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Jarosław Pietrzak[1,A-B,D], **Łukasz Wołowiec**[1,A-B,D], **Joanna Banach**[1,C,E-F], **Wojciech Gilewski**[1,C,E-F], **Władysław Sinkiewicz**[1,A-B,E], **Joanna Osiak**[1,C-D,F], **Anna Krix**[2,D,F], **Anna Wołowiec**[2,D,F], **Jacek Hincz**[3,E-F], **Grzegorz Grześk**[1,A,E-F]

PROGNOSTIC VALUE OF A 6-MINUTE WALK TEST IN PATIENTS WITH CHRONIC HEART FAILURE PREQUALIFIED FOR HEART TRANSPLANTATION IN 12-MONTH FOLLOW-UP.

[1] Department of Cardiology and Clinical Pharmacology, Faculty of Health Sciences, Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University, Toruń, Poland, Polska
[2] Department of Geriatrics, Division of Biochemistry and Biogerontology, Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University, Toruń, Poland, Polska
[3] Pomeranian Rheumatological Center, Dr. Jadwiga Titz-Kosko, Polska

A - Koncepcja i projekt badania, B - Gromadzenie i/lub zestawianie danych, C - Analiza i interpretacja danych, D - Napisanie artykułu, E - Krytyczne zrecenzowanie artykułu, F - Zatwierdzenie ostatecznej wersji artykułu

Abstract (in English):
Aim: A 6-minute walk test (6MWT) is a simple test in the diagnosis of heart failure (HF). The aim of the study was to assess the effect of 6-minute walk distance on the occurrence of a major adverse cardiac event (MACE), defined as cardiovascular death or hospitalization for HF exacerbation in patients with HF, prequalified to heart transplantation.
Material and methods: 46 patients were subjected to a prospective one-year follow-up study. They were diagnosed with HF with reduced left ventricular ejection fraction (LVEF) in NYHA class II and III, with reduced LVEF < 35%. Each patient was initially subjected to a 6MWT, repeated every 3 months during the follow-up visits.

Results: During the 12-month period, a composite endpoint (MACE +) was observed in 23 patients (50.0%), including 17 patients (37.0%) with HF exacerbation, 6 patients (13.0%) died. MACE (+) patients covered a shorter distance than those in the MACE (-) group. A statistically significantly lower mean value of the distance covered in the walk test was observed in the group of patients who died compared to the group of patients without HF exacerbation. Also, at the level of a statistical trend, patients who died had a lower mean value of the distance covered compared to patients with HF exacerbation.
Conclusions: The 6MWT is a useful and simple tool that allows to evaluate the prognosis in patients with chronic HF with reduced LVEF. High specificity of the test is an additional advantage confirming its diagnostic value.

Keywords: prognosis, heart failure, 6-minute walk test, chronic heart failure.

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Short title
6-minute walk test in patients with chronic heart failure

Corresponding author
Łukasz Wołowiec
Department of Cardiology and Clinical Pharmacology, Faculty of Health Sciences, Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University, Toruń, Poland, Polska; email: lukaswolowiec111@gmail.com

Authors (short)
J. Pietrzak et al.

Introduction

Heart failure (HF) is a disease that affects around 1-2% of adults. The prevalence increases with age – in a group of 70-year-olds people or over, reaches the level of >10% [1]. HF consisting of specific symptoms and sings which are caused by structural and/or functional abnormality of the heart. Typical symptoms are breathlessness, ankle swelling, and fatigue. Symptoms initially appear during exercise, with subsequent intensification to symptoms at rest. The basic mechanisms leading to HF are primary contractile failure, pressure or volume overload of the ventricles, impaired diastolic function, and tachyarrhythmias and bradyarrhythmias. HF has been divided on the basis of the measurement of the left ventricular ejection fraction in echocardiography – reduced left ventricular ejection fraction is understood as a value of ≤40%. The most common cause of HF with preserved ejection fraction is arterial hypertension, but in case of HF with reduced ejection fraction - ischemic heart disease. HF is characterized by significant morbidity and mortality and poor functional capacity and quality of life. Nowadays, due to its prevalence, it is a serious problem.

Despite recent advances in the diagnosis and treatment of cardiovascular diseases, the prognosis of HF still remains a challenge for modern medicine and the entire health care system. In the group of patients with advanced HF the risk of death from cardiovascular causes is high, therefore prognostic factors play a very important role allowing the identification of a patient subgroup who require the most intensive treatment, including preparation for heart transplantation. The ECS guidelines from 2021 for the diagnosis and treatment of acute and chronic HF include a comprehensive list of factors with proven diagnostic significance in HF [1]. Newer, recently published studies assessing the diagnostic value of, inter alia, various echocardiographic parameters and markers of inflammation also did not show any significant advantage of a single prognostic factor, proving that the precise assessment of the risk of death or rehospitalization in HF with reduced left ventricular ejection fraction still remains a challenge and requires further observation [2–5].

6-minute walking test consists of measuring the walking distance (6-minute walking distance - 6MWD) with turns in a long, straight corridor (≥30 m), at the patient's own pace[6]. It allows to assess the submaximal exercise capacity corresponding to the ability to perform daily activities. 6MWD in healthy people depends on age and is ~600 m in men and ~500 m in women [7]. It is also useful in assessing and monitoring chronic obstructive pulmonary disease. The test is generally safe, but it is obvious that contraindications must also be taken into account.

The aim of the study is to show a prospective, one-year evaluation of the prognostic value of the 6-minute walk test in the group of patients with chronic HF with reduced left ventricular ejection fraction due to ischemic heart disease and dilated non-ischemic cardiomyopathy, prequalified for heart transplantation.

Patients and methods

The prospective analysis included 46 patients (7 female and 39 male) aged 27-63 years (the mean age at the beginning of the follow-up was 50.7 ± 8.3 years, median 52 years) with advanced HF with reduced left ventricular ejection fraction (mean left ventricular ejection fraction assessed by echocardiography was 22.7 ± 5.1%), clinically stable: 16 patients (35%) in NYHA class II, 30 patients (65%) in NYHA class III, hospitalized to consider prequalification for heart transplantation. The diagnosis of chronic HF with reduced left ventricular ejection fraction was based on the ECS criteria: the symptoms of HF with objectively confirmed impaired left ventricular systolic function at rest. Patients were hemodynamically stable and had been taking stable doses of drugs for at least 2 weeks prior to the examination. Treatment was modified based on the clinical status during further outpatient follow-up. All patients underwent coronary angiography before the test. Ischemic cardiomyopathy was diagnosed in 21 patients and non-ischemic in 25. The exclusion criteria were: pregnancy, breastfeeding, symptoms of an active infection, contraindications to heart transplantation (despite hemodynamic contraindications assessed during cardiac catheterization). The tests were conducted using a 30-meter long section of a hospital corridor in the Department of Cardiology. Before the test, all patients were informed how to perform it and then began walking at their usual pace, covering the distance they could in 6 minutes. When patients felt tired, they could rest and then continued the walk. The test was stopped after 6 minutes or at a patient`s request. After getting acquainted with the terms of the walk test and signing the informed consent, the patients underwent the 6-minute walk test 5 times (during the visit number "0" and after 3, 6, 9 and 12 months).

Statistical analysis

The obtained test results were analyzed statistically. The survival function was estimated using the Kaplan-Meier method. In order to find the best parameters and the optimal cutoff value differentiating the study group in terms of the occurrence and non-occurrence of MACE, ROC curves were plotted and the area under the curve (AUC) was calculated. The p = 0.05 threshold was used as a border of statistical significance. The calculations were made with the use of the STATISTICA v.10.0 PL software by StatSoft, Inc.

Results

The composite endpoint MACE (+) was observed in 23 (50.0%) out of 46 patients enrolled in the study during the 12-month follow-up period, including 17 (37.0%) patients with HF exacerbation and 6 (13.0%) patients who died. At the start of the follow-up period, the patients covered the distance from 180 m to 550 m, on average 378 ± 90 m. The distance covered in the 6MWT (the 6-minute walk test) is presented in figure 1.

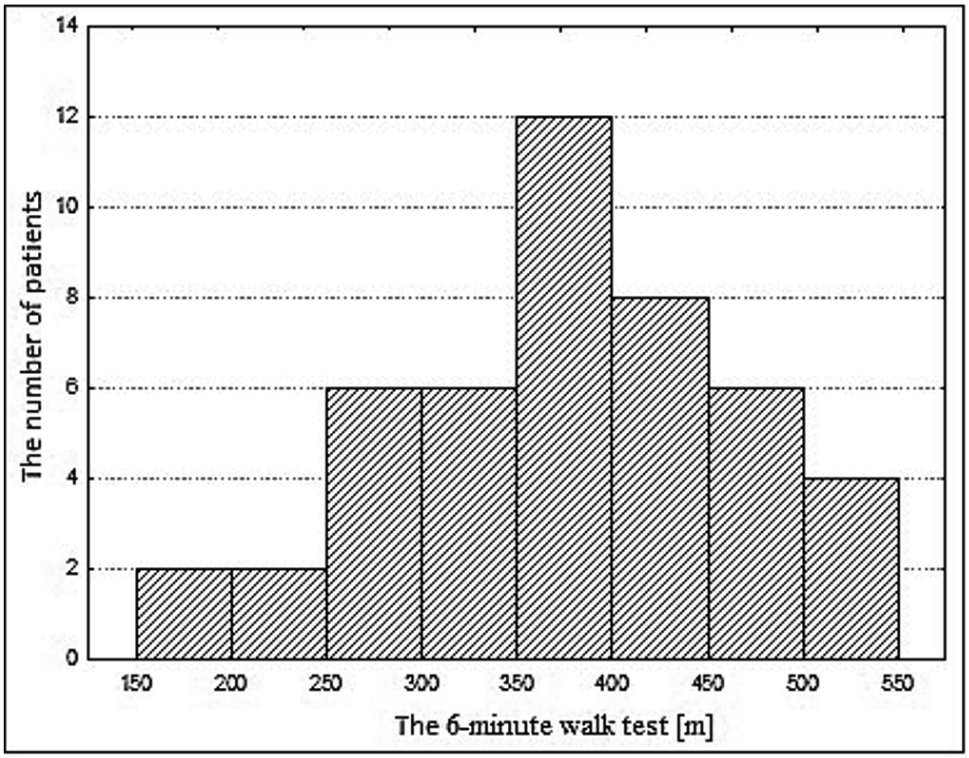

Fig. 1. The distance covered by the patients in the walk test at the beginning of the follow-up period (N = 46).

The walk test results in the MACE (-) and MACE (+) groups of patients at the beginning of the follow-up period is presented In figure 2. The mean result of the walk test at the beginning of the follow-up period in the MACE (-) and MACE (+) groups of patients did not differ significantly (p=0,1391) (table 1).

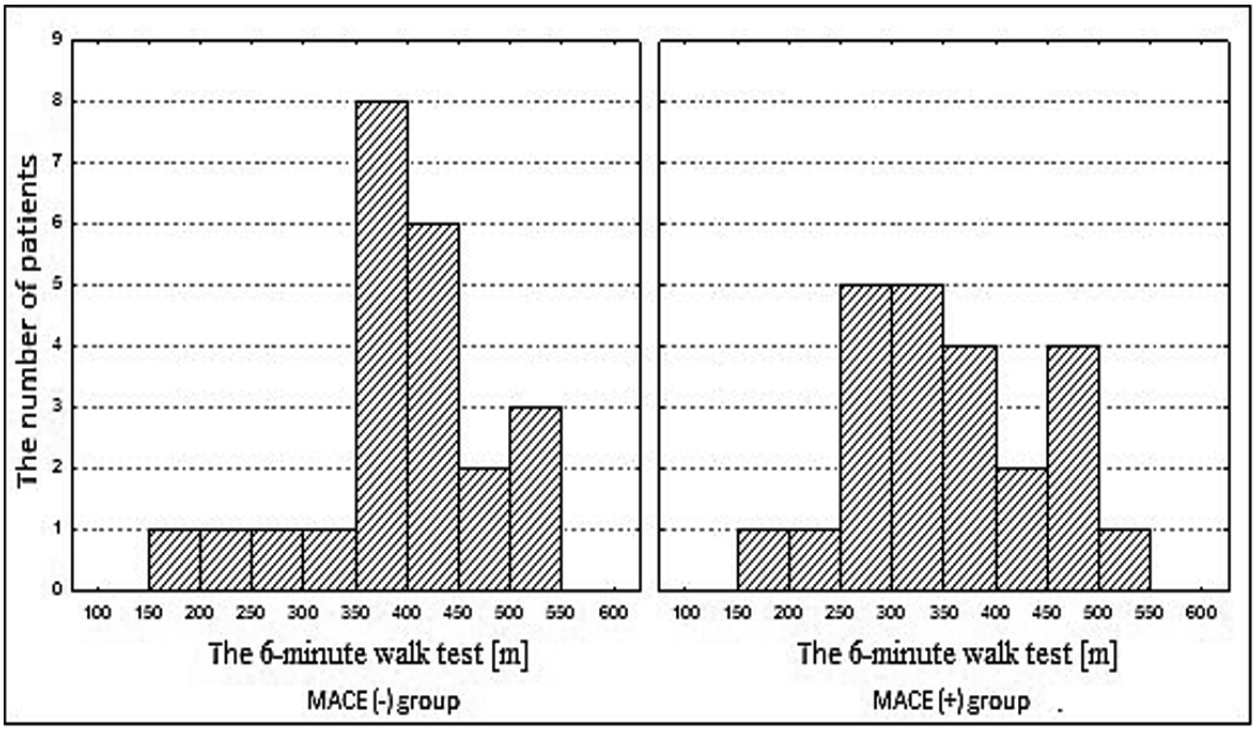

Fig. 2. The walk test results in the MACE (-) and MACE (+) groups of patients at the beginning of the follow-up period.

Table 1. The mean result of the walk test at the beginning of the follow-up period in the MACE (-) and MACE (+) groups of patients.

	MACE(-) N=23	MACE(+) N=23	p
Walk test [m]	398 ± 90	359 ± 88	0.1391

Figure 3 shows the mean value of the walk test results at the beginning of the follow-up period in the group without MACE (-) events, in the MACE (+) group with HF exacerbation and in the group of patients who died during the follow-up period – MACE (+) group (death). Compared to the group without HF exacerbation, patients who died had a statistically significantly lower mean value of the distance covered in the walk test (p = 0.0252) and at the level of a statistical trend they also had a lower mean value of the distance covered than the group with HF exacerbation (p = 0.0729).

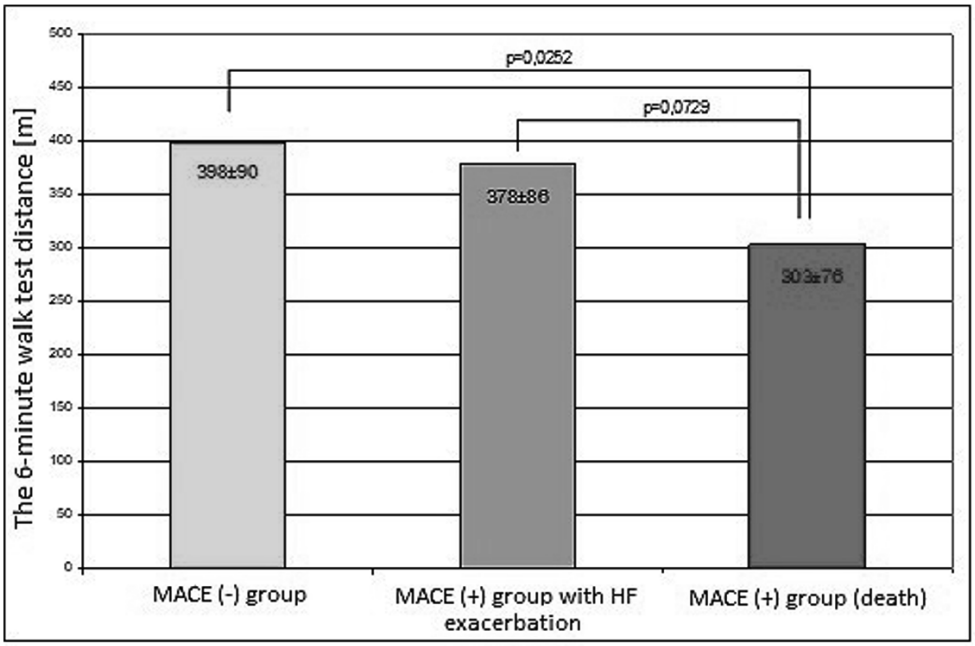

Fig. 3 The mean distance covered by patients in the walk test at the beginning of the follow-up period in MACE (-) group, MACE (+) group with HF exacerbation and MACE (+) group (death).

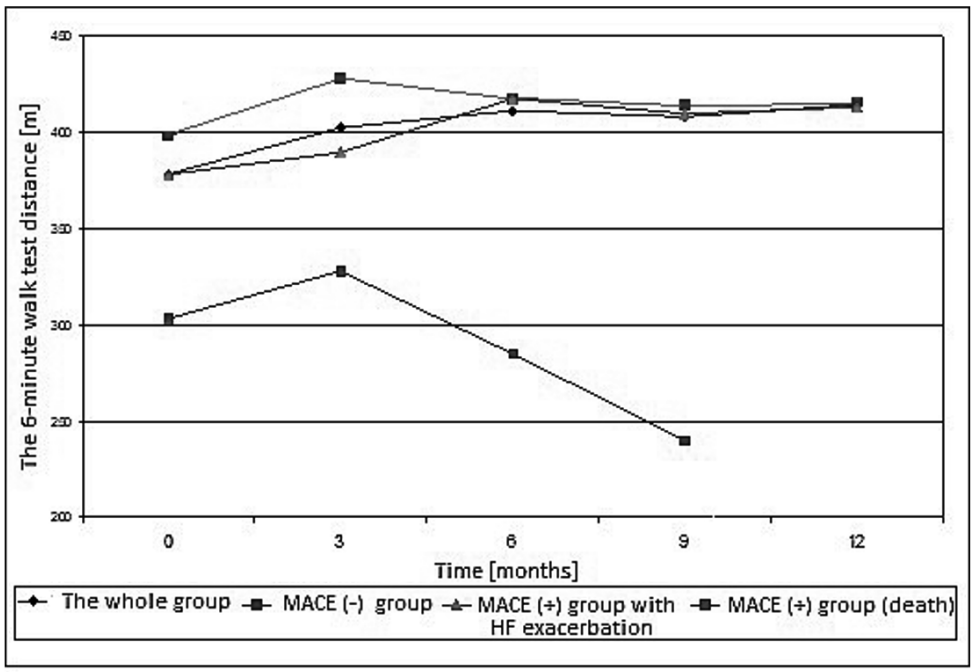

Fig. 4 The distance covered by patients in the walk test during 12 months of follow-up in MACE (-) group, MACE (+) group with HF exacerbation and MACE (+) group (death).

Figure 4 shows the changes in the mean values of the walk test during the 1-year follow up at 3-month intervals. The analysis included 40 patients for whom results were obtained after the 12-month follow-up period. The mean value of the walk test in the MACE (-) group and the MACE (+) group with HF exacerbation did not differ significantly at the beginning ($p = 0.4821$) and after 12 months of follow-up ($p = 0.9392$).

Table 2. The distance covered by patients in the walk test at the beginning and after the 12-month follow-up.

	n	At the beginning of the follow-up	After the 12-month follow-up	p
		Mean ± standard deviation	Mean ± standard deviation	
The whole group	40	390 ± 88	415 ± 97	0.1256
MACE(-)	23	398 ± 90	416 ± 99	0.3727
MACE (+) with HF exacerbation	17	378 ± 86	413 ± 98	0.1761

No statistically significant differences were observed between the mean values of the walk test at the beginning and after 12 months of follow-up both in the whole group and in the group of MACE (-) patients, and MACE (+) patients with HF exacerbation (Table 2).

14 out of 40 patients (35.0%) had worse results in the walk test after the 12-month follow-up period, including 8 patients out of 23 (34.8%) in the MACE (-) group and in 6 out of 17 (35.3 %) in the MACE (+) group with HF exacerbation (p = 0.9733).

ROC curves (Receiver Operating Characteristics Curve) were plotted in order to assess the usefulness of the walk test in determining the probability of MACE. They are based on the determined values of sensitivity and specificity for various cutoff points. The size of the area under the curve above the diagonal illustrates the classification quality of the diagnostic variable. The analysis of ROC curves enables the determination of the optimal values of the analyzed parameters (cutoff points), which best divide the study group into a subgroup at higher risk for MACE and into a subgroup with lower risk of MACE.

Table 3 presents the results of the ROC curve analysis, in which the area under the curve (AUC), sensitivity, specificity, accuracy, positive and negative predictive value as well as likelihood ratio (LR) were calculated for all parameters and their cutoff points.

Table 3. The evaluation of the predictive value of the walk test at the determined cutoff value.

Parameter	Cutoff value	AUC	Sensitivity	Specificity	Accuracy	Positive predictive value	Negative predictive value	LR
The walk test	340	0.648	0.478	0.826	0.652	0.733	0.613	2.8

In the presented study, the AUC value for the walk test indicates the mean value of the decision model based on it. The LR = 2.8 indicates that a walk test result below 340 m is almost 3 times more likely in patients who developed MACE than in those who did not develop it.

Based on the determined cutoff point, the study group was divided and the survival functions were estimated using the Kaplan-Meier method. A difference was observed at the level of a statistical trend between the survival curves for patients in the subgroups of the walk test (p = 0.0862). At the beginning of the follow-up, the course of the survival function was similar. Later, patients, who did not reach 340 m in the walk test, were more likely to develop MACE.

The probability of surviving 365 days without MACE was 0.267 in the group of patients with the baseline walk test result below 340 m and 0.613 in the group of patients with the baseline walk test result above 340 m. The difference between the survival curves for patients in the walk test subgroups reached the level of a statistical trend (p = 0.0862) which is depicted in figure 5.

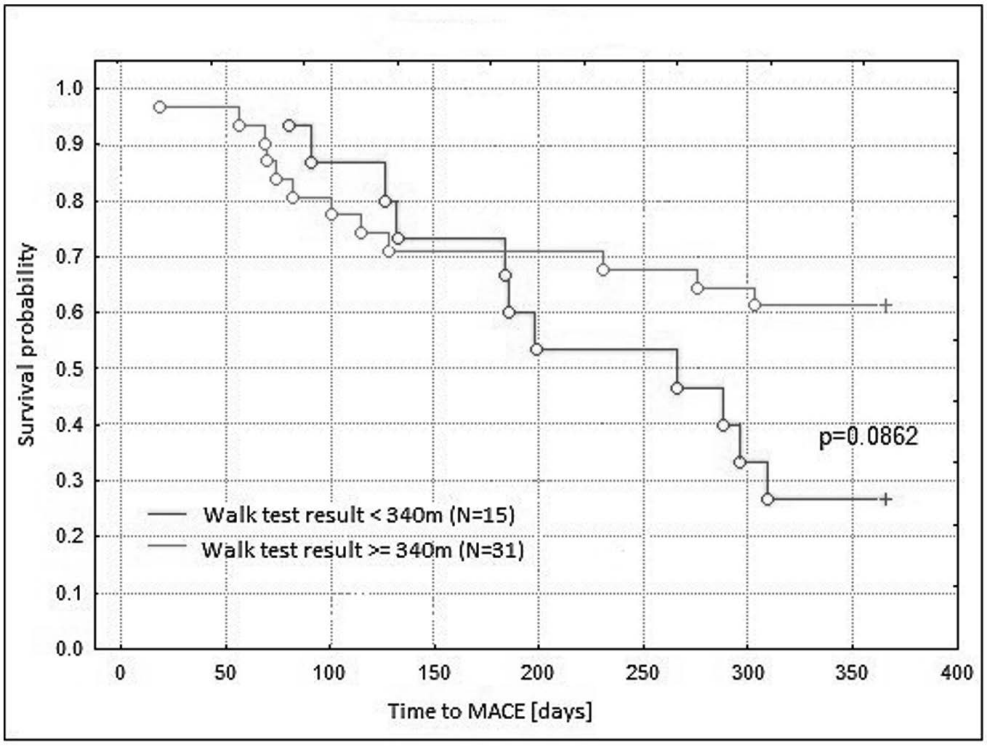

Figure 5. Kaplan-Meier survival functions during the group division based on the designated cutoff point for the walk test

Table 4 shows the numerical distribution of patients who had and did not have MACE, with the walk test results below and above the critical point. MACE (+) was statistically significantly more frequent in the group with the walk test result below 340 m (73.3%) than in patients with the result above 340 m (38.7%) (p = 0.0277).

Table 4. The occurrence of MACE in groups with the walk test results below and above 340 m (p=*0,0277*).

	N	The walk test result	
		< 340 m	≥ 340 m
MACE (-)	23	4 (26.7%)	19 (61.3%)
MACE (+)	23	11 (73.3%)	12 (38.7%)
The whole group	46	15 (100%)	31 (100%)

Discussion

The prognostic value of the walk test among patients with HF in NYHA class II and III has been confirmed in studies dating back to the 1990s [8,9]. In the publication by Ingle et al. regarding the 5-year follow-up in patients with systolic HF, the walk test (similarly to NT-proBNP) turned out to be an independent prognostic factor for all-cause mortality [10].

In our study, a statistically significantly lower mean value of the distance covered in the walk test (303 ± 76 vs 398 ± 90, p = 0.0252) was observed in the MACE (+) group (death) compared to the MACE (-) group. Moreover, at the level of a statistical trend, the MACE (+) group (death) had a lower mean value of the distance covered compared to the group of patients with HF exacerbation (303 ± 76 vs. 378 ± 86 p = 0.0729). The SOLVD study was the first large study in which a relationship between the 6MWT result and the incidence of death / hospitalization due to HF exacerbation in

patients with HF in NYHA class II and III was found [6]. The Polish study by Kidawa et al. assessed the value of various prognostic factors in 56 patients in NYHA class III / IV with systolic (EF <30%) ischemic HF. During the 12-month follow-up, a multivariate analysis showed that the 6MWT was the only significant predictor of the composite endpoint and there was no significant correlation between the occurrence of MACE and, inter alia, systolic blood pressure, CKMB or BNP values. Based on the ROC curves, a threshold value of 380 m was determined, allowing for the differentiation of the MACE (+) and MACE (-) groups with 79% sensitivity and a specificity of 80% [11]. Perhaps the high predictive value of the walk test was caused by the selection of patients – in the study by Kidawa et al., all patients had HF of ischemic origin, so the incidence of different stages of lower limb atherosclerosis was probably higher, which translated into the distance covered in the walk test. The results obtained by Roul [7] in the study, where in a group of 121 patients with systolic HF in NYHA class II / III (mean EF 30%, mean follow-up 1.5 years) the 6MWT distance < or = 300 m predicted the endpoint (death, hospitalization for HF), were similar to the results of our study (mean 6MWT distance in the MACE (+) subgroup (death) was 303 m, where a cutoff point differentiating the MACE groups amounted to 340 m). In addition, the difference in the distance covered in the MACE (+) and (-) groups in the study by Roul and in the presented study was almost identical and amounted to approximately 40 m [9]. Also, in the study by Cahalin et al. the authors noted that the distance of < 300 m was associated with an increased risk of death and hospitalization due to HF exacerbation requiring the administration of positive inotropic drugs [12]. Lower mean values of the 6MWT (310 m) and VO2 peak (12.2 mL / kg / min), compared with our study, may result from a higher NYHA class (3.3 ± 0.6) and a lower LVEF (20 +/- 6%) of patients included in the study. Nevertheless, in the presented paper, similarly as in the observations by Lucas and Pulz, the 6MWT was characterized by worse prognostic power for predicting MACE than VO2 [13,14]. We found that among all assessed prognostic factors, the 6MWT was characterized by the lowest ability to predict the occurrence of MACE. What is worth emphasizing is the high specificity of the walk test, which amounted to 0.826% based on the analysis of ROC curves. In the case of severe chronic diseases, this feature is more important than the sensitivity and therefore the 6-minute walk test is a valuable supplement to other diagnostic methods of HF.

Searching for new prognostic factors, which could be used in diagnostic and therapeutic process in HF is extremely important. In addition to NT-proBNP, the concentration of other markers such as catestatin has also been assessed as a prognostic marker in HF in recent years [15]. The Wołowiec et alia study showed that catestatin concentration is a valuable prognostic parameter in predicting death from any cause and unplanned hospitalization in a group of patients with HF with reduced ejection fraction in a 2-year follow-up [16]. Also, an elevated procalcitonin level may be a predictor of worse prognosis in patients hospitalized with HF with reduced ejection fraction [17]. Other parameters such as red cell distribution width (RDW) or tumor markers such as CA125 as well as the melanoma cell adhesion molecule (MCAM) were also tested [18,19]. For the time being, BNP and NT-proBNP are the most reliable markers for the diagnosis, prognosis and monitoring of HF. However, it is noteworthy that epigenetic tests may be used extensively in the future – different combinations of miRNAs were investigated in the study by Watson et al. – it was noticed that miRNAs may be useful also in the differentiation HF with reduced ejection franction and HF with preserved ejection fraction [20–22]. Abovementioned researches are proof of the great interest of HF among researchers - its diagnosis, monitoring and treatment. So far, the use of tests such as the 6-minute walk test is a simple and cheap method of prognosis in patients with HF.

Conclusion

HF remains a highly prevalent disorder worldwide and it is associated with increase mortality and significantly worsens the quality of life. Despite recent advances in diagnosis and treatment of cardiovascular diseases, the prognosis for HF remains unsatisfactory, therefore, identifying patients with the highest risk of early death is of particular importance. A 6-minute walk test, also known as a corridor test, is a recognized and simple prognostic test for patients with HF. Due to its simplicity, the walk test is a good tool that allows to evaluate the prognosis in patients with chronic HF with reduced left ventricular ejection fraction. The high specificity of the test is an additional advantage confirming its diagnostic value.

Conflicts of Interest

Authors declare no conflict of interest.

References

1. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J 2021;42:3599–726. https://doi.org/10.1093/eurheartj/ehab368.
2. Gilewski W, Pietrzak J, Banach J, Bujak R, Błażejewski J, Karasek D, et al. Prognostic value of selected echocardiographic, impedance cardiographic, and hemodynamic parameters determined during right heart catheterization in patients qualified for heart transplantation. Heart Vessels 2018;33:180–90. https://doi.org/10.1007/s00380-017-1044-x.
3. Rogowicz, D., Wołowiec, Ł., Banach, J., Buszko, K., Mosiądz, P., Gilewski, W., Zukow, W., & Sinkiewicz, W. (2016). Ocena wartości rokowniczej osoczowego stężenia białka C-reaktywnego oznaczonego metodą o wysokiej czułości (hs-CRP) u chorych z przewlekłą niewydolnością serca = Usefulness of serum high-sensitivity C-reactive protein (hs-CRP) level as prognostic factor in patients with chronic heart failure. https://doi.org/10.5281/zenodo.58867
4. Banach J, Grochowska M, Gackowska L, Buszko K, Bujak R, Gilewski W, et al. Melanoma cell adhesion molecule as an emerging biomarker with prognostic significance in systolic heart failure. Biomark Med 2016;10:733–42. https://doi.org/10.2217/bmm-2016-0053.
5. Banach J, Wołowiec Ł, Rogowicz D, Gackowska L, Kubiszewska I, Gilewski W, et al. Procalcitonin (PCT) Predicts Worse Outcome in Patients with Chronic Heart Failure with Reduced Ejection Fraction (HFrEF). Dis Markers 2018;2018:9542784. https://doi.org/10.1155/2018/9542784.
6. Giannitsi S, Bougiakli M, Bechlioulis A, Kotsia A, Michalis LK, Naka KK. 6-minute walking test: a useful tool in the management of heart failure patients. Ther Adv Cardiovasc Dis 2019;13:175394471987008. https://doi.org/10.1177/1753944719870084.
7. Casanova C, Celli BR, Barria P, Casas A, Cote C, de Torres JP, et al. The 6-min walk distance in healthy subjects: reference standards from seven countries. European Respiratory Journal 2011;37:150–6. https://doi.org/10.1183/09031936.00194909.
8. Bittner V, Weiner DH, Yusuf S, Rogers WJ, McIntyre KM, Bangdiwala SI, et al. Prediction of mortality and morbidity with a 6-minute walk test in patients with left ventricular dysfunction. SOLVD Investigators. JAMA 1993;270:1702–7.

9. Roul G, Germain P, Bareiss P. Does the 6-minute walk test predict the prognosis in patients with NYHA class II or III chronic heart failure? Am Heart J 1998;136:449–57. https://doi.org/10.1016/s0002-8703(98)70219-4.
10. Ingle L, Cleland JG, Clark AL. The long-term prognostic significance of 6-minute walk test distance in patients with chronic heart failure. Biomed Res Int 2014;2014:505969. https://doi.org/10.1155/2014/505969.
11. Kidawa M, Wierzchowski T, Rusiecka E, Kłosińska M, Krzemińska-Pakuła M, Drożdż J. Test marszu 6-minutowego - silny niezależny czynnik predykcyjny wystąpienia złożonego punktu końcowego u pacjentów z niewydolnością serca na podłożu choroby niedokrwiennej serca. Polski Przegląd Kardiologiczny. 2008;10:43–47.
12. Cahalin LP, Mathier MA, Semigran MJ, Dec GW, DiSalvo TG. The six-minute walk test predicts peak oxygen uptake and survival in patients with advanced heart failure. Chest 1996;110:325–32. https://doi.org/10.1378/chest.110.2.325.
13. Lucas C, Stevenson LW, Johnson W, Hartley H, Hamilton MA, Walden J, et al. The 6-min walk and peak oxygen consumption in advanced heart failure: aerobic capacity and survival. Am Heart J 1999;138:618–24. https://doi.org/10.1016/s0002-8703(99)70174-2.
14. Pulz C, Diniz R V, Alves ANF, Tebexreni AS, Carvalho AC, de Paola AA V, et al. Incremental shuttle and six-minute walking tests in the assessment of functional capacity in chronic heart failure. Can J Cardiol 2008;24:131–5. https://doi.org/10.1016/s0828-282x(08)70569-5.
15. Weber M, Hamm C. Role of B-type natriuretic peptide (BNP) and NT-proBNP in clinical routine. Heart 2006;92:843–9. https://doi.org/10.1136/hrt.2005.071233.
16. Wołowiec Ł, Rogowicz D, Banach J, Gilewski W, Sinkiewicz W, Grześk G. Catestatin as a New Prognostic Marker in Stable Patients with Heart Failure with Reduced Ejection Fraction in Two-Year Follow-Up. Dis Markers 2020;2020:8847211. https://doi.org/10.1155/2020/8847211.
17. Banach J, Wołowiec, Rogowicz D, Gackowska L, Kubiszewska I, Gilewski W, et al. Procalcitonin (PCT) Predicts Worse Outcome in Patients with Chronic Heart Failure with Reduced Ejection Fraction (HFrEF). Dis Markers 2018;2018. https://doi.org/10.1155/2018/9542784.
18. Woźniak-Wiśniewska A, Błażejewski J, Bujak R, Wołowiec Ł, Rogowicz D, Sinkiewicz W. Wartość oznaczania stężeń antygenu nowotworowego Ca 125 i kopeptyny w monitorowaniu terapii chorych z zaawansowaną niewydolnością serca. Folia Cardiol 2017;12:537–42. https://doi.org/10.5603/FC.2017.0103.
19. Banach J, Grochowska M, Gackowska L, Buszko K, Bujak R, Gilewski W, et al. Melanoma cell adhesion molecule as an emerging biomarker with prognostic significance in systolic heart failure. Biomark Med 2016;10:733–42. https://doi.org/10.2217/bmm-2016-0053.
20. Oeing CU, Pepin ME, Saul KB, Agircan AS, Assenov Y, Merkel TS, et al. Indirect epigenetic testing identifies a diagnostic signature of cardiomyocyte DNA methylation in heart failure. Basic Res Cardiol 2023;118:9. https://doi.org/10.1007/s00395-022-00954-3.
21. Chen Y-T, Wong LL, Liew OW, Richards AM. Heart Failure with Reduced Ejection Fraction (HFrEF) and Preserved Ejection Fraction (HFpEF): The Diagnostic Value of Circulating MicroRNAs. Cells 2019;8. https://doi.org/10.3390/cells8121651.
22. Watson CJ, Gupta SK, O'Connell E, Thum S, Glezeva N, Fendrich J, et al. MicroRNA signatures differentiate preserved from reduced ejection fraction heart failure. Eur J Heart Fail 2015;17:405–15. https://doi.org/10.1002/ejhf.244.