QRS Duration Is Associated With Atrial Fibrillation in Patients With Left Ventricular Dysfunction

Address for correspondence:
Mikhael F. El-Chami, MD
Division of Cardiology, Section of Electrophysiology
Emory University School of Medicine
MOT, 6th Floor
550 Peachtree Street, NE
Atlanta, GA 30308
melcham@emory.edu

Mikhael F. El-Chami, MD; Candace Brancato, MS; Jonathan Langberg, MD; David B. Delurgio, MD; Heather Bush, PhD; Lynne Brosius, MS; Angel R. Leon, MD
Division of Cardiology, Section of Electrophysiology, Emory University School of Medicine, (El-Chami, Langberg, Delurgio, Leon), Atlanta, Georgia; Registrat, Inc., (Brancato, Bush, Brosius), Lexington, Kentucky; Department of Biostatistics, University of Kentucky (Bush), Lexington, Kentucky

ABSTRACT

Background: QRSduration (QRSd) is associated with higher mortality and morbidity in patients with left ventricular (LV) dysfunction. The association between QRSd and atrial fibrillation (AF) has not been studied in this patient population.

Objectives: To investigate the association between QRSd and AF in patients with LV dysfunction.

Methods: Data were obtained from the National Registry to Advance Heart Health (ADVANCENT) registry, a prospective multicenter registry of patients with left ventricular ejection fraction (LVEF) $\leq$40%. A total of 25 268 patients from 106 centers in the United States, were enrolled between June 2003 and November 2004. Demographic and clinical characteristics of patients were collected from interviews and medical records.

Results: Mean age was 66.3 $\pm$ 13 years, 71.5% were males, and 81.9% were white. A total of 14 452 (57.8%) patients had a QRSd <120 ms, 5304 (21.2%) had a QRSd between 120 and 150 ms, and 5269 (21%) had a QRSd >150 ms. Atrial fibrillation occurred in 20.9%, 27.5%, and 35.5% of patients in the QRS groups, respectively ($P < 0.0001$). After adjusting for potential AF risk factors (age, gender, race, body mass index, hypertension, diabetes, renal failure, cancer, lung disease, New York Heart Association [NYHA] class, ejection fraction, etiology of cardiomyopathy) and the use of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, β-blockers, and lipid lowering drugs, QRS duration remained independently associated with AF (odds ratio: 1.20, 95% confidence interval: 1.14–1.25).

Conclusion: In this large cohort of patients, QRSd was strongly associated with AF and therefore may predict the occurrence of this arrhythmia in patients with LV dysfunction. This association persisted after adjusting for disease severity, comorbid conditions, and the use of medications known to be protective against AF.

Introduction

Atrial fibrillation (AF) affects a significant percentage of patients with heart failure ranging from 5% in patients with New York Heart Association (NYHA) class I[1,2] up to 50% in patients with NYHA class IV.[3] The annual incidence of new-onset AF in congestive heart failure (CHF) patients is 2% to 5%.[4–7] This association between AF and CHF is multifactorial. First, several risk factors for CHF such as age,[8,9] coronary artery disease (CAD),[9] hypertension (HTN),[10] diabetes mellitus (DM),[11,12] and obstructive sleep apnea (OSA)[13] are also risk factors for AF.[14–16] Second, structural, hemodynamic, and electrophysiologic changes seen in CHF such as left atrium enlargement, elevated left atrial pressure, and slow heterogeneous intra-atrial conduction,[17] predispose to AF.[17,18] Interestingly, the mere occurrence of AF in this patient population carries an increased risk of morbidity and mortality.[2,19,20] QRS duration (QRSd) is also associated with an increased mortality and morbidity in patients with CHF.[21–23] A wide QRS in this setting is associated with more myocardial disease and worse left ventricular function (LVEF).[21,24,25] We hypothesized that CHF patients with wider QRS will have a higher prevalence of AF.

Methods

Study Population

Patients enrolled in the National Registry to Advance Heart Health (ADVANCENT) registry between June 2003 and November 2004 were included in the study. ADVANCENT is a prospective multicenter, observational registry designed to collect and report data on the histories, diagnostics, and therapies of patients with LV dysfunction (LVEF $\leq$40%). This registry is sponsored by Boston Scientific, Inc and is managed independently by Registrat, Inc. The registry collects detailed medical and demographic information on enrolled subjects. At the time of data analysis, 25 268 patients from 106 centers in the United States had been enrolled. This registry has served as the source of several publications related to AF,[26,27] but none have addressed the association between QRSd and the risk of this arrhythmia.

No conflict of interest to report.

Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20714

Received: September 27, 2009
Accepted with revision: November 2, 2009

Baseline Data Collection

All patients enrolled in this registry were interviewed by medical personnel (physician, nurse practitioner, or physician assistant). Additional data were obtained from reviewing medical records. Demographic information, details on heart disease and its severity, the presence of comorbidities, and cardiovascular medication were collected. Data on QRSd was available from the index ECG on 25 025 of 25 268 patients (99%).

Statistical Analysis

Patients were divided into 3 different QRS duration groups: the narrow QRS group (QRSd <120 ms), the intermediate QRS group (120 ≤ QRSd ≤ 150 ms), and the wide QRS group (QRSd >150 ms). Continuous variables were reported using the mean and standard deviation and categorical variables were reported using counts and percentages. Cochran-Mantel-Haenszel statistics were used for categorical data and 1-way analysis of variance (ANOVA) was used for continuous data. In addition, bivariate analyses were performed to study the effect of QRSd on AF prevalence in the different NYHA classes and in 3 different LVEF groups (<20%, 20% ≤ EF ≤ 30%, EF >30%). A multivariable logistic regression (MLR) model was constructed to assess the independent impact of QRSd on the prevalence of AF. After accounting for missing values, there were 23 840 (95% data completeness) observations used in the MLR model. The following statistically significant variables were included in the model: age, gender, race, hypertension, renal failure, cancer, lung disease, LVEF, angiotensin receptor blocker (ARB) use, lipid lowering agent use (statins), nonischemic cardiomyopathy, valvular heart disease, body mass index (BMI), and New York Heart Association (NYHA) class. Nonstatistically significant variables that were also used in the model included: presence of diabetes, β-blocker, and angiotensin-converting enzyme inhibitor (ACEI) use. Age and LVEF were considered continuous variables and NYHA class was considered an ordinal variable. Gender, race, etiology of cardiomyopathy, active cancer, renal failure, DM, and the use of medications known to be protective against AF (ACEI, ARB, β-blockers, and statins) were considered categorical variables. The analysis was performed with QRSd as a categorical variable (ie, comparing QRSd <120 to QRSd >150 and 120 ≤ QRSd ≤ 150 ms to QRSd >150 ms) and as an ordinal variable (treating QRSd as groups: narrow, intermediate, and wide).

All analyses were completed using SAS version 9.2 and a significance level of 0.05 was used for all statistical tests.

Results

Cohort Characteristics

The characteristics of the entire cohort are summarized in Table 1. The mean age was 66.3 ± 13 years. The mean EF was 31.1% ± 10.47%. Coronary artery disease was the most common cause of LV dysfunction (66%). Slightly less than one-third of patients (27.5%) had moderate to severe CHF (NYHA class III or IV); 58% of patients had a QRSd <120 ms, while the remainder of patients were divided equally among the intermediate and wide QRSd groups (21% for each of those groups).

The characteristics of patients in the different QRSd groups are shown in Table 2. Patients with wide QRS were older ($P < 0.0001$), more likely to be white men ($P < 0.0001$), more likely to have lower EF ($P < 0.0001$), and more severe heart failure ($P < 0.0001$), but less likely to have HTN ($P = 0.0066$) as compared to the intermediate and narrow QRS groups. Also, this group was less likely to have CAD ($P < 0.0001$) as the cause of their cardiomyopathy (63.3%) as compared to the intermediate QRS group (67.3%) and the narrow QRS group (66.3%). Patients with wide QRS were also more likely to have valvular heart disease ($P = 0.0002$). In addition, the groups with intermediate and wide QRS were more likely to have certain comorbidities such as lung disease ($P = 0.0074$), renal failure ($P < 0.0001$), and cancer ($P = 0.0004$) as compared to the narrow QRS group.

The overall use of heart failure medications in the cohort was as follows: 63.4% were on an ACEI, 18.3% were on ARBs, and 79.1% were on β-blockers. There was no difference in the use of ACEI or β-blockers among the 3 groups (Table 2). However, the wide QRS group was more likely to be on an ARB ($P = 0.0009$), but less likely to be treated with a statin ($P = 0.0014$) as compared to the intermediate QRS and narrow QRS groups (Table 2).

Atrial Fibrillation Prevalence

One-quarter of patients (25.5%) had AF. Atrial fibrillation was paroxysmal in 46.4%, persistent in 41.1%, and of unknown pattern in 12.5% of patients. Atrial fibrillation was present in 20.9% of patients with QRSd <120 ms, 27.5% of patients in the intermediate QRSd group, and 35.5% of patients in

Table 1. Cohort Characteristics

Patient number	25 025
Mean age (yrs ± SD)	66.3 ± 13.14
White (%)	20 499 (81.9%)
Male (%)	17 882 (71.5%)
Mean EF ± SD	31.1% ± 10.47%
Nonischemic cardiomyopathy (%)	8543 (34.1%)
QRSd > 150 ms (%)	5269 (21.1%)
Patients in NYHA class III or IV	6826 (27.3%)

Abbreviations: EF, ejection fraction; NYHA, New York Heart Association; QRSd, QRS duration; SD, standard deviation.

Table 2. Cohort Characteristics in Groups of QRS Duration

Parameters	QRSd < 120 n = 14 452	120 ≤ QRSd ≤ 150 n = 5304	QRSd > 150 n = 5269	*P* Value
Age (±SD) yrs	64 (13.51)	68.8 (12.06)	70.3 (11.66)	<0.0001
Male (%)	10 138 (70.1%)	3774 (71.2%)	3970 (75.3%)	<0.0001
White (%)	11 491 (79.5%)	4501 (84.9%)	4507 (85.5%)	<0.0001
EF (±SD) (%)	32.8 (10.49)	29.7 (9.95)	27.7 (9.93)	<0.0001
Nonischemic (%)	4872 (33.7%)	1737 (32.7%)	1934 (36.7%)	<0.0001
Nonischemic/Valvular (%)	545 (3.8%)	251 (4.7%)	258 (4.9%)	0.0002
NYHA class III-IV (%)	3224 (22.3%)	1602 (30.2%)	2000 (37.9%)	<0.0001
HTN (%)	10 528 (72.8%)	3865 (72.9%)	3723 (70.7%)	0.0066
DM (%)	4574 (31.6%)	1685 (31.8%)	1587 (30.1%)	0.0935
Lung disease (%)	2389(16.5%)	977 (18.4%)	896 (17.0%)	0.0074
Renal failure (%)	812 (5.6%)	355 (6.3%)	394 (7.5%)	<0.0001
Cancer (%)	1544 (10.7%)	660 (12.4%)	637 (12.1%)	0.0004
AF (%)	3022 (20.9%)	1461 (27.5%)	1872 (35.5%)	<0.0001
ACEI	9216 (63.8%)	3354 (63.2%)	3306 (62.7%)	0.3921
ARB	2583 (17.9%)	937 (17.7%)	1057 (20.1%)	0.0009
Statins	9736 (67.4%)	3583 (67.6%)	3413 (64.8%)	0.0014
β-Blockers	11 472 (79.4%)	4174 (78.7%)	4153 (78.8%)	0.4824

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; DM, diabetes mellitus; EF, ejection fraction; HTN, hypertension; NYHA, New York Heart Association.

the wide QRSd group ($P < 0.0001$). Also, AF prevalence increased with CHF severity, increasing from 21% to 25%, 30%, and 34% for NYHA classes I to IV, respectively ($P < 0.0001$). In addition, within each NYHA class there was an association found between QRSd and AF prevalence (Figure 1) ($P < 0.0001$ for class I, class II, and class III, $P = 0.0014$ for class IV). For example, AF occurred in 18% of NYHA class I patients with narrow QRS and in 31% of NYHA class I patients with wide QRS. Similarly, within 3 different EF groups (<20%, 20% ≤ EF ≤ 30%, and EF >30%) QRSd was associated with AF prevalence (Figure 2).

Multivariable Regression Analysis

There are several factors that co-vary with QRSd including EF, NYHA class, age, gender, race, etiology of cardiomyopathy, and comorbidities (HTN, CAD, DM, chronic obstructive pulmonary disease [COPD], renal failure, malignancy). These factors are also likely to influence the prevalence of AF. To better determine the independent effect of QRSd on AF prevalence, a multivariate analysis accounting for all potential AF risk factors was constructed (Table 3). The model accounted for demographic risk factors (age, gender, race, BMI, height), comorbidities (HTN, COPD, DM, renal failure, cancer), heart disease etiology and severity (nonischemic cardiomyopathy, valvular heart disease, NYHA class, EF), and medications know to be protective against AF (statins, ACEI, ARB, and β-blockers). Even after accounting for all these confounders, QRSd remained associated with AF (odds ratio [OR]: 0.637, 95% confidence interval [CI]: 0.59–0.688 for QRSd <120 vs QRSd >150 and OR: 0.757 95% CI: 0.692–0.827) when comparing the intermediate QRS group to the wide QRS group. When QRSd was used as an ordinal variable, it remained an independent risk factor for AF (OR: 1.20, 95% CI: 1.14–1.25) which indicates that the estimated odds of AF increases by 20.0% as QRSd increases from one group to the next (ie, 20.0% increase in AF prevalence between narrow and intermediate and a 40.0% increase in AF prevalence when comparing narrow to wide QRSd).

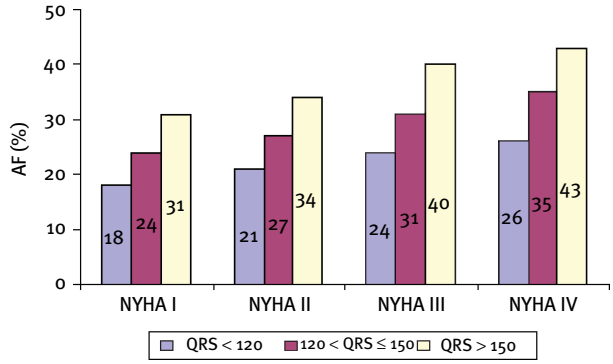

Figure 1. Atrial fibrillation frequency according to NYHA class and QRSd. Abbreviations: NYHA, New York Heart Association; QRSd, QRS duration.

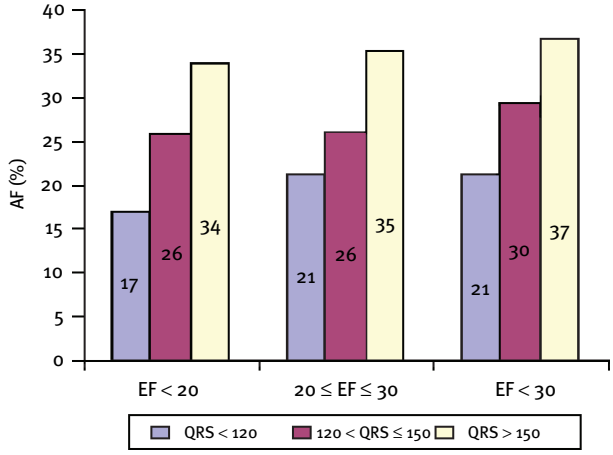

Figure 2. Atrial fibrillation frequency according to EF and QRSd. Abbreviations: EF, ejection fraction; QRSd, QRS duration.

Table 3. Multivariate Analysis Showing the Effect of Different Factors on AF Prevalence

Parameter	Odds Ratio	95% CI
120 ≤ QRSd ≤ 150 vs QRSd > 150	0.757[a]	0.692–0.827
QRSd < 120 vs QRSd > 150	0.637[a]	0.59–0.688
Age	1.535[a]	1.489–1.582
Height	1.025[a]	1.021–1.029
Gender (female vs male)	0.962	0.876–1.057
Race (Black vs white)	0.606[a]	0.546–0.674
Hypertension (HTN vs no HTN)	1.063	0.99–1.141
Diabetes	0.897[a]	0.837–0.962
Renal failure	1.226[a]	1.082–1.39
Cancer	0.926	0.843–1.017
Lung disease	1.119[a]	1.033–1.212
LVEF	1.046[a]	1.014–1.079
β-Blocker	0.874[a]	0.812–0.94
ACE inhibitor	0.877[a]	0.814–0.944
ARB	0.915	0.835–1.003
Lipid lowering agent	0.684[a]	0.638–0.734
Nonischemic	1.321[a]	1.222–1.427
Nonischemic/valvular	1.786[a]	1.543–2.067
BMI	1.016[a]	1.01–1.021
NYHA (ordinal)	1.20[a]	1.14–1.25

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; EF, ejection fraction; HTN, hypertension; NYHA, New York Heart Association; OR, odds ratio; QRSd, QRS duration.
OR for QRSd is comparing: a. QRSd < 120 vs QRSd > 150. b. 120 ≤ QRSd ≤ 150 vs QRSd > 150. OR for age is per 10 years increment. OR for height is per 1 cm increase in height. OR for EF is per 10% increment. OR for BMI is per 1 unit increase in BMI. [a] Denotes statistically significant.

Discussion

Comparison to Previous Registries and Reports

Several findings in this study mirror previous reports. The percentage of patients with QRSd >120 ms in this cohort with LV dysfunction was 42%. Similarly, a post hoc analysis from the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST) showed that 44.6% of patients had a QRSd >120 ms.[22] Overall, the prevalence of a QRSd >120 ms in CHF patients averages 30% (14%–47%).[21] Also, 21% of patients in the current study had a QRSd >150 ms. This is comparable to other reports describing that 19% to 29%[28–31] of CHF patients have a QRSd >150 ms.

In addition, we have found that patients with wider QRSd have lower EF, worse NYHA class, and more comorbidities.[21–23] In fact, an inverse relationship between QRSd and EF has been described.[21] Shenkman et al found a progressive decrease in EF as QRSd lengthened above 120 ms.[32] Furthermore, Sandhu and Bahler noted that mean EF decreased from 41% to 29% and 25% as QRSd increased from <100 ms to 120 ms to 149 ms and >150 ms, respectively.[33] Similarly, QRSd correlated with NYHA class.[34,35] In more than 5000 outpatients with CHF, 32% of patients with complete left bundle branch block (LBBB) were in NYHA class III or IV as compared to 26% of patients with incomplete LBBB.[34] Another study showed that the incidence of QRSd >120 ms increased from 10% to 32% and 53% as NYHA class worsened from I to II and III, respectively.[35]

Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20714

In the current study, more than 80% of the subjects were taking an ACEI or an ARB, and close to 80% were on a β-blocker. This compares favorably to a recently published report from the Acute Decompensated Heart Failure National Registry (ADHERE).[36]

Atrial fibrillation prevalence in this registry (25.5%) was comparable to AF prevalence in the ADHERE registry (30.9%). Previous reports have shown that AF prevalence in the setting of LV dysfunction varies with severity of CHF[37] and that AF occurs in 4% of asymptomatic CHF patients.[2] This prevalence increases to 10% to 26% in NYHA class II-III and 20% to 29% in NYHA class III-IV. Furthermore, it has been reported that up to 50% of NYHA class IV patients have AF. Our data show a higher prevalence of AF in patients with NYHA class I (21%). The lower AF prevalence in NYHA class I patients in the Studies of Left Ventricular Dysfunction (SOLVD) prevention and treatment trials[2] may be due to a different system of classification: patients who had a history of AF but were in sinus rhythm at the time of randomization were considered to be in the sinus rhythm group.

Furthermore, the multivariable analysis results revealed similar findings to previous reports. In our cohort, the odds of AF were less in nonwhite patients compared to white patients (OR: 0.606, 95% CI: 0.546–0.674) and there was a trend in women toward lower AF prevalence compared to men (OR: 0.962, 95% CI: 0.876–1.057). These findings are similar to previous reports.[38,39] Other factors that were shown to be associated with higher AF prevalence in this cohort such as age, BMI, and some comorbid conditions (lung disease and renal failure) are also known risk factors for AF.[37,40–42] In addition, therapy with neurohormonal modulators (ACEI, ARB, and β-blockers) and statins were protective against AF in this patient population. These findings are in agreement with previous publications.[43–46] Surprisingly, DM was associated with lower odds of AF whereas hypertension showed a trend toward higher odds of AF that did not reach statistical significance. While HTN and DM are known risk factors for AF in the general population, our cohort had left ventricular dysfunction. Hence, factors that affect left atrial pressure, stretch, and fibrosis such as severity of heart failure or valvular disease and QRSd are possibly more important as determinants of AF. In fact, data from the Cardiovascular Heart Study support these findings. Diabetes mellitus was a risk factor for AF in the general population, but not in patients with cardiovascular disease.[47]

Interpretation of Main Findings and Clinical Implication

QRSd is associated with lower EF and a worse NYHA class. Hence, the association between QRSd and AF seems evident. However, even after accounting for severity of heart failure, EF, and other covariates, a strong association persisted. QRSd is linked to the extent of ventricular fibrosis in patients with cardiomyopathy.[48,49] It is possible that QRSd also reflects generalized myocardial fibrosis including atrial fibrosis in these patients providing the substrate for AF.

Results of the current study suggest that a simple test (an electrocardiogram) routinely ordered on patients with heart failure could be used to predict the risk of AF. The effect of QRSd on AF prevalence appears to be more potent than NYHA class or EF (Figures 1 and 2). For example, AF prevalence in patients with NYHA class I and wide QRS is 31%, a value that is higher than AF prevalence in patients with NYHA class IV and narrow QRS (26%; Figure 1). The effect of these 2 parameters on AF prevalence appears to be additive (Figure 1). Hence, QRSd can conceivably be used in association with other AF risk factors to predict the occurrence of AF in this patient population.

Study Limitations

Because the ADVANCENT registry was not intended originally to assess the association between QRSd and AF, it is possible that some confounding variables that could affect this association have not been accounted for. For instance, left atrial size and OSA are 2 important AF risk factors that we did not account for. However, we did account for BMI that strongly correlates with the prevalence of OSA. In addition, we have included height in the multilinear regression model. The latter was found to correlate strongly with left atrial diameter in a subgroup of patients enrolled in the ADVANCENT registry.[27] Also, this registry did not include longitudinal data hence it is not possible to determine the association between QRSd and new development of AF.

On the other hand, the large number of patients, the extent and completeness of the data, and the agreement between this study and previous reports on the role of traditional AF risk factors make the conclusion drawn from this study robust and probably reproducible.

Conclusion

To our knowledge, this is the first report in the literature showing an association between QRSd and AF. In this study of more than 25 000 patients with LV dysfunction from more than 100 centers in the United States, QRSd was associated with AF. This association persisted after accounting for several known AF risk factors. Patients with wide QRS and LV dysfunction are at high risk of developing AF. This group of patients could be the subject of future studies addressing AF preventive strategies.

References

1. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. The SOLVD Investigators. *N Engl J Med*. 1991;325(5):293a–302.
2. Dries DL, Exner DV, Gersh BJ, Domanski MJ, Waclawiw MA, Stevenson LW. Atrial fibrillation is associated with an increased risk for mortality and heart failure progression in patients with asymptomatic and symptomatic left ventricular systolic

dysfunction: a retrospective analysis of the SOLVD trials. Studies of Left Ventricular Dysfunction. *J Am Coll Cardiol*. 1998;32(3): 695–703.
3. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). The CONSENSUS Trial Study Group. *N Engl J Med*. 1987;316(23):1429–1435.
4. Deedwania PC, Singh BN, Ellenbogen K, et al. Spontaneous conversion and maintenance of sinus rhythm by amiodarone in patients with heart failure and atrial fibrillation: observations from the veterans affairs congestive heart failure survival trial of antiarrhythmic therapy (CHF-STAT). The Department of Veterans Affairs CHF-STAT Investigators. *Circulation*. 1998;98(23):2574–2579.
5. Stevenson WG, Stevenson LW. Atrial fibrillation in heart failure. *N Engl J Med*. 1999;341(12):910–911.
6. Stevenson WG, Stevenson LW. Atrial fibrillation and heart failure—five more years. *N Engl J Med*. 2004;351(23):2437–2440.
7. Torp-Pedersen C, Moller M, Bloch-Thomsen PE, et al. Dofetilide in patients with congestive heart failure and left ventricular dysfunction. Danish Investigations of Arrhythmia and Mortality on Dofetilide Study Group. *N Engl J Med*. 1999;341(12):857–865.
8. McKee PA, Castelli WP, McNamara PM, Kannel WB. The natural history of congestive heart failure: the Framingham study. *N Engl J Med*. 1971;285(26):1441–1446.
9. Cowie MR, Wood DA, Coats AJ, et al. Incidence and aetiology of heart failure; a population-based study. *Eur Heart J*. 1999;20(6): 421–428.
10. Kannel WB. Incidence and epidemiology of heart failure. *Heart Fail Rev*. 2000;5(2):167–173.
11. Aneja A, Tang WH, Bansilal S, et al. Diabetic cardiomyopathy: insights into pathogenesis, diagnostic challenges, and therapeutic options. *Am J Med*. 2008;121(9):748–757.
12. Cohen-Solal A, Beauvais F, Logeart D. Heart failure and diabetes mellitus: epidemiology and management of an alarming association. *J Card Fail*. 2008;14(7):615–625.
13. Bradley TD, Floras JS. Obstructive sleep apnoea and its cardiovascular consequences. *Lancet*. 2009;373(9657):82–93.
14. Kannel WB, Benjamin EJ. Current perceptions of the epidemiology of atrial fibrillation. *Cardiol Clin*. 2009;27(1):13–24, vii.
15. Schoonderwoerd BA, Smit MD, Pen L, Van Gelder IC. New risk factors for atrial fibrillation: causes of "not-so-lone atrial fibrillation." *Europace*. 2008;10(6):668–673.
16. Stevenson IH, Teichtahl H, Cunnington D, et al. Prevalence of sleep disordered breathing in paroxysmal and persistent atrial fibrillation patients with normal left ventricular function. *Eur Heart J*. 2008;29(13):1662–1669.
17. Li D, Fareh S, Leung TK, Nattel S. Promotion of atrial fibrillation by heart failure in dogs: atrial remodeling of a different sort. *Circulation*. 1999;100(1):87–95.
18. Phang RS, Isserman SM, Karia D, et al. Echocardiographic evidence of left atrial abnormality in young patients with lone paroxysmal atrial fibrillation. *Am J Cardiol*. 2004;94(4):511–513.
19. Corell P, Gustafsson F, Schou M, et al. Prevalence and prognostic significance of atrial fibrillation in outpatients with heart failure due to left ventricular systolic dysfunction. *Eur J Heart Fail*. 2007;9(3):258–265.
20. Parkash R, Maisel WH, Toca FM, et al. Atrial fibrillation in heart failure: high mortality risk even if ventricular function is preserved. *Am Heart J*. 2005;150(4):701–706.
21. Kashani A, Barold SS. Significance of QRS complex duration in patients with heart failure. *J Am Coll Cardiol*. 2005;46(12): 2183–2192.
22. Wang NC, Maggioni AP, Konstam MA, et al. Clinical implications of QRS duration in patients hospitalized with worsening heart failure and reduced left ventricular ejection fraction. *JAMA*. 2008;299(22):2656–2666.
23. Yerra L, Anavekar N, Skali H, et al. Association of QRS duration and outcomes after myocardial infarction: the VALIANT trial. *Heart Rhythm*. 2006;3(3):313–316.
24. De Winter O, Van de Veire N, Van Heuverswijn F, et al. Relationship between QRS duration, left ventricular volumes and prevalence of nonviability in patients with coronary artery disease and severe left ventricular dysfunction. *Eur J Heart Fail*. 2006;8(3):275–277.
25. Murkofsky RL, Dangas G, Diamond JA, et al. A prolonged QRS duration on surface electrocardiogram is a specific indicator of left ventricular dysfunction [see comment]. *J Am Coll Cardiol*. 1998;32(2):476–482.
26. Hanna IR, Heeke B, Bush H, Lipid-lowering drug use is associated with reduced prevalence of atrial fibrillation in patients with left ventricular systolic dysfunction. *Heart Rhythm*. 2006;3(8): 881–816.
27. Hanna IR, Heeke B, Bush H, The relationship between stature and the prevalence of atrial fibrillation in patients with left ventricular dysfunction. *J Am Coll Cardiol*. 2006;47(8):1683–1688.
28. Galizio NO, Pesce R, Valero E, Which patients with congestive heart failure may benefit from biventricular pacing? *Pacing Clin Electrophysiol*. 2003;26(1 pt 2):158–161.
29. Grimm W, Sharkova J, Funck R, et al. How many patients with dilated cardiomyopathy may potentially benefit from cardiac resynchronization therapy? *Pacing Clin Electrophysiol*. 2003;26(1 pt 2):155–157.
30. Kalra PR, Sharma R, Shamim W, et al. Clinical characteristics and survival of patients with chronic heart failure and prolonged QRS duration. *Int J Cardiol*. 2002;86(2–3):225–231.
31. Kearney MT, Zaman A, Eckberg DL, et al. Cardiac size, autonomic function, and 5-year follow-up of chronic heart failure patients with severe prolongation of ventricular activation. *J Card Fail*. 2003;9(2):93–99.
32. Shenkman HJ, Pampati V, Khandelwal AK, et al. Congestive heart failure and QRS duration: establishing prognosis study. *Chest*. 2002;122(2):528–534.
33. Sandhu R, Bahler RC. Prevalence of QRS prolongation in a community hospital cohort of patients with heart failure and its relation to left ventricular systolic dysfunction. *Am J Cardiol*. 2004;93(2):244–246.
34. Baldasseroni S, Opasich C, Gorini M, et al. Left bundle-branch block is associated with increased 1-year sudden and total mortality rate in 5517 outpatients with congestive heart failure: a report from the Italian network on congestive heart failure. *Am Heart J*. 2002;143(3):398–405.
35. Stellbrink C, Auricchio A, Diem B, et al. Potential benefit of biventricular pacing in patients with congestive heart failure and ventricular tachyarrhythmia. *Am J Cardiol*. 1999;83(5B): 143D–150D.
36. Fonarow GC, Heywood JT, Heidenreich PA, et al. Temporal trends in clinical characteristics, treatments, and outcomes for heart failure hospitalizations, 2002 to 2004: findings from Acute Decompensated Heart Failure National Registry (ADHERE). *Am Heart J*. 2007;153(6):1021–1028.
37. Fuster V, Ryden LE, Cannom DS, et al. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: full text: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 guidelines for the management of patients with atrial fibrillation) developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *Europace*. 2006;8(9):651–745.
38. Rienstra M, Van Veldhuisen DJ, Hagens VE, et al. Gender-related differences in rhythm control treatment in persistent atrial fibrillation: data of the Rate Control Versus Electrical Cardioversion (RACE) study. *J Am Coll Cardiol*. 2005;46(7):1298–1306.

Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20714

39. Ruo B, Capra AM, Jensvold NG, Go AS. Racial variation in the prevalence of atrial fibrillation among patients with heart failure: the Epidemiology, Practice, Outcomes, and Costs of Heart Failure (EPOCH) study. *J Am Coll Cardiol*. 2004;43(3):429–435.
40. Hanrahan JP, Grogan DR, Baumgartner RA, et al. Arrhythmias in patients with chronic obstructive pulmonary disease (COPD): occurrence frequency and the effect of treatment with the inhaled long-acting β2-agonists arformoterol and salmeterol. *Medicine (Baltimore)*. 2008;87(6):319–328.
41. Iguchi Y, Kimura K, Kobayashi K, et al. Relation of atrial fibrillation to glomerular filtration rate. *Am J Cardiol*. 2008;102(8):1056–1059.
42. Wanahita N, Messerli FH, Bangalore S, Gami AS, Somers VK, Steinberg JS. Atrial fibrillation and obesity—results of a meta-analysis. *Am Heart J*. 2008;155(2):310–315.
43. Adam O, Neuberger HR, Bohm M, et al. Prevention of atrial fibrillation with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors. *Circulation*. 2008;118(12):1285–1293.
44. Belluzzi F, Sernesi L, Preti P, et al. Prevention of recurrent lone atrial fibrillation by the angiotensin-II converting enzyme inhibitor ramipril in normotensive patients. *J Am Coll Cardiol*. 2009;53(1):24–29.
45. Bourassa MG. Angiotensin II inhibition and prevention of atrial fibrillation and stroke. *J Am Coll Cardiol*. 2005;45(5):720–721.
46. McMurray J, Kober L, Robertson M, et al. Antiarrhythmic effect of carvedilol after acute myocardial infarction: results of the Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction (CAPRICORN) trial. *J Am Coll Cardiol*. 2005;45(4):525–530.
47. Psaty BM, Manolio TA, Kuller LH, et al. Incidence of and risk factors for atrial fibrillation in older adults. *Circulation*. 1997;96(7):2455–2461.
48. Mazzoleni A, Curtin ME, Wolff R, et al. On the relationship between heart weights, fibrosis, and QRS duration. *J Electrocardiol*. 1975;8(3):233–236.
49. Yamada T, Fukunami M, Ohmori M, et al. New approach to the estimation of the extent of myocardial fibrosis in patients with dilated cardiomyopathy: use of signal-averaged electrocardiography. *Am Heart J*. 1993;126(3 pt 1):626–631.

Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20714