Exercise Capacity Is the Most Powerful Predictor of 2-Year Mortality in Patients with Left Ventricular Systolic Dysfunction

Rona Reibis[1, 2], Andras Treszl[3], Karl Wegscheider[3], Bettina Ehrlich[1], Rüdiger Dissmann[4], Heinz Völler[1]

[1] Department of Cardiology, Rehabilitation Center of Cardiovascular Disease, Klinik am See, Rüdersdorf/Berlin, Germany,
[2] Kardiologische Gemeinschaftspraxis Am Park Sanssouci Potsdam, Germany,
[3] Department of Medical Biometry and Epidemiology, University Medical Center Hamburg-Eppendorf, Germany,
[4] Zentralkrankenhaus Reinkenheide, Bremerhaven, Germany.

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Abstract

Background: There are few data about predictors of cardiovascular mortality and rehospitalization rate in patients with left ventricular systolic dysfunction (LVSD) after myocardial revascularization and optimization of pharmacological treatment.

Patients and Methods: 1,346 consecutive patients with left ventricular ejection fraction (LVEF) < 45% (64 ± 10 years, 73% male, LVEF 36.3% ± 8%), who were referred for inpatient cardiac rehabilitation, were followed prospectively for 731 ± 215 days in a unicentric prospective longitudinal registry. Multivariate logistic regression Cox models were used to analyze demographic, echocardiographic and exercise variables in order to determine independent predictors of cardiovascular mortality and rehospitalization.

Results: LVEF failed to show prognostic power (hazard ratio [HR] 0.99 [95% confidence interval, CI, 0.94–1.03]; p = not significant), whereas moderate to severe mitral regurgitation (HR, 5.71 [95% CI 1.75–18.6]; p = 0.004) and atrial fibrillation (HR 1.67 [95% CI 1.15–2.44]; p = 0.008) were associated with a poorer prognosis. In an optimized multivariate model, 6-min walk test (HR 0.93 [95% CI 0.86–1.00] per 50 m; p = 0.049) and symptom-limited maximum exercise capacity test (HR 0.83 [95% CI 0.76–0.91] per 10 W; p < 0.001) as well as female gender (HR 0.58 [95% CI 0.39–0.84]; p = 0.005) were strong predictors for reduced overall mortality.

Conclusion: In patients with LVSD, independently of LVEF, traditional prognostic factors including atrial fibrillation or mitral regurgitation predict poorer survival, whereas symptom-limited exercise capacity and walking distance performed in 6-min walk test were highly predictive for a good prognosis.

Einfluss der körperlichen Leistungsfähigkeit auf die 2-Jahres-Mortalität von Patienten mit systolischer Linksherzinsuffizienz

Schlüsselwörter:
Systolische Linksherzinsuffizienz · Körperliche Leistungsfähigkeit · 6-min-Gehtest · Kardiovaskuläre Mortalität · Rehospitalisationsrate

Zusammenfassung

Hintergrund: Bei revaskularisierten und medikamentös leitlinienorientiert therapierten Patienten mit linksventrikulärer systolischer Dysfunktion sind prognostische Parameter für kardiovaskuläre Mortalität und Rehospitalisierung unzureichend bekannt.

Patienten und Methodik: 1 346 konsekutive Patienten mit einer linksventrikulären Ejektionsfraktion (LVEF) < 45% (64 ± 10 Jahre, 73% männlich, LVEF 36,3% ± 8%) wurden im Rahmen einer kardiologischen Rehabilitation in einem unizentrischen prospektiven Register erfasst und 731 ± 215 Tage nachbeobachtet. In einer multivariaten Cox-Regressionsanalyse wurde der Einfluss demographischer, echokardiographischer und funktioneller Parameter auf die Endpunkte kardiovaskuläre Mortalität und Rehospitalisationsrate beurteilt.

Ergebnisse: Die LVEF zeigte keinen signifikanten prognostischen Einfluss (Hazard-Ratio [HR] 0,99 [95%-Konfidenzintervall, CI, 0,94–1,03]; p = nicht signifikant), wohingegen das Vorliegen einer höhergradigen Mitralklappeninsuffizienz (HR 5,71 [95%-CI 1,75–18,6]; p = 0,004) und eines Vorhofflimmerns (HR 1,67 [95%-CI 1,15–2,44]; p = 0,008) mit einer schlechten Prognose assoziiert war. Im optimierten Gesamtmodell wiesen eine bessere körperliche Leistungsfähigkeit im 6-min-Gehtest (HR 0,93 [95%-CI 0,86–1,00] pro 50 m; p = 0,049) und in der symptomlimitierten Ergometrie (HR 0,83 [95%-CI 0,76–0,91] pro 10 W; p < 0,001) sowie weibliches Geschlecht (HR 0,58 [95% CI 0,39–0,84]; p = 0,005) die höchste Vorhersagekraft für eine reduzierte Gesamtmortalität auf.

Schlussfolgerung: Traditionelle prognostische Risikofaktoren wie Vorhofflimmern oder eine höhergradige Mitralklappeninsuffizienz sind bei Patienten mit systolischer Linksherzinsuffizienz unabhängig von der linksventrikulären Ejektionsfraktion mit einer Steigerung der Mortalitätsrate assoziiert. Demgegenüber sind die maximale Leistungsfähigkeit in der Ergometrie und im 6-min-Gehtest positive Prädiktoren für die Langzeitprognose.

Introduction

A major improvement in the prognosis of heart failure patients, particularly in men and younger patients, could be attained in the last 25 years by optimal revascularization [1], guideline-based pharmacological treatment [2, 3], and application of implantable cardioverter defibrillators for prevention of sudden cardiac death [4]. Nevertheless, depending on clinical severity, prognosis of patients with symptomatic congestive heart failure is rather poor and the mortality rate is similar to that of a malignant disease [5]. Numerous factors including functional, echocardiographic, autonomous and invasive parameters have been analyzed for their impact on mortality in patients with left ventricular systolic dysfunction (LVSD) [6–8]. The present report describes variables predicting rehospitalization rate, 2-year overall and cardiovascular mortality in stable heart failure patients after application of guideline-based pharmacotherapy.

Patients and Methods

Subjects

From January 1998 to December 2000, data from 1,346 consecutive patients (64.3 ± 10 years; 27% women) with echocardiographically quantified biplane left ventricular ejection fraction (LVEF) of < 45% (mean EF 36.3 ± 8%), who were hospitalized for a 3-week inpatient cardiologic rehabilitation was compiled prospectively. The mean follow-up was 731 ± 215 days. 21.5% of the patients were New York Heart Association class I (NYHA I), 54.6% NYHA II, and 23.9% NYHA III/IV. To assess the cardiovascular risk profile, total, LDL and HDL cholesterol, triglycerides and the serum fasting glucose value were determined in all patients. Baseline characteristics and functional parameters at discharge are shown in Table 1.

Table 1. Baseline characteristics and functional parameters. BMI: body mass index; COPD: chronic obstructive pulmonary disease; ECG: electrocardiography; LVEF: left ventricular ejection fraction; MR: mitral regurgitation; nsVT: nonsustained ventricular tachycardia; NYHA: New York Heart Association; SD: standard deviation; TIA: transient ischemic attack; PVC: premature ventricular complexes.

Tabelle 1. Basisparameter und funktionelle Parameter. BMI: Body-Mass-Index; COPD: chronisch-obstruktive Lungenerkrankung; ECG: Elektrokardiographie; LVEF: linksventrikuläre Ejektionsfraktion; MR: Mitralklappeninsuffizienz; nsVT: nichtanhaltende ventrikuläre Tachykardie; NYHA: New York Heart Association; SD: Standardabweichung; TIA: transitorische ischämische Attacke; PVC: ventrikuläre Extrasystolen.

Parameters	Values
Age (years)	64 ± 10
Male (%)	73.0
BMI > 30 kg/m^2 (%)	14.5
LVEF (%, mean ± SD)	36.3 ± 8
Ischemic cardiomyopathy (%)	88.0
NYHA class III/IV (%)	23.9
Hypertension (%)	67.4
Dyslipidemia (%)	76.2
Diabetes mellitus (%)	34.8
Smoking (%)	28.8
COPD (%)	8.6
Stroke/TIA (%)	4.8
MR I/II/III (%)	48.6/12.8/0.4
Permanent atrial fibrillation (%)	11.8
Mean pulse rate (Holter ECG; bpm, mean ± SD)	75 ± 12
Left bundle branch block (%)	9.2
nsVT (Holter ECG) ≥ 3 PVC (%)	14.4
6-min walk test (m, mean ± SD)	350.1 ± 148.6
Symptom-limited maximum exercise capacity on discharge (W, mean ± SD)	75.1 ± 31.5

Functional Parameters

Echocardiography. Biplane LVEF was determined by two-dimensional echocardiographic imaging according to Simpson [9]. For assessing data, 3S probe of Vivid 7 (Vivid 7, GE Ving Med, Horten, Norway) was used. Means of three biplane planimetric measurements were used to determine a mean LVEF value for every patient. Additionally, assessment of mitral valve insufficiency was performed.

ECG/Holter ECG. To stratify the risk of sudden cardiac death, a three-channel Holter ECG including pacemaker analysis (Oxford Medilog Optima, Oxford Medical Systems, UK) was recorded. Nonsustained ventricular tachycardias (duration < 30 s) were documented.

Exercise testing. (1) Standardized 6-min walk tests (6-MWT) were conducted with a distance-measuring device (Nestle Rolltachometer, Dornstetten, Germany) at the beginning and at the end of cardiac rehabilitation. Before starting, the patient was familiarized with the test and the environment [10]. Under the control of a physician, patients were instructed to walk in an indoor corridor and encouraged to walk as far as possible for 6 min. At the end of the 6 min, the physician measured the total distance walked by the patient. The test was repeated at the same day for all patients, the mean value of performed distance was documented.

(2) All patients performed an individualized symptom-limited maximum cycle test on a cycle er-

gometer up to the submaximal predicted heart rate (85% of age-adjusted maximum heart rate) using a stepwise stress-testing protocol, starting with 25 W, followed by 25-W increment every 2nd min until exhaustion. During the tests, a three-lead ECG was recorded continuously. Blood pressure was assessed indirectly by arm cuff sphygmomanometry every 2 min. Standard criteria for termination were employed.

(3) Submaximal cycle ergometric performance was defined as the workload, patients performed in a standardized daily training session for 15 min until exhaustion occurred. The level was primarily defined by 60% of capacity level during the symptom-limited maximum cycle test at admission and was individually increased during the daily training sessions. Submaximal work load at discharge (W) was documented.

Cardiovascular Medication

In respect to medication, the follow-up observation comprised β-blockers, ACE inhibitors, AT_1 receptor blockers, antiplatelet therapy, statins, diuretics, aldosterone antagonists, glycosides, nitrates, and antiarrhythmics. The medication was initially recorded on discharge from rehabilitation and during follow-up observations. The treatment was classified as to comply with the guidelines, if it was defined as being evidence-based at the relevant time in the period investigated [11]. During the follow-up, an adaption of dosage due to side effects was allowed.

Follow-Up Observations

After a mean observation period of 731 ± 215 days, a questionnaire on medication and vital status was sent to the patient and the family doctor at the same time. If no reply was received, the family doctor and the treating hospitals were contacted by telephone. If once more no information was received, vital status was established via the residents' registry office. The overall mortality, cardiac and noncardiac death, as well as death from unknown causes were documented. Questions with regard to clinical events comprised the number and indication of rehospitalization, the occurrence of ischemic stroke, peripheral arterial embolism, venous thromboembolism, cardiac arrhythmias, and worsening heart failure. Six patients (0.4%) were lost to follow-up; therefore, summarized data from 1,340 patients could be analyzed (follow-up: 99.6%).

Statistical Analysis

For sample description, discrete variables are given as counts and percentages, continuous variables as means ± standard deviation. We used adjusted Cox proportional hazards models to examine the association between 19 baseline determinations and overall mortality/rehospitalization. Since seven of 19 baseline variables were not complete, but were considered to be of clinical importance, we performed the analysis by multiple imputation [12]. In age, LVEF, mitral valve insufficiency, 6-MWT, symptoms limiting exercises and ventricular ectopy, two, one, 103, 128, 134, and 18 values had to be imputed, i.e., up to 10.0% of 1,346 patients. Imputation rates < 20% are usually considered acceptable. Of the final imputed model, we present adjusted hazard ratios (HR) with their 95% confidence interval (CI) for all variables and visualized in a forest plot.

Results

Discharge Medication and Accordance with Guidelines

As described in detail elsewhere [13], within the period from 1998 to 2000, an increase in medication prescription in accordance with guidelines was documented from 67.9% to 86.6%. 89% of the patients received ACE inhibitors, 6.7% AT_1 blockers, 90% β-blockers, 62.3% thiazides, and 19% aldosterone antagonists.

Mortality and Rehospitalization

170 of the 1,340 patients died during the follow-up (12.6%). Of these, 40 events (23.5%) were classified as noncardiac death. 98 patients (57.7%) experienced the combined endpoint of cardiovascular death associated with congestive heart failure or sudden cardiac death. 32 patients (18.8%) died of an unknown cause. The indication for nonelective readmission could be confirmed by the hospitals in 1,241 patients (92.6%). 641/1,241 patients (51.6%) had to be rehospitalized during the follow-up period of 2 years, 343/1,241 (27.6%) of them were readmitted to hospital for cardiac reasons. 111/1,241 patients (8.9%) were recorded with acute coronary syndromes and 22/1,241 patients (1.8%) with reinfarction (STEMI [ST segment elevation myocardial infarction] and NSTEMI [non-ST segment elevation myocardial infarction]). Worsening heart failure (i.e., aggravation or new occurrence of heart failure symptoms) was observed in 190/1,241 patients (15.3%).

Predictive Variables for Overall Mortality

Out of 19 baseline and functional parameters, powerful predictors for overall mortality in the stepwise Cox regression procedure were atrial fibrillation (HR 1.67 [95% CI 1.15–2.44]; p = 0.008) and moderate to

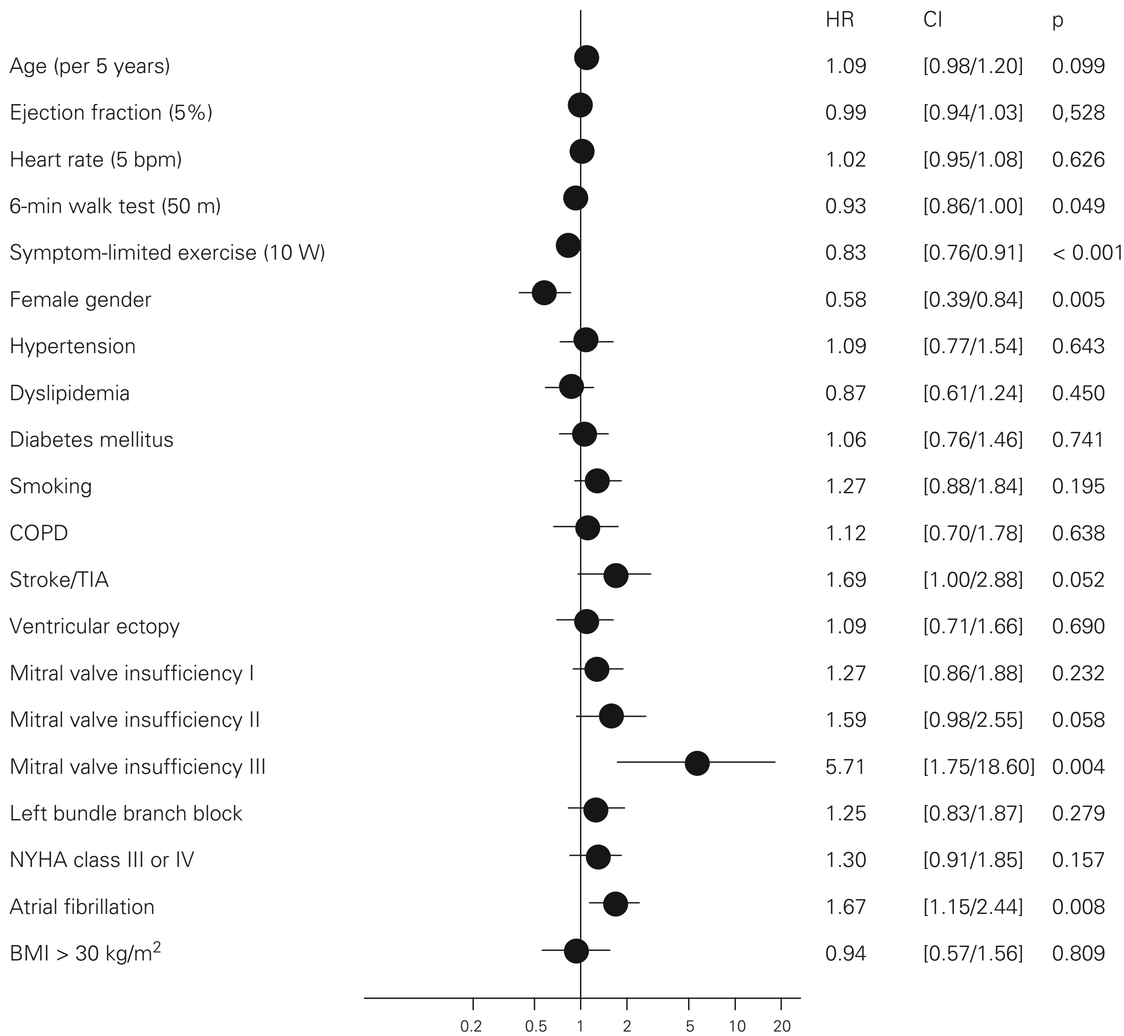

Figure 1. Multivariate predictors of overall mortality. BMI: body mass index; CI: confidence interval; COPD: chronic obstructive lung disease; HR: hazard ratio; NYHA: New York Heart Association; TIA: transient ischemic attack.

Abbildung 1. Multivariate Prädiktoren der Gesamtmortalität. BMI: Body-Mass-Index; CI: Konfidenzintervall; COPD: chronisch-obstruktive Lungenerkrankung; HR: Hazard-Ratio; NYHA: New York Heart Association; TIA: transitorische ischämische Attacke.

severe mitral regurgitation (MR; HR 5.71 [95% CI 1.75–18.6]; p = 0.004; Figure 1).

It could not be demonstrated that LVEF serves as an independent predictor for mortality (HR 0.99 [95% CI 0.94–1.03]; p = 0.528). By contrast, symptom-limited exercise capacity (per 10 W, HR 0.83 [95% CI 0.76–0.91]; p < 0.001) and walking distance performed in 6-MWT (per 50 m, HR 0.93 [95% CI 0.86–1.00]; p = 0.049) as well as female gender (HR 0.58 [95% CI 0.39–0.84]; p = 0.005) were powerful predictors of reduced mortality.

Discussion

The current study is remarkable because of three important findings. First, we present the data of one of the most extensive patient sample sizes for 6-MWT (n = 1,346). Second, we found that on multivariate analysis besides atrial fibrillation as a traditional cardiovascular risk factor a moderate to severe MR was associated with a fivefold increase of overall mortality. Third, we demonstrated that maximum exercise tolerance outperformed conventional cardiovascular risk factors including left ventricular systolic function in prediction of overall mortality and rehospitalization rate. After maximum adjustment, the distance performed during the 6-MWT and symptom-limited maximum cycle exercise capacity on discharge was strongly predictive for a better outcome in patients with LVSD.

Atrial fibrillation is a common comorbidity in patients with left ventricular dysfunction presenting with an incidence up to 26% in an outpatient CHF population [14]. The prognostic power of atrial fibrillation, irrespective of age and NYHA class, as a negative predictive parameter in patients with chronic heart failure is undisputable and not novel [14–17]. The impaired prognosis in CHF patients due to atrial fibrillation is proven in both patients with reduced or preserved ejection fraction [16]. Our results support preceding studies of an almost doubled mortality rate in atrial fibrillation patients [14, 17]. Likewise, our findings of impressive clinical impact of MR go along with earlier reports [18, 19]. In patients with moderate to severe MR, the 5-year survival after percutaneous coronary intervention is reduced by half in comparison to none or mild MR [20]. Thus, even a moderate MR in CHF patients requires frequent observations and, in case of MR progression, a timely valve reconstruction or replacement should be considered.

There is still conflicting evidence regarding gender influence on prognosis in patients with LVSD [21, 22]. The majority of studies have documented an improved survival for women compared to men, which confirm our data of a significantly reduced mortality rate for female gender. However, most prognostic CHF studies have been conducted primarily in men, thus a larger representation of women to objectify the risk situation is desirable.

Survival rate is known to be strongly associated with the degree of clinical heart failure [16, 23]. The 6-MWT, as originally described by Guyatt et al. [10], is widely used to assess physical performance in cardiac rehabilitation settings. 6-MWT has been demonstrated to be significantly correlated with NYHA class [16] and is accepted to be a strong indicator for mortality and morbidity in CHF patients [24–27]. A walking distance of < 300 m was extracted as a predictor of increased mortality and morbidity (hospitalization for worsening heart failure) both in patients with asymptomatic LVSD as well as with mild to moderate and severe heart failure [28]. Bittner et al. [24] reported, from the SOLVD trial, a cutoff value of ≥ 450 m for a good clinical outcome in heart failure patients. Maximum oxygen uptake as well as the VE/VCO_2 slope are traditionally used for risk stratification in systolic [29–31] as well as in diastolic [32] heart failure. The correlation of 6-MWT as an index of daily living activity and VO_{2max} as an index of submaximal exercise capacity yielded inconsistent results in previous trials [25, 33], although a positive correlation was predominantly found [34, 35]. However, the mainly elderly CHF population with complex comorbidities (coxarthrosis, gonarthrosis, muscular atrophy, imbalance, etc.) commonly show a limited exercise level in their daily activity; therefore, it appears to be difficult to perform a maximal effort test. Walking distance may be a more simple, but objective way of stratifying CHF patient risks [36, 37].

The very recently published study from Hsich et al. [38] demonstrated, that instead of cardiopulmonary stress testing the treadmill exercise time with modified Naughton protocol is a reliable prognostic screening tool with a low technical effort in CHD patients. The investigation of Ingle et al. [39] including 1,077 elderly patients demonstrated a high sensitivity of 6-MWT to self-perceived symptoms of heart failure. Demers et al. [40] analyzed data of 768 patients for the RESOLVD study and found a high reproducibility of 6-MWT. Further study indicated, that adjustment for height, weight, body mass index and age did not additionally increase the prognostic power of the 6-MWT for 1-year mortality in heart failure patients [41]. Very similar to 6-MWT, symptom-limited maximum exercise capacity assessed during ergometric exercise was related to a better outcome. Our data are in accordance to those from an extensive investigation by Myers et al. [42], which documented a strong association of exercise capacity and risk of death among both normal subjects and those with cardiovascular disease. Each 1-MET (metabolic equivalent) increase in exercise capacity was associated with a 12% improvement in survival.

In comparison to other groups [10, 13, 43], our survey exhibits a low 2-year overall and cardiovascular mortality (12.6% and 8%). Additionally, our study failed to show a predictive power of LVEF. Both results might be explained by the patient selection by referring to an inpatient cardiac rehabilitation program. The initial LVEF (36.3% ± 8%) could be expected to increase within the recovery process after myocardial revascularization, although the improvement has shown to be rather low [44]. Furthermore, although mean LVEF was markedly reduced, 76.1% of the patients were in NYHA I–II, which reflects an LVSD without symptomatic heart failure and thus the good clinical conditions of these patients.

To summarize, in consideration of multiple modern echocardiographic, electrophysiological and humoral parameters for risk stratification of CHF patients, this study emphasizes the convincingly prognostic role of comparatively simple and inexpensive tools like 6-MWT and maximum cycle ergometry capacity as integrative parameters of cardiovascular fitness.

Study Limitations

The study has several limitations. First, it was conducted as a single-center prospective observational study. The results reflect the conditions and patients, associated with cardiac rehabilitation, i.e., patients with relatively stable CHF. Second, in the given registry women, elderly patients and patients with atrial fibrillation are underrepresented. We were also missing data on details of drug treatment (e.g., dosing and combination therapy). So, a possible influence of these factors on the observed data cannot be ruled out. Finally, regarding the mortality rate, we focused on a highly selected population of almost completely revascularized patients in a follow-up after a cardiologic rehabilitation.

Conclusion

In a CHF population with moderately reduced LVEF after revascularization, the mortality rate is comparatively low. Traditional prognostic factors like atrial fibrillation and MR increase the mortality rate, whereas physical capacity is a strong independent variable for a reduced mortality risk. The 6-MWT and the maximum exercise capacity are valid tools for identifying systolic heart failure patients with a higher risk of cardiovascular morbidity and mortality.

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Address for Correspondence

Rona K. Reibis, MD
Kardiologische Gemeinschaftspraxis Am Park Sanssouci Potsdam
Zimmerstraße 7
14471 Potsdam
Germany
Phone (+49/331) 297629, Fax -2700338
e-mail: rona.reibis@hotmail.de