

Interventions for increasing medication adherence in heart failure patients: A narrative review

Libor Jelinek¹, Jan Vaclavik², Marie Lazarova²

Heart failure is one of the critical and most costly medical challenges of the 21st century. It is a chronic debilitating condition and adherence to medication, a precondition for successful treatment is often poor. There are various interventions for improving the adherence. Depending on the goal of the intervention, these are roughly patient centric, healthcare provider centric and system centric. We provide an overview of these interventions with a focus on effectiveness and appropriateness in different clinical situations. Their use can lead to improved patient outcomes and reduced economic burden of the disease.

Key words: pharmacotherapy, heart failure, barriers to adherence, interventions to improve adherence

Received: April 28, 2024; Revised: June 7, 2024; Accepted: June 17, 2024; Available online: July 16, 2024

<https://doi.org/10.5507/bp.2024.022>

© 2024 The Authors; <https://creativecommons.org/licenses/by/4.0/>

¹Department of Exercise Medicine and Cardiovascular Rehabilitation, University Hospital Olomouc and Faculty of Medicine, Palacky University Olomouc, Olomouc, Czech Republic

²Department of Internal Medicine and Cardiology, University Hospital Ostrava and Faculty of Medicine, University of Ostrava, Ostrava, Czech Republic

Corresponding author: Libor Jelinek, e-mail: libor.jelinek@fnol.cz

INTRODUCTION

Purpose and need of this paper

Our aim was to provide a narrative overview of practices and interventions that have been generally shown to improve medication adherence in patients with chronic heart failure. We focused on methods that have been studied for their impact on patient outcomes based on clinical trials.

Background

Heart failure is one of the most prevalent chronic diseases worldwide¹. Although the incidence has been declining in recent years due to advances in the treatment of acute cardiovascular disease, the overall prevalence is increasing with an ageing population and an increased prevalence of risk factors of heart failure^{2,3}. Khera et al. describe a reduction in the incidence of heart failure in the population of Medicare beneficiaries in the US from 35.7 cases per 1000 population to 26.5 in 2016, independent of race and gender⁴.

Epidemiology and impact of non-adherence in heart failure

The chronic nature of heart disease implies the long-term use of medications. Despite the efficacy of these drugs, the patient does not always adhere to the treatment regimen. Another factor is adherence to lifestyle measures, especially salt and fluid restriction⁵. Medication adherence rates in patients with heart failure are highly variable depending on the population and methods used to assess them. The reported variance can be as high as

10–98% (ref.⁶). Low adherence increases the risk of hospitalisation and death⁷. In addition to the negative effect on patients, non-adherence also has a negative effect on healthcare systems. In a study of Medicare beneficiaries in 4 US states, Esposito et al. found that adherent patients cost the health system 23% less (by \$5,910) (ref.⁸).

Interventions to improve medication adherence in heart failure patients reduce very costly hospital admissions and mortality⁹.

Barriers to medication adherence

Improving adherence to medication is a complex, multi-step process. The adherence level for a particular patient can be thought of as the sum of the individual barriers to adherence and interventions can be interpreted as addressing these individually. The WHO divides them into five groups as socioeconomic, system-related, condition-related, therapy-related and patient-related factors¹⁰.

Different barriers can be addressed in various ways. For example, if the main reason for non-adherence is the financial cost of the treatment, then one can try to replace the medication with cheaper options, or educate the patient about the importance of the treatment and its effect on their health, thereby increasing their willingness to pay for the drugs.

Just as one barrier can be overcome using different methods, one intervention can address multiple barriers. For example, simplifying the medication regimen can reduce the cost, make it easier for the patient to take the therapy, and also minimize the risk of mistaking or omitting prescribed drugs.

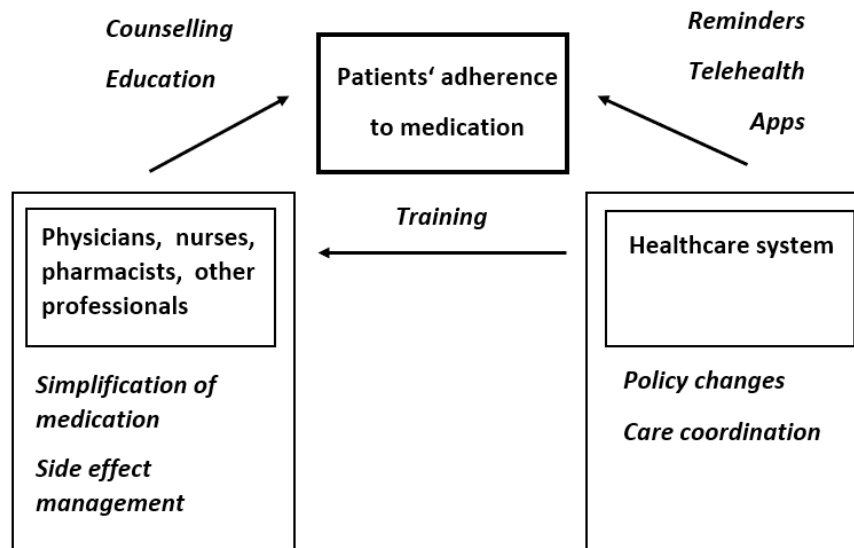


Fig. 1. The complex structure of interventions to improve adherence to medication in heart failure patients.

Table 1. Division of interventions to improve medication adherence.

Patient-Centric Interventions	Healthcare Provider Interventions	System-Level Interventions
Education	Training	Policy changes
Counselling	Simplification of medication	Care coordination
Reminders	Side-Effect Management	
Apps & Telehealth		

INTERVENTIONS TO IMPROVE MEDICATION ADHERENCE

There is an ongoing debate regarding the exact place of interventions to improve medication adherence in the care of patients with heart failure. There is a range of evidence regarding the effectiveness of such methods. These mostly involve working on the soft-skills (like communication counselling) of healthcare providers, or patient education. Both are extensive topics that are difficult to implement outside of clinical trials, heart failure care centres, and above all, are highly dependent on the national system of care (and the system of payment for care).

For the orientation and purposes of this paper, we have simplified a list of WHO defined barriers, and divided the interventions broadly into patient-oriented, health care provider-oriented and health system-oriented, see Table 1. These are interlinked. Interventions targeting the system and healthcare providers lead to increased patient adherence to medication indirectly, see Fig. 1.

Patient-centric interventions

Education

Much of the management of heart failure can and is carried out by patients themselves⁵. Understanding the treatment is a prerequisite for success and this can be achieved through good patient education empowering informed decisions to be made about their own health. This also leads to greater equity and improved clinical outcomes¹¹.

In general, the more time spent with the patient and ideally the involvement of a multidisciplinary team (doctor, nurse, pharmacist), the better the outcome. A meta-analysis by Jonkman et al. involving studies of self-management interventions and education on 5624 heart failure patients showed that the longer the contact of health professionals with the patient, the better the effect on mortality and risk of hospitalization for heart failure, although the cumulative effect was miniscule (roughly 1% decrease per month of intervention) with considerable heterogeneity between studies¹².

Educational interventions may be stepwise. Yu et al. investigated the effect of a multi-step educational strategy on 160 hospitalized heart failure patients. At the beginning, patients were given an educational booklet regarding their disease, created in collaboration with nurses and other patients, so that barriers regarding health literacy were removed. Prior to discharge from hospital, their questions were answered by the investigator and patients were then contacted weekly for one month by telephone. In the event of deterioration, no telephone call was made but a doctor's visit was recommended. The intervention group had significantly better adherence to medication measured by a validated questionnaire at 3-month follow-up¹³.

Counselling

Apart from education about various disease aspects, patient-centred interventions should include further counselling with a focus on a patients' cognitive and psycholog-

ical barriers. This may include the principles of cognitive behavioural therapy (CBT).

Cognitive function is a predictor of outcome in various chronic diseases including heart failure¹⁴. Using 149 patients, Alosco et al. found that cognitive function, as attention, executive, and language functions, was an independent predictor of medication adherence in patients with heart failure¹⁵. Similarly, in a study of 87 left ventricle assist device (LVAD) patients, Casida et al. used questionnaires to show that higher levels of cognitive function were positively correlated with adherence to LVAD measures. This led to better quality of life indicators¹⁶.

Depression and other negative psychosocial factors impair medication adherence in heart failure¹⁷. One effective intervention to reduce these barriers is CBT. In a meta-analysis of studies of the effect of CBT on heart failure patients, Jeyanatham et al. showed that it is an effective intervention for improving a patients' quality of life. The effect lasts mainly during counselling and 3 months thereafter, the strength of the intervention then fades. However, the effect on hard data, mortality and hospital admissions was not statistically significant in the reviewed studies¹⁸.

In another study, Wu et al. counselled heart failure patients using the theory of planned behaviour (TPB). This is a theoretical model that allows prediction of how individuals will behave and then intervening in barriers to desirable behaviour¹⁹. The 82 patients in the study were divided into control and 2 intervention groups that were either only education about the disease and, lifestyle and treatment measures or TPB and adherence feedback measured. Adherence was measured using MEMS. Both intervention groups improved in terms of medication adherence and quality of life. The result also translated into longer event-free survival analysed using cox regression. The intervention was carried out by trained nurses and not doctors²⁰.

Reminders

A major barrier to adherence is the need to remember every day to take the medication. Among ways of facilitating adherence are various pillboxes, alarms or automated messaging systems. In chronic disease in general these measures appear to improve medication adherence²¹.

A study on 61 patients by Travis et al. used an electronic pill box with a notification system to alert patients to take their medication. After a month of use, the authors report high adherence rate and patient satisfaction with the device²².

Apps and telehealth

As part of telemedicine, m-health, defined by the WHO as medical practice supported by mobile devices, is currently developing rapidly²³. A small study by Goldstein et. al compared an mhealth app serving as either a passive recorder or an active reminder with an electronic pillbox again either with an active alarm or in silent mode. Adherence was measured either by opening the pillbox or by electronic self-report by the patient. After 1 month of follow-up, there were no differences in adherence, which

was high, around 80%. Patients themselves preferred the m-health approach²⁴.

Healthcare provider interventions

Interventions targeting healthcare providers also lead to better patient outcomes. To achieve clinical outcomes it is suggested that several such approaches should be combined²⁵.

Training

Training on how to better educate and motivate patients to adhere to their medication regimen ultimately leads to improved adherence. Although this approach is also effective, the main focus should still be on patient education. In general, patient-centred educational interventions are more effective²⁵. In the context of heart failure, Ruppar et al. concluded in a large meta-analysis of interventions to improve heart failure management that healthcare provider training generally has less impact on patient mortality than other interventions studied⁹.

One way is to gradually change the approach of healthcare providers from solely disease education to a motivational approach²⁶. It is advisable to invest enough time to explore the motional, psychological, and socioeconomic barriers of a particular patient and find solutions to them²⁷. A study by Sana et al. on 240 hypertensive patients suggests that programs to improve health care professionals' communication skills improve patients' self-reported adherence to medication. Heart failure-specific randomized controlled trials have not yet been conducted to the best of our knowledge²⁸.

Simplification of medication

As the number of treatment options for chronic diseases increases, so does the number of drugs that patients have to take. This increases the complexity of medication regimens. As the complexity of medication increases, the risk of medical error increases and the risk of hospitalisation increases²⁹. Medication adherence also decreases with increasing complexity of the drug regimen³⁰. The solution is to simplify medication. This can be achieved either by reducing the number of individual tablets using single-pill combination therapy, by reducing the number of daily doses, or by a combination of these two measures. A meta-analysis of 17 studies examining the above measures in patients with chronic diseases demonstrated their effectiveness in increasing adherence. However, increased adherence did not translate into improved clinical outcomes in these studies³¹.

Side-effect management

A larger number of drugs also leads to a higher potential for drug interactions and associated higher number of side effects. Their impact can be reduced by patient education; patients who expect side effects may be better prepared for them and better adhere to the medication³². In a study by Jarab et al. of 427 heart failure patients, it was found that patients who did not suffer from medication side effects had significantly higher odds of having superior levels of adherence, as measured by questionnaires³³.

One possible intervention for the management of typical side effects in heart failure is the use of more modern agents, e.g. replacing spironolactone with eplerenone³⁴.

System-level interventions

Policy changes

The third type of intervention targets the health system as a whole. A major barrier to improving cardiovascular medication adherence in the vast majority of systems is the cost of medicines (and healthcare in general) for individual patients³⁵. Although there is a consensus on the inverse relationship between medication cost and adherence, there are limited data on how strong this relationship is. The heterogeneity of health systems and variability in prices and funding sources makes it difficult to compare studies between systems. The ethics of deciding for whom to reduce the cost if randomisation is used and how to blind such a design is also a significant barrier to study design. In 2010, Maciejewsky et al. published a large retrospective study looking at value-based insurance program design for patients with chronic diseases, including congestive heart failure. Over 1,200,000 patients in two arms, followed for 2 years, were included. Adherence was measured by medication possession ratio. The intervention consisted of reducing patient co-payments for medication. In the control group, adherence decreased significantly more at the end of the follow-up period, by 1.5–3.8%, depending on the disease and drug³⁶.

Care coordination

One of the most important prerequisites for good patient care and a method for improving adherence to medication is coordination of care within a team of health professionals³⁷. Care and treatment are now increasingly the domain not only of the physician, but also of nurses, pharmacists and other supporting professions. This is reflected in various studies and emphasized in one meta-analysis of interventions by Unverzagt et al.³⁷

Challenges and limitations in existing research

A major challenge in the implementation of adherence improvement interventions (especially patient-centric) is the need for long-term action and an individualized approach to the patient in order to achieve a clinical effect³⁷.

A common problem of research interpretation is the heterogeneity of existing studies. Intervention populations differ in baseline clinical characteristics, length of follow-up and, most importantly, in adherence monitoring methods.

There is currently no gold standard of measurement. Although there is considerable popularity of the MEMS method and it is considered a standard by some authors.⁷ However, other authors refer to testing serum drug levels in the same way, but mainly in the context of hypertension. Even so, it is the detection of adherence to the same drugs as in heart failure^{38,39}.

CONCLUSION

With the increasing importance of heart failure within health systems, it is paramount to look for ways to make care more effective. One potentially promising option is to increase patient adherence to medication. Interventions to improve this factor vary according to the target of the intervention, whether it is aimed at the patient, the health-care provider, or the whole system, and the barriers to adherence it seeks to overcome. The complexity of heart failure and its treatment necessitates a multifaceted approach that addresses various barriers to adherence simultaneously.

Although the range of possible interventions is wide and variable, a few key points can be summarised. Studies show that longer engagement with healthcare professionals correlates with improved outcomes. In general, strategies that focus on patient education are more effective than those that focus on health professionals. Further, the use of a team consisting of not only physicians but also other specialties such as pharmacists or nurses is particularly beneficial.

Future research should focus on long-term outcomes of these interventions, addressing the heterogeneity in study designs and adherence measurement methods.

Search Strategy and Selection Criteria

Our research strategy was aimed at evaluating studies on interventions to improve adherence and barriers to adherence in chronic heart failure. Data for this article were identified by search of PubMed database and references from relevant articles using the terms “adherence”, “compliance” “interventions” and “chronic heart failure”. All searches were up to date as of 1. 2. 2024. Only articles published in English were included, abstracts and reports from meetings were not included. We searched for publications in the last 15 years and gave preference to publications from the past 10 years.

Acknowledgement: We would like to thank Alexander Oulton Ph.D. (neurosciences) for professional English language revision and proof-reading.

Author contributions: LJ: manuscript writing; JV, ML: supervision.

Conflict of interest declaration: The authors declare that they have no affiliations with or involvement in any organization or entity with any financial interest in the subject matter or materials discussed in this manuscript

REFERENCES

- Jacob L, Breuer J, Kostev K. Prevalence of chronic diseases among older patients in German general practices. *Ger Med Sci* 2016;14:Doc03. doi: 10.3205/000230
- Ruiz-García A, Serrano-Cumplido A, Escobar-Cervantes C, Arranz-Martínez E, Turégano-Yedro M, Pallarés-Carratalá V. Heart Failure Prevalence Rates and Its Association with Other Cardiovascular Diseases and Chronic Kidney Disease: SIMETAP-HF Study. *J Clin Med* 2023;12(15):4924. doi: 10.3390/jcm12154924
- Virani SS, Alonso A, Aparicio HJ, Benjamin EJ, Bittencourt MS, Callaway CW, Carson AP, Chamberlain AM, Cheng S, Delling FN,

- Elkind MSV, Evenson KR, Ferguson JF, Gupta DK, Khan SS, Kissela BM, Knutson KL, Lee CD, Lewis TT, Liu J, Loop MS, Lutsey PL, Ma J, Mackey J, Martin SS, Matchar DB, Mussolino ME, Navaneethan SD, Perak AM, Roth GA, Samad Z, Satou GM, Schroeder EB, Shah SH, Shay CM, Stokes A, VanWagner LB, Wang NY, Tsao CW; American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart Disease and Stroke Statistics-2021 Update: A Report From the American Heart Association. *Circulation* 2021;143(8):e254-e743. doi: 10.1161/CIR.0000000000000950
4. Khara R, Kondamudi N, Zhong L, Vaduganathan M, Parker J, Das SR, Grodin JL, Halm EA, Berry JD, Pandey A. Temporal Trends in Heart Failure Incidence Among Medicare Beneficiaries Across Risk Factor Strata, 2011 to 2016. *JAMA Netw Open* 2020;3(10):e2022190. doi: 10.1001/jamanetworkopen.2020.22190
5. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumach A, Böhm M, Burri H, Butler J, Čelutkienė J, Chioncel O, Cleland JGF, Coats AJS, Crespo-Leiro MG, Farmakis D, Gilard M, Heymans S, Hoes AW, Jaarsma T, Jankowska EA, Lainscak M, Lam CSP, Lyon AR, McMurray JJV, Mebazaa A, Mindham R, Muneretto C, Francesco Piepoli M, Price S, Rosano GMC, Ruschitzka F, Kathrine Skibellund A; ESC Scientific Document Group. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 2021;42(36):3599-726. doi: 10.1093/eurheartj/ehab368 Erratum in: *Eur Heart J* 2021;42(48):4901. doi: 10.1093/eurheartj/ehab670
6. Cheng C, Donovan G, Al-Jawad N, Jalal Z. The use of technology to improve medication adherence in heart failure patients: a systematic review of randomised controlled trials. *J Pharm Policy Pract* 2023;16(1):81. doi: 10.1186/s40545-023-00582-9
7. Wu JR, Moser DK. Medication Adherence Mediates the Relationship Between Heart Failure Symptoms and Cardiac Event-Free Survival in Patients with Heart Failure. *J Cardiovasc Nurs* 2018;33(1):40-6. doi: 10.1097/JCN.0000000000000427
8. Esposito D, Bagchi AD, Verdier JM, Bencio DS, Kim MS. Medicaid beneficiaries with congestive heart failure: association of medication adherence with healthcare use and costs. *Am J Manag Care* 2009;15(7):437-45.
9. Ruppert TM, Cooper PS, Mehr DR, Delgado JM, Dunbar-Jacob JM. Medication Adherence Interventions Improve Heart Failure Mortality and Readmission Rates: Systematic Review and Meta-Analysis of Controlled Trials. *J Am Heart Assoc* 2016;5(6):e002606. doi: 10.1161/JAHA.115.002606
10. Adherence to long-term therapies: evidence for action. Accessed September 8, 2023. available from: <https://apps.who.int/iris/handle/10665/42682>
11. Dennison Himmelfarb CR, Beckie TM, Allen LA, Commodore-Mensah Y, Davidson PM, Lin G, Lutz B, Spatz ES; American Heart Association Council on Cardiovascular and Stroke Nursing; American Heart Association Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology; Council on Quality of Care and Outcomes Research; Council on Hypertension; Council on the Kidney in Cardiovascular Disease; Council on Lifelong Congenital Heart Disease and Heart Health in the Young; Council on Lifestyle and Cardiometabolic Health; Council on Peripheral Vascular Disease; Council on Epidemiology and Prevention; and Stroke Council. Shared Decision-Making and Cardiovascular Health: A Scientific Statement From the American Heart Association. *Circulation* 2023;148(11):912-31. doi: 10.1161/CIR.0000000000001162
12. Jonkman NH, Westland H, Groenwold RH, Ågren S, Anguita M, Blue L, Bruggink-André de la Porte PW, DeWalt DA, Hebert PL, Heisler M, Jaarsma T, Kempen GL, Leventhal ME, Lok DJ, Mårtensson J, Muñoz J, Otsu H, Peters-Klimm F, Rich MW, Riegel B, Strömberg A, Tsuyuki RT, Trappenburg JC, Schuurmans MJ, Hoes AW. What Are Effective Program Characteristics of Self-Management Interventions in Patients With Heart Failure? An Individual Patient Data Meta-analysis. *J Card Fail* 2016;22(11):861-71. doi: 10.1016/j.cardfail.2016.06.422
13. Yu M, Chair SY, Chan CWH, Choi KC. A health education booklet and telephone follow-ups can improve medication adherence, health-related quality of life, and psychological status of patients with heart failure. *Heart Lung* 2015;44(5):400-7. doi:10.1016/j.hrtlng.2015.05.004
14. Goh FQ, Kong WKF, Wong RCC, Chong YF, Chew NWS, Yeo TC, Sharma VK, Poh KK, Sia CH. Cognitive Impairment in Heart Failure-A Review. *Biology (Basel)* 2022;11(2):179. doi: 10.3390/biology1102017
15. Alosco ML, Spitznagel MB, van Dulmen M, Raz N, Cohen R, Sweet LH, Colbert LH, Josephson R, Hughes J, Rosneck J, Gunstad J. Cognitive function and treatment adherence in older adults with heart failure. *Psychosom Med* 2012;74(9):965-73. doi: 10.1097/PSY.0b013e318272ef2a
16. Casida JM, Wu HS, Abshire M, Ghosh B, Yang JJ. Cognition and adherence are self-management factors predicting the quality of life of adults living with a left ventricular assist device. *J Heart Lung Transplant* 2017;36(3):325-30. doi: 10.1016/j.healun.2016.08.023
17. Poletti V, Pagnini F, Banfi P, Volpato E. The Role of Depression on Treatment Adherence in Patients with Heart Failure—a Systematic Review of the Literature. *Curr Cardiol Rep* 2022;24(12):1995-2008. doi: 10.1007/s11886-022-01815-0
18. Jeyanantham K, Kotecha D, Thanki D, Dekker R, Lane DA. Effects of cognitive behavioural therapy for depression in heart failure patients: a systematic review and meta-analysis. *Heart Fail Rev* 2017;22(6):731-41. doi: 10.1007/s10741-017-9640-5
19. Ajzen I. The theory of planned behavior. *Organ Behav Hum Decis Process* 1991;50(2):179-211. doi: 10.1016/0749-5978(91)90020-T
20. Wu JR, Corley DJ, Lennie TA, Moser DK. Effect of a medication-taking behavior feedback theory-based intervention on outcomes in patients with heart failure. *J Card Fail* 2012;18(1):1-9. doi: 10.1016/j.cardfail.2011.09.006
21. Fenerty SD, West C, Davis SA, Kaplan SG, Feldman SR. The effect of reminder systems on patients' adherence to treatment. *Patient Prefer Adherence* 2012;6:127-35. doi: 10.2147/PPA.S26314
22. Travis L, Hardin S, Champion K, Sananikone V, Clements F, Barker S, Ferguson R, Stamps T, Costa-Stephenson G. A pilot study: Medication reminder technology for those living independently with heart failure. *Geriatr Med Care* 2017;1. doi:10.15761/GMC.1000101
23. Gandapur Y, Kianoush S, Kelli HM, Misra S, Urrea B, Blaha MJ, Graham G, Marvel FA, Martin SS. The role of mHealth for improving medication adherence in patients with cardiovascular disease: a systematic review. *Eur Heart J Qual Care Clin Outcomes* 2016;2(4):237-44. doi: 10.1093/ehjqcco/qcw018
24. Goldstein CM, Gathright EC, Dolansky MA, Gunstad J, Sterns A, Redle JD, Josephson R, Hughes JW. Randomized controlled feasibility trial of two telemedicine medication reminder systems for older adults with heart failure. *J Telemed Telecare* 2014;20(6):293-9. doi: 10.1177/1357633X14541039
25. Conn VS, Ruppert TM, Enriquez M, Cooper PS, Chan KC. Healthcare provider targeted interventions to improve medication adherence: systematic review and meta-analysis. *Int J Clin Pract* 2015;69(8):889-99. doi: 10.1111/ijcp.12632
26. Xu L, Pinxten W, Vandereyck F, Falter M, Scherrenberg M, Kizilkilic SE, Van Erum H, Dendele P, Kindermans H. Motivational communication skills to improve motivation and adherence in cardiovascular disease prevention: A narrative review. *Clin Cardiol* 2023;46(12):1474-80. doi: 10.1002/clc.24128
27. Duffy EY, Ashen D, Blumenthal RS, Davis DM, Gulati M, Blaha MJ, Michos ED, Nasir K, Cainzos-Achirica M. Communication approaches to enhance patient motivation and adherence in cardiovascular disease prevention. *Clin Cardiol* 2021;44(9):1199-207. doi: 10.1002/clc.23555
28. Tavakoly Sany SB, Behzad F, Ferns G, Peyman N. Communication skills training for physicians improves health literacy and medical outcomes among patients with hypertension: a randomized controlled trial. *BMC Health Serv Res* 2020;20(1):60. doi: 10.1186/s12913-020-4901-8
29. Wimmer BC, Cross AJ, Jokanovic N, Wiese MD, George J, Johnell K, Diug B, Bell JS. Clinical Outcomes Associated with Medication Regimen Complexity in Older People: A Systematic Review. *J Am Geriatr Soc* 2017;65(4):747-53. doi: 10.1111/jgs.14682
30. Pantuzzo LL, Ceccato M, das GB, Silveira MR, Junqueira LMR, Reis AMM. Association between medication regimen complexity and pharmacotherapy adherence: a systematic review. *Eur J Clin Pharmacol* 2017;73(11):1475-89. doi: 10.1007/s00228-017-2315-2
31. Elnaem MH, Irwan NA, Abubakar U, Syed Sulaiman SA, Elrggal ME, Cheema E. Impact of Medication Regimen Simplification on Medication Adherence and Clinical Outcomes in Patients with Long-Term Medical Conditions. *Patient Prefer Adherence* 2020;14:2135-45. doi: 10.2147/PPA.S268499
32. Jimmy B, Jose J. Patient Medication Adherence: Measures in Daily Practice. *Oman Med J* 2011;26(3):155-9. doi: 10.5001/omj.2011.38

33. Jarab AS, Al-Qerem WA, Hamam HW, Alzoubi KH, Abu Heshmeh SR, Mukattash TL, Alefishat E. Medication Adherence and Its Associated Factors Among Outpatients with Heart Failure. *Patient Prefer Adherence* 2023;17:1209-20. doi: 10.2147/PPA.S410371
34. Naser N, Durak-Nalbantic A, Sabanovic-Bajramovic N, Karic A. The Effectiveness of Eplerenone vs Spironolactone on Left Ventricular Systolic Function, Hospitalization and Cardiovascular Death in Patients With Chronic Heart Failure-HFrEF. *Med Arch* 2023;77(2):105-11. doi: 10.5455/medarh.2023.77.105-111
35. Khera R, Valero-Elizondo J, Das SR, Virani SS, Kash BA, de Lemos JA, Krumholz HM, Nasir K. Cost-Related Medication Nonadherence in Adults With Atherosclerotic Cardiovascular Disease in the United States, 2013 to 2017. *Circulation* 2019;140(25):2067-75. doi: 10.1161/CIRCULATIONAHA.119.041974
36. Maciejewski ML, Farley JF, Parker J, Wansink D. Copayment Reductions Generate Greater Medication Adherence In Targeted Patients. *Health Aff (Millwood)* 2010;29(11):2002-8. doi: 10.1377/hlthaff.2010.0571
37. Unverzagt S, Meyer G, Mittmann S, Samos FA, Unverzagt M, Prondzinsky R. Improving Treatment Adherence in Heart Failure. *Dtsch Arzteblatt Int* 2016;113(25):423-30. doi: 10.3238/arztebl.2016.0423
38. Berra E, Azizi M, Capron A, Høiegggen A, Rabbia F, Kjeldsen SE, Staessen JA, Wallemacq P, Persu A. Evaluation of Adherence Should Become an Integral Part of Assessment of Patients With Apparently Treatment-Resistant Hypertension. *Hypertension* 2016;68(2):297-306. doi: 10.1161/HYPERTENSIONAHA.116.07464
39. Lane D, Lawson A, Burns A, Azizi M, Burnier M, Jones DJL, Kably B, Khunti K, Kreutz R, Patel P, Persu A, Spiering W, Toennes SW, Tomaszewski M, Williams B, Gupta P, Dasgupta I; Endorsed by the European Society of Hypertension (ESH) Working Group on Cardiovascular Pharmacotherapy and Adherence. Nonadherence in Hypertension: How to Develop and Implement Chemical Adherence Testing. *Hypertension* 2022;79(1):12-23. doi: 10.1161/HYPERTENSIONAHA.121.17596