β_2-agonists during the period three months before and two years after the ECG measurement compared to participants without asthma (n = 130), in asthma patients with exclusion of asthmatics who did not receive any pulmonary drug during this time frame (n = 140), compared to participants without asthma (n = 6303).

	Asthma (n = 158) vs. no asthma (n = 6303)		**Asthma (n = 130, excluding 28 patients who did not receive β_2-agonists) vs. no asthma (n = 6303)**		**Asthma (n = 140, excluding 18 patients who did not receive any respiratory drugs) vs. no asthma (n = 6303)**	
	Adjusted OR[1] (95% CI)	**p-value**	**Adjusted OR[1] (95% CI)**	**p-value**	**Adjusted OR[1] (95% CI)**	**p-value**
Tachycardia (>100 bpm)	5.5 (2.1-14.3)	<0.001	6.7 (2.6-17.3)	<0.001	6.1 (2.4-15.9)	<0.001
Bradycardia (<50 bpm)	0.6 (0.2-1.5)	0.28	0.8 (0.3-1.9)	0.58	0.7 (0.3-1.8)	0.46
PVC	2.5 (1.1-6.0)	0.03	2.5 (1.0-6.3)	0.05	2.3 (0.9-5.8)	0.08
Atrial fibrillation	1.2 (0.2-8.6)	0.89	1.4 (0.2-10.1)	0.77	1.2 (0.2-9.2)	0.83
Any arrhythmia[2]	1.4 (0.8-2.4)	0.21	1.6 (0.9-2.8)	0.08	1.5 (0.9-2.6)	0.15
Mean heart rate (bpm)	-	0.26	-	0.10	-	0.15
Mean QTc length (ms)	-	0.94	-	0.83	-	0.75
Prolonged QTc interval[3]	0.6 (0.2-2.0)	0.42	0.8 (0.2-2.4)	0.63	0.7 (0.2-2.2)	0.51

Bpm: beats per minute, ms: milliseconds, n: number, QTc: corrected QT interval, ECG: electrocardiogram, PVC: premature ventricular contraction.

1. Adjusted for age and sex.
2. Including tachycardia, bradycardia, premature ventricular contraction, atrial fibrillation or flutter. Patients may experience more than one electrocardiographic abnormality, numbers do not add up.
3. Prolonged QTc interval: QTc > 450 ms for males, QTc > 470 ms for females.

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2.3

RESTING HEART RATE IS A RISK FACTOR FOR MORTALITY IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE, BUT NOT FOR EXACERBATIONS OR PNEUMONIA

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Submitted

Abstract

Background

Although it is known that patients with chronic obstructive pulmonary disease (COPD) generally do have an increased heart rate, the effects on both mortality and non-fatal pulmonary complications are unclear. We assessed whether heart rate is associated with all-cause mortality, and non-fatal pulmonary endpoints.

Methods

A prospective cohort study of 405 elderly patients with COPD was performed. All patients underwent extensive investigations, including electrocardiography. Follow-up data on mortality were obtained by linking the cohort to the Dutch National Cause of Death Register and information on complications (exacerbation of COPD or pneumonia) by scrutinising patient files of general practitioners. Multivariate Cox regression analysis was performed.

Results

During the follow-up 132 (33%) patients died. The overall mortality rate was 50/1000 person year (42-59). The major causes of death were cardiovascular and respiratory. The relative risk of all-cause mortality increased with 21% for every 10 bpm increase in heart rate (adjusted HR: 1.21 [1.07-1.36]). The incidence of major non-fatal pulmonary events was 145/1000 person year (120-168). The risk of a non-fatal pulmonary complication increased non-significantly with 7% for every 10 bpm increase in resting heart rate (adjusted HR: 1.07 [0.96-1.18]).

Conclusions

Increased resting heart rate is a strong and independent risk factor for all-cause mortality in elderly patients with COPD. An increased resting heart rate did not result in non-fatal pulmonary complications. This may indicate that the increased mortality in COPD is mainly determined by non-pulmonary causes. Future randomised controlled trials are needed to investigate whether heart rate lowering agents are worthwhile for COPD patients.

Introduction

Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality worldwide.[1] The World Health Organization estimates that by 2020, COPD will be the third most common cause of death in the world.[1,2] Even when COPD is optimally treated, patients periodically experience exacerbations, resulting in decrease of lung function and quality of life, and often requiring costly hospitalisation.[3] COPD and cardiovascular disease share important pathophysiological pathways, and cigarette smoking is a prominent risk factor for both clinical major pulmonary and cardiovascular events. Importantly, in patients with COPD, hospitalisations and deaths are more often caused by cardiovascular events than by respiratory failure.[4]

Previous studies showed that patients with COPD had a significantly higher resting heart rate than patients without COPD.[5-7] Irrespective of this knowledge, the subsequent effects on both mortality and non-fatal major pulmonary complications are unclear. Therefore, we determined whether resting heart rate was associated with cardiovascular, respiratory, and all-cause mortality, but also with non-fatal pulmonary complications (e.g. pneumonia or exacerbation of COPD) in patients with chronic obstructive pulmonary disease.

Methods

Settings and study design

A prospective cohort study was performed in 405 patients recruited between April 2001 and June 2003 from the vicinity of Utrecht, the Netherlands. The patients, aged 65 years or older, had a general practitioner's diagnosis of COPD. The cohort was described in detail elsewhere.[8,9] In short, all patients underwent extensive investigations, including electrocardiography (ECG) and pulmonary function testing. Patients with a cardiologist-confirmed diagnosis of heart failure (5.7% of the participants) were excluded because the main aim of the original study was

to assess the prevalence of unrecognised heart failure. The Medical Ethics Committee of the University Medical Center Utrecht, the Netherlands, approved the study and all participants gave written informed consent.

Electrocardiography

A standard resting 12-lead ECG was recorded (GE electronics, San Diego, California). To obtain the mean RR interval length, hard copy ECGs were scanned and converted to digital ECG files (ECGScan Version 3.0, AMPSLLC, New York).[10] Subsequently the ECGs were processed by a digital calliper software system (CalECG, Version 1.0, AMPSLLC, New York).[11] To determine the heart rate, the following formula was used: heart rate $=$ 60/RR.

Follow-up

In order to obtain information on date and cause of death (in-hospital and out-of-hospital) during follow up, the cohort was linked to the Dutch National Cause of Death Register. Cause of death in this registry is coded according to the 10th revision of the International Classification of Diseases and Related Health Problems (ICD-10).[12] Follow-up data on mortality was collected until January 2011. Eighteen of the 405 patients (4%) could not be linked with the Death Register. For these patients information on cause and date of death was obtained by scrutinising patient files of the general practitioners (maximum follow-up until June 2007).[13]

Information on non-fatal pulmonary endpoints (exacerbation of COPD or pneumonia) was also obtained by scrutinising patient files of the general practitioners, including specialist letters and drug prescriptions. Data was gathered till the patient moved, died or the end of study (June 2007), whatever came first.[13] Exacerbation of COPD was defined as symptomatic deterioration requiring pulsed oral steroids or hospitalisation for an exacerbation.[14] The diagnosis of 'pneumonia' was based on the general practitioner's diagnosis or hospitalisations for pneumonia.

Covariates

As the association between resting heart rate and mortality or nonfatal pulmonary complications may be confounded by patient characteristics, we studied the influence of various covariates on the calculated associations. Potential confounders, measured at baseline, included age, sex, pack-years of smoking, COPD severity (the percentage of predicted forced expiratory volume in 1 second [FEV_1] was used as a proxy), body mass index (BMI), co-morbidities (history of hypertension, diabetes mellitus, cardiovascular disease, hypercholesterolemia, or malignancies), and the use of medication (cardiovascular [β-blockers excluded], β-blockers, and respiratory drugs [β_2-agonists, anticholinergics and inhaled corticosteroids]). Data on co-morbidities were acquired from patient files of the general practitioners. Smoking habits were obtained by a standardised questionnaire. BMI was calculated as weight (kg)/length^2 (m^2). Spirometric measurements were performed in all patients. A bronchodilator reversibility test was executed after inhalation of two puffs of 20 μg ipatropium bromide by inhalation chamber, after a time interval of at least 30 minutes.

Patients were grouped according to fulfilling the criteria of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) for COPD (n $=$ 244, 60%), or not. Patients fulfilled the GOLD criteria for COPD when the ratio of the post-dilatory forced expiratory volume in 1 second and the forced vital capacity ratio (FEV_1/FVC) was $<$ 70%, either with or without complaints.[1]

Statistical analyses

Cox regression analysis was used to calculate the risk for mortality in relation to resting heart rate. We adjusted for two sets of confounders: 1) age and sex, 2) all covariates that influenced the association. All potential confounders that were univariately associated with the outcome and changed the $\beta$of the association with at least 10%, were included in the multivariate analyses. Heart rate was either categorised in steps of 10 beats per minute (bpm) and analysed as a continuous variable or dichotomised in the following categories: $\leq$80 bpm and $>$80 bpm. The

group with a heart rate $\leq$80 bpm was taken as the reference category. A stratified analyses for mortality was performed regarding sex. The presence of interaction on a multiplicative scale between heart rate and sex was estimated by including the cross-product of the two factors as a variable in the model. A separate Cox regression analysis was performed to examine the association between heart rate and non-fatal pulmonary complications.

Sensitivity analyses were conducted to investigate whether the effect of misclassification of COPD and the use of β-blockers influenced the results, by repeating all analyses in subgroups with stricter inclusion criteria: first including only patients with COPD according to the GOLD criteria (n $=$ 244), second including only patients with COPD according to the GOLD criteria who did not receive β-blockers (n $=$ 219). All data were analysed using the statistical software package of SPSS (SPSS for Windows, version 14.0, SPSS Inc.).

Results

The baseline characteristics of the participants are presented in Table 1. The mean age of the patients at the start of the study was 73 (standard deviation [SD] 5) years, and 55% were male. Patients with a heart rate higher than 80 bpm were older and less often male, had a higher median pack-years of smoking, had a lower post-dilatory FEV_1, and used more cardiovascular drugs, but less β-blockers than patients with a heart rate of 80 bpm or lower.

Participants were followed up on mortality for a median period of 7.0 years (range: 7 days to 9.0 years). During follow up 132 (33%) patients died. In 39 (30%) patients cardiovascular diseases were considered the cause of death, and in 36 (27%) respiratory diseases. In the subgroup of patients with COPD according to the GOLD criteria, 97 (40%) patients died. The overall mortality rate was 50/1000 patient-years (py, 42-59). The cardiovascular mortality rate was 15/1000 py (11-20), and the respiratory mortality rate was 14/1000 py (10-19).

Table 1. Baseline characteristics of the 405 patients with a diagnosis of COPD, divided in those with a heart rate of 80 bpm or lower versus those with a heart rate above 80 bpm.

Characteristics	All participants n = 405	Heart rate ≤80 n = 310	Heart rate >80 n = 95	p-value
Male	221 (55%)	174 (56%)	47 (50%)	0.25
Age (years)	73 (5)	73 (5)	74 (6)	0.39
Smoking				
Never smoked	104 (26%)	86 (28%)	18 (20%)	
Past or current smoker				
≤ 15 pack-years	83 (21%)	66 (21%)	17 (18%)	
> 15 pack-years	198 (49%)	145 (47%)	53 (56%)	
Unknown number of pack-years	20 (5%)	13 (4%)	7 (7%)	0.15
FEV_1 (% predicted)	83 (26)	85 (26)	77 (24)	0.01
FEV_1/FVC ratio	0.64 (0.14)	0.65 (0.14)	0.64 (0.15)	0.38
Body mass index (kg/m^2)[1]	27 (4)	26 (4)	28 (4)	0.04
COPD severity				
No COPD according to GOLD criteria	161 (40%)	125 (40%)	36 (38%)	
Stage I	79 (20%)	66 (21%)	13 (14%)	
Stage II	120 (30%)	88 (28%)	32 (34%)	
Stage III-IV	45 (11%)	31 (10%)	14 (15%)	0.22
History of				
Diabetes mellitus	42 (10%)	28 (9%)	14 (15%)	0.11
Hypertension	145 (36%)	98 (32%)	47 (50%)	0.001
Cardiovascular disease[2]	180 (44%)	137 (44%)	43 (45%)	0.85
Malignancies	32 (8%)	23 (7%)	9 (10%)	0.52
Hypercholesterolemia	45 (11%)	36 (12%)	9 (10%)	0.56
Medication				
Cardiovascular drugs[3]	230 (57%)	158 (51%)	72 (76%)	<0.001
- β-blockers	47 (12%)	40 (13%)	7 (7%)	0.14
Inhalatory respiratory drugs				
- β_2-agonists	238 (59%)	176 (57%)	62 (65%)	0.14
- Anticholinergics	192 (47%)	138 (45%)	54 (57%)	0.04
- Corticosteroids	254 (63%)	189 (61%)	65 (68%)	0.19
Heart rate (bpm)	71 (14)	65 (8)	91 (10)	<0.001
Mean RR interval length (ms)[1]	871 (165)	935 (131)	664 (63)	<0.001
All-cause mortality	132 (33%)	87 (28%)	45 (47%)	<0.001
Cardiovascular death	39 (10%)	24 (8%)	15 (16%)	
Respiratory deaths	36 (9%)	19 (6%)	17 (18%)	
Other causes	57 (14%)	44 (14%)	13 (14%)	<0.001
Non-fatal pulmonary complication[4]	179 (44%)	128 (42%)	51 (54%)	0.038

Values are means (SD) for continuous variables, absolute numbers (percentages) for dichotomous variables and median (25-75 percentile) for skewed distributed variables. SD: standard deviation, n: number, COPD: chronic obstructive pulmonary disease, FEV_1: forced expiratory volume in 1 second, FVC: forced vital capacity, bpm: beats per minute, GOLD: global initiative for chronic obstructive lung disease, ms: milliseconds.

1. Body mass index: 4 missing, mean RR: 2 missing.
2. Including prior myocardial infarction, angina pectoris, coronary artery bypass grafting, percutaneous coronary intervention, atrial fibrillation, supraventricular tachycardia, ventricular fibrillation, ventricular tachycardia, other cardiac arrhythmias, stroke, transient cerebral ischaemic attack, peripheral arterial disease, or aortic aneurysm.
3. Including diuretics, digoxin, calcium channel-antagonists, anti-arrhythmics, platelet aggregation inhibitors, ACE inhibitors, angiotensin II receptor blockers, nitrates and statins.
4. Including pneumonia and/or exacerbation.

The relative risk for all-cause mortality in the 405 COPD patients increased with 21% for every 10 bpm increase in resting heart rate (crude hazard ratio [HR]: 1.28 [1.14-1.43], adjusted HR: 1.21 [1.07-1.36], Table 2). Likewise, for every 10 bpm increase in resting heart rate, the risk of cardiovascular mortality increased with 43% (crude HR: 1.44 [1.18-1.75], adjusted HR: 1.43 [1.17-1.76]), and the risk of respiratory mortality increased with 51% (crude HR: 1.54 [1.26-1.89], adjusted HR: 1.51 [1.19-1.90]).

COPD patients with a heart rate of more than 80 bpm had a significant increased risk of death from all causes compared to patients with a heart rate of 80 bpm or lower (adjusted HR: 1.6 [1.1-2.3]). The risk of cardiovascular and respiratory mortality were also increased in COPD patients with a heart rate higher than 80 bpm as compared to those with a heart rate of less than 80 bpm (adjusted HR: 2.3 [1.2-4.5], 2.8 [1.4-5.4], respectively).

Stratification according to sex showed a somewhat stronger effect of heart rate in women (crude HR: 1.37 [1.12-1.68], adjusted HR: 1.28 [1.05-1.57]) than in men (crude HR: 1.23 [1.07-1.40], adjusted HR: 1.15 [0.99-1.33]), but the interaction between sex and heart rate was not statistically significant on a multiplicative scale ($p = 0.14$).

Participants were followed for non-fatal pulmonary complications during a median period of 3.5 years (range: 2 days to 6.1 years). Forty-four percent of the patients experienced at least one episode of exacerbation of COPD or pneumonia during follow-up ($n = 179$). One patient did not have any follow-up data. The incidence of non-fatal pulmonary events was 145/1000 py (95%CI 120-168). COPD patients with a heart rate of more than 80 bpm did not have an increased risk of pneumonia or exacerbation compared to patients with a resting heart rate of 80 bpm or lower (adjusted HR: 1.1 [0.8-2.0], Table 3). A non-significantly increased risk of a non-fatal pulmonary complication was observed in COPD patients with 7% for every 10 bpm of increase in heart rate (adjusted HR: 1.07 [0.96-1.18]).

Table 2. Association of heart rate with all-cause, cardiovascular and respiratory mortality in 405 patients with a diagnosis of chronic obstructive pulmonary disease. Heart rate was categorised in steps of 10 bpm, when analysed as a continuous variable. In total, 310 patients had a heart rate ≤80 bpm and 95 patients had a heart rate >80 bpm.

Heart rate	Person-years	Deaths	Mortality/1000 person-years (95%CI)	Crude HR (95%CI)	Adjusted HR[1] (95%CI)	Adjusted HR (95%CI)
All-cause mortality						
Continuous	2665	132	50 (42-59)	1.28 (1.14-1.43)	1.27 (1.14-1.43)	1.21 (1.07-1.36)[2]
≤80 bpm	2102	87	41 (33-51)	Reference	Reference	Reference
>80 bpm	563	45	80 (59-106)	2.0 (1.4-2.9)	1.9 (1.3-2.8)	1.6 (1.1-2.3)[2]
Cardiovascular mortality[3]						
Continuous	2665	39	15 (11-20)	1.44 (1.18-1.75)	1.42 (1.16-1.75)	1.43 (1.17-1.76)[4]
≤80 bpm	2102	24	11 (7-17)	Reference	Reference	Reference
>80 bpm	563	15	27 (15-43)	2.4 (1.3-4.6)	2.2 (1.1-4.2)	2.3 (1.2-4.5)[4]
Respiratory mortality						
Continuous	2665	36	14 (10-19)	1.54 (1.26-1.89)	1.54 (1.25-1.89)	1.51 (1.19-1.90)[5]
≤80 bpm	2102	19	9 (6-14)	Reference	Reference	Reference
>80 bpm	563	17	30 (18-47)	3.5 (1.8-6.8)	3.3 (1.7-6.4)	2.8 (1.4-5.4)[5]

COPD: chronic obstructive pulmonary disease, HR: hazard ratio, CI: confidence interval, bpm: beats per minute

1. Adjusted for sex, and age.
2. Adjusted for sex, age, pack-years of smoking, FEV_1, and use of cardiovascular drugs (β-blockers excluded).
3. One patient was censored before the earliest event in this stratum occurred and therefore excluded from analysis.
4. Adjusted for sex, age, history of cardiovascular disease, use of cardiovascular medication (β-blockers excluded), and β-blockers.
5. Adjusted for sex, age, pack-years of smoking, and FEV_1 (% predicted).

To account for the effect of misclassification of COPD and use of β-blockers, we performed sensitivity analyses by repeating all analyses in 2 subgroups with different inclusion criteria, which showed similar results as the analyses of the total group of 405 patients. In the subgroup of patients with COPD according to the GOLD criteria (n = 244) the adjusted HR for all-cause mortality was 1.25 (1.07-1.45), and for non-fatal pulmonary complications 1.09 (0.96-1.24). In the subgroup of patients with GOLD-COPD who did not receive β-blockers (n = 219) the adjusted HR for all-cause mortality was 1.15 (0.99-1.35), and for non-fatal pulmonary complications 1.08 (0.95-1.24).

Discussion

We showed that an increased resting heart rate is a strong and independent risk factor for all-cause mortality in elderly men and women with COPD, however, not on non-fatal pulmonary complications. Patients with COPD in general have a higher resting heart rate than patients without COPD,[5,7] and population-based studies clearly showed that elevated resting heart rate is associated with an increased risk of cardiac mortality.[15-18] A recent study of Jensen *et al*. confirmed that these results also apply to patients with COPD. In a prospective study of almost 17,000 subjects and 2645 COPD patients they showed that patients with COPD and a heart rate ≥85 bpm had an increased risk of all-cause and cardiovascular mortality, compared to those with a heart rate of less than 64 bpm (adjusted HR 1.51 [1.43-1.60], 1.57 [1.45-1.71], respectively).[19]

To the best of our knowledge, we are the first who showed that an increased resting heart rate did not result in non-fatal pulmonary complications in patients with COPD. This may indicate that the increased mortality in COPD is mainly driven by non-pulmonary causes. Especially cardiovascular diseases could account for this 'mismatch' because patients with COPD frequently have concurrent cardiovascular disease, often undetected or latent.[8,14] Moreover, both COPD and cardiovascular diseases share a relation with cigarette smoking, a well-known cause of endothelial dysfunction and risk factor for cardiovascular events.

The relation between resting heart rate and respiratory mortality is probably overestimated. Previous studies showed already overestimation of COPD as the cause of death mentioned on death certificates.[20] An effect that certainly is even stronger when patients are known with a pulmonary disease during life.

A potential mechanism of the increased heart rate in patients with COPD is autonomic dysfunction, which may be triggered by longstanding periodically hypoxemia. Autonomic dysfunction contributes to the development of cardiovascular diseases, especially arrhythmias, abnormal conduction, and ectopic beats,[21] but possibly also heart failure.[14] In addition, the use of β_2-agonists could contribute to the elevated resting heart rate, especially the short-acting β_2-agonists. As inhaled β_2-agonists are central to symptom management in COPD, their use could be an additional explanation of the increased heart rate found in COPD patients as compared to an age-matched population at large.

Traditionally, β-blockers, having an opposite effect to β_2-agonists, have been considered contra-indicated in patients with COPD. The first Cochrane review of Salpeter *et al.* was a cornerstone study because it showed that cardio-selective β-blockers were well tolerated by patients with COPD, without adverse effects on FEV_1, respiratory symptoms or response to β_2-agonists.[22] Recent studies showed that beyond safety, long-term treatment with (cardioselective) β-blocking agents even may improve survival of patients with COPD,[14,23] and a reduction in exacerbations.[14] Although, counter intuitive on first glance, combining β_2-agonists and β-blockers seems a good treatment option when both drugs are indicated, because of counterbalancing possible negative effects of each drug.[24] β-blocking agents are known to diminish sympathetic nerve system activity, and thus reduce heart rate and this mechanism may reduce mortality in patients with cardiovascular disease and in those with COPD.[14,25,26]

Randomised controlled trials are needed to confirm if β-blockers, or other heart rate reducing drugs, are beneficial in reducing fatal and nonfatal complications in patients with COPD. Importantly, however, β-blockers could be beneficial on exacerbation because of other mechanism than reduction of heart rate, because we showed that heart rate had no significant effect on non-fatal pulmonary complications.

Some potential limitations of the present study should be taken into account. Only 70% of the 405 patients with a general practitioners diagnosis of COPD had COPD according to the GOLD criteria (post-dilatory $FEV_1/FVC < 70\%$). Importantly, however, a sensitivity analysis in those 244 patients showed similar results as presented in the whole group on both endpoints. Another limitation could be overestimation of pulmonary cause of death on the death certificates because the cause of death of the National Cause of Death Register was not validated by medical records or autopsy reports, although, several studies have shown that in general the validity of the cause of death registration of the Dutch National Cause of Death Register is adequate.[27] Finally, we defined exacerbation as recommended (symptomatic deterioration requiring steroids use or hospitalisation), with the exception that we did not included 'antibiotic use only'.[28] In the Netherlands it is common practice and advocated by Dutch guidelines to treat exacerbations with short-course corticosteroids, and consider to add antibiotics only when a bacterial infection is suspected.

The strength of our study is that we could extensively adjust for potential confounding factors, as we had much information on important potential confounding factors, including detailed information on pack-years of smoking and pulmonary function test parameters. Another advantage of this general practitioners cohort is that it can be considered as population-based, as all community-dwelling persons with COPD, including those treated by a pulmonologist, were included.

Conclusions

Increased heart rate is a strong and independent risk factor for all-cause mortality in patients with a diagnosis of COPD. There was, however, no significant association between heart rate and major respiratory complications, and this may indicate that the increased risk of mortality of patients with COPD is determined by non-pulmonary causes. Especially cardiovascular diseases could account for these findings because of the high concurrency with COPD and its mutual relation with smoking. Future randomised controlled trials are needed to investigate whether heart rate lowering agents, notably β-blockers, would be worthwhile for patients with COPD.

Table 3. Association of heart rate with non-fatal respiratory complications (pneumonia or exacerbation) in 402[1] patients with a diagnosis of chronic obstructive pulmonary disease. Heart rate was categorised in steps of 10 bpm, when analysed as a continuous variable. In total 310 patients had a heart rate ≤80 bpm and 95 patients had a heart rate >80 bpm.

Heart rate	Person-years	Pneumonia or exacerbation	Incidence/1000 person-years (95% CI)	Crude HR (95%CI)	Adjusted HR[2] (95%CI)	Adjusted HR[3] (95%CI)
Continuous	1234	179	145 (120-168)	1.14 (1.03-1.26)	1.13 (1.03-1.25)	1.07 (0.96-1.18)
≤80 bpm	975	128	131 (110-156)	Reference	Reference	Reference
>80 bpm	259	51	197 (148-257)	1.5 (1.1-2.0)	1.5 (1.1-2.0)	1.1 (0.8-1.6)

COPD: chronic obstructive pulmonary disease, HR: hazard ratio, CI: confidence interval, bpm: beats per minute

1. Two patients were excluded as they were censored before the earliest event occurred. In one patient we had no follow-up data.
2. Adjusted for sex, and age.
3. Adjusted for sex, age, pack-years of smoking, FEV_1 (% predicted), use of cardiovascular drugs (β-blockers excluded), and β-blockers.

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3

SUDDEN CARDIAC ARREST IN PATIENTS WITH OBSTRUCTIVE PULMONARY DISEASE

3.1

INCREASED RISK OF SUDDEN CARDIAC ARREST IN OBSTRUCTIVE PULMONARY DISEASE: A CASE-CONTROL STUDY

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Abstract

Background

We aimed to determine whether 1. patients with obstructive pulmonary disease (OPD) have an increased risk of sudden cardiac arrest (SCA) due to ventricular tachycardia or fibrillation (VT/VF), and 2. the SCA risk is mediated by cardiovascular risk-profile and/or respiratory drug use.

Methods

A community-based case-control study was performed, with 1310 cases of SCA of the ARREST study and 5793 age, sex, and SCA-date matched non-SCA controls from the PHARMO database. Only incident SCA cases, aged older than 40 years, that resulted from unequivocal cardiac causes with electrocardiographic documentation of VT/VF were included. Conditional logistic regression analysis was used to assess the association between SCA and OPD. Pre-specified subgroup analyses were performed regarding age, sex, cardiovascular risk-profile, disease severity, and current use of respiratory drugs.

Results

A higher risk of SCA was observed in patients with OPD (n $=$ 190 cases [15%], 622 controls [11%]) than in those without OPD (OR adjusted for cardiovascular risk-profile 1.4 [1.2-1.6]). In OPD patients with a high cardiovascular risk-profile (OR 3.5 [2.7-4.4]) a higher risk of SCA was observed than in those with a low cardiovascular risk-profile (OR 1.3 [0.9-1.9]) The observed SCA risk was highest among OPD patients who received short-acting β_2-agonists (SABA) or anticholinergics (AC) at the time of SCA (SABA OR: 3.9 [1.7-8.8], AC OR: 2.7 [1.5-4.8] compared to those without OPD).

Conclusions

OPD is associated with an increased observed risk of SCA. The most increased risk was observed in patients with a high cardiovascular risk-profile, and in those who received SABA and, possibly, those who received AC at the time of SCA.

Introduction

Sudden cardiac arrest (SCA) most often causes sudden death and is the most common direct cause of death in Western[1] and developing[2] societies. Given the dismal survival rate of SCA,[3,4] identification of patients at risk is crucial to develop preventive measures. Signals have emerged that patients with obstructive pulmonary disease (OPD: asthma and chronic obstructive pulmonary disease [COPD]) do not only have a worse outcome after SCA,[5] but are also at increased risk for the occurrence of SCA.[6] This may be due to an increased risk of concomitant cardiovascular disease,[7] as OPD and cardiovascular disease share risk factors and disease pathways, e.g., smoking (in COPD) and inflammation.[8,9] Accordingly, OPD is associated with a higher risk of cardiac arrhythmias and cardiovascular mortality.[6] Alternatively, increased SCA risk in OPD may stem from drugs used to treat OPD ('respiratory drugs').[10] In particular, inhaled short-acting or long-acting β_2-agonists (SABA, LABA) and anticholinergics (AC) have attracted suspicion, but evidence is conflicting.[11,12]

Reports on SCA often use a practical but inaccurate definition of sudden death: witnessed natural death $<$1 hour of onset of acute symptoms, or unwitnessed unexpected death of someone seen in a stable medical condition $<$24 hours previously.[13] This may cause misclassification, e.g., by inclusion of unwitnessed respiratory failure. Confirmation that SCA was present requires electrocardiogram (ECG) documentation of ventricular tachycardia or ventricular fibrillation (VT/VF), the predominant causative arrhythmias of SCA. The first aim of the present study was therefore to establish whether OPD is associated with an increased risk of SCA with ECG-documented VT/VF. Secondly, we sought to identify subgroups of OPD patients at greatest observed risk, focusing on the possible roles of cardiovascular risk-profile and use of respiratory drugs.

Methods

Ethics statement

The AmsteRdam REsuscitation Study (ARREST) was conducted according to the principles expressed in the Declaration of Helsinki. Written informed consent was obtained from all participants who survived SCA. The Ethics Committee of the Academic Medical Center Amsterdam approved the use of data from patients who did not survive SCA, and approved this study.

Setting and study design

We performed a community-based case-control study. Cases were SCA patients from the ARREST database. Each case was matched to five controls without SCA by age, sex and index date (date of SCA in cases) drawn from the PHARMO record linkage system (`www.PHARMO.nl`).

ARREST is specifically designed to study the causes and outcome of SCA in the community (out-of-hospital). All individual who suffer SCA in the North Holland province of the Netherlands ($>$2.4 million inhabitants) are included.

The ARREST study protocol is described in detail elsewhere.[14] In short, a data collection infrastructure is used to record all SCA parameters, from ambulance dispatch to discharge from the hospital or until death. ECG recordings from the ambulance monitor/defibrillator or automated external defibrillator are used to determine whether VT/VF occurred. Cases were patients older than 40 years with incident SCA; i.e. those with a first diagnosis of SCA, with ECG-documented VT/VF. Patients were excluded when cardiac arrest was caused by trauma, drowning, intoxication, or other unequivocal non-cardiac causes. Patients in whom only asystole (but no VT/VF) was recorded were excluded, because we could not ensure that cardiac arrest stemmed from cardiac causes, as asystole is the end stage of any cardiac arrest, and may be due to non-cardiac causes (e.g., respiratory failure).[15] Of each case, complete medication history of the year before SCA

was retrieved by contacting the patient's pharmacy. Data for the current study were retrieved from July 2005 to December 2008.

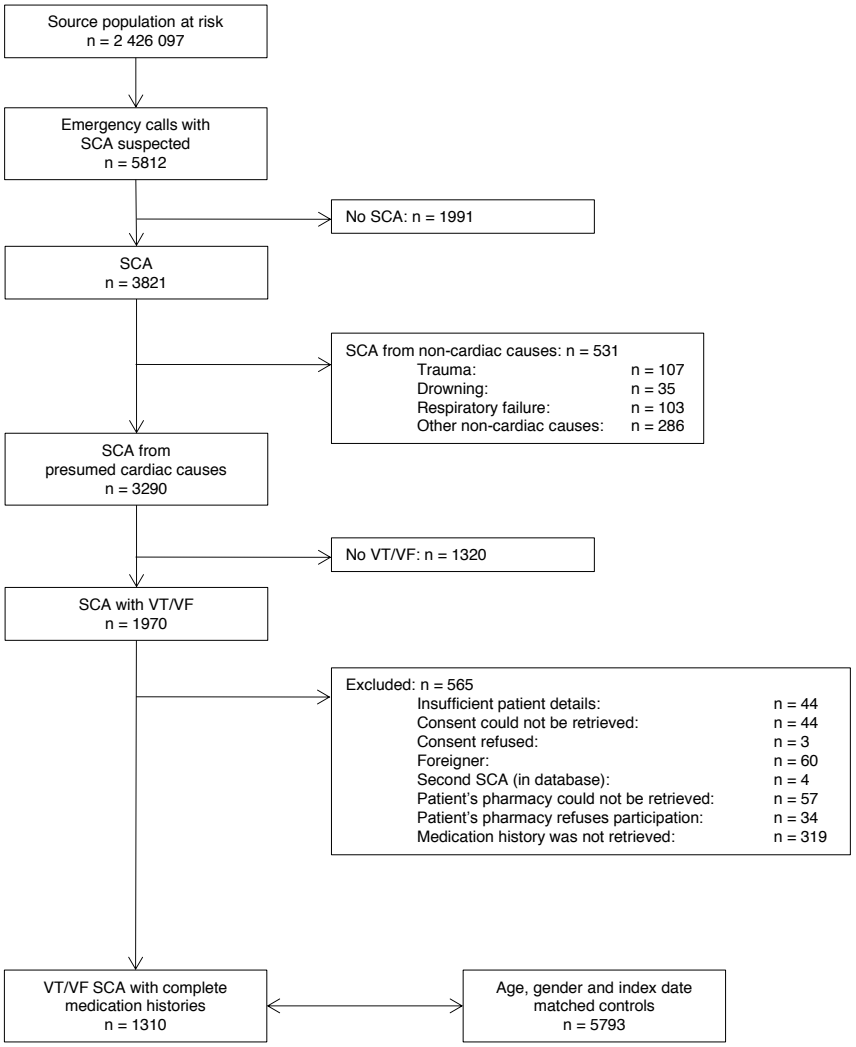
The PHARMO database includes drug-dispensing records from community pharmacies of $>$3 million community-dwelling inhabitants in the Netherlands. The catchment area covers about 12% of the total population of the Netherlands, and is representative of the total population. Since nearly all patients in the Netherlands are registered at a single community pharmacy, independent of prescriber, pharmacy records are essentially complete.[16]

Because it is virtually impossible to disentangle the effects of OPD from those of respiratory drugs, as nearly all OPD patients use such drugs, and those more severely affected generally use more drugs (often from multiple drug classes),[17,18] OPD patients among cases and controls were identified by using the prescription of respiratory medication as proxy; patients were considered to suffer from OPD if they had at least two prescriptions of any drug with Anatomical Therapeutic Chemical classification (ATC) code R03 (drugs for obstructive airway diseases, either oral or inhaled), within one year prior to the index date.

Covariates

As the association between OPD and SCA may be confounded by patient and other characteristics associated with both the presence of OPD and the risk of SCA, we studied the influence of various covariates on the calculated associations. Potential confounders studied were high cardiovascular risk-profile, diabetes mellitus, and current use of antiarrhythmic drugs or non-antiarrhythmic QTc prolonging drugs. High cardiovascular risk-profile was defined as the use of any of the following drugs within 6 months before index date: β-blockers, calcium channel antagonists, angiotensin-converting enzyme inhibitors, diuretics, angiotensin-II receptor blockers, nitrates, platelet aggregation inhibitors, and/or statins.

Figure 1. Flow chart. The source region had a population of 2 426 097 people in 2007 [Netherlands Statistics. http://statline.cbs.nl. Accessed May 15, 2010].



Diabetes mellitus was defined by use of anti-diabetics within six months before index date. Antiarrhythmic drugs were Vaughan-Williams class I or III antiarrhythmic drugs (Appendix 1).[19]

Non-antiarrhythmic QT prolonging drugs were class 1 or 2 QTc prolonging drugs according to the Arizona Center for Education & Research on Therapeutics (Appendix 1). Drug use was defined as current if the index date fell between the prescription date and the end of the prescription period (extended with 10% after the prescribed duration to account for irregular drug use). We defined two age-categories: $<$ 65 years, and $\geq$ 65 years. The number of different respiratory drugs used in the six-month period before index date was used as a proxy for OPD severity.[17,18] OPD patients were grouped according to the current use of respiratory drugs: SABA, LABA, AC, inhaled corticosteroids (ICS), alone or in combinations (mutually exclusive categories). In the Netherlands, OPD is treated almost exclusively with inhaled respiratory medications. Therefore oral medications, such as systemic β_2-agonists, xanthines, or chronic systemic corticosteroid use, were not included in the analyses. In the Netherlands, medications used to treat OPD are not available over-the-counter.

Data analyses

Differences in baseline characteristics were examined with chi-square tests or t-tests. Conditional logistic regression analysis was used to examine the association between SCA and OPD, with adjustment for three sets of confounders: 1) all potential confounders, 2) all covariates that were univariately associated with SCA ($p < 0.05$), 3) all covariates that were univariately associated with SCA and that changed the β-coefficient of the association between OPD and SCA by $\leq$5%. As logistic regression analyses were performed, odds ratios were calculated, which can be interpreted as a risk ratio in case of adequate sampling of controls from the study base. Stratified analyses were performed regarding age category, sex, and cardiovascular risk-profile. The presence of interaction on a multiplicative scale between OPD and cardiovascular risk-profile, was estimated by

Table 1. Baseline characteristics of the study population.

Baseline characteristics	Cases n = 1310	Controls n = 5793	p-value
Mean age (years, standard deviation)	67.1 (12.2)	67.0 (12.2)	n/a
Age group in years			
< 65	546 (42%)	2421 (42%)	
≥65	764 (58%)	3372 (58%)	n/a
Male sex	1015 (78%)	4502 (78%)	n/a
Comorbidities			
High cardiovascular risk-profile[1]	929 (71%)	3049 (53%)	<0.001
Diabetes mellitus[2]	232 (18%)	621 (11%)	<0.001
Current use of concomitant medication[3]			
Antiarrhythmic drugs[4]	60 (4%)	182 (3%)	0.009
β-blockers	463 (35%)	1134 (20%)	<0.001
Class 1 non-antiarrhythmic QT prolonging drugs	21 (2%)	64 (1%)	0.134
Class 2 non-antiarrhythmic QT prolonging drugs	35 (3%)	151 (3%)	0.891
Obstructive pulmonary disease	190 (15%)	622 (11%)	<0.001
Current β-blocker-use in OPD patients	70 (37%)	120 (19%)	<0.001
Current use of inhaled respiratory drugs[3]			
Inhaled short-acting β_2-agonists	62 (5%)	51 (0.9%)	<0.001
Inhaled long-acting β_2-agonists	78 (6%)	127 (2%)	<0.001
Inhaled anticholinergics	78 (6%)	102 (2%)	<0.001
Inhaled corticosteroids	97 (7%)	205 (4%)	<0.001
Other drugs used to treat OPD			
Systemic β_2-agonists[5]	3 (0.2%)	4 (0.1%)	0.096
Xanthines[5]	10 (0.8%)	31 (0.5%)	0.325
Chronically used systemic corticosteroids[6]	18 (1.4%)	93 (1.6%)	0.542

Data are number (%) unless otherwise indicated. OPD: obstructive pulmonary disease.

1. Use of any of the following drugs: β-blockers, calcium channel antagonists, angiotensin converting enzyme inhibitors, diuretics, angiotensin-II receptor blockers, nitrates, platelet aggregation inhibitors, and statins, within six months prior to index date.
2. Use of anti-diabetics within six months prior to index date.
3. Drug use at index date.
4. Class I and III antiarrhythmic drugs and non-antiarrhythmic drugs with (possible) risk of QT prolongation (Appendix 1).
5. Drug use at index date, or within six months prior to index date.
6. Use of systemic corticosteroids with a duration of 90 days or more.

including the cross product of the two factors as a variable in the model. The presence of interaction on an additive scale between OPD and high cardiovascular risk-profile was estimated by determining the synergy index.[20] Subgroup analyses were performed according to disease severity of OPD, and (combinations of) types of current use of respiratory drugs. All data were analysed using the statistical software package SPSS (SPSS for Windows, version 18.0, SPSS Inc.).

Results

During the study period, 3821 instances of cardiac arrest were recorded, of which 1875 cases had ECG-documented VT/VF and were aged >40 years. We excluded 565 patients (Figure 1; excluded vs. included patients: mean age 65.0 [SD 12.2] vs. 67.1 years [SD 12.6], $p < 0.001$; male sex 80% vs. 78%, $p = 0.237$). The study population consisted of 1310 SCA cases; these were matched with 5793 controls without SCA. Characteristics of cases and controls are presented in Table 1. The mean age was 67.1 (SD 12.2, range: 41-99) years, and 78% were male. OPD was more prevalent in cases (15%) than controls (11%, $p < 0.001$).

OPD was independently associated with an increased observed risk of SCA (crude OR 1.4 [1.2-1.7]). The three different models used to adjust for confounding resulted in similar ORs (Table 2). Stratification according to sex showed a stronger effect of OPD in women (adjusted OR 1.8 [1.3-2.6]) than in men (adjusted OR 1.3 [1.03-1.6], Table 3).

The increase in observed SCA risk associated with OPD was slightly stronger in OPD patients younger than 65 (adjusted OR 1.6 [1.2-2.3]) than in OPD patients of 65 years or older (adjusted OR 1.3 [1.03-1.6], Table 3).

Table 2. Determinants of risk of sudden cardiac arrest.

Outcome	Crude OR (95%CI)	Adjusted OR[1] (95%CI)	Adjusted OR[2] (95%CI)	Adjusted OR[3] (95%CI)
Obstructive pulmonary disease	1.4 (1.2-1.7)	1.4 (1.1-1.6)	1.4 (1.1-1.6)	1.4 (1.2-1.6)
High cardiovascular risk-profile[4]	2.5 (2.2-2.9)	2.3 (2.0-2.7)	2.3 (2.0-2.7)	2.5 (2.2-2.9)
Diabetes mellitus[5]	1.8 (1.5-2.1)	1.5 (1.2-1.7)	1.5 (1.2-1.7)	
Use of antiarrhythmic drugs[6]	1.5 (1.1-2.0)	1.2 (0.9-1.6)	1.2 (0.9-1.6)	
Class 1 non-antiarrhythmic QT prolonging drugs[6]	1.4 (0.8-2.3)	1.2 (0.7-2.0)		
Class 2 non-antiarrhythmic QT prolonging drugs[6]	1.0 (0.7-1.5)	1.0 (0.7-1.4)		

CI: confidence interval, OR: odds ratio.

1. Adjusted for all potential confounders.
2. Adjusted for all covariates that were univariately associated with sudden cardiac arrest.
3. Adjusted for all covariates that were univariately associated with sudden cardiac arrest and changed the β with at least 5%.
4. Use of any of the following drugs: β-blockers, calcium channel antagonists, angiotensin converting enzyme inhibitors, diuretics, angiotensin-II receptor blockers, nitrates, platelet aggregation inhibitors, and/or statins, within six months prior to index date.
5. Use of anti-diabetics within six months prior to index date.
6. Class I and III antiarrhythmic drugs and non-antiarrhythmic drugs with (possible) risk of QT prolongation (Appendix 1).

When we studied cardiovascular risk-profile in detail, we found that SCA risk was observed to be most elevated in OPD patients with a high cardiovascular risk-profile (OR 3.5 [2.7-4.4]), and less so in patients without OPD, but with a high cardiovascular risk-profile (OR 2.5 [2.1-2.9]) or in OPD patients with a low cardiovascular risk-profile (OR 1.3 [0.9-1.9]). No significant interaction between cardiovascular risk-profile and OPD was observed on a multiplicative scale, nor on an additive scale. The observed SCA risk increased in parallel with OPD severity: compared to patients without OPD, the observed SCA risk was more elevated in patients with very severe OPD (adjusted OR 1.8 [1.2- 2.7]) than in patients with moderate OPD (adjusted OR 1.4 [1.1-1.7], Table 4).

Table 3. Obstructive pulmonary disease and the risk of sudden cardiac arrest stratified by age group, sex and cardiovascular risk profile.[1]

Outcome		Cases n = 1310	Controls n = 5793	Crude OR (95%CI)	Adjusted OR[2] (95%CI)
By age group (years)					
<65 with OPD		58/546 (11%)	163/2421 (7%)	1.6 (1.2-2.3)	1.6 (1.2-2.3)
≥65 with OPD		132/764 (17%)	459/3372 (14%)	1.3 (1.1-1.6)	1.3 (1.03-1.6)
By sex					
Women with OPD		51/295 (17%)	124/1291 (10%)	2.0 (1.3-2.8)	1.8 (1.3-2.6)
Men with OPD		139/1015 (14%)	498/4502 (11%)	1.3 (1.04-1.6)	1.3 (1.03-1.6)
By cardiovascular risk-profile					
No OPD	Low risk profile	342 (26%)	2505 (43%)	Reference	n/a
	High risk profile	778 (59%)	2666 (46%)	2.5 (2.1-2.9)	n/a
OPD	Low risk profile	39 (3%)	239 (4%)	1.3 (0.9-1.9)	n/a
	High risk profile	151 (12%)	383 (7%)	3.5 (2.7-4.4)[3]	n/a

Data are number (%). CI: confidence interval, CVD: cardiovascular disease, n: number, n/a: not applicable, OPD: obstructive pulmonary disease, OR: odds ratio.

1. Use of β-blockers, calcium channel antagonists, angiotensin converting enzyme inhibitors, diuretics, angiotensin-II receptor blockers, nitrates, platelet aggregation inhibitors, and/or statins within six months prior to index date.
2. Adjusted for cardiovascular risk profile.
3. Interaction on a multiplicative scale: OR 1.1 (0.7-1.6), on an additive scale: synergy index 1.4 (0.7-2.6).

Analysis of current use of respiratory drug revealed that increased SCA risk was associated with the use of SABA only (adjusted OR 3.9 [1.7-8.8]) or AC only (adjusted OR 2.7 [1.5-4.8]), but not ICS only, while use of LABA only was too rare to draw any conclusions (Table 4). Use of SABA or AC in combination with other

respiratory drugs was also associated with increased SCA risk. Patients who used both SABA and AC, in combination with LABA and/or ICS, had the highest observed SCA risk (adjusted OR 7.6 [3.7-15.6], Table 4). SCA risk associated with SABA or AC use (alone or in combination with other respiratory drugs) was particularly elevated in the presence of a high cardiovascular risk-profile (SABA: 45 cases [3%], 33 controls [0.6%], adjusted OR 6.0 [3.8-9.5], AC: 61 cases [5%], 80 controls [1%], adjusted OR 3.5 [2.4-4.9]).

Discussion

This is the first study to show that OPD is associated with a 40% increased risk of ECG-confirmed SCA. Multiple analytical approaches were applied to account as much as possible for confounding. These analyses consistently demonstrated a statistically significantly increased observed risk of SCA in OPD patients, with an OR of 1.4. This provides some evidence of the robustness of our findings, but residual confounding cannot be completely ruled out, because of potential misclassification in some of our measurements. The increase in observed SCA risk is most pronounced in OPD patients with a high cardiovascular risk-profile. Use of SABA increases SCA risk among OPD patients, particularly in patients with a high cardiovascular risk-profile: in these patients a six-fold increased SCA risk was observed compared to patients without OPD.

The observed increased risk of SCA in OPD patients may be, in part, due to the higher prevalence of concomitant cardiovascular disease and cardiac arrhythmias, as these are risk factors for VT/VF. However, adjusting our analyses for cardiovascular risk-profile, current use of anti-arrhythmic drugs (as a proxy for pre-existing cardiac arrhythmias), and QT prolonging drugs (which may evoke cardiac arrhythmias) did not alter the OR for SCA risk. Still, the strongest association with SCA was observed in OPD patients with a high cardiovascular

Table 4. The risk of sudden cardiac arrest in obstructive pulmonary disease categorized in subgroups by disease severity and current use of respiratory medication.

Outcome		Cases n = 1310	Controls n = 5793	Crude OR (95% CI)	Adjusted OR[1] (95% CI)
Disease severity of OPD[2]					
No OPD		1120 (86%)	5171 (89%)	Reference	Reference
OPD	Mild (0 drugs)	12 (1%)	61 (1%)	0.9 (0.5-1.7)	0.9 (0.5-1.7)
	Moderate (1-2 drugs)	99 (8%)	334 (6%)	1.4 (1.1-1.7)	1.4 (1.1-1.7)
	Severe (3 drugs)	45 (3%)	147 (3%)	1.4 (1.01-2.0)	1.3 (0.9-1.9)
	Very severe (>3 drugs)	34 (3%)	80 (1%)	1.9 (1.3-2.9)	1.8 (1.2-2.7)
Current use of respiratory drugs					
No OPD		1120 (86%)	5171 (89%)	Reference	Reference
OPD	No SABA, AC, LABA or ICS	52 (4%)	358 (6%)	0.7 (0.5-0.9)	0.7 (0.5-0.9)
	SABA only	12 (0.9%)	13 (0.2%)	4.1 (1.9-9.0)	3.9 (1.7-8.8)
	LABA only	2 (0.2%)	5 (0.1%)	1.7 (0.3-9.0)	1.8 (0.3-9.2)
	AC only	19 (2%)	30 (0.5%)	2.8 (1.6-5.0)	2.7 (1.5-4.8)
	ICS only	11 (0.8%)	78 (1.3%)	0.6 (0.3-1.2)	0.7 (0.4-1.3)
	SABA + AC	8 (0.6%)	10 (0.2%)	3.5 (1.4-8.9)	2.6 (1.02-6.7)
	ICS + LABA	26 (2%)	57 (1.0%)	2.0 (1.3-3.3)	2.0 (1.2-3.2)
	SABA + LABA and/or ICS	14 (1%)	11 (0.2%)	5.5 (2.5-12.1)	5.3 (2.4-12.0)
	AC + LABA and/or ICS	23 (2%)	46 (0.8%)	2.3 (1.4-3.8)	2.0 (1.2-3.4)
	SABA + AC + LABA and/or ICS	23 (2%)	14 (0.2%)	7.9 (3.9-16.0)	7.6 (3.7-15.6)

Data are number (%) or odds ratios (95%CI). Categories are mutually exclusive.
ATC: Anatomical Therapeutic Chemical classification system, AC: anticholinergics, CI: confidence interval, ICS: inhaled corticosteroids, LABA: long-acting β_2-agonists, n: number, OPD: obstructive pulmonary disease, OR: odds ratio, SABA: short-acting β_2-agonists.

1. Adjusted for concomitant cardiovascular disease.
2. Number of different respiratory drugs used (ATC code R03) in the six-month period before index date. Patients with mild OPD are patients who received at least two prescriptions of any drug ATC code R03 (drugs for obstructive airway diseases), within one year prior to the index date, but who did not use any of these drugs in the six-month period before index date.

risk-profile, particularly, in those who used SABA. Other shared risk factors for OPD and cardiovascular disease may also play a role, but we were unable to assess them. Smoking, a common cause of COPD, is clearly also associated with ischaemic heart disease.[21] Similarly, systemic inflammation, an important pathophysiologic mechanism in OPD,[8,9] has emerged from epidemiologic studies as a causative factor for atherosclerosis and ischaemic heart disease.[22]

To further support the role of OPD in SCA risk, we found that more severe OPD was more strongly associated with SCA risk than mild OPD. Possibly, chronic hypoxemia, more likely to occur in those with more severe OPD, may contribute to the development of cardiac arrhythmias by increasing resting heart rates, as increased heart rate is associated with increased mortality in both the general population as well as in patients with COPD.[23-25] These cardiac arrhythmias may cause episodes of cardiac ischaemia, which is related to an increased SCA risk.[26] Paradoxically, we found that use of β-blockers among OPD patients was more common in cases than controls. One would probably expect the reverse, as β-blockers are the only drugs proven to prevent sudden death (possibly, in part, through heart rate slowing).[27-30] Moreover, these drugs have long been considered contra-indicated in COPD patients, particularly in those with severe COPD and larger SCA risk. Yet recent evidence indicates that cardio-selective β-blockers are well tolerated by COPD patients, in daily practice the potential disadvantages of making COPD worse by prescribing β-blockers and making cardiac disease worse by refraining from prescribing these drug should be weighed to optimally decide on the use of β-blockers in patients with OPD.[31]

Interestingly, although not statistically significantly, we found a stronger association between OPD and SCA in women than in men. This contrasts with the general population, where the observed SCA risk among women is only a third of that in men.[32] It may be speculated that this difference is, in part, mediated by concomitant, yet unrecognised and thus untreated, cardiovascular disease in women.

The clinical presentation of ischaemic heart disease in women differs from that in men. Symptoms of myocardial infarction are often labelled as "atypical" in women, as women are less likely to report the key symptom, chest pain or discomfort, than men.[33] We observed that, in the studied population, patients who received SABAs at the time of SCA, especially when combined with other respiratory drugs, had a higher SCA risk than patients who received other respiratory drugs. For LABAs, this association was less clear. The association between SABA use and SCA may be explained as follows. β_2-agonists act on the β_2-adrenergic receptors of bronchial smooth muscle, leading to dilatation of the bronchi, which results in relief of symptomatic wheeze and dyspnoea, and improvement of lung function.[34-25] However, β_2-adrenergic receptors are also present in the heart. Here, their stimulation results in increased myocardial contractility and heart rate.[34] An elevated heart rate is associated with an increased risk of cardiac mortality in the general population,[36] and in COPD patients. Moreover, β_2-agonists lower serum potassium levels due to intracellular uptake of potassium by stimulation of membrane-bound Na/K-ATPase; this may cause cardiac arrhythmias.[34 37] Finally, inhaled β_2-agonists prolong the ECG QT interval, a risk factor for mortality,[38] and this effect is dose-dependent.[35]

Consequently, soon after their availability in the 1960s, concerns have emerged about potentially serious adverse effects of β_2-agonists on the heart, although the currently available studies and meta-analyses yield conflicting results. The meta-analysis of Salpeter *et al*. showed that use of β_2-agonists in OPD patients increases the risk of cardiovascular events.[11] In contrast, a review of Wood-Baker *et al*. concluded that there is no evidence of increased mortality associated with the use of SABAs in COPD patients,[39] and Suissa *et al*. suggest that the use of β_2-agonists only increases the risk of cardiac mortality in certain administration forms.[40] An alternative explanation for the association of β_2-agonist use with cardiovascular mortality is that the intensity of use, and combined use with other respiratory drugs, reflects the severity of OPD. Our study adds to this discussion by the observation that, while elevated SCA risk is, in general, associated with SABA use, this is particularly true for patients with high cardiovascular risk-profile.

In accordance with previous studies which showed that AC use was associated with an increased risk of cardiovascular death,[12] we found that OPD patients who received AC showed an overall increased risk of SCA, although to a lesser extent than patients receiving SABA. In contrast, the UPLIFT-trial did not show an increased risk of cardiovascular mortality in COPD patients using AC (tiotropium).[41] Based upon this trial, the Food and Drug Administration in 2010 concluded that current studies did not support the notion that there is an increased risk of death associated with tiotropium.[42] In accordance with this conclusion, we cannot rule out that our observed increase in SCA risk of OPD patients who receive AC may reflect COPD severity, rather than a pro-arrhythmic effect of AC per se, as AC are mainly used by COPD patients (not by patients with asthma), especially those with advanced disease. In any case, SCA risk associated with AC use was largest in OPD patients with a high cardiovascular risk profile.

Strengths and limitations

A major strength of our study is that ARREST was specifically designed to study the determinants of SCA. This ensured that SCA diagnosis was accurate. SCA was validated by the presence of VT/VF on the ECG. This is especially important in OPD patients, because sudden death caused by cardiac arrest may easily be confused with sudden death caused by respiratory failure.[15] Another strength is that our findings are representative for the community at large, because we studied the general population, including both urban and rural areas, and captured $>$90% of all SCA cases.[14] We only excluded eligible cases and controls because of incompleteness of data. If such incompleteness is associated with the determinant of interest (i.e. OPD) this may lead to (selection) bias. Since the main reasons of incompleteness (e.g. consent could not be retrieved or was refused, patient's pharmacy could not be retrieved or refused participation) were highly unlikely to be related to the presence of OPD, such bias does not play an important role in our study.

A limitation is that, as this is an observational study, we were unable to completely distinguish between the effects of OPD per se and those of the respiratory drugs used to treat OPD. We addressed this problem by performing subgroup analyses according to disease severity, and current use of respiratory medication. Misclassification in the diagnosis of OPD could have occurred, as we defined the presence of the disease by the use of two prescriptions of respiratory drugs within one year before index date. Still, the risk of misclassification is probably limited, as these drugs are indicated exclusively for OPD, and patients with OPD who received less than two prescriptions of any respiratory drug in the past year most likely are patients with very mild disease. Besides, such a misclassification is most likely to be non-differential, i.e. not related to the risk of SCA and thus most likely results in an underestimation of the true association between OPD and SCA. Similarly, as we defined the presence of the disease by the use of medication, it was impossible to distinguish between asthma and COPD. However, we defined subgroups based on age, with the 65-years-or-younger group most likely to be asthma patients, and the 65-years-or-older group most likely to be COPD patients. Also, there may be some misclassification on drug exposure, as it is impossible to ascertain whether the patients who received a prescription for inhalation medication actually used these drugs on the index date. This may especially be true for SABA, as these are generally intermittently used as symptomatic treatment. Finally, SCA is the first clinically identified expression of heart disease in up to one-half of the instances of SCA.[43] Therefore, many important clinical measurements, such as information on smoking and alcohol use, or history of syncope or arrhythmias have never been made before the SCA episode. Smoking is an important risk factor for both COPD and cardiovascular disease, and we assume that smoking rates were higher among OPD patients than controls.

Conclusions

We observed that the overall risk of SCA is 40% higher in patients with OPD than in patients without OPD, and we were able to identify subgroups of OPD patients in whom this risk was most elevated: those with a high cardiovascular risk-profile, those who receive SABA, and possibly those who receive AC at the time of SCA. Our findings may provide the basis for refinements in treatment strategies for OPD patients. We therefore would recommend a prospective trial to evaluate the effectiveness of more integrated pulmonary and cardiovascular care (e.g., investigations to detect previously unrecognised cardiovascular disease) in these high-risk patients.

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Appendix 1. Class I and III antiarrhythmic drugs, according to the classification of Vaughan-Williams[19] (ATC code: C01B, C07AA07), and non-antiarrhythmic drugs with (possible) risk of QT prolongation according to the Arizona Center for Education & Research on Therapeutics (http://www.azcert.org/medical-pros/drug-lists/bycategory.cfm, accessed on December 2, 2011).

Class I and III antiarrhythmic drugs	Class 1 non-antiarrhythmic QT prolonging drugs[1]	Class 2 non-antiarrhythmic QT prolonging drugs[2]	
Class Ia	Arsenic trioxide	Alfuzosin	Perflutren lipid
Quinidine	Astemizole	Amantadine	microspheres
Procainamide	Bepridil	Atazanavir	Quetiapine
Disopyramide	Chloroquine	Azithromycin	Ranolazine
Sparteine	Chlorpromazine	Chloral hydrate	Risperidone
Ajmaline	Cisapride	Clozapine	Roxithromycin
Prajmaline	Citalopram	Dolasetron	Sertindole
Lorajmine	Clarithromycin	Escitalopram	Sunitinib
Class Ib	Domperidone	Famotidine	Tacrolimus
Lidocaine	Droperidol	Felbamate	Tamoxifem
Mexiletine	Erythromycin	Foscarnet	Telithromycin
Tocainide	Halofantrine	Fosphenytoin	Tizanidine
Aprindine	Haloperidol	Gatifloxacin	Vardenafil
Class Ic	Levomethadyl	Gemifloxacin	Venlafaxine
Propafenone	Mesoridazine	Granisetron	Voriconazole
Flecainide	Methadone	Indapamide	Ziprasidone
Lorcainide	Moxifloxacin	Isradipine	
Encainide	Pentamidine	Lapatinib	
Class III	Pimozide	Levofloxacin	
Amiodarone	Probucol	Lithium	
Bretylium tosilate	Sparfloxacin	Moexipril/HCTZ	
Bunaftine	Terfenadine	Nicardipine	
Dofetilide	Thioridazine	Nilotinib	
Ibutilide	Vandetanib	Octreotide	
Tedisamil		Ofloxacin	
Dronedarone		Ondansetron	
Sotalol		Oxytocin	
Moricizine		Paliperidone	
Cibenzoline			
Vernakalant			

1. Drugs with Risk of torsade de pointes and QT prolongation
2. Drugs with Possible Risk of torsade de pointes and QT prolongation

3.2

REDUCED IN-HOSPITAL SURVIVAL RATES OF OUT-OF-HOSPITAL CARDIAC ARREST VICTIMS WITH OBSTRUCTIVE PULMONARY DISEASE

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Abstract

Background

Out-of-hospital cardiac arrest (OHCA) due to sustained ventricular tachycardia/fibrillation (VT/VF) is common and often lethal. Patient's comorbidities may determine survival after OHCA, and be instrumental in post-resuscitation care, but are poorly studied. We aimed to study whether patients with obstructive pulmonary disease (OPD) have a lower survival rate after OHCA than non-OPD patients.

Methods

We performed a community-based cohort study of 1172 patients with non-traumatic OHCA with ECG-documented VT/VF between 2005 and 2008. We compared survival to Emergency Room (ER), to hospital admission, to hospital discharge, and at 30 days after OHCA, of OPD-patients and non-OPD patients, using logistic regression analysis. We also compared 30-day survival of patients who were admitted to hospital, using multivariate logistic regression analysis.

Results

OPD patients ($n = 178$) and non-OPD patients ($n = 994$) had comparable survival to ER (75% vs. 78%, OR 0.9 [0.6-1.3]) and to hospital admission (56% vs. 57%, OR 1.0 [0.7-1.4]). However, survival to hospital discharge was significantly lower among OPD patients (21% vs. 33%, OR 0.6 [0.4-0.9]). Multivariate regression analysis among patients who were admitted to hospital (OPD: $n = 100$, no OPD: $n = 561$) revealed that OPD was an independent determinant of reduced 30-day survival rate (39% vs. 59%, adjusted OR 0.6 [0.4-1.0, $p = 0.035$]).

Conclusions

OPD-patients had lower survival rates after OHCA than non-OPD patients. Survival to ER and to hospital admission was not different between both groups. However, among OHCA victims who survived to hospital admission, OPD was an independent determinant of reduced 30-day survival rate.

Introduction

Out-of-hospital cardiac arrest (OHCA) due to ventricular tachycardia/fibrillation (VT/VF) is common and often lethal in both affluent and developing countries.[1,2] Despite much effort, survival after OHCA remains poor, even when cardiopulmonary resuscitation (CPR) by emergency medical services (EMS) personnel is attempted. Survival rate to hospital discharge is generally low and varies greatly, ranging from 3 to 40%.[3,4] This variability is largely attributable to differences in the chain of survival: location of OHCA, presence of a witness, use of automated external defibrillator (AED), and time of onset of CPR, defibrillation, and advanced care.[5-7] However, these factors do not entirely explain the variability in survival after OHCA. Rea *et al*. showed that these links in the pre-hospital chain of care (termed the Utstein measures) collectively predicted 72% of survival variability among all OHCAs, and 40% among bystander-witnessed OHCA with VF.[6] This indicates that patient characteristics may also play an important role. Clearly, recognising the role of these characteristics can have important implications for therapy strategies for OHCA. Yet, reports on the effects of patient characteristics are scarce (on comorbidities)[8, 9] and contradicting (on age[10,11] and sex[12,13]). It is conceivable that obstructive pulmonary disease (OPD; i.e., asthma and/or chronic obstructive pulmonary disease [COPD]) may affect survival rate from OHCA. Adverse effects of ventilation and endotracheal intubation during the resuscitation efforts, and increased hypoxemia in OPD patients may negatively impact the patient's chance on survival. Also, concomitant (yet often unrecognised) cardiac disease in OPD patients may play a role.[14]

Yet, systematic studies on the relation between OPD and survival rates from OHCA are lacking. The primary aim of our study was to assess whether OPD patients have a lower survival rate after OHCA than non-OPD patients. We studied in detail at which point in the course of post-resuscitation care survival rates between both groups diverge by comparing survival to emergency room (ER), survival to hospital admission, survival to hospital discharge, and 30-day survival.

Secondly, we aimed to compare the duration of hospital care and the quality of outcome (neurologic outcome) between OPD patients and non-OPD patients who were discharged from hospital alive.

Methods

Setting and study region

The AmsteRdam REsuscitation STudy (ARREST) research group prospectively collects data of all OHCA since June 2005 in the North Holland province of the Netherlands. This region covers 2404 km^2 (urban and rural communities) and had a population of 2,426,097 in 2007.[15] In case of a medical emergency, people dial the national emergency number. Calls are transferred to the regional EMS dispatch centre. When suspecting a cardiac arrest, the EMS dispatcher sends out 2 ambulances from a single tier.[16] Further details of the EMS system were described elsewhere.[17]

Study design

Data of all resuscitations during the study period, from arrival of EMS personnel until hospital discharge or death, were collected according to Utstein recommendations.[18] To determine the survival of OHCA victims with or without OPD, a prospective cohort study was performed. This study was conducted according to the principles expressed in the Declaration of Helsinki. Written informed consent was obtained from all participants who survived OHCA. The Ethics Committee of the Academic Medical Center Amsterdam approved the study, including the use of data from patients who did not survive OHCA.

Patient selection

Of each patient in whom a resuscitation attempt was undertaken by EMS personnel, the ECG from the ambulance or AED was retrieved and analysed. Patients

were included for the present study if they had OHCA with ECG-documented VT/VF from presumed cardiac causes. All OHCAs were considered to be from cardiac causes unless an unequivocal non-cardiac cause was documented (i.e., drowning or trauma). This was verified by reviewing all case files. We excluded EMS-witnessed OHCAs, since emergency call - response intervals and immediate resuscitation by EMS personnel have enormous impact on survival chances,[6] and excluded aborted resuscitation efforts in individuals with a "do not resuscitate" status. As we aimed to perform a complete case analysis, we excluded patients of whom the medication history of the year before OHCA could not be retrieved, and those of whom data on the chain of resuscitation care were missing.

Definitions and covariates

OHCA was defined as the cessation of cardiac mechanical activity as confirmed by the absence of signs of circulation,[18] occurring out-of-hospital. Patients were considered to have OPD if they had at least two prescriptions of any medication with Anatomical Therapeutic Chemical classification system (ATC) code R03 (drugs for obstructive airway diseases) in the year before OHCA. Data of medication use at the time of OHCA, and in the year before OHCA, were obtained from the patient's community pharmacy. Survival was assessed at different time points: survival to emergency room (ER), survival to hospital admission, survival to hospital discharge (information retrieved from hospital records), and 30-day survival (retrieved from the civic registry). Duration of hospital care (in days) was retrieved from hospital records. Two researchers (JB and AB) classified neurologic outcome on the Cerebral Performance Category (CPC) scale by reviewing hospital charts of patients who survived until hospital discharge. Category 1 represents good cerebral performance; category 2 moderate cerebral disability; category 3 severe cerebral disability; category 4 coma or vegetative state; and category 5 death.[19] Neurologically intact survival was defined as CPC category 1 or 2.[18]

The following prognostic factors were considered to be potential confounding factors: older age ($>$65 years), sex, cardiovascular co-morbidity (defined by medi-

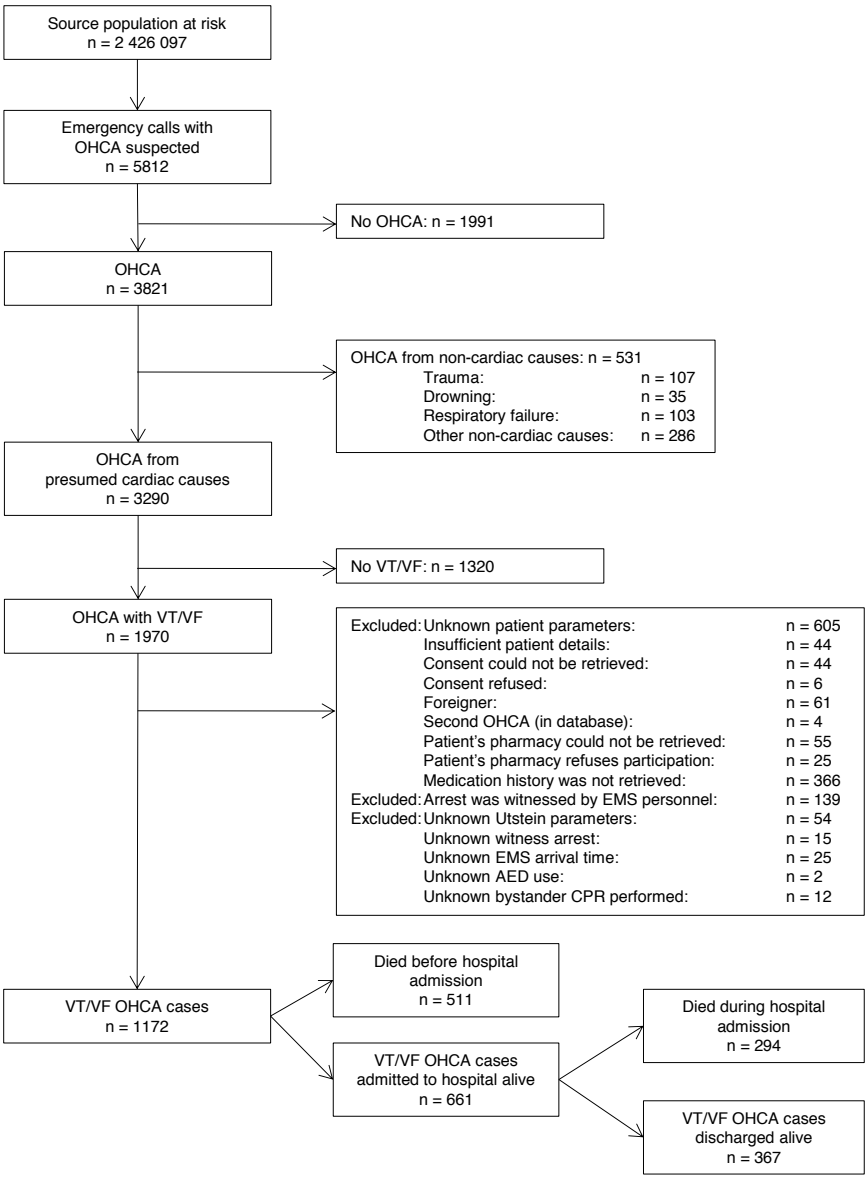
cation use: β-blockers, calcium antagonists, angiotensin converting enzyme inhibitors, diuretics, angiotensin-II receptor blockers, platelet aggregation inhibitors, nitrates and/or statins within 6 months before OHCA), bystander witnessed OHCA, public location of OHCA, bystander CPR performed, use of AED, and time interval from emergency call to arrival of EMS personnel.

Data analysis

To establish the association between OPD and survival after OHCA, we first studied all OHCA patients with documented VT/VF (n = 1172, Figure 1). As primary outcome measure in this analysis, we used 30-day survival, as this can be determined for all patients regardless of hospitalisation status. Secondary outcome measures were survival rates at succeeding stages in the chain of care: 1. survival to arrival at the ER, 2. survival to hospital admission, and 3. survival to hospital discharge. We performed logistic regression analysis for survival at all stages, adjusting for age and sex.

Next, we determined at which stage of the chain of care survival diverged between OPD patients and non-OPD patients. We then selected all patients who survived up to that stage, and performed multivariate logistic regression analysis, using 30-day survival as outcome measure. We applied two multivariate models: 1. with adjustment for all covariates that were univariately associated with OHCA with VT/VF, and 2. with adjustment for all covariates that were univariately associated with OHCA with VT/VF and changed the point estimate of the association between OPD and outcome with at least 5%.[20] Interaction between OPD and either older age, sex or concomitant cardiovascular disease was estimated by including the cross product of the two factors as a variable in the model. Results are presented as odds ratio (OR) and 95% confidence intervals (95% CI).

Figure 1. Flow chart of patient inclusion



VT/VF: ventricular tachycardia/ventricular fibrillation, OHCA: out-of-hospital cardiac arrest, EMS: emergency medical services, AED: automated external defibrillator, CPR: cardiopulmonary resuscitation.

To compare duration of hospital care and quality of outcome between OPD patients and non-OPD patients who were discharged from the hospital alive, we studied duration of hospital care (in days) and neurologic status at hospital discharge of the patients who were discharged from the hospital alive.

Continuous variables were described as means and standard deviations (SD), or medians and interquartile range where appropriate, and categorical variables as absolute numbers and percentages. Comparisons between groups were performed with chi-square test or analysis of variance were appropriate. All data were analysed using the statistical software package of SPSS (SPSS for Mac, version 18.0, SPSS Inc.).

Results

During the 43-month study period, there were 5812 emergency calls with EMS dispatchers suspecting OHCA. In 3821 instances, EMS personnel attempted to resuscitate. There were 3290 patients with OHCA from presumed cardiac causes, including 1970 with documented VT/VF. After exclusion of non-eligible patients (in 605 patient data unavailable, in 139 EMS-witnessed OHCA, in 54 data on circumstances of OHCA unavailable), the analysis cohort consisted of 1172 patients (Figure 1). Age and sex of included and excluded patients were not meaningfully different: age 63.5 (14.5) vs. 65.8 (14.3) years, respectively, $p < 0.001$; male sex 78% in both groups, $p = 0.78$.

Baseline characteristics of OHCA patients with OPD ($n = 178$) and without OPD ($n = 994$) are shown in Table 1. OPD patients were older (70 [12] vs. 65 [15] years, $p < 0.001$), less often male (71 vs. 79%, $p = 0.02$), and more often used (any type of) cardiovascular medication (80 vs. 67%, $p = 0.001$). In OPD patients, OHCA occurred less often at a public location (28 vs. 39%, $p = 0.007$), AED use was less common (17 vs. 26%, $p = 0.02$), and EMS response time was longer (10.4 vs. 9.6 min, $p = 0.02$). Survival rates of OPD and non-OPD patients are

shown in Figure 2 and Table 2. Thirty-day survival was lower in OPD patients than in non-OPD patients (23 vs. 34%, OR 0.7 [0.5-0.97]). However, survival to ER was comparable (75 and 78%, respectively, OR 0.9 [0.6-1.3]), as was survival to hospital admission (56 and 57%, OR 1.0 [0.7-1.4]). In contrast, survival to hospital discharge was lower in OPD patients (21 vs. 33%, OR 0.6 [0.4-0.9]).

Since survival rates of OPD patients became lower than those of non-OPD patients only after admission to the hospital, we studied the cohort of patients who were admitted to the hospital alive (n = 661, Figure 1, Table 1) to establish whether OPD was an independent determinant of lower survival rate. Within this cohort, OPD patients were older than non-OPD patients (69 [12] vs. 65 [14] years, p = 0.006), less often male (66 vs. 78%, p = 0.008), and more often received (any) cardiovascular medication (79 vs. 69%, p = 0.043). While all resuscitation parameters were less favourable for OPD patients, only the lower rate of bystander CPR reached statistical significance. Table 3 shows ORs for 30-day survival in this cohort, calculated with univariate and multivariate regression analysis (two models). OPD patients had a lower chance of survival (39% vs. 59%, p $<$ 0.001; adjusted OR [first model] 0.6 [0.4-0.99], p = 0.047, adjusted OR [second model] 0.6 [0.4-0.95], p = 0.035). No significant interaction between age, sex or concomitant cardiovascular disease and OPD was observed.

Among patients who were discharged from hospital alive, duration of hospital care was not different between OPD patients and non-OPD patients (26 vs. 27 days, p = 0.825, Table 4). Also, CPC scores were similar (Table 4), as was the proportion of neurologically intact survival (95% and 94%, p = 0.787).

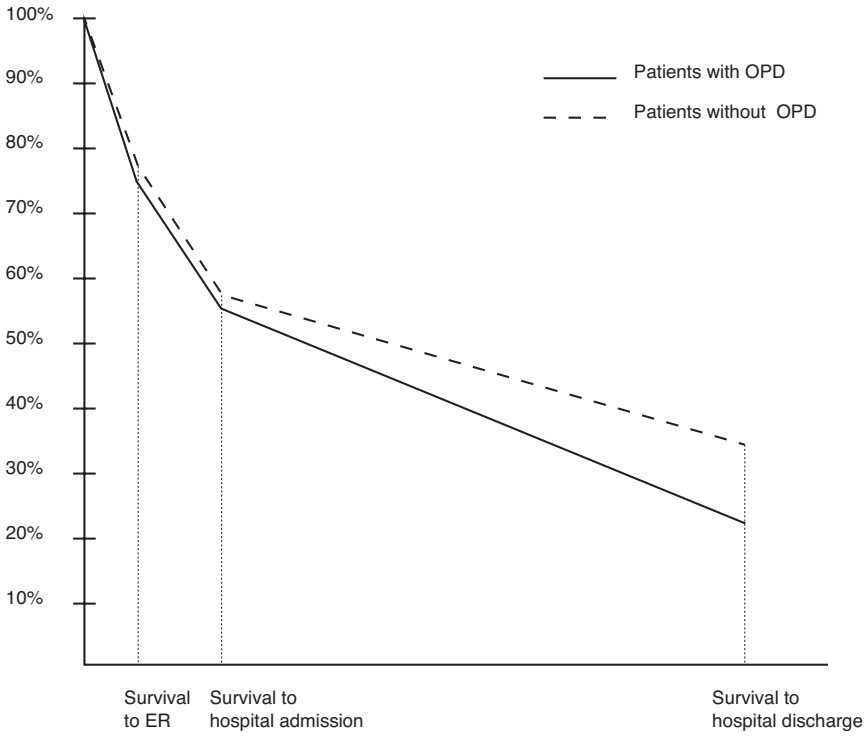
Table 1. Baseline characteristics of the study population (all patients: n = 1172, patients admitted to hospital alive: n = 661).

Baseline characteristics	All patients			Patients admitted to hospital alive		
	OPD	No OPD	p-value	OPD	No OPD	p-value
Number of events	178	994		100	561	
Mean age (years)	70 (12)	65 (15)	<0.001	69 (12)	64 (14)	0.006
Older age (≥65 years)	123 (69%)	545 (55%)	<0.001	67 (67%)	295 (53%)	0.008
Male sex	127 (71%)	785 (79%)	0.024	66 (66%)	439 (78%)	0.008
Cardiovascular disease[1]	142 (80%)	668 (67%)	0.001	79 (79%)	387 (69%)	0.043
Resuscitation parameters						
Collapse at public location	50 (28%)	385 (39%)	0.007	34 (34%)	249 (44%)	0.053
Witnessed collapse	152 (85%)	855 (86%)	0.826	86 (86%)	512 (91%)	0.099
Bystander CPR performed	122 (69%)	734 (74%)	0.142	68 (68%)	436 (78%)	0.035
AED used	31 (17%)	258 (26%)	0.015	21 (21%)	168 (30%)	0.068
EMS response time in min, median (Q1-Q3)	10.4 (8.0-13.1)	9.6 (7.5-11.9)	0.021	9.9 (7.4-13.1)	9.0 (6.8-11.5)	0.075

Values are means (SD) for continuous variables and absolute numbers (percentages) for dichotomous variables. Comparisons of continuous variables were made with ANOVA; the chi-square test was used when binary variables were compared. All statistical tests were 2 tailed.
AED: automated external defibrillator, CPR: cardiopulmonary resuscitation, EMS: emergency medical services, OPD: obstructive pulmonary disease, Q: quartile, SD: standard deviation.

1. Use of β-blocker, calcium antagonist, angiotensin converting enzyme inhibitor, diuretic, angiotensin-II receptor blocker, platelet aggregation inhibitors, nitrate and/or statin within 6 months prior to out-of-hospital cardiac arrest.

Figure 2. Survival rates after OHCA of OPD patients and non-OPD patients, at Emergency Room, hospital admission, and hospital discharge.



Discussion

Patients with OPD had a 40% lower chance on 30-day survival after OHCA than patients without OPD. Survival rates were similar for OPD patients and non-OPD patients at the first stages of resuscitation care (survival to ER and survival to hospital admission); it is only after admission to hospital that the survival rate of OPD patients became lower than of non-OPD patients. These findings support

the idea that survival at early stages is mostly determined by pre-hospital chain of care factors, while patient characteristics play a larger role in late (eventual) survival.

In accordance with our findings, Carew *et al.*[8] reported that the chance of survival after OHCA declines as the number of co-morbidities (including lung disease) increases. However, co-morbidities in the study of Carew were not so well ascertained as in our study because they were collected solely from EMS reports. Moreover, their analysis included ambulance witnessed arrests, which arguably could be considered as in-hospital cardiac arrests when analysing survival. Most importantly, we discovered that reduction in survival rate of OPD patients (relative to non-OPD patients) occurs when these patients are already admitted to hospital.

Table 2. Survival rates and Odds Ratios for survival at various stages, patients with and without OPD (n = 1172).

Outcome	Patients with OPD n = 178	Patients without OPD n = 993	OR[1] (95%CI)
30-day survival	40 (23%)	333 (34%)	0.7 (0.5-0.97)
Survival to ER	134 (75%)	779 (78%)	0.9 (0.6-1.3)
Survival to hospital admission	100 (56%)	561 (57%)	1.0 (0.7-1.4)
Survival to hospital discharge	38 (21%)	329 (33%)	0.6 (0.4-0.9)

Values are numbers (percentage).
CI: confidence interval, ER: emergency room, OPD: obstructive pulmonary disease, OR: odds ratio.
1. ORs are corrected for age and sex.

This finding indicates that it should be feasible to modify treatment strategies in such a way that this mortality gap can be closed (treatment strategies for pre-hospital or in-community care would be much more difficult to implement). Such efforts should be targeted at the pathophysiologic mechanisms that underlie the lower survival rates in OPD patients.

While we did not study these mechanisms, various explanations may be proposed. Firstly, OPD patients have a lower potential for oxygen uptake, and may there-fore have lower 'oxygen reserve', and be more vulnerable to the deleterious effects of hypoxemia during cardiac arrest and resuscitation. Also, endotracheal intubation and ventilation during the resuscitation efforts might enhance the inflammatory response in their already affected airways. Both mechanisms may adversely influence survival. Clearly, future studies must address these issues. Still, improved pre-hospital or in-community treatments to reduce risk of OHCA or survival from OHCA in OPD patients must also be considered. For instance, at present, β-blockers are the only drugs that have shown to prevent sudden cardiac death in some patient categories, notably cardiomyopathy, heart failure, coronary artery disease, and hemodialysis.[21-23] Traditionally, β-blockers have been considered contra-indicated in COPD patients, although evidence indicates that at least cardioselective β-blockers are well tolerated by COPD patients.[24] Interestingly, recent observational studies suggest that long-term treatment with β-blockers may improve survival of COPD patients, including those without known cardiovascular disease.[25,26] As COPD patients have a worse prognosis after OHCA, future research must establish whether or not β-blockers should be given to COPD patients with an indication for these drugs.

Table 3. Thirty-day survival for patients with or without OPD who were admitted to the hospital alive (n = 661).

	30-day survival		Crude OR	Adjusted[1] OR	Adjusted[2] OR
	Yes (n = 371)	No (n = 290)	(95%CI)	(95%CI)	(95%CI)
OPD	39 (11%)	61 (21%)	0.4 (0.3-0.7)	0.6 (0.4-0.99)	0.6 (0.4-0.95)
Age (years)	62 (14)	70 (13)	0.95 (0.94-0.97)	0.96 (0.94-0.97)	0.96 (0.95-0.97)[3]
Male sex	302 (81%)	203 (70%)	1.9 (1.3-2.7)	1.7 (1.1-2.5)	1.6 (1.1-2.4)[4]
Cardiovascular disease[5]	236 (64%)	230 (79%)	0.5 (0.3-0.7)	0.8 (0.5-1.2)	0.8 (0.5-1.2)
OHCA at public location	191 (52%)	92 (32%)	2.3 (1.7-3.1)	1.7 (1.2-2.4)	1.7 (1.2-2.4)
Witnessed OHCA	353 (95%)	245 (85%)	3.6 (2.0-6.4)	3.1 (1.7-5.8)	
Bystander CPR performed	305 (82%)	199 (69%)	2.1 (1.5-3.0)	1.2 (0.8-1.9)	1.5 (1.0-2.2)
AED used	131 (35%)	58 (20%)	2.2 (1.5-3.1)	1.7 (1.1-2.5)	
EMS response time in min[6]	8.4 (6.0-10.7)	10.0 (8.0-12.7)	0.93 (0.90-0.97)	0.95 (0.91-0.99)	0.94 (0.90-0.98)

Values are means (SD) for continuous variables and absolute numbers (percentages) for dichotomous variables.
AED: automated external defibrillator, CI: confidence interval, CPR: cardiopulmonary resuscitation, EMS: emergency medical services, min: minutes, n: number, OHCA: out-of-hospital cardiac arrest, OPD: obstructive pulmonary disease, OR: odds ratio, SD: standard deviation.

1. Adjusted for all covariates that were univariately associated with outcome.
2. Adjusted for all covariates that were univariately associated with outcome and that changed the β with at least 5% (age, sex, cardiovascular medication, collapse at public location, bystander CPR performed, EMS response time).
3. Interaction OPD and older age on a multiplicative scale: OR 0.9 (95% CI 0.3-2.4), p = 0.832.
4. Interaction OPD and sex on a multiplicative scale: OR 1.0 (95% CI 0.4-2.7), p = 0.980.
5. Use of β-blocker, calcium antagonist, angiotensin converting enzyme inhibitor, diuretic, angiotensin-II receptor blocker, platelet aggregation inhibitors, nitrate and/or statin within 6 months prior to out-of-hospital cardiac arrest.
6. Median (first to third quartile).

A major strength of our study is that ARREST was specifically designed to study the determinants and outcomes of OHCA. This ensured that OHCA diagnosis was accurate. A cardiac cause of OHCA was validated by the presence of VT/VF on the ECG. This is especially important in patients with OPD, because sudden death caused by cardiac arrest may easily be confused with sudden death caused by respiratory failure.[14] Another strength is that our findings are representative for the community at large, because we studied the general population, including both urban and rural areas, and captured ~90% of all OHCA cases.[27]

Table 4: Neurologic outcome and duration of hospital admission for patients with and without OPD who were discharged from hospital alive (n = 367).

	OPD (n = 38)	**No OPD (n = 329)**	**p-value**
CPC-score			0.507
CPC=1: Good cerebral performance	31 (82%)	265 (81%)	
CPC=2: Moderate cerebral disability	5 (13%)	43 (13%)	
CPC=3: Severe cerebral disability	1 (3%)	19 (6%)	
CPC=4: Coma or vegetative state	1 (3%)	2 (1%)	
Duration of hospital admission (days)	26 (17)	27 (19)	0.825

Values are means (SD) for continuous variables and absolute numbers (percentages) for dichotomous variables.
CPC: cerebral performance category, OPD: obstructive pulmonary disease, SD: standard deviation.

Some limitations of our study should also be discussed. Non-differential misclassification in the diagnosis of OPD could have occurred, as we defined the presence of the disease by the use of two prescriptions of respiratory drugs within 1 year before OHCA. However, these drugs are indicated exclusively for OPD, and patients with OPD who received less than two prescriptions of any respiratory drug most likely are patients with very mild disease; the misclassification therefore would result in underestimation of the effect. Similarly, our diagnosis of CVD was based on the use of β-blockers, calcium antagonists, angiotensin converting enzyme inhibitors, diuretics, angiotensin-II receptor blockers, platelet aggregation inhibitors, nitrates and/or statins within 6 months before OHCA. Other definitions, e.g. the use of anti-diabetic medication, anti-arrhythmic drugs or digitalis, may lead to different classifications. Still, it may be assumed that patients with a recog-

nised high cardiac risk profile will use at least one of the drugs in the categories of our definition. Furthermore, our findings may partly be explained by the possibility that some patients have been misdiagnosed as OPD, due to misinterpretation of their dyspnoea or other symptoms, while in fact they had unrecognised heart failure.[14] Finally, OPD treatment withdrawal subsequent to the resuscitation may explain part of the observed difference in survival, but was not assessed in our study. Future studies should establish whether in-hospital post-resuscitation care includes sufficient attention for OPD treatment.

In conclusion, we found that OPD patients have a 40% lower chance on 30-day survival after OHCA than non-OPD patients. Survival rates were similar in both groups at the first stages of resuscitation care (survival to ER and survival to hospital admission); it is only after admission to hospital that survival rates of OPD patients became lower than those of non-OPD patients. Our findings suggest that in-hospital post-resuscitation care of OPD patients who suffered OHCA should be adapted in order to close this mortality gap. We aim to raise awareness of the lower survival chances of OPD patients after OHCA; closer monitoring of these patients may provide insight into the pathophysiologic basis of this difference.

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4

PREVENTION OF CARDIAC ARRHYTHMIAS IN DAILY CLINICAL PRACTICE

4.1

SMOKING CESSATION STRATEGIES IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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Abstract

Background

Smoking cessation is the cornerstone of treatment of chronic obstructive pulmonary disease (COPD) patients. This systematic review evaluates the effectiveness of behavioural and pharmacological smoking cessation strategies in COPD patients.

Methods

MEDLINE was searched from January 2002 to October 2011. Randomised controlled trials evaluating the effect of smoking cessation interventions for COPD patients, published in English or Dutch, were selected. The methodological quality of included trials was assessed using the Delphi list by two reviewers independently. The relative risks of smoking cessation due to the intervention, compared with controls, were calculated.

Results

Eight studies met the inclusion criteria. Heterogeneity was observed for study population, the intervention strategy, the follow-up period and the outcome. According to the Delphi list methodological quality scores, five studies were considered to be of acceptable quality. Pharmacological therapy combined with behavioural counselling was more effective than each strategy separately. In COPD patients, the intensity of counselling did not seem to influence the results, nor did the choice of drug therapy make a difference.

Conclusions

This systematic review makes clear that in COPD patients, pharmacological therapy combined with behavioural counselling is more effective than each strategy separately. Neither the intensity of counselling nor the type of anti-smoking drug made a difference.

Introduction

The single most common cause of chronic obstructive pulmonary disease (COPD) is cigarette smoking.[1] About 15 to 20% of smokers develop COPD[2,3] and 37% of the COPD patients are current smokers.[4] Because almost all patients with COPD smoke or have smoked in the past, they are also at increased risk for developing lung cancer[5] as well as cardiovascular diseases (e.g. coronary, peripheral and cerebral artery diseases) and an eventually higher cardiovascular mortality rate.[6-8]

Smoking cessation,[9-11] as well as pharmacological treatment of COPD,[12] improves symptoms and quality of life. However, only smoking cessation substantially changes the clinical course of COPD by reducing the rate of decline of pulmonary function and all-cause mortality.[9,13,14] Additionally, smoking cessation reduces the risk of developing and eventually dying from lung cancer, cardiovascular disease and other tobacco-related illnesses.[15,16] Patients with COPD therefore have a greater and more urgent need to stop smoking than the average smoker. For this, the European Respiratory Society Task Force guidelines for smoking cessation in patients with respiratory disease recommend integration of smoking cessation treatment into the management of the patients' condition.[17,18] However, COPD patients are far more resistant to smoking cessation treatment than "healthy" smokers, partly because of older age, higher pack-year history and stronger physical dependence on nicotine.[19] Because COPD patients have a higher risk for depressive symptoms,[20-25] smoking cessation attempts may be less successful and proportion of relapses may be higher.[21,23]

In 2002, van der Meer *et al.* conducted a Cochrane review to determine the effectiveness of smoking cessation interventions in COPD patients, concluding that a combination of psychosocial and pharmacological interventions is superior to no treatment or to psychological interventions alone. They recommended more randomised controlled trials, investigating whether tailoring interventions to the needs of COPD patients improves quit rates in these patients.[21]

During the last decade, the attitude of physicians towards smoking has changed. More attention has been drawn to the biomedical aetiology of tobacco addiction, perceiving tobacco addiction more as a neuropsychological disease instead of simply an unhealthy lifestyle.[26] Awareness of the importance of smoking cessation medication has not only increased among health professionals, but also among responsible persons in most western governments. New laws have been introduced banning smoking from public places in Europe, Australia, Canada and the USA, and, in addition, the public opinion of smoking has shifted to regard it as something that is not socially acceptable.[27-29]

The aforementioned changes might have affected the randomised controlled trials on smoking cessation intervention programmes tailored to the needs of COPD patients. In order to facilitate implementation of the newest insights in smoking cessation treatment of COPD patients, the aim of this systematic review was to investigate the efficacy and effectiveness of different behavioural and pharmacological smoking cessation strategies in COPD patients since 2002.

Methods

Search strategy

MEDLINE was searched from January 1, 2002 to October 20, 2011. The keywords (Medical Subject Headings and text search terms) describing the study population were 'chronic obstructive pulmonary disease', 'chronic obstructive lung disease', 'COLD', 'emphysem∗', 'bronchit∗', 'COPD', 'emphysema' and 'chronic obstructive airway disease'. The keywords describing smoking cessation interventions were 'smoking', 'smoking cessation', 'tobacco', 'tobacco use cessation', 'tobacco use disorder', 'nicotine', 'cessation intervention', 'smoking cessation program', 'quit∗', 'smok∗' and 'cessation'. All these were combined with keywords referring to outcome 'abstain∗', 'abstin∗', 'abstinence', 'abstination', 'quit∗', 'stop∗', 'cessat∗' and 'ceas∗'. To identify randomised controlled trials validated search terms for MEDLINE searches were used.[30] The search was limited to articles

published in English or Dutch. For determining additional studies, reference lists of review articles and included studies were scrutinised.[21,31-35]

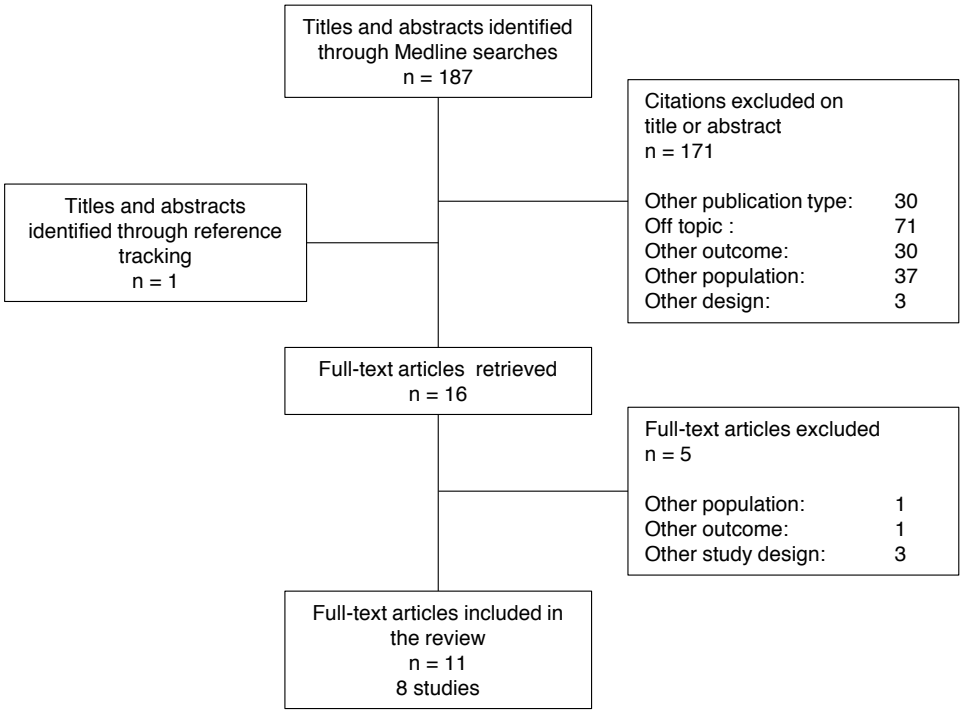
Study selection

Abstracts of identified publications were screened for eligibility. If potentially relevant abstracts did not provide enough information, full papers were retrieved. Studies were selected by applying the inclusion criteria: 1. COPD patients, 2. randomised controlled trial, 3. evaluation of smoking cessation intervention, and 4. published in English or Dutch.

Data extraction and quality assessment

A structured data extraction was performed, focusing on design, setting, type of intervention, patient characteristics, outcome measures and results. Methodological quality of included studies were rated, applying the Delphi list.[36] Items were scored 'yes', 'no', or 'don't know'. Only items that were assessed with 'yes' were given a score of 1 point. A total score for overall methodological quality out of a maximum of 9 points was obtained by applying equal weights to all items. For the definition of 'acceptable methodological quality', an arbitrary but generally accepted cut-off value of 5 points was used. If enough data were available in the original article, i.e. absolute numbers of smoking cessation in each treatment group, the relative risk (RR) with corresponding 95% confidence intervals were calculated by determining the rate of smoking cessation in both the treated group and the untreated group. When both point prevalence and continuous abstinence were provided, only continuous abstinence was reported. Two reviewers (M.J. Warnier and E.E.S. van Riet) independently screened and selected the publications, as well as extracting data and assessing methodological quality. Consensus was used to resolve disagreement. If consensus could not be reached, a third reviewer (A.P.E. Sachs) was consulted.

Figure 1. Flowchart showing results of the search strategy.



Results

Identification of studies

Results of the search strategy are presented in Figure 1. In total, eight randomised controlled trials (11 publications) were included.[9,25,37-45] As these studies were very heterogeneous regarding study population, type of intervention, duration of follow-up and outcome measure, no pooling of data was carried out. Characteristics of the included studies and of the participants within each study are shown in Tables 1 and 2, respectively.

Methodological assessment

According to the Delphi List methodological quality scores, five studies were considered to be of acceptable quality (5 points, Table 3). The scores for methodological quality varied between 3 and 9 points. The study of Wagena *et al.*[25] had a maximum score of 9 points, indicating a low probability of bias. The most prevalent methodological shortcomings were an absence of blinding of the care provider, patient and outcome assessor, and a lack of concealment of the randomisation method. All studies used biochemical validation to confirm self-reported smoking cessation (Table 1). The three studies that did not have an acceptable quality score (5 points) presented the following shortcomings: none of the three studies concealed the treatment allocation or blinded the care provider, patient and outcome assessor. In addition, in the studies by Christenhusz and coworkers[43,44] and Hilberink and co-workers[41,42], the groups were not comparable at baseline. In addition, Christenhusz and co- workers[43,44] did not use an intention-to-treat analysis and Wilson *et al.*[37] did not provide point estimates of smoking cessation.

Behavioural intervention

Borglykke *et al.*[45] showed that patients hospitalised with symptoms of acute exacerbation of COPD who participated in a smoking cessation group significantly

more often stopped smoking after 1 year (29.8%), compared with hospitalised patients who only received information on the benefits of smoking cessation (12.7%, RR 2.3 [1.3- 4.2]).

Combining a pharmacological and behavioural intervention

Added value of a pharmacological intervention

Tashkin *et al*.[49] evaluated the effect of varenicline treatment compared with placebo. After 1 year, the use of varenicline (18.5%) resulted in significantly higher continuous abstinence rates (RR 3.3 [1.9-5.9]) compared with placebo (5.6%).

Wagena *et al*.[25] evaluated the smoking cessation effect of bupropion or nortriptyline. Out of the 225 participants, 44% were at risk for COPD (Global Initiative for Chronic Obstructive Lung Disease stage 0[46]). After 6 months, the use of bupropion (28%) as well as nortriptyline (25%) resulted in higher prolonged abstinence rates compared with placebo (15%). Only the difference between bupropion and placebo reached statistical significance (RR 1.91 [1.04-3.50]). Bupropion and nortriptyline were equally effective (RR 1.12 [0.67-1.86]).

Additional value of a combined intervention

Kotz *et al*.[39] evaluated the effect of confrontational counselling and regular counselling, both combined with nortriptyline, compared with usual care. Compared with usual care, regular counselling with nortriptyline (11.6%) as well as confrontational counselling with nortriptyline (11.2%) increased the prolonged abstinence rates after 1 year, although not statistically significant, compared to usual care (5.9%, RR 2.1 [0.7-5.8] and RR 1.9 [0.7-5.6], respectively). Confrontational counselling and regular counselling plus nortriptyline were equally effective (RR 1.0 [0.5-2.0]).

Table 1. Characteristics of the studies.

First author, year	Methods[1]	Duration of exposure/ follow up	Intervention	Partici-pants, n	Primary endpoint/biochemical validation technique	Results	
						n (%)	RR (95% CI)
Wagena 2005[25]	population based, the Netherlands, RCT, double blind, placebo controlled	12 weeks/ 6 months	I1: bupropion I2: nortriptyline C: placebo All groups: individual face-to-face counselling + supportive telephone calls	255	prolonged abstinence, week 4 to 26/urinary cotinine <60 ng/ml	I1: 24/86 (27.9%) I2: 20/80 (25.0%) C3: 13/89 (14.6%)	I1 vs. C: 1.9 (1.0-3.5) I2 vs. C: 1.7 (0.9-3.2) I1 vs. I2: 1.1 (0.7-1.9)
Tønnesen 2006[9]	hospital outpatients, Denmark, RCT, placebo controlled	1 year/ 1 year	I1: nicotine sublingual tablet + low support I2: nicotine sublingual tablet + high support I3: placebo sublingual tablet + high support C: placebo sublingual tablet + low support	370	sustained abstinence, week 2 to 52/CO-measurement <10 ppm	NRT vs. placebo: NRT: 26/185 (14.1%) Placebo: 10/185 (5.4%) High vs. low support: High: 19/187 (10.2%) Low: 17/183 (9.3%)	NRT vs. placebo: 2.6 (1.3-5.2) High vs. low support: 1.1 (0.6-2.0)
Christenhusz 2007[43,44]	hospital outpatients, the Netherlands, RCT	3 months/ 1 year	I: SmokeStopTherapy (SST) = group and individual counselling, telephone contacts, free bupropion C: MIS for lung patients	225	continuous abstinence, 1 year/salivary cotinine <20 ng/ml	I: 20/114 (17.5%) C: 9/111 (8.1%)	2.2 (1.0-4.5)
Wilson 2008[37]	hospital outpatients, Ireland, RCT	5 weeks/ 1 year	C: usual care, brief advice to stop smoking I1: individual support, 5 individual sessions with nurse + free NRT offered I2: group support, brief advice to stop smoking + 5 group sessions with nurse + free NRT offered	91	complete cessation, 1 year/CO-measurement ≤10 ppm + salivary cotinine ≤10 ng/ml	C: 0 I1: 0 I2: 0	NS

Table 1. Characteristics of the studies (continued).

First author, year	Methods[1]	Duration of exposure/ follow up	Intervention	Partici-pants, n	Primary endpoint/ biochemical validation technique	Results	
						n (%)	RR (95% CI)
Borglykke 2008[45]	hospitalized patients, Denmark, RCT	5 weeks/ 1 year	C: no additional intervention I: participation in smoking cessation group, weekly 2 hour sessions, 5 weeks All groups: information on benefit of smoking cessation at admission	223	point abstinence, 1 year/ carbohemoglobin measurement <2%	C:13/102 (12.7%) I: 36/121 (29.8%)	2.3 (1.3-4.2)
Kotz 2009[39]	population based, the Netherlands, RCT	4 weeks/ 1 year	C: usual care I1: confrontational counselling by nurse + nortriptyline I2: health education and promotion by nurse + nortriptyline	296	prolonged abstinence week 5 to 52/urinary cotinine <50 ng/ml	C: 4/68 (5.9%) I1: 13/116 (11.2%) I2: 13/112 (11.6%)	I1 vs. I2: 1.0 (0.5-2.0) I1 vs. C: 1.9 (0.7-5.6) I2 vs. C: 2.0 (0.7-5.8)
Tashkin 2011[38]	hospital outpatients, United States, Spain, France, Italy, RCT	12 weeks/ 1 year	C: Placebo I: Varenicline All groups: educational booklet, brief counselling sessions at telephone call (n = 6) and clinic visits (n = 19)	499	continuous abstinence, 1 year/ CO measurement ≤10 ppm	I: 46/248 (18.5%) C: 14/251 (5.6%)	3.3 (1.9-5.9)
Hilberink 2011[41,42]	GP practices, the Netherlands, cluster RCT	depending on motiva-tional stage/ 1 year	I1: counselling strategy + NRT I2: counselling strategy + NRT + bupropion C: usual care Counselling strategy: intensified MIS according to motivational stage	667	point prevalence, 1 year/urinary cotinine lever <50 ng/ml	I1: 18/243 (7.4%) I2: 21/276 (7.6%) C: 5/148 (3.4%)	I2 vs. I1: 1.0 (0.6-1.9) I1 vs. C: 2.2 (0.8-5.8) I2 vs. C: 2.3 (0.9-5.9)

n: number, 95% CI: 95% confidence interval, I: intervention group, C: control group, GP: general practitioner, RR: relative risc, NRT: nicotine replacement tharpy, NS: not significant, ppm: parts per million, ng/ml: nanogram per millimetre, RCT: randomized controlled trial, CO: carbon monoxide, MIS: minimal intervention strategy.

1. Setting, country, and design.

Hilberink *et al*.[41,42,50] evaluated the effect of a behavioural intervention combined with nicotine replacement therapy (NRT) alone or with NRT plus bupropion, compared with usual care, in patients with a clinical diagnosis of COPD. The point prevalence of abstinence after 1 year was non significantly higher in both intervention groups (NRT group, 7.4%; NRT plus bupropion group, 7.6%) than in the usual care group (3.4%, RR 2.2 [0.8-5.8] and RR 2.3 [0.9-5.9], respectively).

Factorial design evaluating both a behavioural and pharmacological intervention

Tønnesen *et al*.[9] evaluated the efficacy of nicotine sublingual tablet or placebo combined with either high or low behavioural support. After 1 year, significantly higher quit rates were observed in the group using sublingual nicotine tablets (14%) compared with placebo (5%, RR 2.60 [1.29-5.24]). However, no significant difference in sustained abstinence rate between the groups receiving low (9%) or high behavioural support (10%, RR 1.12 [0.60- 2.09]), was observed.

Behavioural intervention combined with free pharmacotherapy

Christenhusz *et al*.[43,44] evaluated the effect of SmokeStop therapy (SST) with free bupropion compared with the minimal intervention strategy. The SST group received bupropion for free while in the control group, pharmacological support was recommended but voluntary and at the patient's costs. After 12 months, the continuous abstinence rate was significantly higher in the SST group (19% versus 9%, RR 2.22 [1.06-4.65]).

Wilson *et al*.[37] evaluated whether an intensive individual or group behavioural intervention increased smoking cessation rates compared with usual care. As only 91 hospital outpatients participated, the number of patients in each subgroup was small. The trial failed to find a statistically significant difference between the treatment groups, as after 1 year, none of the patients achieved complete smoking cessation.

Table 2. Characteristics of participants.

First author, year	Patients, n	Age (years)	Male, n (%)	Definition of COPD	FEV_1 (% pred.)
Wagena 2005[25]	I1: 86 I2: 80 C: 89	I1: 51.1 (8.3) I2: 51.2 (9.1) C: 51.3 (8.4)	I1: 34 (40%) I2: 44 (55%) C: 46 (52%)	GOLD criteria, stage 0 (at risk for) included[46]	I1: 86.3 (21.0) I2: 83.1 (21.7) C: 87.4 (23.0)
Tønnesen 2006[9]	I1: 95 I2: 90 I3: 97 C: 88	I1: 59.2 (10.3) I2: 61.3 (9.6) I3: 61.2 (9.4) C: 62.5 (9.3)	I1: 45 (47%) I2: 46 (51%) I3: 46 (47%) C: 40 (46%)	Post-bronchodilator $FEV_1/FVC < 70\%$ FEV_1 <90% pred.	I1: 55.1 (15.4) I2: 53.4 (19.4) I3: 58.2 (17.8) C: 56.0 (19.1)
Christenhusz 2007[43,44]	I: 114 C: 111	I: 57.0 (8.4) C: 59.6 (8.5)	I: 55 (48%) C: 63 (57%)	FEV_1 <69% pred.[1]	I: 65.6 (27.4) C: 62.8 (25.7)
Wilson 2008[37]	I1: 27 I2: 29 C: 35	I1: 61.0 (8) I2: 60.4 (9) C: 61.4 (8)	I1: 14 (52%) I2: 12 (41%) C: 18 (51%)	$FEV_1/FVC < 0.7$ FEV_1 < 80% pred.[2]	I1: 52.1 (20) I2: 54.6 (23) C: 54.3 (20)
Borglykke 2008[45]	I:121 C: 102	I: 65 C: 67	I: 42 (35%) C: 37 (36%)	Patients having symptoms of COPD	Not available
Kotz 2009[39]	I1: 116 I2: 112 C: 68	I1: 53.8 (7.0) I2: 54.9 (8.0) C: 53.0 (7.6)	I1: 71 (61%) I2: 74 (66%) C: 40 (59%)	Post-bronchodilator $FEV_1/FVC<70\%$ FEV1 ≥ 50% pred.	I1: 80.5 (14.7) I2: 83.7 (16.8) C: 79.7 (14.0)
Tashkin 2011[38]	I: 248 C: 251	I: 57.2 (9.1) C: 57.1 (9.0)	I: 155 (63%) C: 156 (62%)	Post-bronchodilator $FEV_1/FVC < 70\%$ FEV_1 ≥ 50% pred.	I: 70.8 (17.0) C 69.1 (16.9)
Hilberink 2011[41,42]	I1: 243 I2: 276 C: 148	I1: 58.0 (12.2) I2: 60.7 (11.2) C: 60.1 (11.5)	I1: 113 (47%) I2: 132 (48%) C: 82 (55%)	Clinical criteria by GP	Not available

Data are presented as mean (standard deviation), unless otherwise stated.
n: absolute number, I: intervention group, C: control group, COPD: chronic obstructive pulmonary disease, GP: general practitioner, FEV_1: forced expiratory volume in 1 second, % of pred.: percentage of predicted.
1. Moderate or severe COPD according to American Thoracic Society criteria.[56]
2. COPD according to National Institute for Health and Clinical Excellence (NICE) guidelines.[57]

Discussion

This is the first systematic review since 2002 evaluating the efficacy and effectiveness of pharmacological and behavioural smoking cessation interventions in COPD patients. Eight studies fulfilled the inclusion criteria. The results of the included studies indicate that pharmacological therapy, combined with behavioural counselling, is still the most effective smoking cessation strategy for COPD patients. The intensity of counselling did not seem to influence the results. Neither did the choice of drug therapy make a difference. These findings are in line with the results of the Cochrane review of Van der Meer *et al*.[21] published in 2002.

Compared with the review of Van der Meer *et al*.[21], the studies included in our review were of higher methodological quality; in the review of Van der Meer *et al*.[21], only two (40%) of the five included studies had five or more 'yes' scores on the Delphi list, compared with 63% (five out of eight) in this review. Studies included in the review of Van der Meer *et al*.[21] only determined the effectiveness of NRT and bupropion, while this review also included studies investigating the newer drugs varenicline and nortriptyline. Another difference is that the behavioural interventions in this review are more tailored to the needs of the COPD patient compared with the behavioural interventions included in the review of Van der Meer *et al*.[21].

Pharmacological interventions

Four of the included studies mainly evaluated the effect of pharmacological treatments. Pharmacological support with bupropion, nortriptyline, NRT or varenicline results in higher smoking cessation rates compared with placebo, an effect also seen in non-COPD smokers.[9,25,38,41,42,49] Importantly, none of the RCTs showed a significant difference in smoking cessation rates between different drugs. This is in contrast to studies in smokers without COPD. Studies comparing drugs and a meta-analysis suggest that varenicline would be more effective for smoking cessation than the antidepressants nortriptyline and bupropion and NRT,[51,52] while bupropion, nortriptyline and NRT were equally effective.[53] Interestingly, a recent

meta-analysis by Shah *et al*.[54] showed that combining NRT with one of the other agents resulted in significantly higher abstinence rates if compared with any of the mono-therapies in non-COPD smokers.

Behavioural interventions

Four of the included studies evaluated the effect of a behavioural intervention. Tønnesen *et al*.[9] found no significant difference in abstinence rates between low or high behavioural support, possibly because of too much similarity of the two regimens. Christenhusz *et al*.[43,44] and Borglykke *et al*.[45] showed that group therapy increases smoking cessation rates in COPD patients. Counselling combined with pharmacotherapy was more effective than usual care in the studies of Hilberink *et al*.[41,42] and Kotz *et al*.[39] However, these results were not statistically significant, which may be due to the high treatment standard of usual care and low statistical power of the studies. In non COPD smokers, the results of different studies and meta-analyses suggest that all behavioural interventions are more effective when combined with pharmacotherapy to accomplish smoking cessation. A recent study by Hoogendoorn *et al*.[34] compared the costs of intensive counselling and pharmacotherapy. They showed that compared with usual care, intensive counselling and pharmacotherapy resulted in low costs per quality adjusted life-year gained, and pharmacotherapy was cost saving compared with intensive counselling.

Limitations

Interpretation of the results of the studies was challenging. First, only five out of eight studies were of acceptable methodological quality, applying a well-accepted cut-off value of 5 points to the Delphi list. Next, the numbers of patients included in the studies were small, resulting in broad confidence intervals. Furthermore, different types of outcome measures were used, making it impossible to directly compare study results. Besides, the majority of the studies failed to detect a statistically significant difference between the various smoking cessation strategies

and usual care stop smoking guidance; this may be due to the high standard of usual care nowadays. Lastly, no clear uniform definition of COPD was provided.

Recommendations

Compared with the review of Van der Meer *et al.*[21], the studies included in this 2002-2011 review are of higher methodological quality, investigated more different and newer drug therapies, and the behavioural interventions studied were more tailored to the needs of the COPD patients. However, in order to be able to identify optimal smoking cessation strategies for patients with COPD, we would like to propose some recommendations. First, more high-quality, well-powered randomised controlled trials with a minimal follow up of 1-year and continuous abstinence from target quit date as the primary outcome measure should be performed. In order to obtain high quality, randomised controlled trials should be performed according to the Consolidated Standards of Reporting Trials statements in future research.[55] Secondly, to realise uniformity between smoking cessation studies, the duration of follow-up should be 1 year and continuous abstinence from target quit date should be used as primary outcome measure. West *et al.*[56] proposed six standard criteria to realise uniformity between smoking cessation studies: the Russell Standard. We recommend the use of these criteria to enable meaningful comparison between studies.

Subsequently, we would like to recommend a meta-analysis of individual patient data (individual data analysis) of RCTs, in order to identify subgroups of patients with COPD with specific patient characteristics (e.g. pack-years of smoking, age, sex, comorbidities and number of quit attempts) that might benefit from various smoking cessation strategies.[57] Smoking COPD patients are known to be a difficult target for smoking cessation, being more resistant to smoking cessation therapies. In order to amplify the development of patient-tailored smoking cessation strategies, it would be very useful to identify the characteristics of smokers with COPD and to evaluate how these characteristics may affect smoking cessation strategies (e.g. COPD patients have a higher risk for depressive symptoms

and COPD smokers who are depressed at the same time may benefit more from antidepressant smoking cessation therapy). Finally, we recommend integrating smoking cessation treatment into regular COPD care, to lower barriers for smoking cessation treatment and to advocate a proactive role of physicians in motivating COPD patients to quit smoking.[18]

Table 3. Quality assessment based on the Delphi List.[36] Items of the Delphi List were scored 'yes', 'no' or 'don't know'. Only items that were assessed with 'yes' were given a score of 1 point. A total score for overall methodological quality of maximum 9 points was obtained by applying equal weights to all items. "?" denotes unclear, + denotes yes, - denotes no.

Author	Randomization method	Concealment treatment allocation	Similarity groups at baseline	Eligibility criteria specified	Blinding outcome assessor	Blinding care provider	Blinding patient	Outcome: point estimates and measures of variability	Intention to treat analysis	Total score
Wagena[25]	+	+	+	+	+	+	+	+	+	9
Tønnesen[9]	+	?	+	+	?	-	-	+	+	5
Christenhusz[43,44]	+	?	-	+	?	-	-	+	-	3
Wilson[37]	+	?	+	+	?	-	-	-	+	4
Borglykke[45]	+	-	+	+	?	-	?	+	+	5
Kotz[39]	+	+	+	+	?	?	+	+	+	7
Tashkin[38]	+	?	+	+	?	?	+	+	+	6
Hilberink[41,42]	+	?	-	+	?	-	-	+	+	4

Conclusions

To conclude, results of this 2002-2011 systematic review of smoking cessation strategies for patients with COPD indicate that pharmacological therapy, in addition to behavioural counselling, is the most effective smoking cessation strategy for COPD patients. In contrast to non-COPD smokers, neither the intensity of counselling nor the type of anti-smoking drug made a significant difference in smoking quit results.

Patients with COPD, being more resistant to smoking cessation therapies, could benefit significantly from smoking cessation, as smoking cessation is currently the only evidenced-based intervention to change the clinical course of the disease. Further research should focus on identifying subgroups that benefit most of patient-tailored smoking cessation strategies.

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4.2

ARE ECG MONITORING RECOMMENDATIONS BEFORE PRESCRIPTION OF QT PROLONGING DRUGS APPLIED IN DAILY PRACTICE? THE EXAMPLE OF HALOPERIDOL

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Submitted

Abstract

Background

To assess whether physicians follow the recommendation to perform an electrocardiogram (ECG) before prescribing haloperidol, an antipsychotic drug with QT prolonging properties.

Methods

A prospective cohort study was performed with primary care based data from the UK Clinical Practice Research Datalink. Patients aged 18 years or older with a first prescription of haloperidol between January 1, 2009 and May 1, 2013 were included. The proportion of ECGs made was determined in two blocks of four weeks; during the exposure period when haloperidol was initiated, and during the control period, one year before. Conditional logistic regression analysis was applied to calculate the relative risk of having an ECG in the exposure period compared to the control period. Subgroup analyses were performed to assess the outcome in patients with one or more additional risk factors for QT prolongation; age 65 years or older, history of heart failure, ischaemic heart disease, QT prolongation or congenital long QT syndrome, or concurrent use of antiarrhythmics or other QT prolonging drugs.

Results

In total, 3420 patients were prescribed haloperidol during the exposure period, and 1.8% of them had an ECG at initiation, compared to 0.8% during the control period (relative risk [RR] 2.4 [1.5-3.8]). Of the patients with additional risk factors for QT prolongation 1.9% of the patients had an ECG at initiation of the prescription, compared to 1.0% during the control period (RR 2.1 [1.2-3.5]).

Conclusions

Compliance with recommendations to perform an electrocardiogram when starting a new QT prolonging drug is extremely low, when haloperidol is taken as an example. This result and the fact that the QT interval is only a weak marker of future torsade des pointes, ventricular tachycardia, and sudden cardiac death, the general recommendation to perform an ECG before prescribing QT prolonging drugs such as haloperidol should be reconsidered.

Introduction

Drugs are a frequent cause of QT interval prolongation on the electrocardiogram (ECG), a sign of increased cardiac repolarisation time that may facilitate the development of torsade de pointes.[1] Torsade de pointes is a transient polymorphic ventricular tachycardia that, when sustained, may evolve into ventricular fibrillation and potentially cause sudden cardiac arrest, but it may also revolve, leaving no trace. The risk of developing torsade de pointes and cardiac arrest is higher in patients with additional risk factors for QT prolongation, such as prior myocardial infarction, heart failure, hypokalaemia, concomitant use of other arrhythmogenic drugs, and a (family) history of congenital long QT syndrome.[2] The estimated incidence of torsade de pointes in the population at large is 0.5 per 10,000 person-years,[3] while the estimated incidence of out-of-hospital cardiac arrest is approximately 10 per 10,000 person-years.[4-6] The study of Straus *et al.* shows that QT prolonging drugs increase the risk of sudden cardiac death with about 3 times compared to no use (adjusted odds ratio 2.7 [1.6-4.7]).[6] Although this relative risk of sudden cardiac death is substantial, the absolute risk is low, and therefore sudden cardiac death remains rare also in patients taking QT prolonging drugs.

Nevertheless, QT prolongation is one of the most common adverse drug reactions leading to regulatory action, including withdrawal of a drug from the market.[7,8] Several drugs have been reported to increase the risk of QT prolongation and ventricular arrhythmia; e.g. the relative risk for sudden cardiac death with ciprofloxacin was 2.4 (0.5-11.7) and with the use of risperidon 3.9 (1.1-13.5).[9] Still, prolongation of the QT interval is anything but an ideal marker for the risk of torsade de pointes or sudden cardiac death. Not all drugs that prolong the QT interval increase the risk of torsade de pointes or sudden cardiac death to an equivalent degree, and importantly, on the other hand, not all drugs that increase the risk of torsade de pointes or sudden cardiac death, prolong the QT interval.[10,11]

Irrespective of the low absolute risk related to QT interval prolongation,[1,12] the regulatory authorities have adopted stringent requirements for pre-marketing testing

of pro-arrhythmic effects of new drugs over the last decade, with a focus on QT interval duration. In 2005, the Food and Drug Administration (FDA), the European Medicine Agency (EMA), and the Japanese Pharmaceutical and Medical Devices Agency (PMDA) adopted the ICH E14 guideline that recommends performing a 'thorough QT study' for all new drugs, as a basis to conclude on a compounds ability to cause QT prolongation.[13,14] Apart from these recommendations on how and when to perform thorough QT studies, the ICH E14 guideline provides guidance on how information on QT prolongation should be addressed in the drug labelling. One of the risk minimisation measures suggested in the ICH E14 is to include "Recommendations for patient monitoring (ECG and electrolytes) and management of patients with QT/QTc prolongation or symptoms suggestive of an arrhythmia" in the labelling of QT prolonging drugs. A previous study from our group showed that currently in 63% of the QT prolonging drugs, and 29% of the potentially QT prolonging drugs, ECG monitoring prior to treatment is recommended in the drug label (Chapter 5.1).

Box 1. Recommendation in the summary of product characteristics (SPC) to perform an ECG prior to starting haloperidol.[21]

4.4 Special warnings and precautions for use

"Baseline ECG is recommended prior to treatment in all patients, especially in the elderly and patients with a positive personal or family history of cardiac disease or abnormal findings on cardiac clinical examination. During therapy, the need for ECG monitoring (e.g. at dose escalation) should be assessed on an individual basis. Whilst on therapy, the dose should be reduced if QT is prolonged, and haloperidol should be discontinued if the QTc exceeds 500 ms."

QTc: QT interval corrected for heart rate

Haloperidol is a widely prescribed antipsychotic agent in both hospital and primary care settings to manage agitation, delirium, and psychosis. Haloperidol has been linked to QT prolongation and torsade de pointes in case reports[15-19] and post-marketing studies.[20] The UK product label of the innovator of haloperidol currently states: 'Baseline ECG is recommended prior to treatment in all patients, especially in the elderly and patients with a positive personal or family history of

cardiac disease or abnormal findings on cardiac clinical examination' (Box 1).[21] It is, however, unknown how adequate these risk minimisation measures, as called by the regulatory authorities, are being adhered to in daily clinical practice. Therefore, the objective of this study was to assess whether the advice of the drug label to perform an ECG in patients before prescribing a QT prolonging drug is followed in daily practice, and we took haloperidol as the example.

Methods

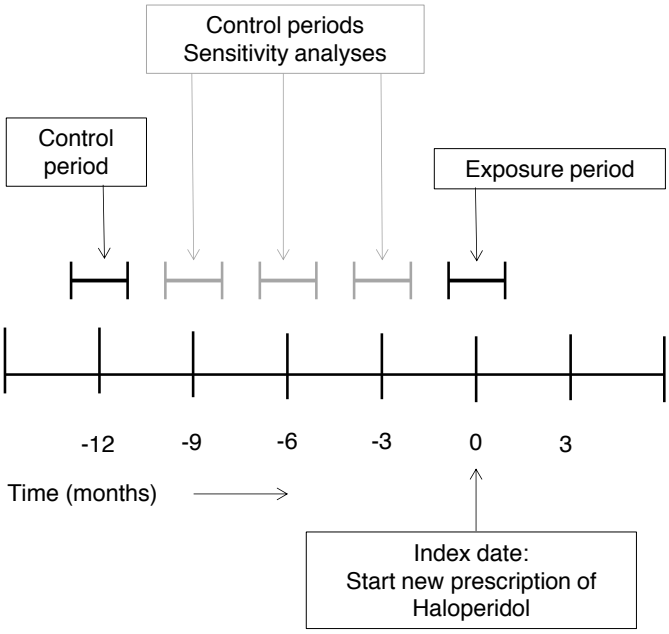
Setting and study design

We performed a prospective cohort study. Data for this study were obtained from the Clinical Practice Research Datalink (CPRD). CPRD comprises the computerised medical records of patients derived from primary care practices throughout the United Kingdom (UK). These longitudinal data are coded using the Read code system, which is validated and individualised for over 46 million person years since 1987.[22] The records include the patient's demographic information and data on routine care such as prescription details, clinical events, preventive care provided, specialist referrals, hospital admissions and major clinical outcomes. General practitioners play a key role in the UK health care system, as they are responsible for primary health care and specialist referrals.[22,23]

Study population and measures

All patients aged 18 years and older with a new prescription of haloperidol between January 1, 2009 and May 1, 2013, were identified. We started with the data collection in 2009 to allow enough time for adherence to the ECG monitoring recommendation, which was reported in the label for the first time in 2006. The date of the start of the first prescription of haloperidol was defined as the index date. A new prescription of haloperidol (exposure of interest) was defined as not having had a prescription of the drug in the 365 days before the index date. For each patient we assessed whether an ECG was performed or a referral for an

Figure 1. Study design.



ECG (outcome of interest) was provided during two measurement periods of four weeks (Figure 1). The first measurement period was the exposure period, i.e. the period 2 weeks before until 2 weeks after the index date. The control period when the patient did not use haloperidol was taken as the period from 2 weeks before till 2 weeks after the date that fell 12 months before the index date (Figure 1). Patients were included when at least 379 days of valid data collection before the index date was available, as the control period started 1 year and 2 weeks before the index date. Patient that had less than 365 days of valid follow-up after the index date were excluded, as we intended to exclude prescriptions in terminally ill patients or those with a shorter life expectancy.

Subgroups with risk factors for QT prolongation

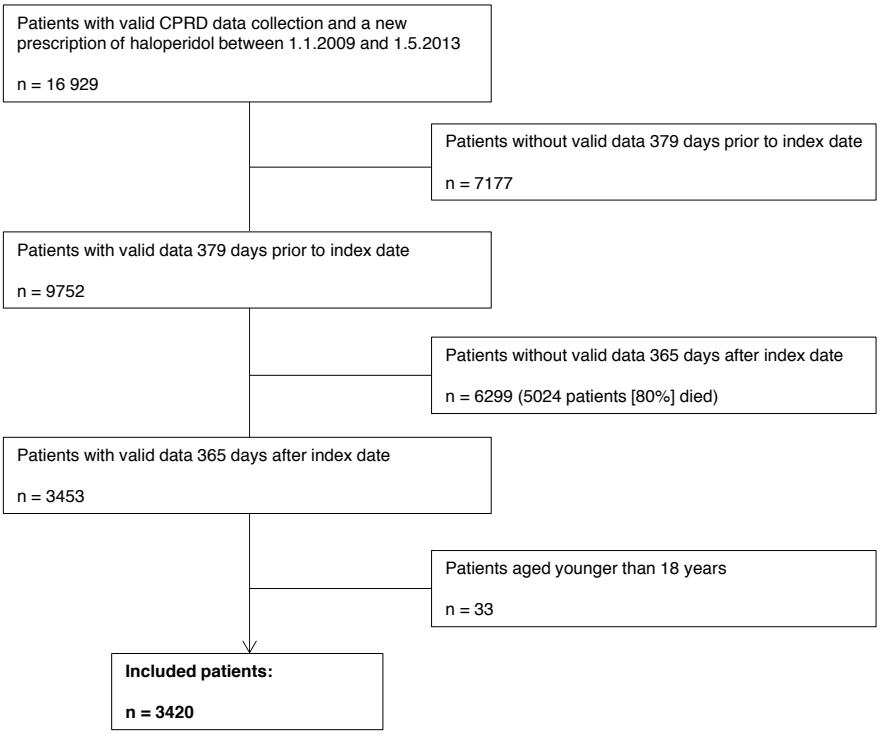
We assessed whether patients with at increased risk of QT prolongation were more likely to have an ECG prior to starting haloperidol. Increased risk was defined as the presence of one or more of the following risk factors on the index date: age 65 years or older, history of heart failure, ischaemic heart disease, QT prolongation, or congenital long QT syndrome, or the concurrent use of antiarrhythmic or class 1 QT prolonging drugs. We defined four age-categories: 18-44 years, 45-64 years, 65-84, and $\geq$85 years. Patients were defined as having a history of QT prolongation, congenital long QT syndrome, ischaemic heart disease, or heart failure when they had a diagnosis coded in the database ever before the index date. Drug use was defined as concurrent if the prescription date fell in a period of 90 days before the index date or the reference date, one year earlier. We considered drugs that met the criteria of Vaughan-Williams class I or III as antiarrhythmic drugs.[24] QT prolonging drugs were subdivided in class 1 or 2 QT prolonging drugs according to the Arizona Center for Education & Research on Therapeutics (Appendix 1).[25]

Data analysis

Absolute numbers and proportions of ECGs performed during the index period and the control period were evaluated. Conditional logistic regression analysis was used to calculate the relative risk of having an ECG in the exposure period compared to the control period. In order to show an incidence curve, the proportion of ECGs performed per month before and after index date (start haloperidol prescription) was calculated from 12 months before the index date to 6 months after the index date. In addition, we calculated the proportion of ECGs performed each calendar year to assess time trends.

Three sensitivity analyses were conducted. First, we performed the aforementioned analyses without excluding patients with less than one year of follow-up. Next, sensitivity analyses were performed with three other 4 week control periods (3, 6, and 9 months before the index date, instead of 12 months, Figure 1).

Figure 2. Flowchart of included and excluded patients.



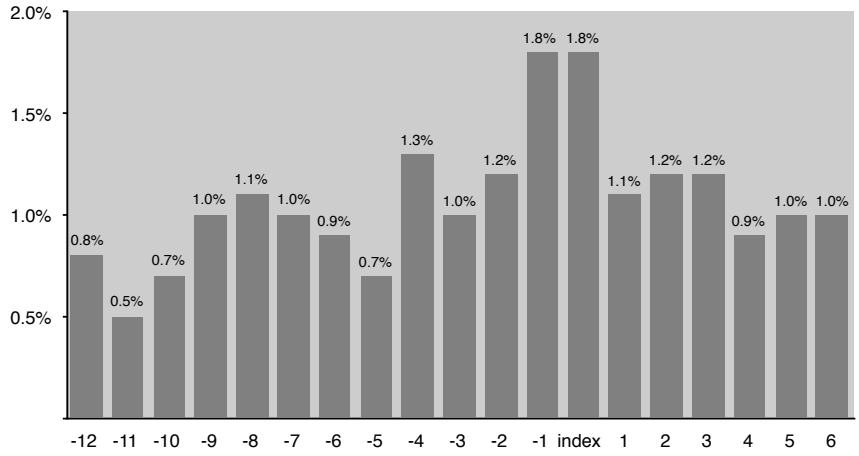
Finally, a sensitivity analysis was conducted defining concurrent drug use as having a prescription in a period of 30 days before the index date instead of 90 days. All data were analysed using the statistical software package of SPSS (SPSS for Windows, version 20.0, SPSS Inc.).

Results

During the study period, 3420 patients aged 18 years or older, with a new prescription of haloperidol were included (Figure 2). The mean age was 65.3 (SD 20.4, range: 18-106) years, and 58% was female (Table 1). Of those receiving a new prescription of haloperidol, 1.8% had an ECG recorded (n = 63) as compared to 0.8% during the control period one year earlier (n = 27, relative risk [RR] 2.4 [1.5-3.8], Table 2). Figure 3 indicates the proportion of ECGs per month and shows that the proportion of ECGs was highest at the index date (1.8%) and one month before the index date (1.8%). The proportion of ECGs in the remaining months ranged from 0.5% to 1.3%. Of the patients with at least one additional risk factor for QT prolongation 1.9% had an ECG at the start of haloperidol as compared to 1.0% during the control period (RR 2.1 [1.2-3.5]). Of the patients without additional risk factors for QT prolongation 1.6 % received an ECG prior to the start of haloperidol as compared to 0.4% during the control period (RR 2.8 [1.0-7.8]).

Patients aged 45-64 or 65-84 years more often had an ECG performed prior to starting with haloperidol (exposure period 2.3% and 2.6%, control period 0.4% and 1.2%, RR 5.3 [1.6-18.3] and 2.3 [1.2-4.3], respectively) than younger patients (18-44 years, exposure period 1.2%, control period 0.5, RR 4.0 [0.8-18.8]) or the very old (>84 years, exposure period 0.6%, control period 0.7%, RR 1.0 [0.3-4.0]). In women ECGs were performed less often during both the exposure and control period (1.4% and 0.5%, respectively, RR 2.7 [1.3-5.6]) than men (2.5% and 1.2%, RR 2.2 [1.2-4.0]), respectively. No clear increase or decrease of the proportions of ECGs performed during initiation of haloperidol was shown over time.

Figure 3. Proportion of ECGs performed per month before and after index date (start haloperidol prescription).



As expected, sensitivity analyses performed in the full cohort of 9719 new haloperidol users (including patients with less than one year of follow up) resulted in lower proportions of ECGs (exposure period: 1.4%, control period: 1.1%, RR 1.3 [1.0-1.6]). Sensitivity analyses performed with three other control periods (3, 6, and 9 months before the index date, instead of 12 months) and with another definition of concurrent drug use (i.e. a prescription during a 30-day period instead of a 90-day period, before the index date) yielded comparable results.

Table 1. Baseline characteristics of the study population: all incident haloperidol users between 1.1.2009 and 1.5.2013 (n = 3420).

Baseline characteristics	**Study population**	
Mean age (years, SD)	65.3	(20.4)
Age category (years)		
18-44	693	(20.3%)
45-64	750	(21.9%)
65-84	1312	(38.4%)
>84	665	(19.4%)
Female sex	1984	(58.0%)
Smoking		
Current	751	(22.0%)
Former	1129	(33.0%)
Never	862	(15.2%)
Unknown	678	(19.8%)
History of		
Ischaemic heart disease	585	(17.1%)
Heart failure	168	(4.9%)
Diabetes mellitus	627	(18.3%)
Chronic obstructive pulmonary disease	243	(7.1%)
QT prolongation or long QT syndrome	1	(0.03%)
Current use of concomitant QT prolonging drugs		
Class 1 QT prolonging drugs[1]	903	(26.4%)
Class 2 QT prolonging drugs[1]	739	(21.6%)
Class I/III anti-arrhythmic drugs[2]	47	(1.4%)

Data are number (%) unless otherwise indicated. SD: standard deviation.

1. Drugs with (possible) risk of QT prolongation according to the Arizona Center for Education & Research on Therapeutics.[25]
2. Class I and III antiarrhythmic drugs, according to the classification of Vaughan-Williams.[24]

Discussion

Our study shows that less than 2% of the patients who had a new prescription of haloperidol received an ECG at initiation (exposure period: 1.8%, control period: 0.8%, RR 2.4 [1.5-3.8]). This was also the case in patients with at least one additional risk factor for QT prolongation (exposure period: 1.9%, control period 1.0%, RR 2.1 [1.2-3.5]). To the best of our knowledge, our study is the first to report on compliance with recommendations on ECG monitoring upon starting with a QT prolonging drug in the population at large. Recently Muzyk *et al.* examined in a hospital environment the effects of implementation of a computerized physician order entry on adherence to monitoring, of among others, the QT interval after intravenous haloperidol prescription. During the study period (2007-2010) 40% of the patients who received intravenous haloperidol had an ECG, which increased to 61% after the implementation of the intervention.[26]

Our study has several limitations. First, haloperidol is often prescribed in the very old and terminally ill patients to manage agitation and delirium, especially in primary care, and for understandable reasons these patients are less likely to have an ECG. We therefore only included patients with a follow up time of at least one year after the start of haloperidol in our main analysis. Sensitivity analyses performed in the full cohort (including patients with less than one year of follow up) resulted in lower proportions of ECGs (1.4%). Second, as in some cases a medical specialist may have initiated haloperidol and ordered an ECG, this may not have been recorded in the medical files of the general practitioner. When the continued supply subsequently was managed by the general practitioner, as is common practice, this may have incorrectly been recorded as a first prescription of haloperidol in our study. This may have resulted in an underestimation of ECG recordings in de CPRD data base. Any underestimation is likely to be very small, however, as the vast proportion of haloperidol prescriptions included in our study were initiated in the primary care setting.

In view of the extremely low compliance with the drug label recommendation to record an ECG before initiation of a QT prolonging drug such as haloperidol, a critical reappraisal of this recommendation seems warranted. Importantly, the QT prolongation is a poor marker of the risk of torsade de pointes, ventricular arrhythmia and sudden cardiac death. According to the ICH E14 guideline, a thorough QT study is negative when a drug increases the mean QT interval less than 10 ms. In clinical studies, a QT interval of 500 ms or more is accepted as a threshold of an increased risk of torsade de pointes.[13,14] However, the association between the risk of torsade de pointes and the length of the QT interval seems not to be linear.[13,14] A prolonged QT by no means will imply that a drug per se causes torsade de pointes, while some drugs have been removed from the market because of a high risk of torsade de pointes, although the mean QT interval was only moderately increased (5-10 ms).[27]

For example, terfenadine, a widely used antihistamine drug was withdrawn from the market in 1998 because of its ability to induce torsade de pointes (incidence rate 1.0 per 10,000 person-years, RR compared to no use 2.1 [0.5- 8.5]),[28] while this drug only has a minimal QT prolonging effect (mean increased QT interval of approximately 6 ms).[10] On the other hand amiodarone, a class III anti-arrhythmic drug, routinely prolongs the QT interval to more than 500 ms, while this drug only rarely causes torsade de pointes.[10]

An important aspect in the discussion on safety is that the absolute risk of torsade de pointes is very low. Haloperidol is associated with relatively mild QT prolongation, especially the oral formulation and at low dose. The use of 15 mg haloperidol (orally) causes an average increase in QT of 7 ms.[20] However, this drug has clearly been linked to torsade de pointes in a post-marketing analysis of the adverse effects of haloperidol, especially when used intravenously.[20] Between 1972 and 2010, 365 cases of QT prolongation, torsade de pointes or cardiac arrest were spontaneously reported in the WHO global individual case safety report database (mean of 9.6 cases yearly) to be associated with haloperidol, of which 42% was fatal (mean of 3.8 deadly cases per year).[29]

Table 2. The proportion of electrocardiographs performed in the exposure period (from 2 weeks prior to 2 weeks after start of index date [new prescription of haloperidol]) compared to control period (from 2 weeks prior to 2 weeks after one year before the index date), stratified according to risk factors for QT prolongation.

	Exposure period n = 3420	Control period n = 3420	Relative risk (95% CI)
All patients	63 (1.8%)	27 (0.8%)	2.5 (1.5-3.8)
Any additional risk factor for QT prolongation[1]			
Yes	47 (1.9%)	22 (1.0%)	2.1 (1.2-3.5)
No	16 (1.6%)	5 (0.4%)	2.8 (1.0-7.8)
Age category in years			
18-44	8 (1.2%)	4 (0.5%)	4.0(0.9-18.8)
45-64	17 (2.3%)	4 (0.4%)	5.3 (1.6-18.3)
65-84	34 (2.6%)	16 (1.2%)	2.3 (1.2-4.3)
>84	4 (0.6%)	4 (0.7%)	1.0 (0.3-4.0)
Sex			
Male	36 (2.5%)	17 (1.2%)	2.2 (1.2-4.0)
Female	27 (1.4%)	10 (0.5%)	2.7 (1.3-5.6)
History of ischaemic cardiac disease or heart failure			
Yes	14 (2.1%)	9 (1.5%)	1.4 (0.6-3.4)
No	49 (1.8%)	18 (0.6%)	2.9 (1.7-5.0)
Concurrent use of class 1 QT prolonging drugs and/or antiarrhythmic drugs[2]			
Yes	17 (1.9%)	8 (1.3%)	1.2 (0.4-3.9)
No	46 (1.8%)	19 (0.7%)	2.4 (1.4-4.1)

CI: confidence interval

1. At least one of the following risk factors: age >65 years, history of heart failure, ischaemic heart disease, or concurrent use of class 1 QT prolonging drugs or anti-arrhythmic drugs.
2. Drugs with risk of QT prolongation according to the Arizona Center for Education & Research on Therapeutics,[25] and class I and III antiarrhythmic drugs, according to the classification of Vaughan-Williams.[24]

The study of Meyer-Massetti *et al*. identified 70 cases of intravenous haloperidol associated torsade de pointes (n = 54) and/or QT prolongation (n = 42), of whom 3 experienced sudden cardiac arrest. However, 97% of the patients had additional risk factors for QT prolongation and all received high doses of intravenous administered haloperidol (lowest cumulative dose: 2 mg or more; the majority of the cases received cumulative doses of 10 mg or more).[30] In a study of Hennessy *et al*. incidence rate of 42 (35-50) per 10,000 person-years for the composite endpoint of cardiac arrest and ventricular arrhythmia in haloperidol users with schizophrenia was reported. The two control groups, patients with

psoriasis or glaucoma, showed an incident rate of 18 (11-28) and 34 (28-41) per 10,000 person-years (adjusted rate ratios 2.4 [1.5-3.9] and 2.2 [1.7-3.0]).[31] Other studies reported incidence rates of composite endpoints combining sudden arrest and ventricular arrhythmia of 18 to 83 per 10,000 person-years for users of haloperidol.[32,33]

A limitation of these studies is the imprecise definition of sudden death, including for example patients with the following diagnostic codes: sudden death (cause unknown), instantaneous death, death occurring in less than 24 hours from onset of symptoms (not otherwise explained), and unattended death.[31-33] Such an imprecise definition most probably caused considerable misclassification, as dying from arrhythmia not always occurs suddenly, and a sudden death may well be of a non-arrhythmic cause, such as aortic rupture or massive pulmonary embolism.[34] Consequently, applying diagnostic codes for sudden death and ventricular arrhythmia has considerable limitations in identifying outpatient events. According to the study of Hennessy *et al.* these diagnostic codes used for sudden cardiac arrest correlated poorly with the cause of death according to the death certificates when validated;[35] for example, in only 26% of those with unexplained or unattended death, the cause of death according to the death certificate was of cardiac origin.[33] In addition, in primary care only 19% of the users of haloperidol had a schizophrenia diagnosis and 30% of the users were aged 75 or older and at average,[33] which implies that many of the users have considerable comorbidities and thus additional risk factors for sudden cardiac arrest.

In users of antipsychotics (not specified which one), the proportion of patients that develop QT prolongation (> 500 ms) is estimated between 0 and 2%, and the reported frequency of torsade de pointes was approximately 1 in 10,000 users.[36] About one-fifth of the cases of torsade de pointes convert into ventricular fibrillation (1 in 50,000 users), which in 85% of the cases was fatal.[36,37] On the basis of these findings, Bouvy *et al.* showed that for the current QT prolonging antipsychotics on the market, routine ECG monitoring of all new users in clinical practice is not cost-effective.[36]

As the results of our study show, physicians do not comply with the ECG monitoring recommendations stated in the drug labels of QT prolonging drugs. This may be due to two important barriers. First, lack of awareness among physicians, about the recommendation, and about the association between QT prolonging drugs and sudden cardiac arrest. The knowledge on QT prolongation risks among physicians has been shown to be suboptimal.[38] Although, haloperidol has been on the market since 1958,[39] and has been prescribed since, physicians may never have observed a QT related side effect in their practice. Moreover, the ultimate negative effect of QT prolongation, amely ventricular arrhythmia and sudden cardiac death, will not always be linked to the prescription of a QT prolonging drug.

A second barrier may be the lack of feasibility. It could be argued that physicians, in contrast to regulatory authorities, find it not feasible to perform ECGs in every patient who starts a QT prolonging drug. Several QT prolonging drugs are widely prescribed by general practitioners, such as domperidone, (es)citalopram, and haloperidol. It may very well be that clinicians consider the risk of QT prolongation acceptable, or they are willing to take the risk that this potentially fatal, but very rare side effect occurs. Besides, in the case of haloperidol, alternative therapies carry the same risks as most antipsychotic medications have been shown to cause some degree of QT prolongation.[20]

Finally, it can be questioned whether inclusion of such a recommendation in the drug labelling is effective, when not accompanied by more direct communication to prescribing physicians. Changing prescribing behaviour is extremely difficult. Even strong actions may have only a moderate impact on prescription patterns. For example, Piening *et al*. evaluated the effect of direct healthcare professional communications or “dear doctor letters”. In the European Union, these warning letters are sent to health care professionals when important new safety issues for drugs are identified that warrant strong regulatory action. The authors found that such a letter caused a long-term change of use of only one-third of the drugs in question and a mean decrease of 27% in the use of such drugs.[40] As another example, in September 2007 the Irish Medicines Board issued a warning regard-

ing the use of, among others, haloperidol in patients with cardiovascular disease, additionally recommending that patients should undergo ECG prior to treatment. Musleh *et al*. determined prescribing rates 12 months before and after the warning, which showed that the warning had no significant effect on prescribing of the drug, although alternative therapy is available.[41]

Conclusion

Our study showed that the compliance with recommendations to perform ECGs when starting a new QT prolonging drug, in our example haloperidol, is extremely poor. In view of this and the fact that the QT interval is a weak marker of future torsade des pointes and sudden cardiac death and these adverse events are very rare, the recommendation to record an ECG before prescribing QT prolonging drugs such as haloperidol should be reconsidered.

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Appendix 1. List of QT prolonging drugs and class I and III antiarrhythmic drugs.

Class I and III antiarrhythmic drugs[1]	Class 1 QT prolonging drugs[2]	Class 2 QT prolonging drugs[2]	
Class Ia	Amiodarone[4]	Alfuzosin	Risperidone
Quinidine	Arsenic trioxide	Artenimol+piperaquine[3]	Roxithromycin[3]
Procainamide	Astemizole	Atazanavir	Saquinavir
Disopyramide	Azithromycin	Bedaquiline[3]	Sertindole
Sparteine[3]	Bepridil[3]	Clozapine	Sunitinib
Ajmaline[3]	Chloroquine	Dolasetron	Tacrolimus
Prajmaline[3]	Chlorpromazine	Eribulin[3]	Tamoxifem
Lorajmine[3]	Cisapride	Famotidine	Telavancin[3]
Class Ib	Citalopram	Felbamate	Telithromycin
Lidocaine	Clarithromycin	Fingolimod	Tizanidine
Mexiletine	Disopyramide[4]	Foscarnet	Tolterodine
Tocainide	Dofetilide[3,4]	Fosphenytoin	Vardenafil
Aprindine[3]	Domperidone	Gatifloxacin[3]	Venlafaxine
Class Ic	Dronedarone[4]	Gemifloxacin[3]	Voriconazole
Propafenone	Droperidol	Granisetron	Vorinostat[3]
Flecainide	Erythromycin	Iloperidone[3]	
Lorcainide[3]	Escitalopram	Indapamide	
Encainide[3]	Flecainide[4]	Isradipine	
Class III	Halofantrine	Lapatinib	
Amiodarone	Vandetanib[3]	Levofloxacin	
Bretylium tosilate[3]	Ibutilide[3,4]	Lithium	
Bunaftine[3]	Levomethadyl[3]	Mirtazapine	
Dofetilide[3]	Mesoridazine[3]	Moexipril/HCTZ	
Ibutilide[3]	Methadone[3]	Nicardipine	
Tedisamil[3]	Moxifloxacin	Nilotinib	
Dronedarone	Ondansetron	Ofloxacin	
Sotalol	Pentamidine	Olanzapine	
Moracizine	Pimozide	Oxytocin	
Cibenzoline[3]	Probucol	Paliperidone	
Vernakalant[3]	Procainamide[4]	Pasireotide[3]	
	Quinidine[4]	Perflutren lipid microspheres	
	Sevoflurane		
	Sotalol[4]	Promethazine	
	Sparfloxacin	Quetiapine	
	Terfenadine	Ranolazine	
	Thioridazine	Rilpivirine[3]	

1. Antiarrhythmic drugs, class I and III, according to the classification of Vaughan-Williams.
2. Drugs with (Possible) Risk of torsade de pointes and QT prolongation according to an internet-based registry of QT prolonging drugs (http://www.azcert.org/medical-pros/drug-lists/bycategory.cfm, accessed on July 18, 2013). Haloperidol is classified as a class I QT prolonging drug, but is left out of this table as it is the exposure of interest.
3. No prescription records in GPRD during study period.
4. Anti-arrhythmic QT prolonging drugs.

5

DRUG LABELLING TO MINIMISE THE RISK FOR DRUG-INDUCED ARRHYTHMIAS

5.1

QUALITY OF DRUG LABEL INFORMATION ON QT INTERVAL PROLONGATION

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Abstract

Background

Information regarding QT prolongation in the drug label may vary between products. This could lead to suboptimal risk minimisation strategies. Therefore the objective was to systematically assess the variation in the extent and content of information on QT prolongation in the summary of product characteristics (SPC) of recently approved medicinal products.

Methods

The drug labels of products centrally approved in Europe between 2006 and 2012 were screened. Of drugs including the term 'QT' in the SPC, the message on QT prolongation (categorised as 'no prolongation' / 'unclear drug-QT association' / 'possibly QT prolongation' / 'QT prolongation') and the advice on cautionary measures pertaining to QT prolongation in the label were examined, as well as their association.

Results

Of the 175 screened products, 44 contained information on QT in the SPC ('no QT prolongation': 23%, 'unclear drug-QT association': 43%, 'possibly QT prolongation': 16%, 'QT prolongation': 18%). Sixty-two percent of the SPCs (27/44) contained advices to act with caution in patients with additional risk factors for QT prolongation. Products that more likely to have QT prolonging properties according to the SPC provided more information on QT prolongation in the SPC (for the category 'no prolongation': 10% and for the category 'QT prolongation': 100%).

Conclusions

The extent and content of information on QT prolongation varies considerably between SPCs, and in almost half of the drugs a clear message on QT prolongation was lacking in the SPC. We advocate providing more structured phrasing of information and unambiguous interpretation of evidence on QT prolongation in the SPC, to optimise risk minimisation strategies.

Introduction

Prolongation of cardiac repolarisation, manifested as a prolonged QT interval on the surface electrocardiogram (ECG) may predispose to fatal ventricular arrhythmias such as torsade de pointes, ventricular tachycardia or fibrillation, and sudden cardiac death.[1,2] At present, cardiac arrhythmia associated with QT interval prolongation is one of the most common adverse drug reactions leading to regulatory action, including withdrawal of a drug from the market.[3,4] Although the occurrence of QT interval prolongation is generally rare, it can be potentially fatal.[1,2] As a result, the regulatory authorities have strengthened the requirements for premarketing testing of pro-arrhythmic effects of new drugs, over the last decade. In 2005, the Food and Drug Administration (FDA), the European Medicine Agency (EMA), and the Japanese Pharmaceutical and Medical Devices Agency (PMDA) adopted the ICH E14 guideline, which recommends to perform a 'thorough-QT study' for all new drugs, as a basis to conclude on a compounds ability to cause QT prolongation.[5,6]

In case of any suspicion of QT prolongation before, but also after marketing authorisation of a drug, information about this is commonly mentioned in specific sections of the drug labelling, also called the summary of product characteristics (SPC). The SPC is a legal document that sets out the conditions under which a certain medicinal product can be used safely and effectively.[7,8] It contains a description of the products (chemical, pharmacological and pharmaceutical) properties as well as information on the clinical use including sections on e.g. contraindications, special warnings and precautions, interactions and undesirable effects. The SPC forms the basis of information for health professionals on how to use the specific product safely and effectively.[7]

It has been noticed, however, that the quality of information on QT prolongation varies between products. This could hamper the usefulness of this information for health care providers and lead to suboptimal risk minimisation strategies. Therefore, the aim of this study was to systematically assess the variation in the extent

and content of information on QT prolongation in the SPC, in relation to the QT prolonging effects described in the SPC.

Methods

Study design and data collection

A descriptive study was performed. Medicinal products centrally approved in the European Union (EU) between January 1, 2006 and June 1, 2012 were included. Duplicates, generics, fixed-dose combinations, and vaccines were excluded. The SPCs of the included products were identified from the European Medicines Agency (EMA) database of European public assessment reports[9] and screened to determine if the product included the word 'QT' in the SPC.

Characteristics of the selected products

The following characteristics of the included products were recorded: indication (cardiovascular, endocrinology and metabolic, infectious disease, musculoskeletal and nervous system, oncology, immunology or 'other'), year of registration, and orphan drug status (yes/no). The size of the company of the marketing application holder was, in line with other studies, determined as small, medium-sized, or large, based on ranking by total revenue as reported in Script's Pharmaceutical Company League Tables 2008. Companies were defined as large if ranked 1-20, medium-sized if ranked 21-150, and small if the company was not on the ranking list.[10,11]

Information on QT prolongation in the SPC

Of all products that mentioned 'QT' in the SPC, data on QT prolongation were extracted from the SPC. In order to evaluate the content of information on QT prolongation in the SPCs, the message on QT prolongation in the drug label was categorised into four subsets: 1. 'Drug does not prolong QT interval', 2. 'Unclear

if the drug prolongs the QT interval', 3. 'Drug possibly prolongs QT interval', 4. 'Drug prolongs QT interval', based on the phrasing used to report on the degree of QT prolonging properties of the compound (Appendix 1). As we aimed on addressing the usefulness of drug labels for health care providers, we did not interpret the results of studies on QT prolongation reported in the label. MW and MDB independently categorised the drug labels of the included products into the four subsets. Consensus was used to resolve disagreement. If consensus could not be reached, discrepancies were resolved in discussion with PM.

In order to evaluate the extent of information on QT prolongation in the SPCs, we examined in which of the following sections of the SPC QT prolongation was mentioned: 4.3 contra-indications, 4.4 special warnings and precautions, 4.5 interactions, 4.8 undesirable effects, 4.9 overdose, 5.1 pharmacodynamics and 5.3 preclinical safety data. In addition, we determined whether the SPC provided information on the following three topics: 1. Advices to act with caution in patients with (additional) risk factors for QT prolongation, 2. An explanation for the association of QT prolongation with ventricular arrhythmia, torsade de pointes, and sudden cardiac arrest, and 3. Advices on monitoring of patients using the product. In addition we assessed whether the label contained information on thorough-QT studies. Subsequently, the association between the content (message on QT prolongation in the drug label according to the 4 subcategories) and the extent (information on QT prolongation in the label according to 3 information topics mentioned above) was determined.

Data analysis

Values were presented as absolute numbers and proportions. All data were analysed using the statistical software package SPSS (SPSS for Windows, version 20.0, SPSS Inc.).

Figure 1. Flowchart of inclusion of products.

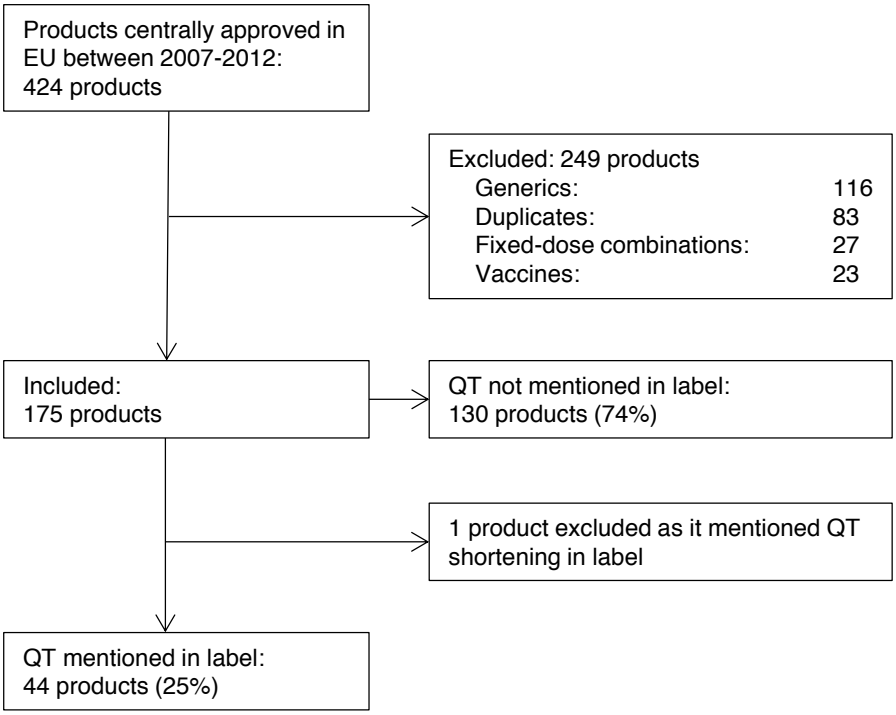


Table 1. Characteristics of the included products (n = 44).

Characteristics	QT mentioned in SPC n = 44	
Indication:		
Cardiovascular	6	(14%)
Endocrinology and metabolic	4	(9%)
Infectious disease	6	(14%)
Musculoskeletal and nervous system	6	(14%)
Oncology	12	(27%)
Immunology	3	(7%)
Others	7	(16%)
Year of registration:		
2006	3	(7%)
2007	11	(25%)
2008	5	(11%)
2009	8	(18%)
2010	5	(11%)
2011	9	(21%)
2012[1]	3	(7%)
Orphan drug	8	(18%)
Company size:		
Large	30	(68%)
Medium	10	(23%)
Small	4	(9%)

1. Until June 1, 2012

Results

Characteristics of the selected products

Of the 424 identified medicinal products, centrally approved in the EU between January 1, 2006 and June 1, 2012, we excluded 249 products (59%) for the following reasons: SPC duplicates (n = 83), generics (n = 116), fixed-dose combinations (n = 27), and vaccines (n = 23, Figure 1). Of the remaining 175 products, one product that mentioned the word 'QT' in the SPC (rufinamide) was excluded as the warning was not on QT prolongation, but on QT shortening, and 44 (25%) of the SPCs mentioned QT prolongation (Appendix 2). Characteristics of the 44 selected products are presented in Table 1. The most common indication was oncology (n = 12, 27%). Eighteen percent of the products was registered as orphan drugs. In the majority of the selected products a large company was involved (n = 30, 68%).

Information on QT prolongation in the SPC

In one-third of the 44 products, the main message on QT prolongation in the SPC was that either the drug prolongs the QT interval (18%), or that the drug possibly prolongs the QT interval (16%). In about a quarter of the products (23%) the SPC contained the message that the drug does not prolong the QT interval. For the remaining products (43%) no clear message on QT prolongation was included in the SPC (Table 2).

QT related issues were most commonly reported in section 4.4 (special warnings and precautions, 66%) and section 4.8 (undesirable effects, 57%, Figure 2).

Concordantly, the products that either prolong or possibly prolong the QT interval according to the SPC most often reported QT related issues in section 4.4 (both 100%) and 4.8 (88% and 57%, respectively). In contrast, for products that mentioned 'no QT prolongation' in the SPC, QT prolongation was most often stated in section 5.1 (pharmacodynamics properties, 60%).

Sixty-two percent of the SPCs contained the advice to act with caution in patients with additional risk factors related to QT prolongation (n = 25, Table 2), and 16% of the SPCs explained the association of QT prolongation with ventricular arrhythmias (n = 27). The advice on monitoring of patients using the product was given in 34% of the SPCs (n = 15). The most frequently reported item was 'Use with caution concurrently with other drugs that prolong the QT interval or anti-arrhythmics' (n = 24, 55%).

Products that were more likely to have QT prolonging properties according to the SPC provided more information on QT prolongation in the SPC. The proportion of products that provided information on at least one of the informative topics increased from 10% of the drugs that 'does not prolong the QT interval' according to the SPC to 100% of the drugs that either 'prolong' or 'possibly prolong' the QT (Table 2, Figure 3). In contrast, the label of drugs that claimed to have 'no QT prolonging properties' in the label more often reported on thorough-QT studies (60%), than the labels of drugs that either 'prolong' (13%) or 'possibly prolong' (14%) the QT interval according to the SPC.

Discussion

Our study shows that the extent and content of information on QT prolongation varies considerably between drug labels, and in 43% of the drugs that mention the QT interval in the SPC, no clear statement on whether a drug prolongs the QT interval is mentioned in the SPC. Products that are more likely to have QT prolonging properties according to the SPC also provide more specific information on QT prolongation in other sections of the SPC.

Almost half of the SPCs that reported on QT prolongation, did not present a clear conclusion whether the drug induces QT prolongation, which is noteworthy. According to the guideline on summary of product characteristics the SPC or drug label is considered 'the basis of information for healthcare professionals on how

Table 2. Information and advices on QT prolongation reported in the drug label according to the message on QT prolongation according to the drug label (n = 44).

Information and advice on QT prolongation	Nature of the message on QT prolongation				
	All	**Drug does not prolong QT**	**Unclear if drug prolongs QT**	**Drug possibly prolongs QT**	**Drug prolongs QT**
	44 (100%)	**10 (23%)**	**19 (43%)**	**7 (16%)**	**8 (18%)**
Advice to act with caution or contraindicated in patients with risk factors related to QT prolongation:	27 (62%)	1 (10%)	11 (56%)	7 (100%)	8 (100%)
- Patients who have or may develop a prolonged QT	18 (41%)	0	6 (32%)	5 (71%)	7 (88%)
- Patients with congenital long QT syndrome	16 (36%)	0	6 (32%)	6 (86%)	4 (50%)
- Patients with a family history of congenital long QT syndrome	4 (9%)	1 (10%)	1 (5%)	2 (29%)	0
- Concurrently with other drugs that prolong the QT interval or anti-arrhythmics	24 (55%)	1 (10%)	10 (53%)	5 (71%)	8 (100%)
- Patients with electrolyte disturbances	14 (32%)	0	5 (26%)	3 (43%)	6 (75%)
- Patients with bradycardia	8 (18%)	0	3 (16%)	3 (43%)	2 (25%)
- Patients with cardiac disease	15 (34%)	1 (10%)	6 (32%)	4 (57%)	4 (50%)
Explaining the association of QT prolongation with ventricular arrhythmia, torsade de pointes, and sudden cardiac arrest	7 (16%)	0	2 (11%)	1 (14%)	4 (50%)
Advice on monitoring of patients using the product	15 (34%)	0	4 (21%)	4 (57%)	7 (88%)
- ECG prior to administration should be considered	8 (18%)	0	1 (5%)	2 (29%)	5 (63%)
- Monitoring with ECGs during treatment should be considered	12 (27%)	0	2 (11%)	4 (57%)	6 (75%)
- Electrolyte disturbances should be corrected prior to treatment	8 (18%)	0	2 (11%)	3 (43%)	3 (38%)
- Monitoring of electrolytes during treatment should be considered	8 (18%)	0	1 (5%)	2 (29%)	5 (63%)
- If the QT interval is prolonged the product should be stopped	4 (9%)	0	1 (5%)	0	3 (38%)

Values are numbers (percentages).

to use the medicinal product safely and effectively' and 'the SPC should be worded in clear and concise language'.[7] The ICH E14 European Medicine Agency (EMA) guideline on the clinical evaluation of QT prolongation and proarrhythmic potential which aims to promote drug safety and prevent drug-induced sudden cardiac death,[6] contains a short section on labelling issues for drugs that prolong the QT interval. It recommends that the following is considered: a warning/precautionary statement about the risk; a description of the design and results of the trials investigating the effect on the QT/QTc interval, including the absence of demonstrated effect; the dosage recommendations; a list of conditions known to increase the proarrhythmic risk (e.g., congestive heart failure, Long QT Syndrome, hypokalaemia); a precautionary statement regarding the concomitant use of two or more QT/QTc interval prolonging drugs and other interactions increasing the risk; recommendations for patient monitoring (ECG and electrolytes) and management of patients with QT/QTc prolongation or symptoms suggestive of an arrhythmia.[6] However, no guidance on how to formulate the message on QT prolongation is included. It is also not explicitly recommended to include an interpretation of the results, rather than a summary of the findings of the various trails.

We recommend to further update the ICH E14 guidelines to ensure more structured wordings on QT prolongation. In addition, we recommend an unambiguous interpretation of evidence, resulting in a clear 'message' on whether or not the products prolongs the QT, since the plain numbers of results of the trials investigating the effect on the QT interval may be hard to interpret for prescribing physicians. In addition, we recommend to present the associations between QT prolongation and ventricular arrhythmia, torsade de pointes, and sudden cardiac arrest more explicitly in the drug label. Only a minority of the SPCs (16%) provides such information. To reduce the risk of torsade de pointes and sudden cardiac arrest, physicians should be aware that a prolonged QT interval is a potential indicator of cardiovascular risk. Importantly, a study of Al-Khatib *et al.* showed that the knowledge on QT prolongation among health care providers is still unsatisfactory, illustrating the importance of clear and concise information in the SPC.[12]

Figure 2. Frequency of reporting on QT prolongation per section of the drug label, by the message on QT prolongation in the SPC

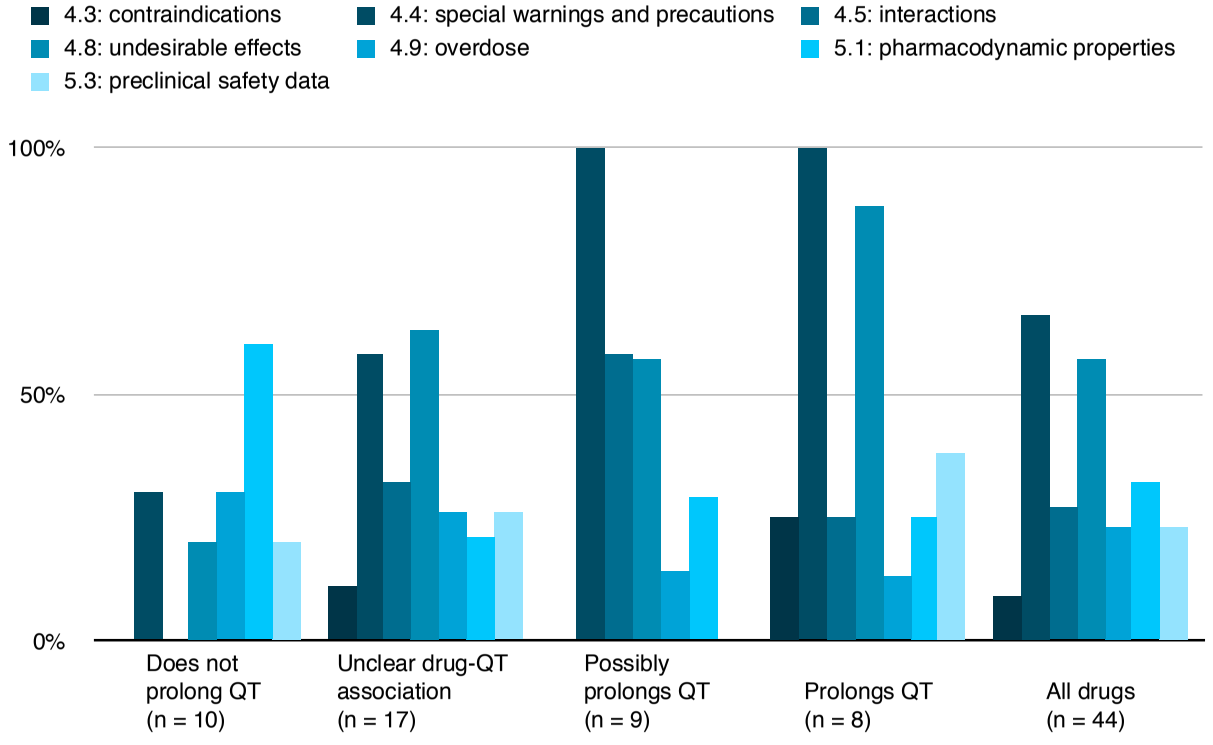
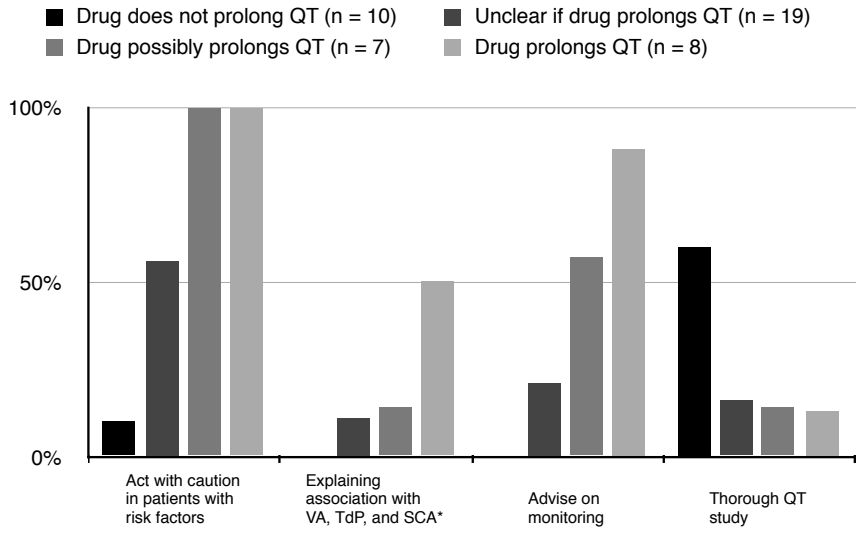


Figure 3. Information on QT prolongation reported in the summary of product characteristics (n = 44).



*VA: ventricular arrhythmia, TdP: torsade de pointes, SCA: sudden cardiac arrest.

According to Bastholm Rahmner *et al*. there is a need for databases that provide consistent information about new and existing drugs.[13] Inconsistencies in the SPC information undoubtedly reduce the utility of such systems when incorporating in these systems. Moreover, a more structured wording of the SPC on QT prolongation renders the recommendations in the SPC suitable for electronic prescribing systems and clinical decision support systems.[14,15]

We conclude that the extent and content of information on QT prolongation varies considerably between drug labels, and that in almost half of the drugs that mention the QT interval in the SPC, no clear statement on whether a drug prolongs the QT interval is mentioned in the SPC. The SPC is an important, albeit indirect, source of information for health care providers. Ambiguous information may

hamper the usefulness of the information for prescribing physicians and lead to suboptimal risk minimisation strategies. We therefore advocate to provide more structured phrasing of information and unambiguous interpretation of evidence on QT prolongation in the drug label, and provide clear instructions for prescribers how to deal with such risk.

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Appendix 1. Information on QT prolonging properties mentioned in the drug label, categorised into four subsets, based on the phrasing used to report on the degree of QT prolonging properties of the compound.

Drug does not prolong QT interval

- No events of clinically relevant QT prolongation have occurred (at supra-therapeutic or therapeutic doses, in clinical studies)

Unclear if the drug does prolong the QT interval

- Preclinical studies suggest that the drug has the potential to prolong the QT interval (Clinical studies: not stated or no (clinically relevant) effect on QT prolongation)
- Label contains conflicting statements on QT prolongation
- Events of QT prolongation have occurred, only at supra-therapeutic doses
- Numbers of events of QT prolongation occurred in clinical studies are stated, but no conclusion is drawn or interpretation is given concerning the ability to cause QT prolongation
- Label mentions QT prolongation *only* in section 4.8 in tabulated summary of adverse reactions
- Label does *only* mention warnings ("contra-indicated or use with caution when the patient has risk factors for QT prolongation")

Drug does potentially prolong QT interval

- Events of QT prolongation have occurred in clinical studies, but the clinical significance of this prolongation is unknown.
- Few clinically relevant events of QT prolongation have occurred in clinical studies
- Events of QT prolongation have occurred in clinical studies, so an effect on QT interval cannot be ruled out

Drug does prolong QT interval

- Dose and/or concentration-related increases in the QT interval have been observed.
- Events of QT prolongation have occurred (in clinical studies, at therapeutic doses)

Appendix 2. List of included products which mentioned QT in the SPC (n = 44) according to the message on QT prolongation in the SPC.

Not QT prolonging n = 10	Unclear drug-QT association n = 19	Possibly QT prolonging n = 7	QT prolonging n = 8
Aliskiren	Amifampridine	Fingolimod	Dronedarone
Asenapine maleate	Boceprevir	Lapatinib	Nilotinib
Azilsartan medoxomil	Darunavir	Pasireotide	Pazopanib
Indacaterol	Dasatinib	Ranolazine	Retigabine
Methylnaltrexone	Degarelix	Tacrolimus	Sorafenib tosylate
Prucalopride	Eltrombopag	Telaprevir	Sunitinib
Saxagliptin	Eribulin	Vinflunine ditartrate	Vandetanib
Sitagliptin	Fampridine		Vemurafenib
Sugammadex	Fesoterodine		
Trabectedin	Gadoversetamide		
	Gefitinib		
	Lenalidomide		
	Maraviroc		
	Olanzapine		
	Paliperidone		
	Regadenoson		
	Rilpivirine		
	Telavancin		
	Vernakalant		

SPC : summary of product characteristics

5.2

SAFETY INFORMATION ON QT INTERVAL PROLONGATION: VARIATION IN EUROPEAN AND AMERICAN DRUG LABELLING

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Abstract

Background

Prolongation of the QT interval may predispose to fatal ventricular arrhythmias. Information regarding QT prolonging properties of drugs seems inconsistent between different regulatory authorities, which may hamper the usefulness of the information and jeopardise risk minimisation strategies. Therefore the objective was to systematically compare the phrasing used to communicate on QT prolonging properties of drugs in the European and American drug labelling.

Methods

New unique medicinal products centrally approved in the European Union between January 1, 2006 and June 1, 2012, that were also approved in the US, were included. The European and American drug labels of included products were identified from the European Medicines Agency database of European public assessment reports and from the 'Drugs@FDA Search' database. Of those mentioning 'QT' in the drug label, the information on QT prolongation was categorised in four subsets (no QT prolongation / unclear drug-QT association / possibly QT prolongation / QT prolongation). The kappa statistic was calculated to estimate the agreement between the message in the European and American drug label.

Results

Of the 144 included unique medicinal products, 36 (25%) reported on QT prolongation in both the European and American drug label, and 30 (21%) in just one of the labels (28 American, 2 European). The agreement about the message on QT prolongation between the European and American drug labels was moderate (kappa 0.434). Six percent of the American drug labels had an unclear message on QT prolongation (i.e. some information from studies was provided, but no clear conclusion was drawn) compared to 12% of the European labels. The majority of the products (24/28) where only the American drug label reported on QT prolongation contained the message that the drug *does not* prolong the QT interval. When these 24 products were excluded, the kappa increased to 0.646.

Conclusions

There was only moderate agreement between the European and American drug label in how the QT prolonging effect was described. The American drug label tended to be more explicit, and more often contained a message excluding QT prolongation than the European drug label, showing that despite harmonisation of regulations drug labels are not uniform.

Introduction

Prolongation of cardiac repolarisation, manifested as a prolonged QT interval on the surface electrocardiogram (ECG) may predispose to ventricular arrhythmias, torsade de pointes, and sudden cardiac arrest.[1,2] Over the last decades, it was one of the most common adverse drug reactions leading to regulatory action, including withdrawal of a drug from the market.[3,4] As a result, the regulatory authorities have strengthened the requirements for premarketing assessment of proarrhythmic effects of new drugs, e.g. requesting 'thorough-QT studies'.[5]

Once a drug is approved the drug label forms the basis of information for health professionals on how to use the specific product safely and effectively.[6] It has been noticed, however, that the labelling information regarding QT prolonging properties of drugs varies between products, despite the fact that the administrative process for creating the document is similar: the document is written by the manufacturer and then formally approved by the governmental drug regulatory authority. The aim of this study was to systematically compare the phrasing used to communicate QT prolonging properties of drugs registered in the European and the US.

Methods

Study design and data collection

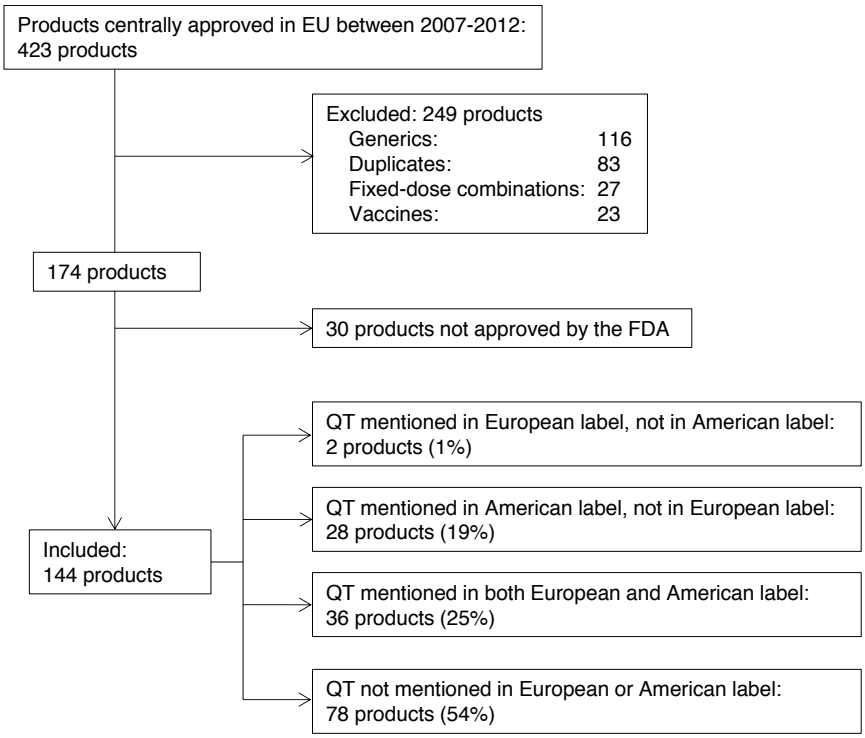
A descriptive study was performed, including new medicinal products centrally approved in the European between January 1, 2006 and June 1, 2012 that were also approved in the US. Duplicates, generics, fixed-dose combinations, and vaccines were excluded. The most recent European and American drug labels (March 2013) were identified from the European Medicines Agency database of European public assessment reports[7] and the 'Drugs@FDA Search' database of the Food and Drug Administration, respectively.[8] Of all included products, the indication and the year of registration in Europe were recorded.

Of all products that mentioned 'QT' in the label of either the European or American label (or both), the paragraphs that mentioned QT prolongation were extracted and assessed. Information on QT prolonging properties mentioned in the drug label was categorised into four subsets: 1. 'Drug does *not* prolong QT interval', 2. '*Unclear* if the drug prolongs the QT interval', 3. 'Drug *possibly* prolongs QT interval', 4. 'Drug *prolongs* QT interval', based on the semantics of the phrasing used to report on the degree of QT prolonging properties of the compound (Appendix 1). As we aimed to address the usefulness of drug labels for health care providers, we did not interpret the actual results of studies on QT prolongation noted in the label, but merely followed the semantics of the phrasings used to indicate the QT prolonging properties. MJW and MLDB independently categorised the drug labels into the four subsets. In addition, we assessed if the label contained information on thorough-QT studies.

Data analysis

The kappa statistic was calculated to estimate the agreement between the message (categorised in four subsets) on QT prolongation in the European and American drug label. A separate analysis was performed, in which a drug that according to the US label does 'not prolong the QT interval' while the European label provides no information on QT prolongation, were considered as concordant, because essentially no information warning for increased QT interval properties is included in either label. The kappa statistic was interpreted according to the classification system by Landis and Koch.[9] All data were analysed using the statistical software package SPSS (SPSS for Windows, version 20.0, SPSS Inc.).

Figure 1. Product inclusion and presence of information on QT in the drug label.



Results

Of the 174 products centrally approved in Europe between January 1, 2006 and June 1, 2012, 30 were not registered in the US (17%, Figure 1). Characteristics of the 144 included products are presented in Table 1. A quarter of the products (n=36, 25%) reported on QT prolongation in both the European and the American drug label, while more than half of the products contained information on QT prolongation in neither the American, nor the European label (n=78, 54%, Figure 1, Table 2).

Table 1. Characteristics of the included medicinal products centrally registered in the EU.

Characteristics	n	%
Indication:		
Cardiovascular	9	6%
Endocrinology and metabolic	12	8%
Infectious disease	24	17%
Immunology	19	13%
Haematology	11	8%
Musculoskeletal and nervous system	17	12%
Oncology	24	17%
Other	28	19%
Year of registration in Europe:		
2006	24	17%
2007	31	22%
2008	22	15%
2009	25	17%
2010	14	10%
2011	23	16%
2012[1]	5	4%

Until June 1, 2012

There was a tendency for the American drug label to be more explicit on drug associated QT prolongation than the European label (Table 2). Only 6% of the American drug labels had an unclear message on QT prolongation compared to 12% of the European drug labels (i.e. some information on studies was provided, but no clear conclusion was mentioned). In 19% of the products (n=28), only the American drug label reported on QT prolongation and not the European. Of these products, the majority (n=24) contained a message that the drug *does not* prolong the QT interval. One product (asenapine) had no QT prolonging properties according to the European label, while, according to the semantics in the American label, this drug possibly prolongs the QT interval.

In total 34 out of the 64 (53%) American labels that reported on QT prolongation contained information on a thorough-QT study. Of these products, 74% (n=25/34) of the drug labels contained the message that the drug *does not* prolong the

QT interval. In contrast, only 8 out of the 38 (21%) of the European labels that mention QT contained information on a thorough-QT study, of which 38% (n=3/8) were stated in labels with a negative message on QT prolongation. In 6 instances both the American and the European label mentioned a thorough-QT study.

Overall, the agreement on the message about QT prolongation between the European and American drug label was moderate (kappa 0.434). When the 24 products, of which the US label stated 'does not prolong QT interval' while the European label provided no information, were considered as concordant, the kappa increased to 0.646 (substantial agreement).

Discussion

To the best of our knowledge, this study is the first to investigate how information on QT prolongation is covered in European and US drug labels. The overall results show that the European and American drug label only moderately agree in their semantics used to phrase QT prolonging properties of a drug; kappa 0.434 and when drugs with 'does not prolong QT interval' in the American label while the European label did not provide any information on QT prolongation, were considered concordant, kappa was 0.646. The American drug label tends to be more explicit. In addition, the American drug label more often contained a message excluding a risk of QT prolongation, usually supported by evidence obtained from a thorough-QT study. Although the administrative process creating drug labels is similar in both continents, a negative thorough-QT study, or a lack of drug effect on QT prolongation, seems for the European regulators often no reason to let these negative findings be reflected in the drug label.

Table 2. Agreement between the message on QT prolongation in the European and American drug label based on the semantics of the phrasings used to indicate the QT prolonging properties.

Message on QT prolongation in American drug label	Message on QT prolongation in European drug label					
	Drug does not prolong QT	Unclear if drug prolongs QT	Drug possibly prolongs QT	Drug prolongs QT	QT not mentioned	Total
Drug does not prolong QT	6 (4%)	8 (6%)	0	0	24 (17%)	38 (26%)
Unclear if drug prolongs QT	0	4 (3%)	1 (0.7%)	0	4 (3%)	9 (6%)
Drug possibly prolongs QT	1 (0.7%)	3 (2%)	2 (1%)	0	0	6 (4%)
Drug prolongs QT	0	1 (0.7%)	2 (1%)	8 (6%)	0	11 (8%)
QT not mentioned	0	1 (0.7%)	1 (0.7%)	0	78 (54%)	80 (56%)
Total	7 (5%)	17 (12%)	6 (4%)	8 (6%)	106 (74%)	144 (100%)

Values are absolute numbers (percentages of total)

Recently, Shimazawa and Ikeda concluded that although the mean proportion (number of words) of safety information is similar in American, European and Japanese drug labels, substantial differences exist for several therapeutic classes.[10] Kesselheim *et al*. conducted a study comparing prescribing information (i.e. drug labels) approved by the FDA with that approved by the European, Canadian, and Australian regulatory authorities. They found that significantly fewer adverse drug reactions were listed in the UK label compared to the US label and concluded that the international variations in the presentation of safety data in the drug label, may have important implications for patient safety.[11]

The global harmonisation activities of the regulatory authorities of the US, Europe, and Japan have resulted in a guideline on Clinical Evaluation of QT Interval Prolongation and Proarrhythmic Potential (ICH E14) that amongst others calls for harmonised implications for drug labelling.[5,12] However, the results of our study show that the harmonised approach is not reflected in uniform drug labels with respect to QT prolongation.

Noteworthy, the following example displays the irregularity in how QT information is handled in the European and American drug label. Asenapine, which is a sublingually administered atypical antipsychotic that has no QT prolonging properties according to the European label (stating 'QT prolongation does not appear to be associated with asenapine'), while this drug does prolong the QT interval according to the American label (stating 'Increases in QT interval'). Whereas the European label does not report on a thorough-QT study, the American label reports on such a thorough-QT that showed a 2 to 5 ms increase of the QT interval.[13,14] Although the clinical interpretation may indicate that there was no clinically relevant QT prolongation observed, the semantics used to phrase the findings do not incorporate this clinical interpretation. Hence, clinicians are just confronted with a phrase that states that QT prolongation was observed, resulting in a different message on QT prolonging properties in both continents.

Some limitations of our study should be discussed. We studied a subset of re-

cently approved products for which harmonisation may be relatively high. The kappa is likely to be lower when a wider range of products is studied. In addition, the method to categorise the message on QT prolonging properties of the drug described in the drug label into four subsets was subjective and not validated by other studies, as a validated categorising system does not exists.

Conclusions

This study showed that the European and American drug label only moderately agree in their semantics used to phrase QT prolonging properties. The American drug label tended to be more explicit, and more often contained a message stating that the drug does not prolong the QT interval. The results of our study show that despite shared knowledge and harmonisation of drug safety regulations safety information related to QT prolongation in the drug label is not uniform, and should be optimised.

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Appendix 1. Information on QT prolonging properties mentioned in the drug label, categorised into four subsets, based on the phrasing used to report on the degree of QT prolonging properties of the compound.

Drug does not prolong QT interval

- No events of clinically relevant QT prolongation have occurred (at supra-therapeutic or therapeutic doses, in clinical studies)

Unclear if the drug does prolong the QT interval

- Preclinical studies suggest that the drug has the potential to prolong the QT interval (Clinical studies: not stated or no (clinically relevant) effect on QT prolongation)
- Label contains conflicting statements on QT prolongation
- Events of QT prolongation have occurred, only at supra-therapeutic doses
- Numbers of events of QT prolongation occurred in clinical studies are stated, but no conclusion is drawn or interpretation is given concerning the ability to cause QT prolongation
- Label mentions QT prolongation *only* in section 4.8 in tabulated summary of adverse reactions
- Label does *only* mention warnings ("contra-indicated or use with caution when the patient has risk factors for QT prolongation")

Drug does potentially prolong QT interval

- Events of QT prolongation have occurred in clinical studies, but the clinical significance of this prolongation is unknown.
- Few clinically relevant events of QT prolongation have occurred in clinical studies
- Events of QT prolongation have occurred in clinical studies, so an effect on QT interval cannot be ruled out

Drug does prolong QT interval

- Dose and/or concentration-related increases in the QT interval have been observed.
- Events of QT prolongation have occurred (in clinical studies, at therapeutic doses)

6

GENERAL DISCUSSION

ARRHYTHMIAS IN PATIENTS WITH OBSTRUCTIVE PULMONARY DISEASE: SHOULD WE BOTHER?

Chronic obstructive pulmonary disease (COPD) and asthma are both obstructive pulmonary diseases characterised by inflammation of the bronchi causing airway obstruction. Whereas in asthma the obstruction is largely reversible,[1] in COPD the airway obstruction is irreversible and progressive.[2] The most important risk factor for COPD is smoking of tobacco.[3,4] Unlike COPD, asthma is not caused by cigarette smoking, but by a genetic predisposition to atopy and airway hyperresponsiveness.[5] While asthma primarily is a childhood disease, that in approximately 80% persists as mild asthma in adulthood,[6] COPD is mainly a disease of the elderly. Both COPD and asthma have been associated with an increased risk of cardiac arrhythmias, but underlying mechanism and the role of pulmonary medication remains unclear. In both diseases, inhaled bronchodilators, e.g. anticholinergics and β_2-agonist, are essential in the pharmacological treatment. β_2-agonists are used for both asthma and COPD, but anticholinergics almost exclusively for COPD.[1,2] Although both are established drugs for obstructive pulmonary disease, there are concerns about their pro-arrhythmic effects. In this chapter we will discuss the risk of cardiac arrhythmias in obstructive pulmonary disease, and the possible role of the aforementioned inhalatory drugs, and other drugs, in this association.

Obstructive pulmonary disease, heart rate, and cardiac arrhythmia

Epidemiological studies show that patients with COPD have an increased risk of (any type of) cardiac arrhythmias compared to those without COPD. The prevalence of arrhythmia in patients with COPD varies according to setting, population characteristics such as age and severity of pulmonary disease, and definition of arrhythmia. It ranges from 11% to 29% in various studies, as compared to 5% to 14% in those without COPD (relative risks [RR] ranging from 1.2 to 2.8).[7-11] Patients with asthma seem to have an increased risk of arrhythmia as well, when compared to those without asthma, although this relationship is less strong. A

recently published population-based study showed that the prevalence of arrhythmia (type not specified) was 8.7% in patients with asthma aged 35 or older, compared to 6.1% in those without asthma of the same age (crude odds ratio [OR]: 1.47 [1.42-1.53]).[9]

Increased resting heart rate and tachycardia

In one or our studies (chapter 2.2) we showed that asthma was associated with an increased risk of tachycardia (resting heart rate $>$100 beats per minute) as compared to those without asthma (3% vs. 0.6%, age and gender adjusted OR 5.5 [2.1-14.3]), although the mean resting heart rate was similar in those with and without asthma (66 beats per minute [SD 11] and 65 beats per minute [SD 11], respectively, $p = 0.26$). The increased risk of tachycardia in patients with asthma was more pronounced in those who used β_2-agonists, when compared to those without asthma (7% vs. 0.6% in those without asthma, RR 12.4 [4.7-32.8]).[12]

Previous studies, including one of our own (chapter 2.1), showed that COPD is associated with an increased resting heart rate as compared to age- and sex-matched controls, and that the heart rate increases with increasing severity of the disease.[13,14] Heart rate is an important predictor of all-cause and cardiovascular mortality in the population at large,[15-18] but also, as we and others showed recently (chapter 2.3), in those with COPD.[13] The pathophysiologic mechanism of this association is unknown, although Levine proposed that the effect of the resting heart rate on mortality may be explained by basal metabolic effects. He showed that the number of heart beats per lifetime is the same across a wide range of mammals, and that slower heart rates are associated with greater longevity.[19]

Ventricular arrhythmia and sudden cardiac arrest

Patients with obstructive pulmonary disease have an increased risk of ventricular arrhythmia and cardiac arrest. The cohort study of Sidney *et al*. showed

that patients with COPD experienced an almost three-fold increased risk of hospitalisation for ventricular tachycardia and cardiac arrest,[20] and Engström *et al*. demonstrated that reduced lung function was associated with an increased risk of ventricular arrhythmia.[21] In one of our studies (chapter 3.1), we observed that patients with obstructive pulmonary disease had a 40% higher risk of sudden cardiac arrest, compared to those without this disease (adjusted OR 1.4 [1.2-1.6]).[22] The association with sudden cardiac arrest was most pronounced in the subgroup of patients receiving short-acting β_2-agonists at the time of the sudden cardiac arrest. This was also observed, albeit to a lesser extent, in the subgroup of patients receiving anticholinergic drugs.

Potential explanatory mechanisms

Proposed explanatory mechanisms of the increased risk of cardiac arrhythmias in COPD include smoking, systemic inflammation, and autonomic dysfunction. Smoking is a common and important risk factor for COPD as well as for coronary artery disease, and coronary artery disease increases the risk of arrhythmia and sudden cardiac death.[23] Systemic inflammation, an important pathophysiologic mechanism in disease progression of chronic obstructive pulmonary disease, seems to play a crucial role in the development of atherosclerosis and ischaemic heart disease.[24,25] In asthma also background systemic inflammation may be present which may contribute to the development of cardiac arrhythmias in these patients, although evidence confirming this hypothesis is limited.[26-28] Finally, hypoxemia together with dyspnoea and increased respiratory drive is associated with elevated sympathetic activity (autonomic dysfunction) in asthma and COPD which in turn may contribute to the development of cardiac arrhythmias by increasing the resting heart rate.[21,29,30] Besides these mechanisms related to the disease, there is a growing concern that pulmonary medication - most notably β_2-agonists and anticholinergics - increase resting heart rate and may promote cardiac arrhythmias.[31-37] We will subsequently discuss the potential role of drug therapy in the increased risk of cardiac arrhythmias in patients with asthma and COPD.

Drug therapy and risk of arrhythmias

β_2-agonists

Already soon after their availability in the 1960s, concerns emerged about potentially serious adverse effects of β_2- agonists on the heart. β_2-agonists act on the β_2-adrenergic receptors of bronchial smooth muscle cells, resulting in dilatation of the bronchi and thus relief of symptomatic wheeze and dyspnoea, and improvement of the lung function.[38,39] However, β_2-adrenergic receptors are also present in the heart, where stimulation of the receptor results in increased myocardial contractility and heart rate.[38] In addition, β_2-agonists lower serum potassium levels due to intracellular uptake of potassium by stimulation of membrane-bound Na/K-ATPase, which may also cause cardiac arrhythmias, especially when combined with (sulfonamides and thiazides) diuretics.[38,40] Finally, β_2-agonists may prolong the QT interval measured on a standard electrocardiography (ECG) in a dose-dependent manner.[39] The mean maximum changes from baseline in QT interval were 61.4, 40.2, 32.5, and 7.1 ms for respectively fenoterol, formoterol, salbutamol, and placebo in the study of Bremner *et al*.[41]

The currently available studies and meta-analyses yield conflicting results on the association of β_2-agonists with cardiac arrhythmias. The meta-analysis of randomised, placebo-controlled trials of Salpeter *et al*. showed that use of β_2-agonists in patients with asthma and COPD increases the risk of sinus tachycardia (RR 3.06 [1.70-5.50]).[31] In addition, the risk of major cardiovascular events (ventricular tachycardia, atrial fibrillation, syncope, cardiac arrest, and sudden cardiac death) increased, although non-significantly, with the use of β_2-agonists (RR 1.61 [0.76-3.42]). However, some remarks about the methodology of this meta-analysis have to be made. First, in about a quarter of the included studies (8/33), dating back to 1966, the β_2-agonists were administered orally, intramuscular and nebulised, which may result in a higher risks of side effects compared to more locally administered, inhalator therapy, which is nowadays the usual form of administration in many countries. This is illustrated by a case-control study observing an increased risk of cardiovascular death in users of β_2-agonists taken

orally or by nebuliser (RR 2.4 [1.0-5.4]), but not in users of β_2-agonists administered by metered-dose inhaler (RR1.2 [0.5-2.7]).[42] In addition, several of the included studies were phase II trials that were designed to evaluate the maximum tolerated dose, and many of the adverse events occurred at doses higher than currently approved.[43] Finally, most included trials excluded patients with concomitant cardiovascular disease, abnormal ECG, and other comorbidities. Hence, the results of this meta-analysis should be interpreted with caution.

In contrast, the Cochrane review of Sestine *et al.* found no serious side effects during treatment with inhaled short-acting β_2-agonists, although the duration of all the included trials was short, ranging from 1 to 9 weeks.[44] A recent review of 20 placebo-controlled studies that also included trials in patients with pre-existent cardiovascular disease, evaluated long-term use of long-acting β_2-agonists in patients with COPD. The authors showed that none of the included randomised controlled trials reported on an increased incidence of cardiac arrhythmias with the use of long-acting β_2-agonists.[45] However, many of the included studies did not report on specific causes of serious adverse events. This may have resulted in an underestimation of the arrhythmogenic effect of long-acting β-agonists.

Observational studies were less consistent. In two recent case-control studies an increased risk of cardiac arrhythmia was observed with new use of long-acting β-agonists in patients with COPD $>$ 55 and $>$ 66 years (RR 4.55 [1.43-14.45] and RR 1.47 [1.01-2.15], respectively).[46] A major limitation of both studies is, however, that disease severity was not taken into account, as spirometry and other clinical data used to assess COPD severity were not available for patients of both cohorts, which may have introduced bias. Other observational studies did not show an increased risk of (any) cardiac arrhythmia.[34,47]

In conclusion, although evidence is conflicting and the interpretation of the studies are hampered by methodological limitations, β_2-agonists are likely to add - at least to some degree - to the increased risk of cardiac arrhythmias in patients with obstructive pulmonary disease.

Anticholinergics

Anticholinergic drugs, or anti-muscarinic agents, inhibit the muscarinic acetylcholine receptors, which results in a decrease in contractility of smooth muscle in the bronchi of the lung and an inhibition of (chronic) bronchoconstriction and mucus secretion.[48] In contrast, to β_2-agonists, anticholinergics were not under the suspicion of causing cardiovascular side effects some decades ago, thus anticholinergic agents traditionally were more readily prescribed to patients at increased risk of cardiovascular disease. However, more recently, there have been concerns that anticholinergics also may cause cardiovascular disease. In addition to their local effects on the lungs, anticholinergic agents reduce the systemic parasympathetic activity, which may cause tachyarrhythmias and myocardial ischaemia.[48]

The currently available epidemiologic studies show an overall trend towards an increased risk of cardiac morbidity and mortality in patients prescribed short-acting anticholinergics, while the risk seems lower for long-acting anticholinergics. Evidence, however, is conflicting and lately concerns have been raised about the cardiovascular risk associated with the anticholinergic tiotropium mist inhaler. The meta-analysis of Singh *et al*. showed that the use of short-acting anticholinergics was associated with an increased risk of an composite endpoint including cardiovascular death, myocardial infarction and stroke (RR 1.70 [1.19-2.42]), but this risk was non-significantly increased in long-term anticholinergics (RR 1.43 [0.95-2.16]).[49] Selection bias may have occurred in this meta-analysis as 83% of the studies (86/103) was excluded because no cardiovascular averse events were reported. Also other meta-analyses,[50] reviews,[25,51] and observational studies,[34,52] showed that the risk of arrhythmias and cardiovascular mortality is increased in short-acting anticholinergics. It is yet unknown why the risk on cardiac arrhythmias seems to be more pronounced in short-acting than in long-acting anticholinergics. It may be argued that, the rapid, but short, action of the short-acting anticholinergics may cause instability of the cardiovascular system. Also the fact that short-acting anticholinergics are used as rescue therapy may result in higher total doses and increased risk of cardiac arrhythmias.[25]

The meta-analysis of Singh *et al*. also showed that the use of inhaled anticholinergics (short and long-acting together) increased the risk of cardiovascular death (0.9% vs. 0.5% in controls, RR 1.80 [1.17-2.77]).[49] In contrast, the UPLIFT-trial (pharmaceutical industry sponsored) did not show an increased risk of cardiovascular mortality in COPD patients using long-acting anticholinergics (tiotropium dry-powder inhaler), but patients prior cardiovascular disease such as recent myocardial infarction, unstable cardiac arrhythmias, or hospitalizations for heart failure were not included in this trial.[53] Based upon this trial, the Food and Drug Administration in 2010 concluded that tiotropium was not associated with an increased mortality risk.[54] Then, however, concerns were raised on the tiotropium mist inhaler. Three systematic reviews and meta-analyses of randomised controlled trials[55-57] by various groups of independent investigators concluded that the tiotropium mist inhaler increased the risk of cardiovascular and all-cause mortality, compared to placebo (RR 2.05 [1.06-3.99] and 1.52 [1.06-2.16], respectively),[55] but also compared to other inhaled bronchodilators (all-cause mortality compared to placebo: OR 1.51 [1.06-2.19], to the tiotropium dry powder inhaler: OR 1.65 [1.13-2.43], to long-acting β_2-agonists: OR 1.63 [1.10-2.44], to long-acting β_2-agonists combined with inhaled corticosteroids: OR 1.90 [1.28-2.86]).[57] Because of the safety concerns of tiotropium mist inhaler, a large-scale randomized controlled trial was conducted (sponsored by the pharmaceutical company that produces tiotropium) including 17,135 patients with COPD, which showed no increased risk of all-cause and cardiovascular death compared to the tiotropium dry powder inhaler (RR 0.96 [0.84-1.09] and 1.11 [0.85-1.45], respectively), also not in the 1825 patients with previous cardiac arrhythmia (RR 0.81 [0.58-1.12]).[58]

Still, the recently published opinion paper of Singh *et al*. urges caution in the prescription of inhaled anticholinergics for patients with pre-existing arrhythmias or cardiac disorders, as according the authors inhaled anticholinergics have an pro-arrhythmic and pro-ischaemic effect. They insist on an adequately powered cardiovascular safety trial of short and long acting anticholinergic inhalers, including patients with a history of cardiovascular disease.[59]

QT prolonging drugs

Several drugs are able to increase the QT interval. This may, although rarely, result in drug-induced arrhythmia such as torsade de pointes, ventricular fibrillation, and sudden cardiac death.[60] Anti-arrhythmic drugs such as sotalol commonly cause QT prolongation, but also non-antiarrhythmic drugs may induce QT prolongation, for instance macrolide antibiotics, such as azithromycin and clarithromycin, or anti-psychotics, such as haloperidol.[61] Also β_2-agonists (e.g. salmeterol, fenoterol, and salbutamol) are reported to increase the QT interval in a dose-dependent manner.[41, 62-64]

Patients with additional risk factors for QT prolongation, such as prior myocardial infarction, heart failure, concomitant use of other arrhythmogenic drugs, and a history of congenital long QT syndrome experience an extra increased risk of cardiac arrhythmias when the QT interval is prolonged.[65] Patients with obstructive lung disease, particularly those with COPD, may often use QT interval prolonging drugs. Moreover, they frequently have additional risk factors for QT prolongation. For example, more than 20% of the COPD patients, aged 65 year or older, concomitantly suffer from heart failure.[66]

Previous studies showed that patients with asthma were more prone to develop cardiac arrhythmia than people without this condition, when using QT interval prolonging drugs.[67] We, however, did not find evidence that this is a result of an increased baseline prolongation of the QT interval in such patients. In one of our studies (chapter 2.2) the mean QT interval length and prevalence of QT interval prolongation were similar in those with and without asthma.[12] In our study among patients with COPD (chapter 2.1) QT prolongation was even less prevalent than in those without a diagnosis of COPD, and the mean QT interval length was shorter in those with COPD as compared to those without such a diagnosis.[14] Until now, there is no indisputable evidence that patients with obstructive pulmonary disease are more prone to the QT prolonging effect of some drugs, than those without obstructive pulmonary disease.

However, the use of QT prolonging drug may add to the increased risk of cardiac arrhythmias of patients with asthma and COPD, although to what degree remains unclear.

Methodological issues

Although the preceding indicates that pulmonary drug therapy, at least to some extent, plays a role in the association between obstructive pulmonary disease and cardiac arrhythmias, the question remains to what extent this is caused by the disease (obstructive pulmonary disease), or by the drugs prescribed to treat these diseases (β_2-agonists and anticholinergics).

Randomised controlled trials

A considerable part of the knowledge on the arrhythmogenic effects of respiratory drugs originates from randomised controlled trials and meta-analyses of randomised controlled trials. However, although randomised controlled trials are often considered to produce the highest level of evidence, they do have limitations. Participants of randomised controlled trials in general have less or no (cardiovascular) comorbidities and are often younger than the population at large with a certain disease, and have a higher drug adherence.[68,69] In addition, as most trials are only evaluating a drug during a short period of time, lasting usually only a few weeks or months, long-term effects are not evaluated with this type of study.

Moreover, trials are often not powered to identify an (unexpected) side effect of a drug, or such adverse effects are not registered.[69] For instance, an increased risk of arrhythmia associated with the use of long-acting anticholinergics (tiotropium) has been reported consistently in many clinical trials, but none of the trials reached statistically significance.[59]

In theory, randomised controlled trials specially designed and conducted to evaluate a suspected side effect would be desirable. In reality, these trials seldom are conducted, because of the ethical objections, although the study comparing the mortality risk in patients using tiotropium mist inhaler or tiotropium dry powder inhaler.

Observational studies

When it is not possible or ethical to perform randomised controlled trials, observational studies are the best alternative, although also observational studies have their shortcomings for the evaluation of arrhythmogenic drug effects in patients with obstructive pulmonary disease. One of the pitfalls of studying drug effects in observational studies is confounding by indication.[70] The preferences of physicians to prescribe (or not prescribe) a certain drug depends on the type of patient. In other words, the characteristics of those who receive a certain drug always differ from those who do not. Therefore, patients with a certain disease receiving a certain drug differ from those with the same disease not prescribed this drug, and differences in the occurrence of the outcome observed in a study comparing those receiving the drugs or not can be either caused by the drug or by the differences in patient characteristics. Also disease severity may cause confounding in such studies.[71] Physicians prescribe drugs to patients in whom they consider it to be indicated. Bronchodilators are almost exclusively used by patients with obstructive pulmonary disease, but patients who suffer from more severe disease will receive more types and higher dosages of bronchodilators than patients with milder disease. Moreover, physicians do not prescribe drugs to patients who have a contra-indication, which may result in confounding by contra-indication.[72] For example, in the 1990s β_2-agonsists were assumed to cause serious cardiovascular side effects, while anticholinergics were considered not to have such adverse effects, and thus anticholinergic agents were more readily prescribed as alternative bronchodilator to patients with COPD and concomitant cardiac problems. Thus, the association between bronchodilators and cardiac arrhythmias reported in observational studies, may - at least partially - be caused by bias and in particular confounding.

Clinical implications

Whilst the risk of cardiac arrhythmia, especially tachycardia, seems to be only moderately increased, and most likely is mainly caused by bronchodilator treatment, patients with COPD unequivocally have an increased risk of cardiac arrhythmia, which appears to be the result of a complex interaction between disease (severity), concomitant heart disease, also often caused by smoking and therapy for the disease. As patients with COPD have an increased risk of cardiovascular disease, including cardiac arrhythmia, smoking cessation remains one of the most important treatment options, to reduce the deleterious effects of smoking on both heart (mainly ischaemic heart disease) and lung (COPD, but also lung cancer). In addition, as bronchodilators are essential to reduce symptoms for patients with obstructive pulmonary disease, not using these drugs is not an option.[1,2] However, the possibility of cardiac arrhythmias needs to be considered in the management of patients with obstructive pulmonary disease, and special attention in the diagnostic work-up of these patients is needed, especially in patients with COPD, to detect previously unrecognised cardiovascular disease.

Furthermore, β-blockers may have a role in the treatment of COPD. β-blockers can counter-act the increased generalised sympathetic over-activity present in COPD. Despite the substantial benefit of β-blockers, these drugs have long been considered contra-indicated in COPD patients. Particularly in COPD patients with severe disease, many of whom have substantial concomitant cardiovascular disease, physicians tend to refrain from prescribing β-blockers. This is strange in a way, because especially those with severe COPD do not have any reversibility and thus are unlikely to react on the potential broncho-constrictive effects of β-blockers. Evidence indicates that cardio-selective β-blockers are well tolerated by COPD patients. The Cochrane review of Salpeter *et al*. showed that cardio-selective β-blockers are well tolerated by patients with COPD, without adverse effects on FEV_1, respiratory symptoms or response to β_2-agonists.[73]

In addition, several large observational studies showed that long-term treatment with (cardio-selective) β-blockers even may improve survival of patients with chronic obstructive pulmonary disease,[74,75] and also reduce exacerbations.[74]

Although, counter intuitive at first glance, combining β_2-agonists and β-blockers seems a good treatment option for patients with COPD when both drugs are indicated, because of counterbalancing possible negative effects of each drug.[76] Until now the effect of β-blockers on mortality in patients with COPD has only been demonstrated in observational studies, and thus the results are prone to confounding. Therefore randomised controlled trials are needed to confirm if β-blockers, or other heart rate lowering drugs, are beneficial in reducing fatal and nonfatal complications in patients with COPD.

In order to manage the risk of drug-induced arrhythmias in daily clinical practice, the drug label plays a central role. The drug label forms the basis of information for health care professionals on how to use the specific product safely and effectively, also regarding information on arrhythmogenic properties of drugs.[77] Inconsistencies in drug labelling may hamper the usefulness of the information and jeopardise risk minimisation strategies.

In our study we found that the extent and content of information on QT prolongation varied considerably between drug labels, and that many drug labels did not mentioned a clear message on whether the drug does or does not prolong the QT interval (chapter 5.1). Furthermore, there are quite some inconsistencies between the American and European drug labels with respect to how QT-prolonging effects are described (chapter 5.2).

In a separate analyses we looked at how the recommendations concerning preventive measures for drug-induced arrhythmias are followed in routine care (chapter 4.2). We found that compliance of general practitioners to ECG monitoring recommendations stated in the label of the QT prolonging drug haloperidol was extremely low (1.8%). These results show that careful consideration of too little

and too much information and recommendations in the drug label is essential. Next, structured phrasing and unambiguous interpretation of evidence, to provide clear instructions for prescribers in the drug label on how to deal with arrhythmogenic properties and side effects is preferable.

Conclusions

We should bother about possible cardiac arrhythmias in patients with obstructive pulmonary disease. Although it is impossible to fully disentangle the effects of the disease (COPD and asthma) and the treatment for the disease (β_2-agonists and anticholinergics), current evidence shows that patients with obstructive pulmonary disease, and especially COPD, are at increased risk of cardiac arrhythmias. In asthma the risk of cardiac arrhythmia appears to be only moderately increased, and most likely mainly related to bronchodilator treatment, while patients with COPD clearly have an increased risk of cardiac arrhythmia, which appears to be the result of a complex interaction between disease (severity), concomitant smoking related ischaemic heart disease, and therapy for the disease. Physicians should be aware that patients with obstructive pulmonary disease have an increased risk of cardiac arrhythmia, and that bronchodilator treatment may cause cardiac arrhythmia in patients with asthma and COPD. Especially for patients with COPD, but also in selected patients with asthma, a more integrated pulmonary and cardiovascular care with special attention to previously unrecognised cardiovascular disease, is preferable.

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ADDENDUM

Summary

In the introduction, **chapter 1**, we discuss that notwithstanding the clinical importance of cardiac arrhythmias, relevant information about the background risk and the exact underlying mechanisms of cardiac arrhythmias in patients with obstructive pulmonary disease (asthma and chronic obstructive pulmonary disease [COPD]) is still lacking. During the last decade it became increasingly clear that patients suffering from COPD are at increased risk of cardiovascular morbidity and mortality, including cardiac arrhythmia. In patients with asthma the relation with cardiovascular disease is less unequivocal, although asthma patients as well appeared to have an increased risk of arrhythmia. Proposed explanatory mechanisms of the increased risk of cardiac arrhythmias in COPD are smoking, systemic inflammation, and autonomic dysfunction. Besides these mechanisms related to the disease, there is a growing concern that drug therapy - most notably β_2-agonists and anticholinergics, but also QT interval prolonging drugs - may promote cardiac arrhythmias. New evidence on these issues may create new opportunities to prevent of cardiac arrhythmias in patients with obstructive pulmonary disease.

In **chapter 2** the association between obstructive pulmonary disease and the risk of electrocardiographic (ECG) abnormalities was evaluated. In **chapter 2.1** the occurrence of ECG characteristics among COPD patients was determined, and we assessed whether the prevalence of various ECG characteristics was related to severity of pulmonary obstruction. ECG abnormalities, especially conduction abnormalities were common in COPD patients (50% and 28%, respectively, compared to respectively 36% [$p = 0.054$] and 11% [$p < 0.001$] in patients without COPD), and the prevalence of ECG abnormalities increased with severity of COPD according to the global initiative for chronic obstructive lung disease (GOLD) criteria (GOLD I: 46%, GOLD II: 50%, GOLD III: 58%, adjusted odds ratio [OR] III vs. I: 1.5 [0.7-3.3]). These results showed that COPD patients more often have ECG abnormalities than those without this disease, including abnor-

malities that have been shown to increase the risk of future cardiovascular events and mortality. Therefore, special attention in the diagnostic work-up of these patients is needed, including ECG and in selected cases echocardiography, coming to a more integrated pulmonary and cardiovascular care. In **chapter 2.2**, we studied the association between asthma and the risk of cardiac arrhythmias and ECG characteristics of arrhythmogenicity, using data from the cohort of the Utrecht Health Project - an on-going, longitudinal, primary care-based study. In addition, we explored the role of β_2-agonists in this association. The adult patients with asthma more commonly showed tachycardia and premature ventricular contractions (PVCs) on the ECG (3% and 4%, respectively) than those without asthma (0.6%, $p < 0.001$; 2%, $p = 0.03$, respectively). In asthma patients, who received β_2-agonists, the risk of tachycardia and PVCs was even more pronounced (OR: 12.4 [4.7-32.8] and 3.7 [1.3-10.5], respectively). Elevated heart rate is associated with an increased risk of cardiac mortality in epidemiological studies in the population at large and we therefore suggested future research to evaluate whether the increased heart rate is related to the disease itself or the use of inhalers, notably β_2-agonists. **Chapter 2.3** focussed on prognostic significance of heart rate in patients with COPD. Patients with COPD often have coexisting cardiovascular disease and in general they have higher heart rates than the population at large. However, the effects on both mortality and non-fatal pulmonary complications was still unknown. Hence the aim of this study was to assess whether heart rate is associated with all-cause mortality, and non-fatal pulmonary endpoints. The results of this prospective cohort study among 405 patients aged 65 years or older showed that increased resting heart rate is a strong and independent risk factor for all-cause mortality in elderly patients with COPD, although resting heart rate did not result in non-fatal pulmonary complications. The relative risk of all-cause mortality increased with 21% for every 10 bpm increase in heart rate (adjusted hazard rate [HR]: 1.21 [1.07-1.36]), while the risk of a non-fatal pulmonary complication increased non-significantly with 7% for every 10 bpm increase in resting heart rate (adjusted HR: 1.07 [0.96-1.18]).

This may indicate that the increased mortality in COPD is mainly determined by non-pulmonary causes. We therefore suggested that future randomised controlled trials are needed to investigate whether patients with COPD may benefit from heart rate lowering agents.

Chapter 3 provided new insights into sudden cardiac arrest in patients with obstructive pulmonary disease. In **chapter 3.1** we studied whether patients with obstructive pulmonary disease have an increased risk of (ECG-confirmed) sudden cardiac arrest. Next, we attempted to identify subgroups of patients with obstructive pulmonary disease at greatest risk, focusing on the possible roles of cardiovascular risk-profile and use of respiratory drugs. We observed that obstructive pulmonary disease was associated with a 40% increased risk of ECG-confirmed sudden cardiac arrest (n = 190 cases [15%], 622 controls [11%]). The increase in sudden cardiac arrest risk was most pronounced in obstructive pulmonary disease patients who received short-acting β_2-agonists (SABA) or anticholinergics (AC) at the time of sudden cardiac arrest (SABA OR: 3.9 [1.7-8.8], AC OR: 2.7 [1.5-4.8] compared to those without obstructive pulmonary disease). These findings may provide the basis for refinements in treatment strategies for patients with obstructive pulmonary disease; for instance, in patients who receive short-acting β_2-agonists or anticholinergics, investigations to detect previously unrecognized cardiovascular disease may be recommended. In **chapter 3.2** we studied whether patients with obstructive pulmonary disease have a lower survival rate after out of hospital cardiac arrest than patients without obstructive pulmonary disease. We observed that patients with obstructive pulmonary disease had a 40% lower chance on 30-day survival after out of hospital cardiac arrest than patients without obstructive pulmonary disease (21% vs. 33%, OR 0.6 [0.4-0.9]). Survival rates were similar for patients with and without obstructive pulmonary disease at the first stages of resuscitation care (survival to ER: 75% vs. 78%, OR 0.9 [0.6-1.3], and survival to hospital admission: 56% vs. 57%, OR 1.0 [0.7-1.4]); it was only after admission to hospital that the survival rate of patients with obstructive pulmonary disease became lower than of those without this disease. These findings suggested that in-hospital post-resuscitation care of patients with obstructive pul-

monary disease who suffered out of hospital cardiac arrest should be adapted in order to close this mortality gap. Closer monitoring of these patients may provide insight into the pathophysiologic basis of this difference.

In **chapter 4** we focused on the prevention of cardiac arrhythmias in patients with obstructive pulmonary disease in daily clinical practice. **Chapter 4.1** aimed to systematically review the efficacy and effectiveness of different behavioural and pharmacological smoking cessation strategies in patients with COPD since 2002. This systematic review made clear that in COPD patients, pharmacological therapy combined with behavioural counselling is more effective than each strategy separately. Neither the intensity of counselling nor the type of anti-smoking drug made a difference. Patients with COPD, being more resistant to smoking cessation therapies, could benefit significantly from smoking cessation, as smoking cessation is currently the only evidenced-based intervention to change the clinical course of the disease. The objective of **chapter 4.2** was to assess whether general practitioners in the UK adhere to the recommendation to perform an ECG before starting with the drug that is often stated in the drug label of QT prolonging drugs. We used haloperidol as an example, and the results of the study made clear that less than 2% of the patients who had a new prescription of haloperidol received an ECG at initiation (exposure period: 1.8%, control period: 0.8%, RR 2.4 [1.5-3.8]). This was also the case in patients with at least one additional risk factor for QT prolongation (exposure period: 1.9%, control period 1.0%, RR 2.1 [1.2-3.5]). Taking into account this extremely low compliance to the recommendation, the low absolute risk of torsade de pointes, ventricular tachycardia, and sudden cardiac death, as well as the fact that the QT interval prolongation is a weak marker of such future events, we argued to reconsider the recommendation to record an ECG before prescribing QT prolonging drugs such as haloperidol.

In **chapter 5** we focused on the utilisation of drug labelling to minimise the risk of drug-induced arrhythmias. The aim of **chapter 5.1** was to systematically assess the variation in the extent and content of information on QT prolongation in the label. In almost half of the drugs that mentioned the QT interval in the label,

no clear statement on whether a drug prolongs the QT interval was mentioned in the label (43%). 62% percent of the drug labels (27/44) contained advices to act with caution in patients with additional risk factors for QT prolongation. Products that more likely to have QT prolonging properties according to the SPC provided more information on QT prolongation in the SPC (for the category 'no prolongation': 10% and for the category 'QT prolongation': 100%). We concluded that the extent and content of information on QT prolongation varied considerably between drug labels. The drug label is an important, albeit indirect, source of information for health care providers. Ambiguous information may hamper the usefulness of the information for prescribing physicians and lead to sub optimal risk minimisation strategies. We therefore advocated to provide more structured phrasing of information and unambiguous interpretation of evidence on QT prolongation in the drug label, and provide clear instructions for prescribers how to deal with such risk. In **chapter 5.2** we aimed to systematically compare the phrasing used to communicate on QT prolonging properties of drugs in the European and American drug labelling. We found that the agreement about the message on QT prolongation between the European and American drug labels was moderate (kappa 0.434), and that 6% of the American drug labels had an unclear message on QT prolongation (i.e. some information from studies was provided, but no clear conclusion was drawn) compared to 12% of the European labels. The majority of the products (24/28) of which only the American drug label reported on QT prolongation contained the message that the drug does not prolong the QT interval. We concluded that the European and American drug label only moderately agree in their semantics used to phrase QT prolonging properties. The American drug label tended to be more explicit, and more often contained a message stating that the drug does not prolong the QT interval, showing that despite harmonisation of regulations drug labels are not uniform.

Chapter 6 provided a general discussion on the risk of cardiac arrhythmias in obstructive pulmonary disease, and we discussed the impact of drug therapy (β_2-agonists, anticholinergics, and QT prolonging drugs). The advantages and limitations of various epidemiological study designs were considered. Although it is

impossible to fully disentangle the effects of the disease (COPD and asthma) and the treatment for the disease (β_2-agonists and anticholinergics), current evidence shows that patients with obstructive pulmonary disease have an increased risk of cardiac arrhythmias, especially patients with COPD. For patients with COPD, but also in selected patients with asthma, a more integrated pulmonary and cardiovascular care with special attention to previously unrecognised cardiovascular disease, is preferable.

Samenvatting

Ondanks de klinische relevantie van hartritmestoornissen bestaat er nog steeds gebrek aan informatie over het achtergrond-risico en de onderliggende mechanismen van hartritmestoornissen bij patiënten met obstructief longlijden (astma en 'chronic obstructive pulmonary disease' [COPD]). De laatste decennia is steeds duidelijker geworden dat patiënten met COPD een verhoogd risico hebben op cardiovasculaire mortaliteit en morbiditeit, waaronder hartritmestoornissen. Hoewel ook astmapatiënten een verhoogd risico op hartritmestoornissen lijken te hebben, is de relatie minder duidelijk. Mechanismen die het verhoogd risico op hartritmestoornissen bij patiënten met astma en COPD kunnen verklaren zijn roken, systemische inflammatie en autonome dysfunctie. Naast deze ziekte-gerelateerde mechanismen, zou medicatie - met name β_2-mimetica en anticholinergica, maar ook QT-verlengende medicatie - mogelijk ook een rol kunnen spelen. Deze middelen kunnen het risico op ritmestoornissen vergroten. Het doel van het onderzoek in dit proefschrift is meer inzicht te creëren en daarmee handvatten te bieden voor de preventie van hartritmestoornissen bij patiënten met obstructieve longaandoeningen.

In **hoofdstuk 2** wordt de relatie tussen obstructieve longziekten en het risico op afwijkingen op het elektrocardiogram (ECG) bestudeerd. In **hoofdstuk 2.1** wordt onderzocht hoe vaak verschillende afwijkende ECG karakteristieken voorkomen bij patiënten met COPD. Daarnaast wordt bestudeerd of er samenhang is tussen de prevalentie van deze ECG-karakteristieken en de ernst van de longfunctiestoornis. Bij patiënten met COPD komen ECG-afwijkingen (50%), met name geleidingsstoornissen (28%), vaker voor dan bij patiënten zonder COPD (respectievelijk 36% [$p = 0{,}054$] en 11% [$p < 0{,}001$]). De prevalentie van ECG afwijkingen stijgt met toenemende ernst van COPD volgens de GOLD (Global initiative for chronic Obstructive Lung Disease) criteria (GOLD I: 46%, GOLD II: 50%, GOLD III: 58%, odds ratio [OR] III vs. I: 1,5 [0,7-3,3]). Hieruit concluderen wij dat patiënten met COPD vaker ECG-afwijkingen hebben dan mensen zonder deze aandoen-

ing. Speciale aandacht in het diagnostisch proces en een meer geïntegreerde cardiovasculaire en pulmonale zorg van deze patiënten lijkt daarom wenselijk. In **hoofdstuk 2.2** wordt de relatie tussen astma en het risico op hartritmestoornissen en aritmogene ECG-afwijkingen onderzocht. Tevens wordt bestudeerd welke rol β_2-mimetica spelen in deze associatie. Daarbij is opnieuw gebruik gemaakt van data van het Leidsche Rijn GezondheidsProject, een populatie onderzoek van de inwoners van Leidsche Rijn, een wijk in Utrecht. We vonden dat volwassen astmapatiënten vaker een tachycardie (3%) of premature ventriculaire contracties (PVC, 4%) op het ECG vertonen dan de deelnemers zonder astma (respectievelijk 0,6% [p $<$ 0,001] en 2% [p $=$ 0,03]). Bij astmapatiënten die β_2-mimetica gebruiken is het risico op tachycardie en PVCs zelfs nog uitgesprokener (OR: 12,4 [4,7-32,8] en 3,7 [1,3-10,5]). Een verhoogde hartslag is geassocieerd met een toegenomen risico op cardiale mortaliteit in epidemiologische studies van de algemene bevolking. Toekomstig onderzoek zal moeten uitwijzen of een verhoogde hartslag veroorzaakt wordt door de ziekte zelf of door het gebruik van inhalatiemedicatie, met name β_2-mimetica. **Hoofdstuk 2.3** bestudeert de prognostische waarde van hartslag in rust bij COPD-patiënten. Patiënten met COPD hebben vaak cardiovasculaire co-morbiditeiten en over het algemeen hebben ze een hogere hartslag in rust dan de algemene bevolking. Echter, de effecten op mortaliteit en niet-fatale pulmonaire complicaties zijn nog onbekend. De resultaten van dit prospectieve cohort onderzoek laten zien dat een verhoogde rusthartslag een sterke en onafhankelijke voorspeller is van mortaliteit in oudere patiënten met COPD. Daarentegen leidt een verhoogde hartslag in rust niet tot meer non-fatale pulmonale complicaties (pneumonie en exacerbatie van COPD). Het relatief risico op mortaliteit neemt met 21% toe met elke 10 slagen per minuut (spm) die de hartslag toeneemt (geadjusteerde hazard ratio [HR]: 1,21 [1,07-1,36]), terwijl het risico op niet-fatale pulmonale complicaties 7% toeneemt bij een toename van de rusthartslag van 10 spm (HR: 1,07 [0,96-1,18]). We concluderen hieruit dat de verhoogde mortaliteit in COPD waarschijnlijk vooral wordt bepaald door niet-pulmonale oorzaken. Gerandomiseerd gecontroleerd onderzoek is nodig om aan te tonen of COPD-patiënten baat kunnen hebben bij hartslag-verlagende medicatie.

Hoofdstuk 3 schetst nieuwe inzichten op het gebied van plotse hartstilstand bij patiënten met obstructieve longziekten. In **hoofdstuk 3.1** onderzoeken we of patiënten met obstructieve longziekten een verhoogd risico op een hartstilstand (ventrikeltachycardie of ventrikelfibrilleren op ECG). De resultaten van dit onderzoek laten zien dat obstructief longlijden een 40% hoger risico op een hartstilstand geeft (n = 190 cases [15%], 622 controles [11%]). Het verhoogde risico op een hartstilstand is het meest uitgesproken bij patiënten met obstructief longlijden die kortwerkende β_2-mimetica of anticholinergica gebruiken (kortwerkende β_2-mimetica OR: 3,9 [1,7-8,8], anticholinergica OR: 2,7 [1,5-4,8] ten opzichte van patiënten zonder obstructieve longziekten). Deze bevindingen kunnen een basis vormen voor verfijning van behandelstrategieën van patiënten met obstructief longlijden. Een aanbeveling zou bijvoorbeeld kunnen zijn om patiënten die kortwerkende β_2-agonisten of anticholinergica gebruiken onbekende cardiovasculaire aandoeningen op te sporen. In **hoofdstuk 3.2** wordt onderzocht of patiënten met obstructief longlijden een lagere overlevingskans hebben na een hartstilstand vergeleken met patiënten zonder obstructieve longaandoeningen. De resultaten van deze studie wijzen uit dat patiënten met obstructief longlijden een 40% lagere overlevingskans hebben in de eerste 30 dagen na hun hartstilstand vergeleken met patiënten zonder obstructieve longziekten (21% vs. 33%, OR 0,6 [0,4-0,9]). Op de zeer korte termijn verschilt de overleving van patiënten met en zonder obstructieve longziekten niet van elkaar. Overleving tot de spoedeisende hulp is 75% vs. 78%, OR 0,9 (0,6-1,3) en overleving tot ziekenhuisopname is 56% vs. 57%, OR 1,0 (0,7-1,4). Pas na ziekenhuisopname wordt de overleving van patiënten met obstructief longlijden lager dan de overleving van patiënten zonder deze aandoening. De klinische zorg voor patiënten met obstructieve longaandoeningen die een reanimatie hebben doorgemaakt zou moeten worden aangepast aan de behoeften van deze patiënten om zo het verschil in overleving te verminderen.

Hoofdstuk 4 richt zich in het bijzonder op de preventie van hartritmestoornissen bij patiënten met obstructieve longaandoeningen in de dagelijkse klinische praktijk. **Hoofdstuk 4.1** geeft een overzicht van onderzoeken naar de werkzaamheid

en effectiviteit van verschillende stoppen-met-roken strategieën gebaseerd op gedragsveranderingen en/of farmacologische ondersteuning toegepast bij patiënten met COPD. De resultaten van de geïncludeerde onderzoeken maken duidelijk dat bij COPD-patiënten medicamenteuze behandeling gecombineerd met gedragstherapie effectiever is dan wanneer slechts één van beide strategieën wordt toegepast. Noch de intensiteit van de gedragstherapie, noch het type of stoppen-met-roken medicatie maakt verschil in de effectiviteit van de behandeling. In **hoofdstuk 4.2** wordt onderzocht in welke mate huisartsen in het Verenigd Koninkrijk de aanbeveling opvolgen om een ECG te maken voor het starten met QT-verlengende medicatie, zoals vaak vermeld staat in de 'summary of product characteristics' (SPC, samenvatting van productinformatie) van deze middelen. Haloperidol wordt gebruikt als voorbeeldmiddel. De resultaten van deze studie laten zien dat bij minder dan 2% van de patiënten die start met haloperidol een ECG gemaakt wordt (periode van start haloperidol: 1,8%, controle periode: 0,8%, RR 2,4 [1,5-3,8]). Bij patiënten met tenminste één andere risicofactor voor QT-verlenging werd niet vaker een ECG gemaakt (periode van start haloperidol: 1,9%, controle periode: 1,0%, RR 2,1 [1,2-3,5]). Het absolute risico op ventriculaire tachycardie en plotse hartdood is laag en QT-verlenging slechts een zwakke voorspeller voor het optreden van potentieel fatale ritmestoornissen. Mede omdat de aanbevelingen voor het maken van een ECG slechts in zeer geringe mate worden opgevolgd, pleiten we voor heroverweging van deze aanbevelingen bij het starten van QT-verlengende medicatie, zoals haloperidol.

In **hoofdstuk 5** richten we ons op het gebruik van bijsluiters om het risico op geneesmiddel-geïnduceerde hartritmestoornissen te minimaliseren. In **hoofdstuk 5.1** wordt de variatie in omvang en inhoud van informatie over QT-verlenging in de SPC onderzocht. In bijna de helft van de middelen waar iets over het QT interval in de SPC staat, wordt niet expliciet vermeldt of het middel het QT interval daadwerkelijk verlengt (43%). Bij 62% van de middelen (27/44) zegt de SPC dat voorzichtigheid geboden is bij patiënten met bijkomende risicofactoren voor QT-verlenging. Wanneer we de producten indelen op basis van de (in de SPC vermelde) toenemende waarschijnlijkheid dat ze QT-verlengend zijn (niet

QT-verlengend / onduidelijk of het QT-verlengt / mogelijk QT-verlengend / QT-verlengend), zien we dat meer additionele adviezen en uitleg worden gegeven naarmate het middel met grotere waarschijnlijkheid QT-verlengend is (voor de categorie 'niet QT-verlengend': 10% en voor de categorie 'QT-verlengend': 100%). We concluderen dat de omvang en inhoud van informatie over QT-verlenging aanzienlijk verschilt tussen de SPCs van verschillende middelen. De SPC is een belangrijke, doch indirecte, bron van informatie voor artsen. Dubbelzinnige informatie kan de bruikbaarheid van deze informatie verminderen. We adviseren daarom de informatie over QT-verlenging in de SPC beter te structureren. Daarnaast raden we aan om in de SPC een ondubbelzinnige interpretatie van het bewijs over QT-verlengende eigenschappen en een duidelijke instructie aan voorschrijvers over hoe om te gaan met het risico op QT-verlenging te geven in de SPC. In **hoofdstuk 5.2** wordt de manier om QT-verlengende eigenschappen van een middel te beschrijven vergeleken tussen de Europese SPC en het Amerikaanse 'drug label'. De overeenkomst tussen de Europese SPC en het Amerikaanse 'drug label' is matig (kappa 0,434). Van de Amerikaanse 'drug labels' bevat een 6% onduidelijke boodschap over QT-verlenging (bijv. er wordt enige informatie van studies gegeven maar er wordt geen duidelijke conclusie getrokken) vergeleken met 12% van de Europese SPCs. De meerderheid van de producten (24/28) waarbij alleen het Amerikaanse 'drug label' rapporteert over QT-verlenging, beschrijft dat het middel het QT-interval niet verlengt. We concluderen dat de Europese SPC en het Amerikaanse 'drug label' maar matig overeenkomen wat betreft de semantiek van de bewoording over QT-verlengende eigenschappen. Het Amerikaanse 'drug label' lijkt explicieter te zijn en bevat vaker de boodschap dat het middel niet QT-verlengend is. Hoewel de SPC regelgeving in grote mate is geharmoniseerd, blijken de Europese SPC en het Amerikaanse 'drug label' niet uniform te zijn.

In de het laatste hoofdstuk, **hoofdstuk 6**, gaan we in op het risico op hartritmestoornissen bij obstructief longlijden en we bespreken de invloed van medicatie (β_2-mimetica, anticholinergica, en QT-verlengende medicatie). De voor- en nadelen van verschillende epidemiologische onderzoeksopzetten komen ter sprake. Of-

schoon het bijna onmogelijk is om de effecten van de ziekte (COPD en astma) en de behandeling voor deze aandoeningen (β_2-mimetica en anticholinergica) geheel van elkaar te onderscheiden, concluderen we op basis van de huidige inzichten dat patiënten met obstructief longlijden een verhoogd risico hebben op hartritmestoornissen, met name de patiënten met COPD. Voor COPD-patiënten, maar ook voor sommige patiënten met astma, lijkt een meer geïntegreerde cardiopulmonale zorg met speciale aandacht voor nog onontdekte cardiovasculaire ziekten wenselijk.

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Zomer 2009 had ik een gesprek met promotoren en copromotor ‘om eens over een nieuw onderzoek te praten’. Ik was bezig aan het eerste jaar van de huisartsenopleiding maar miste de wetenschappelijke diepgang hierin en was daarom op zoek gegaan naar een promotieonderzoek dat ik zou kunnen combineren met de huisartsenopleiding. We besloten dat ik na het einde van het eerste jaar en de geboorte van mijn zoon aan het onderzoek over hartritmestoornissen bij longpatiënten zou gaan beginnen.

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About the author

Miriam Warnier was born on August 11th, 1980 in Maastricht, the Netherlands. She attended secondary school (Atheneum B) at the Trichter College in Maastricht and graduated in 1999. She studied Anthropology and Development Studies at the Radboud University Nijmegen during one year, before entering medical school at the Radboud University Nijmegen in 2000. For her doctoral thesis she worked 6 months in the Institute Curie in Paris, France, under supervision of dr. L. Johannes, and 3 months in the University Medical Center Nijmegen, under supervision of prof. L. Monnens from the department of paediatrics, conducting a study on trafficking of Shiga toxin in human kidney cells.

After receiving her medical degree in 2007 she was involved in a study on smoking cessation strategies in patients with chronic obstructive pulmonary disease at the Julius Center for Health Sciences and Primary Care (dr. A.P.E. Sachs, prof. T. Verheij), University Medical Center Utrecht. In 2008 she started her vocational training at the department of General Practice in Utrecht, and in 2009 she started combining this with the doctoral research described in this thesis, which she performed at the Utrecht University, department of Pharmacoepidemiology and Clinical Pharmacology under supervision of prof. A. de Boer, prof. A.W. Hoes, dr. M.L. De Bruin and dr. F.H. Rutten. During this combined programme she obtained a Master of Science degree in pharmacoepidemiology at Utrecht University in august 2012. At present, she is in her third and final year of the general practitioner vocational training.