

Quinidine for Pharmacological Cardioversion of Atrial Fibrillation: A Retrospective Analysis in 501 Consecutive Patients

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Background: Although quinidine has been used to terminate atrial fibrillation (AFib) for a long time, it has been recently classified to be used as a third-line-drug for cardioversion. However, these recommendations are based on a few small studies, and there are no data available of a larger modern patient population undergoing pharmacological cardioversion of AFib. Therefore, we evaluated the safety of quinidine for cardioversion of paroxysmal AFib in patients after cardiac surgery and coronary intervention.

Methods: In 501 consecutive patients (66 ± 9 years, 32% women), 200–400 mg of quinidine were administered every 6 hours until cardioversion or for a maximum of 48 hours. Patients were included with QT interval ≤ 450 ms, ejection fraction (EF) $\geq 35\%$, and plasma potassium > 4.3 mEq/L. Exclusion criteria were: unstable angina, myocardial infarction < 3 months, and advanced congestive heart failure. Patients received verapamil, beta-blockers, or digitalis to slow down ventricular rate < 100 bpm.

Results: Quinidine therapy did not have to be stopped due to adverse drug reactions (ADR), and no significant QTc interval prolongation (Bazett and Fridericia correction) and no life-threatening ventricular arrhythmia occurred. Mean quinidine dose was 617 ± 520 mg and 92% of the patients received verapamil or beta-blocker to decrease ventricular rate. Cardioversion was successful in 84% of patients. All ADRs were minor and transient. Multivariate analysis revealed female gender (OR 2.62, CI 1.61–4.26, $P < 0.001$) and EF 45–54% (OR 1.97, CI 1.15–3.36, $P = 0.013$) as independent risk factors for ADRs.

Conclusions: Quinidine for pharmacological cardioversion of AFib is safe and well tolerated in this subset of patients.

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atrial fibrillation; quinidine; pharmacological cardioversion; drug safety; adverse drug reaction

Class I antiarrhythmic drugs have been used to terminate atrial fibrillation (AFib) for nearly a century. However, the results of the Cardiac Arrhythmia Suppression Trial (CAST) in patients with structural heart disease and asymptomatic ventricular arrhythmias, showing a significant increase in mortality and nonfatal cardiac arrest rate, have highlighted our growing awareness of the proarrhythmic potential of class I antiarrhythmic drugs, especially class IC. Even though, the ap-

plicability of these results to other populations or other antiarrhythmic agents (such as class IA) is uncertain. At present, it is of course prudent to consider these results when also using class IA antiarrhythmic agents. Among the drugs listed in the ACC/AHA/ESC 2006 guidelines for the management of patients with AFib, quinidine is classified as "to be used with caution," and "safer methods with alternative agents" are recommended for pharmacological cardioversion.¹

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Especially in patients with coronary artery disease, quinidine is considered as a third-line treatment choice because of a greater potential for adverse drug reactions (ADR).¹ These recommendations, however, are based on a few studies of the early-to-mid 1990s, investigating only a small cohort of patients undergoing pharmacological cardioversion with quinidine.^{2–10}

Our clinic is an inpatient cardiac rehabilitation center, conducting multidisciplinary and comprehensive therapy for secondary prevention after cardiac surgery or coronary intervention. In this setting, quinidine has been used for pharmacological cardioversion of AFib over a longer period without any serious side effects. Therefore, we hypothesized that cardioversion of paroxysmal AFib with quinidine may be safe and effective, and tested this assumption by retrospectively analyzing our database of 503 patients with modern interventional or surgical cardiac treatment undergoing cardioversion of paroxysmal AFib with quinidine.

PATIENTS AND METHODS

A total of 503 consecutive patients with symptomatic paroxysmal AFib undergoing cardioversion with quinidine were identified retrospectively from our database. All patients met the following inclusion criteria: electrocardiogram (ECG) document of paroxysmal AFib, plasma potassium level >4.3 mEq/L, absolute QT duration ≤ 450 ms during AFib before quinidine administration, and left ventricular ejection fraction (LVEF) $\geq 35\%$. Exclusion criteria for quinidine therapy were: chronic AFib, unstable angina, acute myocardial ischemia (12-lead ECG, cardiac markers), myocardial infarction within 3 months, congestive heart failure NYHA classes III and IV, hepatic insufficiency, and concomitant therapy with other class I or class III antiarrhythmic drugs.

All patients underwent an initial diagnostic evaluation including baseline demographic data, all relevant cardiac diagnoses, a physical examination as well as echocardiography¹¹ to assess left atrial (LA) diameter and LVEF. LVEF was divided into group A $\geq 55\%$, B 45–54%, and C 35–44%, and LA diameter was classified into group A ≤ 40 mm, B 41–54 mm, and C ≥ 55 mm.

Before quinidine therapy was initiated, plasma creatinine and potassium levels were determined. If K^+ was ≤ 4.3 mEq/L, potassium was adminis-

tered intravenously or per os until plasma levels met the inclusion criteria. Using an ECG paper speed of 50 mm/s, the duration of the QT interval was measured (ms) in lead II from 12-lead ECG before quinidine therapy, and it was corrected for heart rate according to the formulas of Bazett¹² and Fridericia¹³ using average RR intervals during AFib. The QT interval was controlled between 2 and 4 hours after the initial (test) drug dose, every 12 hours thereafter, and finally after conversion to sinus rhythm. Quinidine therapy was stopped in case of serious ADR or when the absolute QT prolongation was >500 ms. During quinidine therapy, patients were closely observed and the ECG was monitored continuously at all times to detect asymptomatic arrhythmia. Plasma potassium levels were determined every day.

Peripheral or pulmonary congestion was treated by loop diuretics. During tachyarrhythmia, patients received concomitant medication (verapamil, beta-blockers, and digitalis) to slow down the ventricular rate to below 100 bpm before quinidine therapy was started. A test dose of quinidine sulfate 200 mg was administered, followed by a slow-release preparation of 200–400 mg (Chinidin duriles, Astra Zeneca, Wedel, Germany) every 6 hours, lasting for a maximum of 48 hours or until conversion to sinus rhythm. Patients were monitored by continuous ECG for at least 6 to 8 hours after completing antiarrhythmic treatment.

Statistics

Values are given as mean \pm standard deviation. Two-sided univariate analyses are performed by using Wilcoxon test for paired data and by using Mann-Whitney *U* test for unpaired data. Multivariate analyses are performed by logistic regression with stepwise forward selection of parameters, and odds ratios (OR) with 95% confidence intervals (CI) are given. *P* values < 0.05 are considered significant.

RESULTS

This study investigated 503 consecutive cardiac inpatients of a large specialized cardiac rehabilitation clinic, undergoing pharmacologic cardioversion of paroxysmal AFib. Two patients were excluded from further analysis because quinidine therapy had to be stopped before conversion to

Table 1. Baseline Clinical Characteristics of 501 Patients Undergoing Pharmacological Cardioversion of Atrial Fibrillation

Underlying Heart Disease	Patients	
	n	(%)
Coronary artery disease (CAD)	293	(58.4)
Old myocardial infarction	127	(25.3)
CABG	225	(44.9)
PCI	68	(13.5)
Valvular heart disease (VHD)	139	(27.8)
Valve surgery	139	(27.8)
CAD + VHD	44	(8.8)
Valve surgery + CABG	44	(8.8)
Other structural heart disease	25	(5.0)

n = number of patients, % in relation to n = 501.

CABG = coronary artery bypass graft surgery; PCI = percutaneous coronary intervention.

sinus rhythm within 12 hours after initiation of therapy (one patient due to feverish pneumonia and another due to severe diarrhea with *Clostridium difficile*). Both cases were classified as not to be related to quinidine administration. Mean age of the remaining 501 patients was 66.4 ± 9.0 years (median 67, range 26–93 years) including 343 men and 158 women (32%). Diagnosis and interventions are displayed in Table 1.

LVEF was $\geq 55\%$ in 390 patients (78%), in 103 patients (21%) it was 45–54%, and only 5 patients (1%) exhibited an LVEF of 35–44%. In three patients, LVEF could not be determined exactly. LA diameter was ≤ 40 mm in 227 patients (45%), between 41 and 54 mm in 223 patients (45%), and only 29 patients (6%) exhibited an LA diameter ≥ 55 mm. In 22 patients, LA diameter could not be measured exactly. Before starting with quinidine therapy, the average plasma potassium level was 4.3 ± 0.5 mEq/L, and in 404 out of 501 patients (81%), a potassium substitution was necessary to keep the plasma level >4.3 mEq/L during quinidine administration. Concomitant medication comprised digitalis (83%), verapamil (79%), and beta-blockers (13%) alone or in combination, and loop diuretics (41%).

The average quinidine dose administered was 617 ± 520 mg, range 200 to 2800 mg, median 400 mg. In 90% of the patients (449 of 501), the maximum dose was below 1400 mg. During quinidine therapy, the absolute QT interval (ms) increased significantly, whereas the corrected QT intervals

according to Bazett and Fridericia did not exhibit any significant difference before and after quinidine administration. Corrected QT intervals were above 440 ms in 47.9% of patients using the formula of Bazett and in 8.8% of patients, respectively, using the formula of Fridericia. Only in three patients (0.6%), a prolongation of the absolute QT interval up to 500 ms was observed during quinidine therapy. QT intervals and heart rates are displayed in Table 2, and in Figures 1 and 2.

In 403 patients (80%), it was the first episode of AFib. Only 98 patients (20%) exhibited recurrent AFib. The average duration of symptomatic AFib was 18.6 ± 55 hours with the longest episode lasting for 22 days. In 453 patients (90%), AFib persisted for a maximum of 24 hours before initiation of quinidine therapy. Conversion into sinus rhythm was achieved in 423 out of 501 patients (84%) within 11.1 ± 11.6 hours after initiation of quinidine therapy. Among patients with successful cardioversion, sinus rhythm was restored in 90% within 24 hours. Univariate predictors of cardioversion were a shorter duration of AFib (15.2 ± 51.2 vs 36.7 ± 71.5 hours; $P = 0.002$), a higher heart rate during AFib (128 ± 26 vs 118 ± 25 bpm; $P = 0.002$), coronary artery disease versus valvular heart disease (89% vs 77%; $P = 0.001$), no loop diuretics versus with loop diuretics (88% vs 79%; $P = 0.008$), LVEF $\geq 55\%$ versus 54–45% (87% vs 74%; $P = 0.004$), LA diameter ≤ 40 mm versus 40–54 mm versus ≥ 55 mm ($P = 0.001$ for all groups), and first episode versus recurrent episode of AFib (87% vs 74%; $P = 0.002$). Independent predictors for cardioversion identified by multivariate analysis are displayed in Table 3.

In none of the patients, quinidine therapy had to be stopped due to ADR. Furthermore, no prolongation of QT interval duration >500 ms was observed and no life-threatening ventricular arrhythmia was documented. Minor (and transient) ADR are depicted in Table 4. Univariate predictors of these minor ADR were gender (female 27% vs male 13%; $P < 0.0001$), body weight (lower 73.6 ± 13.1 vs higher 77.9 ± 12.7 kg; $P = 0.005$), and LVEF $\geq 55\%$ versus 45–54% (15% vs 25%; $P = 0.026$). There was a trend toward a more frequent use of loop diuretics in patients with ADR (21% vs 14%; $P = 0.054$). No association was observed between ADR and age, cumulative dosage of quinidine, plasma potassium and creatinine levels, potassium substitution, heart rate, QT and QTc intervals, structural heart disease, cardiac intervention or

Table 2. QT Intervals Are Displayed as Absolute Value (ms) and Corrected (QTc) According to the Formulas of Bazett and Fridericia before and Immediately at the End of Quinidine Administration for All Patients (n = 501), for Patients Converting into Sinus Rhythm during Quinidine Therapy (n = 423), and for those Remaining in Atrial Fibrillation (n = 78).

	Before Quinidine Administration	After Quinidine Administration	Statistics
QT interval (ms)			
All patients (n = 501)	306 ± 40	371 ± 43	P < 0.01
In sinus rhythm (n = 423)	304 ± 39	375 ± 41	P < 0.01
In AFib (n = 78)	314 ± 43	350 ± 49	P = 0.052
QTc Bazett (ms)			
All patients (n = 501)	438 ± 52	426 ± 44	n.s.
In sinus rhythm (n = 423)	439 ± 50	424 ± 40	n.s.
In AFib (n = 78)	435 ± 60	441 ± 62	n.s.
QTc Fridericia (ms)			
All patients (n = 501)	388 ± 43	407 ± 40	n.s.
In sinus rhythm (n = 423)	388 ± 42	407 ± 37	n.s.
In AFib (n = 78)	390 ± 49	407 ± 51	n.s.
Heart rate (min ⁻¹)			
All patients (n = 501)	127 ± 26	81 ± 17	P < 0.01
In sinus rhythm (n = 423)	128 ± 26	78 ± 12	P < 0.01
In AFib (n = 78)	118 ± 25	98 ± 25	P < 0.01

Values are given as mean value ± one standard deviation.
AFib = atrial fibrillation; n.s. = not significant.

surgery, former myocardial infarction, medication with beta-blocker, verapamil or digitalis, LA diameter, and history of AFib (first vs recurrent AFib). Results of multivariate analysis for ADRs are displayed in Table 4.

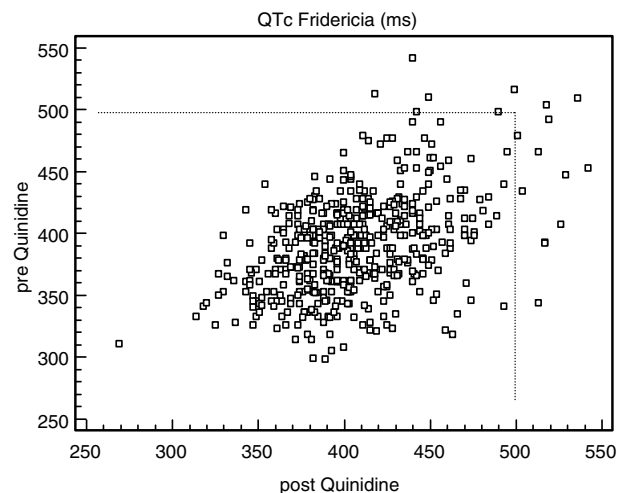


Figure 1. Relationship between Fridericia-corrected QT intervals before and after quinidine administration. The dotted line represents the upper limit for QTc prolongation.

DISCUSSION

Traditionally, quinidine has been the class I antiarrhythmic agent of choice for pharmacological cardioversion of atrial fibrillation.^{2,9,14} Reports of an unacceptably high incidence of ADR such as gastrointestinal symptoms, dizziness, profound

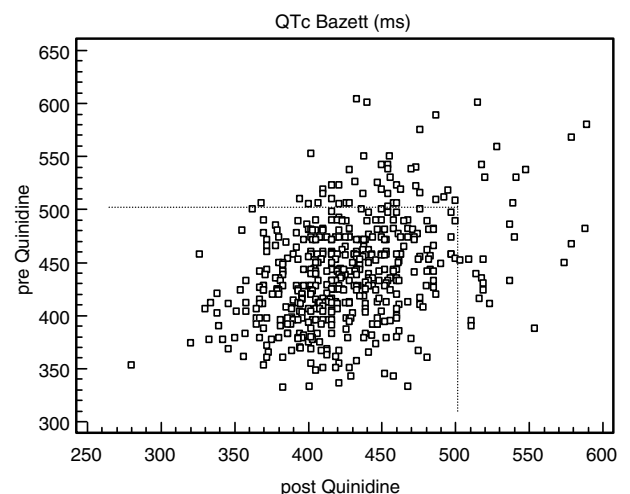


Figure 2. Relationship between Bazett-corrected QT intervals before and after quinidine administration.

Table 3. Multivariate Regression Analysis of Independent Parameters Affecting Success of Cardioversion and of Independent Parameters Affecting Adverse Drug Reactions during Quinidine Administration

	Odds Ratio	95% CI	P Value
Unsuccessful cardioversion			
Coronary artery disease	0.42	0.24–0.73	0.002
Loop diuretics	1.77	1.02–3.71	0.044
Recurrent AFib	2.00	1.08–3.71	0.028
Adverse drug reaction			
Female gender	2.62	1.61–4.26	<0.001
EF 45–54%	1.97	1.15–3.36	0.013

AFib = atrial fibrillation; CI = confidence interval; EF = left ventricular ejection fraction.

prolongation of the QT interval, torsade de pointes tachycardia, and even increased total mortality^{6,15,16} have displaced quinidine as a first-line drug for pharmacological restoration of sinus rhythm in patients with atrial fibrillation.¹

These concerns were derived particularly from the meta-analysis of Coplen et al.¹⁵ who reported a significant three-fold increase in total mortality in quinidine-treated patients as compared with control group (95% CI 1.07–8.33; $P < 0.05$; absolute mortality rate 3% vs 1%, respectively) and five patients receiving quinidine but none of the controls had cardiac arrest. However, the precise cause of death in the quinidine-treated patients was only known in 7 out of 12 cases, including 3 noncardiac deaths (suicide, $n = 1$; cerebrovascular, $n = 2$), and important concurrent medical illness was

present in 5 patients whose cause of death was not clear (carcinoma, $n = 2$; pneumonia, $n = 1$; hepatic failure, $n = 1$). In this meta-analysis,¹⁵ studies were only included if they had administered quinidine chronically for maintenance of sinus rhythm for at least 3 months after cardioversion. As the time of death is not reported and as the exact cause of death was not known in 42% of the quinidine-treated patients, it can be assumed that the patients died during chronic quinidine therapy and not during acute restoration of sinus rhythm that was achieved in 82–86% of cases by electrical cardioversion.¹⁵

In addition, parameters affecting the risk of proarrhythmia such as plasma potassium, QT interval, and LVEF were not used as inclusion or exclusion criteria in the studies^{17–22} of this meta-analysis,¹⁵ normal serum electrolytes were reported in only one trial,²² and digoxin was the only other antiarrhythmic agent allowed simultaneously.¹⁵ In all studies included,^{17–22} Digoxin was discontinued between 1 to 4 days prior to cardioversion, but in none of the trials, chronic digoxin dosage was reduced during concomitant quinidine medication and measurements of plasma glycoside concentrations were not reported.¹⁵ Hence, it is questionable, whether quinidine toxicity or glycoside overdose^{23,24} might have caused increased mortality during chronic treatment. This is in contrast to our evaluation, where potassium, QT interval, and LVEF were controlled, where 92% of the quinidine-treated patients received concomitant verapamil or beta-blockers for reducing proarrhythmic effects of class I antiarrhythmic drugs,^{25,26} and finally, where quinidine therapy was discontinued after 48 hours. Thus, the negative results of the aforementioned meta-analysis¹⁵ may not be transferred to the patient population of the present investigation.

In a study of Hohnloser et al.,⁶ quinidine therapy was also associated with a high risk of proarrhythmic side effects: in three patients torsade de pointes tachycardia was documented and one patient had sustained ventricular tachycardia. In three of these patients, the arrhythmia occurred shortly after cardioversion during slow sinus rhythm on day 4, 5, and 7 of quinidine therapy, respectively.⁶ The fourth patient experienced the ventricular tachyarrhythmia on day 1 of quinidine treatment being still in AFib, but exhibiting a QT interval of 520 ms before the event.⁶ In addition, one of these four patients had a maximum QT interval of 550 ms,

Table 4. Adverse Drug Reactions (ADR) during Administration of Quinidine and Concomitant Medication. All ADR Were Transient and of Minor Impact on the Patients' Well-Being

Adverse Drug Reactions	Patients	
	n	(%)
Diarrhea	64	(13)
First-degree AV block	19	(4)
Symptomatic hypotension	9	(2)
Supraventricular premature beats	7	(1)
Nausea	6	(1)
Ventricular premature beats	5	(1)
Exanthema of the skin	1	(<1)

n = number of patients, % in relation to n = 501.

another showed a LVEF of 27% and plasma potassium levels were substituted only if they were below 4.0 mEq/l.⁶ In our evaluation, quinidine administration was stopped immediately after cardioversion, and it remains unclear, whether the previously reported proarrhythmic side effects could have been prevented, if the same inclusion criteria would have been used as in this evaluation (plasma potassium > 4.3 mEq/l, maximum QT interval 500 ms, and LVEF \geq 35%).

The report of Selzer et al.¹⁶ is based on eight cases out of an estimated 200–300 patients treated with quinidine for cardioversion of atrial fibrillation. In none of these eight patients, plasma potassium, QT interval, and LVEF was reported and a very high dosage up to 4.0 g of quinidine per day was used. Seven patients had rheumatic valvular disease with significant clinical symptomatology and persistent cardiac failure until orthopnea. One patient showed congenital heart disease with atrial septal defect and pulmonary hypertension.¹⁶ Patients received quinidine before or after valvotomy or open heart surgery using extracorporeal circulation in the year 1962. In one case, quinidine therapy was continued despite a “markedly prolonged QT-interval” and another patient received quinidine and procainamid in combination.¹⁶ This case series is not at all comparable with today’s practice and the patients presented here. Hence, its negative results may not be generalized as well.

In the other studies on pharmacological cardioversion using quinidine^{2–5,7–10} that are cited in the present guidelines,¹ relevant parameters associated with the risk of proarrhythmia such as plasma potassium levels,^{2–5,7,9} QT interval duration,^{2,5,9} and LVEF^{2,3,5,9} were also not reported. In addition, the only concomitant medication that was allowed with quinidine therapy was digitalis.^{2,4,7–10} Only in few patients, additional verapamil^{3,5} or beta-blockers were used.⁵ Furthermore, as most of the literature cited was published in the prethrombolytic and thrombolytic era, patients in the early phase after coronary interventions or cardiac surgery (those with a high incidence of AFib) were not investigated in most of the trials^{2–10} and were excluded in the meta-analysis of Coplen et al.¹⁵ Even though quinidine dosage and treatment schedule are comparable, it is highly questionable whether the results derived from the studies above may be transferred to a modern cardiac patient population such as reported here, in

which very strict inclusion and exclusion criteria were used during short-term quinidine therapy and continuous monitoring.

In the review of Slavik et al.,²⁷ another six small studies, not cited before, enrolling between 15 and 237 patients (median, $n = 40$) are introduced. The heterogeneity described before also applies to these predominantly older studies.^{28–33} Again, plasma potassium,^{28–31} QT interval duration,^{28–33} and LVEF^{28–33} were not used as inclusion or exclusion criteria. In some studies, quinidine was even administered alone, without medication to decrease atrioventricular conduction velocity³¹ or digitalis being the only concomitant medication allowed.^{29,33} In three trials, propranolol was added to quinidine therapy with two studies showing this regimen to be efficacious and safe^{28,32} whereas Hillestad et al.³⁰ reported this combination to be ineffective and dangerous.

There are even additional small and heterogeneous studies in the literature exhibiting inconclusive data regarding both the true efficacy as well as the true toxicity of quinidine.^{34–43} As a consequence, in the ACC/AHA/ESC 2006 guidelines, quinidine is listed among the “incompletely studied agents for cardioversion of atrial fibrillation.”¹

In the study of Naccarelli et al.,⁴⁴ randomly assigning 117 patients to quinidine therapy for cardioversion of paroxysmal AFib, inclusion criteria (LVEF \geq 35%, maximum corrected QT interval < 500 ms, normal routine clinical laboratory results) and quinidine drug dosing (500 mg to 1500 mg per day) was very similar to our protocol. As in our evaluation, there was no life-threatening proarrhythmic effect, no torsade de pointes tachycardia, and no death in the quinidine-treated group.⁴⁴ In addition, cardiac ADR responded to drug discontinuation, reduction in dose, or any other acute treatment and most of the general ADR did not require drug discontinuation⁴⁴ as it was the case in our study.

To our knowledge, this study describes the largest patient population assigned to quinidine treatment for cardioversion of paroxysmal AFib. In contrast to most of the previous trials, parameters known to reduce the risk of proarrhythmia during quinidine therapy were carefully and consequently controlled: LVEF \geq 35%,^{44,45} QT interval < 500 ms,^{46,47} plasma potassium levels > 4.3 mEq/L,^{41,46} and concomitant medication with verapamil or beta-blockers.^{25,26} In addition,

exclusion criteria were advanced heart failure or acute angina, history of myocardial infarction <3 months, hepatic insufficiency, and concomitant therapy with other antiarrhythmic drugs. Considering these precautions, oral quinidine therapy was safe in this patient population and as the patients were monitored by ECG at all times, no episodes of asymptomatic torsade were missed. All ADR (Table 4) were transient and tolerable in each patient. As described in the literature,^{48,49} ADR were significantly associated with female gender in this study as well (Table 3).

There were significant differences between Fridericia- and Bazett-corrected QTc intervals durations, both before and after quinidine administration (Figs. 1 and 2). Bazett's formula is frequently used in clinical practice and in the medical literature. In general, however, Bazett's correction overcorrects at elevated heart rates and undercorrects at heart rates below 60 bpm and hence, is not an ideal correction. Fridericia's correction is more accurate than Bazett's correction in subjects with such altered heart rates, that is, patients with atrial fibrillation and fast ventricular rates as included in this study. The absolute QT interval was significantly increased by quinidine therapy, whereas the corrected QT intervals (Bazett and Fridericia) were not significantly prolonged by the antiarrhythmic drug, neither in the patients remaining in AFib nor in those converting into sinus rhythm (Table 2), showing that the concomitant medication (Verapamil, beta-blockers) effectively slowed down ventricular rate during AFib and that the RR interval was prolonged after conversion to sinus rhythm as well.

Limitations

This study has several limitations. First, as a retrospective study, our database is limited to the variables that were collected for clinical management. However, the quality of our database allowed to identify all patients in a consecutive way within the time period studied, and 98.7% of our data were complete. In addition, the large number of patients may balance at least partly the bias of retrospective analysis. This study did not evaluate the efficacy of quinidine for cardioversion as the drug was not randomized against control. In addition, spontaneous conversion to sinus rhythm, which is very common in postoperative patients,⁵⁰ was not taken

into account in the treatment protocol explaining the "high success rate" of 84% in this evaluation. As the results of this evaluation were obtained in the early postoperative period after cardiac surgery and after coronary intervention, they may not be transferred to the general patient population exhibiting AFib.

CONCLUSION

Considering the small number of patients studied so far, the heterogeneity in study design, and inclusion criteria as well as the conflicting results of the prevailing older studies, literature available about quinidine is inconclusive. As described above, it might not only be the drug but also a wrong patient selection that caused the unfavorable position of quinidine as compared with other antiarrhythmic medication for pharmacological cardioversion of AFib.¹ This view is supported by current randomized controlled trials, showing that quinidine is even safe during long-term treatment in carefully selected patients.^{51,52} Assuming, that quinidine is similar to other antiarrhythmic drugs with respect to efficacy and toxicity,^{53,54} its true potential for cardioversion should be evaluated in a suitable patient cohort according to the principles of evidence-based medicine. Using the inclusion and exclusion criteria of this evaluation, quinidine seems safe enough to be tested in a large randomized controlled trial.

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