

CO-MORBIDITIES

Cardiac Arrhythmias in Adult Patients with Asthma

MIRIAM J. WARNIER, M.D.,^{1,2} FRANS H. RUTTEN, M.D., PH.D.,¹ JAN A. KORS, PH.D.,³ JAN WILLEM J. LAMMERS, M.D., PH.D.,⁴ ANTHONIUS DE BOER, M.D., PH.D.,² ARNO W. HOES, M.D., PH.D.,¹ AND MARIE L. DE BRUIN, PHARM.D., PH.D.^{1,2}

¹Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands.

²Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht, The Netherlands.

³Division of Medical Informatics, Erasmus University Medical Center, Rotterdam, The Netherlands.

⁴Department of Pulmonary Diseases, Heart Lung Center Utrecht, University Medical Center Utrecht, Utrecht, The Netherlands.

Objective. The pathogenesis of cardiac arrhythmias in asthma patients has not been fully elucidated. Adverse drug effects, particularly those of β_2 -mimetics, may play a role. The aim of this study was to determine whether asthma is associated with the risk of cardiac arrhythmias and electrocardiographic characteristics of arrhythmogenicity (ECG) and to explore the role of β_2 -mimetics. **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 ongoing, longitudinal, primary care-based study. All patients underwent extensive examinations, including resting 12-lead electrocardiogram (ECG) 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%, $p < .001$; 2%, $p = .03$, respectively). The prevalence of QTc interval prolongation was similar in participants with (2%) and without asthma (3%, odds ratio [OR]: 0.6 and 95% confidence interval [95% CI]: 0.2–2.0). In 74 asthma patients, who received β_2 -mimetics, tachycardia and PVCs were more common (OR: 12.4 [95% CI: 4.7–32.8] and 3.7 [95% CI: 1.3–10.5], respectively). **Conclusions.** The adult patients with asthma more commonly show tachycardia and PVCs on the ECG than those without asthma. The patients with asthma received β_2 -mimetics; the risk of tachycardia and PVCs is even more pronounced.

Keywords β_2 -mimetic agents, electrocardiography, obstructive pulmonary disease, premature ventricular contractions, tachycardia

INTRODUCTION

Asthma is a chronic condition, characterized 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 -mimetics, 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 -mimetics, in this association.

METHODS

We performed a cross-sectional population study within the Utrecht Health Project (UHP) cohort. The UHP is an ongoing, 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 labeled with the International

*Corresponding author: Marie L. De Bruin, Pharm.D., Ph.D., Department of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, PO Box 80082, 3508 TB Utrecht, The Netherlands; Tel: +31 30 253 7324; Fax: +31 30 253 9166; E-mail: m.l.debruin@uu.nl

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 all of 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 analyzed for recording errors and manually classified according to the Minnesota coding criteria by an experienced cardiologist (9). Then, the ECGs were digitally analyzed 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 s (FEV1) 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 analyzed with multivariate logistic regression to compute odds ratios (ORs). Linear regression analysis was used for analyzing continuous outcome variables. 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 -mimetic 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 labeled with the ICPC code R96 (asthma), who did not receive any β_2 -mimetics in this 2.25-year-period, and repeated the multivariable analyses after excluding these 28 patients. Next, we identified 18 patients labeled with the ICPC code R96 (asthma), who did not use any respiratory medications (β_2 -mimetics, 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 analyzed 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).

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

TABLE 1.—Baseline characteristics of the study population.

	Participants without asthma <i>N</i> = 6303	Participants with asthma <i>N</i> = 158	Participants with asthma	
			Receiving β_2 -mimetics ^a <i>N</i> = 73	Not receiving β_2 -mimetics ^a <i>N</i> = 85
Age (years, SD)	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 ^b	620 (10%)	17 (11%)	6 (8%)	11 (13%)
Use of respiratory drugs ^c	232 (4%)	88 (56%)	73 (100%)	15 (18%)
β_2 -Mimetics	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%)
FEV1/FVC ^d	0.85 (0.09)	0.81 (0.09)	0.80 (0.10)	0.83 (0.08)
FEV1/FVC $< 0.70^d$	237 (4%)	16 (10%)	12 (16%)	4 (5%)
FEV1 (% of predicted) ^d	0.96 (0.15)	0.89 (0.18)	0.86 (0.20)	0.92 (0.15)

Notes: Values are means (SD) for continuous variables and absolute numbers (%) for dichotomous variables. COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroids; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity.

^a β_2 -Mimetics received during a time period of 3 months and until 3 months after the baseline assessments.

^bIncluding diuretics, β -blockers, dioxin, calcium-antagonists, anti-arrhythmics, platelet aggregation inhibitors, ACE inhibitors, ATII receptor blockers, nitrates, and statins.

^cIncluding β_2 -mimetics, anticholinergics, or ICSs. Patients may be treated with multiple drugs, numbers do not add up.

^dPredilatory values of spirometry are presented, missing $n = 5$.

TABLE 2.—ECG characteristics of participants with and without asthma.

	No asthma N = 6303	Asthma N = 158	Adjusted OR ^a (95% CI)	P-value
Tachycardia (>100/min)	37 (0.6%)	5 (3%)	5.5 (2.1–14.3)	<.001
Bradycardia (<50/min)	320 (5%)	5 (3%)	0.6 (0.2–1.5)	.28
PVC	97 (2%)	6 (4%)	2.5 (1.1–6.0)	.03
Atrial fibrillation or flutter	34 (0.5%)	1 (0.6%)	1.2 (0.2–8.6)	.89
Any arrhythmia ^b	473 (8%)	16 (10%)	1.4 (0.8–2.4)	.21
Mean heart rate (bpm)	65 (11)	66 (11)	—	.26
Mean QTc length (ms)	415 (23)	415 (23)	—	.94
Prolonged QTc interval ^c	194 (3%)	3 (2%)	0.6 (0.2–2.0)	.42

Notes: Values are means (SD) for continuous variables and absolute numbers (%) for dichotomous variables. Bpm, beats per minute; ms, milliseconds; QTc, corrected QT interval.

^aAdjusted for age and sex.

^bIncluding tachycardia, bradycardia, PVC, atrial fibrillation, or flutter. Patients may experience more than one electrocardiographic abnormality, numbers do not add up.

^cProlonged QTc interval: QTc > 450 ms for males, QTc > 470 ms for females.

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 and 95% confidence interval [95% CI]: 0.8–2.4). Tachycardia and PVCs were significantly more common in asthma patients (age- and sex-adjusted ORs: 5.5 [95% CI: 2.1–14.3] and 2.5 [95% CI: 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 $p = .26$). The prevalence of QTc interval prolongation was similar in patients with asthma (2%) and without asthma (3%) (adjusted OR: 0.6 and 95% CI: 0.2–2.0) and the mean QTc interval length was comparable between both the groups (adjusted $p = .94$).

In 73 patients with asthma, who received β 2-mimetics, tachycardia was more common (7%) than those who did not receive β 2-mimetics (0%) and the group without asthma (0.6%; adjusted OR β 2-mimetic users with asthma vs. no asthma 12.4 [95% CI 4.7–32.8]; Table 3). In addition, β 2-mimetics-receiving asthma patients more often showed PVCs on the ECG (6%) than those not prescribed

TABLE 3.—Tachycardia and PVC of participants with and without asthma, receiving β 2-mimetics or not during a time period of 3 months and until 3 months after the baseline assessments.

	Total number	Number of events (%)	Adjusted OR ^a (95% CI)
Tachycardia			
No asthma	6303	37 (0.6%)	Reference
Asthma, no β 2-mimetics	85	0 (0%)	—
Asthma, β 2-mimetics	73	5 (7%)	12.4 (4.7–32.8)
PVC			
No asthma	6303	97 (2%)	Reference
Asthma, no β 2-mimetics	85	2 (2%)	1.6 (0.4–6.5)
Asthma, β 2-mimetics	73	4 (6%)	3.7 (1.3–10.5)

Note: ^aAdjusted for age and sex.

with β 2-mimetics (2%) and than those without asthma (2%) (adjusted OR β 2-mimetic users with asthma vs. no asthma 3.7 [95% CI: 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-mimetics 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-mimetics 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 $p < .001$ and 2%; adjusted $p = .03$, respectively). In 73 patients with asthma, who received β 2-mimetics in the 6-month period around the ECG measurements, tachycardia (7%) and PVCs (6%) were more common (adjusted ORs vs. no asthma: 12.4 [95% CI: 4.7–32.8] and 3.7 [95% CI: 1.3–10.5], respectively).

When patients have severe acute asthma, they have an increased risk of potentially fatal arrhythmias and death due to ischemic heart disease, caused by the effects of medications (predominantly high dosages of [oral] β 2-mimetics), 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).

We demonstrated that the asthma patients had an increased risk of PVCs (adjusted OR: 2.5; 95% CI: 1.1–6.0) and that this risk is even more pronounced in asthma patients who received β 2-mimetics 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

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 -mimetics during the period 3 months before and 2 years after the ECG measurement compared with 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 with 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 -mimetics) 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 (95% CI) ^a	P-value	Adjusted OR (95% CI) ^a	P-value	Adjusted OR (95% CI) ^a	P-value
Tachycardia (>100/min)	5.5 (2.1–14.3)	<.001	6.7 (2.6–17.3)	<.001	6.1 (2.4–15.9)	<.001
Bradycardia (<50/min)	0.6 (0.2–1.5)	.28	0.8 (0.3–1.9)	.58	0.7 (0.3–1.8)	.46
PVC	2.5 (1.1–6.0)	.03	2.5 (1.0–6.3)	.05	2.3 (0.9–5.8)	.08
Atrial fibrillation	1.2 (0.2–8.6)	.89	1.4 (0.2–10.1)	.77	1.2 (0.2–9.2)	.83
Any arrhythmia ^b	1.4 (0.8–2.4)	.21	1.6 (0.9–2.8)	.08	1.5 (0.9–2.6)	.15
Mean heart rate (bpm)	—	.26	—	.10	—	.15
Mean QTc length (ms)	—	.94	—	.83	—	.75
Prolonged QTc interval ^c	0.6 (0.2–2.0)	.42	0.8 (0.2–2.4)	.63	0.7 (0.2–2.2)	.51

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

^aAdjusted for age and sex.

^bIncluding tachycardia, bradycardia, PVC, atrial fibrillation, or flutter. Patients may experience more than one electrocardiographic abnormality, numbers do not add up.

^cProlonged QTc interval: QTc > 450 ms for males, QTc > 470 ms for females.

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 -Mimetics, 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 -mimetics. Importantly, several studies and meta-analyses showed that adult asthma patients using β_2 -mimetics 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 postdilatory 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. 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 -mimetics 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 -mimetics, 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 -mimetics, the results shown are most likely an underestimation of the actual association between β_2 -mimetics 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 -mimetic use and disease severity. However, after the correction of the underlying disease severity, by adjusting the predilatory values of FEV1/FVC ratio and FEV1 (% 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 -mimetics, 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 -mimetics.

ACKNOWLEDGMENTS

We thank Prof. ME Numans, M.D., Ph.D. from the Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands, for providing access to the data of the UHP. We also thank the participating inhabitants of Leidsche Rijn, Utrecht, The Netherlands and the GPs working in this area for providing research data from their routine care.

DECLARATION OF INTEREST

The authors MJ Warnier, FH Rutten, JA Kors, JWJ Lammers, A de Boer, AW Hoes, and ML De Bruin declare that they have no conflicts of interest in relation to this article.

FUNDING

This study was supported by Utrecht University. The UHP received grants from the Ministry of Health, Welfare, and Sports (VWS), the Utrecht University, the Province of Utrecht, the Dutch Organisation of Care Research (ZON), the University Medical Center Utrecht (UMC Utrecht), and the Dutch College of Healthcare Insurance Companies (CVZ). The funding source had no involvement in the study design; in the collection, analysis, and interpretation data; in the writing of the report; and in the decision to submit the article for publication.

The Department of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, has received unrestricted research funding from the Netherlands Organisation for Health Research and Development (ZonMW), the Dutch Health Care Insurance Board (CVZ), the Royal Dutch Pharmacists Association (KNMP), the private-public-funded Top Institute Pharma (www.tipharma.nl, includes co-funding from universities, government, and industry), the EU Innovative Medicines Initiative (IMI), EU 7th Framework Program (FP7), the Dutch Medicines Evaluation Board, and the Dutch Ministry of Health and industry (including GlaxoSmithKline, Pfizer, and others).

REFERENCES

- Parker MJ. Asthma. *Otolaryngol Clin North Am* 2011; 44(3):667–684, ix.
- De Bruin ML, Hoes AW, Leufkens HG. QTc-prolonging drugs and hospitalizations for cardiac arrhythmias. *Am J Cardiol* 2003; 91(1): 59–62.
- Rosero SZ, Zareba W, Moss AJ, Robinson JL, Hajj Ali RH, Locati EH, Benhorin J, Andrews ML. Asthma and the risk of cardiac events in the long QT syndrome. Long QT syndrome investigative group. *Am J Cardiol* 1999; 84(12):1406–1411.
- Kramer D, Zimetbaum P. Long-QT syndrome. *Cardiol Rev* 2011; 19(5): 217–225.
- Salpeter SR, Ormiston TM, Salpeter EE. Cardiovascular effects of beta-agonists in patients with asthma and COPD: a meta-analysis. *Chest* 2004; 125(6):2309–2321.
- Appleton SL, Ruffin RE, Wilson DH, Taylor AW, Adams RJ; North West Adelaide Cohort Health Study Team. Cardiovascular disease risk associated with asthma and respiratory morbidity might be mediated by short-acting beta2-agonists. *J Allergy Clin Immunol* 2009; 123(1):124,130.e1.
- Ahonen A, Sovijärvi AR, Karhumäki L. ECG changes in exercise-induced asthma. *Respiration* 1982; 43(3):186–193.
- Grobbee DE, Hoes AW, Verheij TJ, Schrijvers AJ, van Ameijden EJ, Numans ME. The Utrecht Health Project: optimization of routine health-care data for research. *Eur J Epidemiol* 2005; 20(3):285–287.
- Rose GA, Blackburn H. Cardiovascular Survey Methods. Geneva: World Health Organisation, 1983.
- van Bommel JH, Kors JA, van Herpen G. Methodology of the modular ECG analysis system MEANS. *Methods Inf Med* 1990; 29(4):346–353.
- Bazett HC. An analysis of time relations of the electrocardiogram. *Heart* 1920; 7:353–370.
- CPMP/986/96. The Assessment of the Potential for QT Interval Prolongation by Non-Cardiovascular Medicinal Products. London: The European Agency for the Evaluation of Medicinal products, 1997.
- Molfino NA, Nannini LJ, Martelli AN, Slutsky AS. Respiratory arrest in near-fatal asthma. *N Engl J Med* 1991; 324(5):285–288.
- Osuorji I, Williams C, Hessney J, Patel T, Hsi D. Acute stress cardiomyopathy following treatment of status asthmaticus. *South Med J* 2009; 102(3):301–303.
- RuDuksy B. Acute myocardial infarction and status asthmaticus: a case report. *Angiology* 2006; 57(5):655–658.
- Appleton SL, Ruffin RE, Wilson DH, Taylor AW, Adams RJ. Asthma is associated with cardiovascular disease in a representative population sample. *Obes Res Clin Pract* 2008; 2(2):91–99.
- Schanen JG, Iribarren C, Shahar E, Punjabi NM, Rich SS, Sorlie PD, Folsom AR. Asthma and incident cardiovascular disease: the atherosclerosis risk in communities study. *Thorax* 2005; 60(8):633–638.
- Onufrak SJ, Abramson JL, Austin HD, Holguin F, McClellan WM, Vaccarino LV. Relation of adult-onset asthma to coronary heart disease and stroke. *Am J Cardiol* 2008; 101(9):1247–1252.
- Iribarren C, Tolstykh IV, Eisner MD. Are patients with asthma at increased risk of coronary heart disease? *Int J Epidemiol* 2004; 33(4): 743–748.
- Enright PL, Ward BJ, Tracy RP, Lasser EC. Asthma and its association with cardiovascular disease in the elderly. The cardiovascular health study research group. *J Asthma* 1996; 33(1):45–53.
- Engstrom G, Wollmer P, Hedblad B, Juul-Möller S, Valind S, Janzon L. Occurrence and prognostic significance of ventricular arrhythmia is related to pulmonary function: a study from “men born in 1914,” Malmö, Sweden. *Circulation* 2001; 103(25):3086–3091.
- Kannel WB, Kannel C, Paffenbarger RS Jr, Cupples LA. Heart rate and cardiovascular mortality: the Framingham study. *Am Heart J* 1987; 113(6):1489–1494.
- Morshedi Meibodi A, Evans J, Levy D, Larson M, Vasan R. Clinical correlates and prognostic significance of exercise-induced ventricular premature beats in the community: the Framingham heart study. *Circulation* 2004; 109(20):2417–2422.
- Cheriyath P, He F, Peters I, Li X, Alagona P Jr, Wu C, Pu M, Cascio WE, Liao D. Relation of atrial and/or ventricular premature complexes on a two-minute rhythm strip to the risk of sudden cardiac death (the atherosclerosis risk in communities [ARIC] study). *Am J Cardiol* 2011; 107(2):151–155.
- Nelson HS, Weiss ST, Bleecker ER, Yancey SW, Dorinsky PM; SMART Study Group. The salmeterol multicenter asthma research trial: a comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus Salmeterol. *Chest* 2006; 129(1):15–26.
- de Vries F, Setakis E, Zhang B, van Staa TP. Long-acting beta2-agonists in adult asthma and the pattern of risk of death and severe asthma outcomes: a study using the GPRD. *Eur Respir J* 2010; 36(3):494–502.
- Cazzola M, Matera MG, Donner CF. Inhaled beta2-adrenoceptor agonists: cardiovascular safety in patients with obstructive lung disease. *Drugs* 2005; 65(12):1595–1610.
- Shaper AG, Wannamethee G, Macfarlane PW, Walker M. Heart rate, ischaemic heart disease, and sudden cardiac death in middle-aged British men. *Br Heart J* 1993; 70(1):49–55.
- Jouven X, Empana JP, Schwartz PJ, Desnos M, Courbon D, Ducimetiere P. Heart-rate profile during exercise as a predictor of sudden death. *N Engl J Med* 2005; 352(19):1951–1958.
- Fox K, Ford I, Steg PG, Tendera M, Robertson M, Ferrari R; BEAUTIFUL investigators. Heart rate as a prognostic risk factor in patients with coronary artery disease and left-ventricular systolic dysfunction (BEAUTIFUL): a subgroup analysis of a randomised controlled trial. *Lancet* 2008; 372(9641):817–821.

Copyright of Journal of Asthma is the property of Taylor & Francis Ltd and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.