Multiple interventions following an acute coronary syndrome event increase uptake into cardiac rehabilitation

Lawless M1, Harrison AS1, Doherty P1

**Affiliation**

1The University of York

**Authorship Statement**

This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation

**Keywords**

Treatment, Acute coronary Syndrome, Cardiac Rehabilitation, Uptake

**Word Count**

3080

**Address of corresponding author**

[Alexander.harrison@york.ac.uk](mailto:Alexander.harrison@york.ac.uk)

Research Fellow,

Area 4, Seebohm Rowntree Building

The University of York

York

YO105DD

# Abstract

## Aims

Cardiac rehabilitation (CR) improves morbidity and mortality. Uptake varies for patients following acute coronary syndrome (ACS). Entry into CR is often dependent on the management strategy received, lower following percutaneous coronary intervention (PCI), higher following coronary artery bypass grafting (CABG). This study sought to investigate differences in CR uptake following an ACS event for those patients receiving multiple treatments.

## Methods

Data was from the National Audit of CR between 2016-2019. Patients with ACS were categorised as: no intervention; one treatment (such as any PCI, CABG, any valve surgery and any device therapy); two treatments; or three or more treatments. Baseline demographics and logistic regression were used to analyse the effect of multiple treatment intervention on uptake into CR.

## Results

A total of 6833 ACS patients were included in the analysis (0 treatments 2014, 1 treatment 3104, ≥2 treatments 2799). Patients who received ≥2 therapeutic interventions were more likely to be male, partnered and >2 comorbidities. Logistic regression showed a positive relationship between uptake total intervention. Similar associations were seen: being younger, male, partnered and having any comorbidity. The hospital stay, history of angina, diabetes and stroke was negatively correlated with an uptake.

## Conclusion

This study showed for the first time that multiple interventions following ACS is a significant predictor of uptake into CR. The findings align with recent trends with medically managed myocardial infarction uptake. Our findings identify factors associated with poor uptake to CR which should be considered as part of strategy to increase participation.

# Introduction

Cardiac rehabilitation (CR) is a comprehensive intervention delivered by a multi-disciplinary team known to improve the physical, mental and social consequences of cardiovascular disease (1). CR reduces cardiovascular mortality and decreases rates of hospital readmission (2-4). CR is currently listed as a Class 1a recommendation in European Society of Cardiology guidelines. The NHS England Long Term Plan has set an ambitious target of 85% of patients participating in a CR programme post-myocardial infarction (MI) by 2028, however, uptake rates currently attain only 50% across the UK (5). Numerous strategies have been proposed to encourage greater patient uptake into CR (6).

Acute coronary syndrome (ACS) is defined as any myocardial infarction (ST-elevated, STEMI, and non ST-elevated, NSTEMI) and unstable angina. There are over 80000 ACS admissions per year in UK (7) and NICE guidelines recommend that CR should be offered to all patients post-MI. Following an ACS event CR reduces cardiac death and lowers the risk of recurrence of MI and stent (8, 9).

Management of ACS depends on cause, effectiveness of treatment and patient preference. Early therapeutic intervention is required to reduce the risk of future morbidity and mortality (10). All patients are offered combination medical therapy including dual antiplatelets, statin, beta-blocker, nitrates and analgesia as required. The majority of patients are vascularised with percutaneous coronary intervention (PCI) and some receive coronary artery bypass grafting (CABG) depending on outcomes of further investigation such as angiography. In addition to these common treatment strategies patients may also receive valve replacement or device therapy following the ACS event.

CR following PCI or CABG reduces all-cause mortality (11), future cardiac events and readmission rates (12). Patients who received CR following valvuloplasty, both open and percutaneous procedures, as well as those who received left ventricular assist device therapy were shown to have an increased exercise capacity than those who did not (13-17). Despite the benefits of CR post ACS treatment, there are notable differences in CR uptake following different treatment modalities. In the UK in 2019 75% of patients who received CABG entered into CR, in contrast to only 52% of those who received PCI (5). The difference in severity and impact on the patient of the two treatments may influence uptake; in addition, increased length of stay in hospital could also contribute.

In order to understand the relationship between uptake to CR and treatment modality received following an ACS event, this current study aimed to investigate the effects of multiple treatments on the uptake to CR services in the UK.

**Methods**

## Data interpretation was performed in concordance with STROBE guidelines (18).

## Data

Data analysed in the present study was sourced from the British Heart Foundation National Audit of Cardiac Rehabilitation (NACR). The main aim of the audit is to monitor the CR service and provide information on inequality and sufficiency of rehabilitation programmes in order to increase availability, uptake and output of CR. Clinical data is obtained from both clinical practitioners and patient-led questionnaires. The data is entered by local CR teams with authorisation approved by Caldicot Guardian and a lead clinician who is responsible for service quality. Patient demographics, behaviour, mental health, wait times, uptake and completion are all recorded. The secure database is managed by NHS Digital who supply NACR with anonymised data approved annually under authorisation of Health Research Authority Confidentiality Group. The audit has been established for over 10 years and is embedded into routine practice collecting information on close 100,000 cardiac events per year.

This is a retrospective observational study utilising patient and service level data selected based on those presenting with an initiating ACS event between 1st April 2016 and 31st March 2019. This was determined in those patients coded as presenting with any of the following: myocardial infarction (MI) type unknown, ST-elevated MI, non-ST elevated MI, heart failure with MI, unstable angina and ACS. Patient treatment was considered either medical management or interventional management. For those patients who received interventional management, four individual groups of treatment were created (see supplementary materiel for detail): Percutaneous coronary intervention, coronary artery bypass graft, valvular surgery and device therapy. Patients receiving 2 or more treatments could have any combination of these therapies.

## Study flow and sample size

Across the study period the NACR database contained data from 580433 patients. Following an ACS event, 2799 patients received ≥2 interventions, leaving 311647 patients who received ≤1 intervention. In order to attain true predictions using a logistic regression model the treatment groups were adjusted to matched sample sizes. Thus, in order to minimise selection bias, a random selection of patients was generated from those who received ≤1 intervention, resulting in a total population of 24704, of whom 8342 had an ACS event, Figure 1. The total number of patients following ACS entering into CR was 4034.

## Cardiac rehabilitation engagement

Patients having an ACS event either proceeded to enter into a CR programme or not following a formal referral post-discharge from hospital. Previous research had identified several variables may have a direct impact on the decision to engage in CR these included age (continuous), gender (male/female), marital status (single/partnered), comorbidity (above or below 2 comorbidities), ethnicity (white/non-white) (19).

## Statistical analysis

Analysis was conducted in SPSS 25. Baseline data characteristics were generated for each relevant variable as described previously (19). Continuous variables were described as per treatment group and differences defined through t-test and odds ratio computed by logistic regression. Categorical variables were described and tested using chi squared and odds ratio. In both cases a p value < 0.05 was considered statistically significant.

Those patients receiving three or more treatments represented a smaller group in comparison to the other treatment groups. This empowered a decision to combine those receiving 2 or more treatments as a multiple treatment group enabling comparisons to be made between those receiving no intervention (medical therapy alone), 1 treatment (any treatment), and multiple treatment (≥2 treatments). A binary logistic regression forward stepwise model was used to predict the uptake to a CR programme and examine the association between the variables described above. The model was tested for sensitivity and specificity, as well as a goodness-of-fit analysis. Odds ratios are presented with confidence intervals. For univariate analysis a Bonferroni correction was used to counteract any problems with multiple comparisons, significance threshold was considered p < 0.01.

# Results

## Patient demographics and the effect of increased intervention

The sample population had a mean age of 67(12) 27% female. Table 1 and Table 2 show descriptive statistics and odds ratio for continuous and categorical variables.

Patients who received medical therapy alone were older, mean age 71 years. This was significantly older than those patients who received one (64 years) or more treatments (69 Years), p<0.002.

Following an ACS event 78% of males and 65% of females received more than one intervention. When compared with those receiving only medical therapy, the number of males receiving a combination of intervention was greater than females (medical vs >2 Treatments: males 21% vs 36%; females 35% vs 27%). The odds of being male and receiving any treatment was significantly increased (1.21, 95% CI 1.13, 1.31), which was further enhanced when receiving multiple treatment (1.38, 95% CI 1.24, 1.53).

The number of patients who were reportedly single was higher in the medical therapy group (single 28%, partnered 22%). The odds ratio of receiving any intervention was significantly increased if the patient was partnered (1.08, 95% CI 1.01, 1.16), an effect which was exacerbated if receiving multiple treatments (1.18, 95% CI 1.08, 1.28).

The number of comorbidities a patient presented with was tested against the number of interventions they received. The odds of receiving multiple interventions was significantly increased if two or more comorbidities were present (1.21, 95% CI 1.10, 1.34).

For the purposes of this study ethnicity was described as white versus non-white. The proportion of the non-white population receiving 1 intervention was higher than the white population, 49% and 41% respectively, which was the converse for more than two interventions (white 34%, non-white 29%). Overall the odds of receiving either any or multiple intervention was not significantly affected by ethnicity.

## Uptake to cardiac rehabilitation

This study has sought to investigate the effect of therapeutic intervention on the uptake to a cardiac rehabilitation programme. Those patients who received medical therapy alone were less likely to enter CR (no CR 70% vs yes CR 30%). The odds ratio of entering into cardiac rehabilitation is significantly increased by any treatment intervention (1.28, 95% CI 1.20, 1.37). Patients were 3% more likely to uptake rehabilitation if they received multiple therapy.

## Predicting uptake into cardiac rehabilitation programme

Logistic regression was used to compare uptake into CR by treatment intervention, patient characteristics and length of stay with the odds ratio and p value presented for each variable Table 3.

This regression analysis shows that there is a significant increase in uptake to CR with increasing number of interventions (p < 0.001). The included covariates of age, gender, marital status and comorbidity were all shown to be significantly associated with an increased uptake to rehabilitation (p < 0.001). The model showed that uptake to rehabilitation was more likely if the patient was younger, male, partnered and having the presence of at least one comorbidity. The assumptions of uniform variance and linearity for the regression model have all been met.

Some comorbidities (coded no/yes) were more likely to be associated with an increase in uptake into cardiac rehabilitation programme (arthritis, claudication, emphysema, asthma, chronic back pain, osteoporosis), whereas others were associated with a reduced uptake into rehabilitation (angina, diabetes, stroke).

Length of stay (days) in hospital was shown to be negatively correlated with uptake Table 3, suggesting that the longer a patient stays in hospital the less likely they are to enter into the service.

# Discussion

This study has, for the first time shown that multiple treatment intervention increases the likelihood of a patient entering into a CR programme following an ACS event.

CR is well known to be beneficial to patients following ACS regardless of treatment strategy (2). Interestingly, uptake into CR is dependent on the mode of treatment strategy adopted, thus those patients who received PCI are less likely to enter into CR than those who receive CABG (5, 20). We could speculate as to the reasons behind this discrepancy; patient preference; increased contact with healthcare services; the risks and burden of having undergone major surgery rather than receiving PCI, which is often viewed and described as a ‘procedure’. Nevertheless, the present study shows that those who receive more than one intervention will more likely uptake a CR service.

This study has shown that the association of uptake to CR and treatment number is associated with an important demographic of patients: patients being younger, male, partnered and having more than one comorbidity.

Patient age is correlated with increased chance of comorbidity and complexity of coronary vascular lesion, which is further complicated by the direct effects of age on the myocardium (reduced elasticity, endothelial dysfunction, pro-coagulative pro-inflammatory). Moreover, the older patient often poses problems associated with frailty, polypharmacy, decreased functional and cognitive status, social implications (21). The present study has shown that patients who received any intervention were younger, <70 years. Current guidelines indicate that any patient presenting with ACS should be offered revascularisation regardless of age, the caveat being this is dependent on patient preference, risk and benefit, comorbidity and quality of life. It has been extensively reported that mortality and risk of repeat MI, rehospitalisation and death are all significantly reduced following intervention after an ACS event (22, 23). However, it still remains that there is a deficit in the proportion of elderly patients receiving intervention (24, 25). It is possible that one reason for this deficit is that it is much harder to define acute ischaemia in the elderly patient based on current diagnostic aid. ECG changes in an older patient may be masked by concomitant changes such as left ventricular hypertrophy, left bundle branch block or pacemaker complexes. Furthermore, high sensitive troponin measurement may be less sensitive due to heart failure or renal dysfunction (26). Furthermore, elderly patients may have less typical symptoms of acute myocardial ischaemia (25, 27).

Differences in prognosis following ACS between males than females has been known for over thirty years (28), with little understanding to the cause of this difference. This study has found that men are more likely to receive intervention following ACS, an effect which is exacerbated when factoring in multiple interventions. Similar observational studies have previously described female patients receiving less intensive therapeutic interventions than male patients (29-31). Females are more likely to have a longer time-to-treatment following arrival in hospital than males (32) and therefore unfortunately may suffer longer ischaemic times. Moreover, female patients are less likely to accept intervention in the form of PCI and CABG, 6% and 7% less than males respectively, preferring medical management (33-35). Despite this difference in uptake to treatment, it has been shown that females are more likely to have a better long-term outcome than males following matched intervention. The differences observed in the present study could indicate patient choice. We report that the number of males receiving a combination of interventions was greater than females, which likely reflects the greater number of males in the dataset, furthermore males are generally younger at time of acute coronary events. Regardless of this, it is maintained that it we must attract more females to CR programmes in order to facilitate uptake.

Studies have previously shown that being single or living alone increases risk of ACS and cardiovascular mortality (36). Furthermore prognosis following MI is poorer in those who were unmarried or living independently regardless of age or gender (37). Prognosis may be explained by significant differences in adherence to secondary prevention medications of patients who live unmarried or independently (38). To our knowledge this is the first study to show partnered patients are more likely to receive intervention following ACS, which may indicate an advantage of a direct social support network on the outcome of therapy in ACS.

Risk factors for cardiovascular diseases include increasing comorbidity. The literature describes risk of ACS therapy being based upon ACS related and non ACS related risk factors, with certain comorbidities carrying greater risk of contraindication for intervention than others (39). This study has shown that those patients who have >2 comorbidity are more likely to receive multiple treatments following an ACS event. It is known that ACS rates increase with increasing comorbidity (25, 40), however there are no guidelines to suggest that intervention should be provided based on comorbidity alone and is therefore guided by clinical discretion. This may present a limitation to the present study as our umbrella term of ACS may indicate clinical decision determining different management strategies for those with comorbidities suffering STEMI, versus a patient with the same comorbidities suffering an NSTEMI.

We conclude that the findings of the present study therefore suggest that these important patient characteristics make it more likely for a patient to enter into CR following increased intervention.

# Limitations

The data available to us is derived from data inputted by clinical personnel and service user questionnaires. Thus, the first limitation of the present study is the potential presence of data entry errors and missing data. Increasing the quantity of data through future audit iterations can reduce the number of errors and maximise the relevance of conclusions to influence future cardiac rehabilitation services. Furthermore, to limit bias, we utilised a random sample of the complete data set, which aimed to enable more robust comparisons to be made using the regression analysis. No difference was observed between the characteristics of patients used in the random sample an those in the total population.

Another important limitation of our study is that we used a combination of ACS as the investigated disease, however, a lot of the literature focuses specifically on STEMI or NSTEMI/unstable angina cohorts. This may reflect the current thinking of viewing an acute pathology under the umbrella of ACS, rather than a more chronic pathology of chronic angina. This suggests that our study is perhaps more relevant to patients following an acute event.

Our study has focussed on quantitative measures and predictors of uptake to cardiac rehabilitation programmes; however, this does not truly represent the real-world patient decisions to enter or not enter CR. It would be important to explore qualitatively patient choice and their thought process behind consideration of CR services following ACS. This future work would enable direct comparisons between the patient demographics and the predictors described in this study with the personal factors that influence patient choice. After all, striking the balance of both understanding statistically significant predictors of healthcare access and actual patient choice is the future of healthcare service provision.

# Conclusion

This is the first study to test the association of multiple treatment interventions following ACS and the uptake to CR services. An increase in the number of interventions received following any ACS is a significant predictor of uptake into a CR programme. The effect of increased treatment number on uptake to rehabilitation is however less associated with those patients who have increasing age, unpartnered and female. We would suggest that clinical cardiology practitioners and CR services should therefore be mindful of patient characteristics, treatment number and type when offering CR, in order to attract more of this “known but lost” population to the CR service. In hospital patient education led by the recruitment teams would be an ideal opportunity to identify patients less likely to start CR and tailor the CR offer to their need and preferences.

**Acknowledgements**

The authors acknowledge the support of the NACR team.

**Funding**

This study and the NACR data is funded by the British Heart Foundation grant (040/PSS/17/18/NACR).

**Conflicts of Interest**

No conflicts of interest were present

**Author Contributions**

All authors were involved in the conception, design, analysis and writing of the research project.

# References

1. Cowie A, Buckley J, Doherty P, Furze G, Hayward J, Hinton S, et al. Standards and core components for cardiovascular disease prevention and rehabilitation. Heart. 2019;105(7):510-+.

2. Anderson L, Oldridge N, Thompson DR, Zwisler AD, Rees K, Martin N, et al. Exercise-Based Cardiac Rehabilitation for Coronary Heart Disease Cochrane Systematic Review and Meta-Analysis. Journal of the American College of Cardiology. 2016;67(1):1-12.

3. Sumner J, Harrison A, Doherty P. The effectiveness of modern cardiac rehabilitation: A systematic review of recent observational studies in non-attenders versus attenders. PLoS One. 2017;12(5).

4. Rauch B, Davos CH, Doherty P, Saure D, Metzendorf MI, Salzwedel A, et al. The prognostic effect of cardiac rehabilitation in the era of acute revascularisation and statin therapy: A systematic review and meta-analysis of randomized and non-randomized studies - The Cardiac Rehabilitation Outcome Study (CROS). European Journal of Preventive Cardiology. 2016;23(18):1914-39.

5. BHF. The National Audit of Cardiac Rehabilitation (NACR) Annual Statistics Report UK. 2019.

6. Karmali KN, Davies P, Taylor F, Beswick A, Martin N, Ebrahim S. Promoting patient uptake and adherence in cardiac rehabilitation. Cochrane Database of Systematic Reviews. 2014(6).

7. Quinn T, Johnsen S, Gale CP, Snooks H, McLean S, Woollard M, et al. Effects of prehospital 12-lead ECG on processes of care and mortality in acute coronary syndrome: a linked cohort study from the Myocardial Ischaemia National Audit Project. Heart. 2014;100(12):944-50.

8. Ji HG, Fang L, Yuan L, Zhang Q. Effects of Exercise-Based Cardiac Rehabilitation in Patients with Acute Coronary Syndrome: A Meta-Analysis. Medical Science Monitor. 2019;25:5015-27.

9. Lawler PR, Filion KB, Eisenberg MJ. Efficacy of exercise-based cardiac rehabilitation post-myocardial infarction: A systematic review and meta-analysis of randomized controlled trials. American Heart Journal. 2011;162(4):571-U25.

10. Hellermann JP, Goraya TY, Jacobsen SJ, Weston SA, Reeder GS, Gersh BJ, et al. Incidence of heart failure after myocardial infarction: Is it changing over time? American Journal of Epidemiology. 2003;157(12):1101-7.

11. Goel K, Lennon RJ, Tilbury RT, Squires RW, Thomas RJ. Impact of Cardiac Rehabilitation on Mortality and Cardiovascular Events After Percutaneous Coronary Intervention in the Community. Circulation. 2011;123(21):2344-U49.

12. Pack QR, Goel K, Lahr BD, Greason KL, Squires RW, Lopez-Jimenez F, et al. Participation in Cardiac Rehabilitation and Survival After Coronary Artery Bypass Graft Surgery: A Community-Based Study. Circulation. 2013;128(6):590-7.

13. Sibilitz KL, Berg SK, Tang LH, Risom SS, Gluud C, Lindschou J, et al. Exercise-based cardiac rehabilitation for adults after heart valve surgery. Cochrane Database of Systematic Reviews. 2016(3).

14. Voller H, Salzwedel A, Nitardy A, Buhlert H, Treszl A, Wegscheider K. Effect of cardiac rehabilitation on functional and emotional status in patients after transcatheter aortic-valve implantation. European Journal of Preventive Cardiology. 2015;22(5):568-74.

15. Zanettini R, Gatto G, Mori I, Pozzoni MB, Pelenghi S, Martinelli L, et al. Cardiac rehabilitation and mid-term follow-up after transcatheter aortic valve implantation. Journal of Geriatric Cardiology. 2014;11(4):279-85.

16. Pressler A, Christle JW, Lechner B, Grabs V, Haller B, Hettich I, et al. Exercise training improves exercise capacity and quality of life after transcatheter aortic valve implantation: A randomized pilot trial. American Heart Journal. 2016;182:44-53.

17. Grosman-Rimon L, Lalonde SD, Sieh N, Pakosh M, Rao V, Oh P, et al. Exercise rehabilitation in ventricular assist device recipients: a meta-analysis of effects on physiological and clinical outcomes. Heart Failure Reviews. 2019;24(1):55-67.

18. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: Guidelines for reporting observational studies. International Journal of Surgery. 2014;12(12):1495-9.

19. Harrison AS, Doherty P. Does the mode of delivery in routine cardiac rehabilitation have an association with cardiovascular risk factor outcomes? European Journal of Preventive Cardiology. 2018;25(18):1925-33.

20. Suaya JA, Shepard DS, Normand SLT, Ades PA, Prottas J, Stason WB. Use of cardiac rehabilitation by medicare beneficiaries after myocardial infarction or coronary bypass surgery. Circulation. 2007;116(15):1653-62.

21. T V. Non-ST elevation acute coronary syndrome in women and the elderly: recent updates and stones still left unturned. In: NK W, editor.: f1000Research; 2018.

22. Tegn N, Abdelnoor M, Aaberge L, Endresen K, Smith P, Aakhus S, et al. Invasive versus conservative strategy in patients aged 80 years or older with non-ST-elevation myocardial infarction or unstable angina pectoris (After Eighty study): an open-label randomised controlled trial. Lancet. 2016;387(10023):1057-65.

23. Savonitto S, Cavallini C, Petronio AS, Murena E, Antonicelli R, Sacco A, et al. Early Aggressive Versus Initially Conservative Treatment in Elderly Patients With Non-ST-Segment Elevation Acute Coronary Syndrome A Randomized Controlled Trial. Jacc-Cardiovascular Interventions. 2012;5(9):906-16.

24. Devlin G, Gore JM, Elliott J, Wijesinghe N, Eagle KA, Avezum A, et al. Management and 6-month outcomes in elderly and very elderly patients with high-risk non-ST-elevation acute coronary syndromes: The Global Registry of Acute Coronary Events. European Heart Journal. 2008;29(10):1275-82.

25. Rosengren A, Wallentin L, Simoons M, Gitt AK, Behar S, Battler A, et al. Age, clinical presentation, and outcome of acute coronary syndromes in the Euroheart acute coronary syndrome survey. European Heart Journal. 2006;27(7):789-95.

26. Reiter M, Twerenbold R, Reichlin T, Haaf P, Peter F, Meissner J, et al. Early diagnosis of acute myocardial infarction in the elderly using more sensitive cardiac troponin assays. European Heart Journal. 2011;32(11):1379-89.

27. Canto JG, Shlipak MG, Rogers WJ, Malmgren JA, Frederick PD, Lambrew CT, et al. Prevalence, clinical characteristics, and mortality among patients with myocardial infarction presenting without chest pain. Jama-Journal of the American Medical Association. 2000;283(24):3223-9.

28. Kannel WB, Sorlie P, McNamara PM. PROGNOSIS AFTER INITIAL MYOCARDIAL-INFARCTION - FRAMINGHAM-STUDY. American Journal of Cardiology. 1979;44(1):53-9.

29. Dey S, Flather MD, Devlin G, Brieger D, Gurfinkel EP, Steg PG, et al. Sex-related differences in the presentation, treatment and outcomes among patients with acute coronary syndromes: the Global Registry of Acute Coronary Events. Heart. 2009;95(1):20-6.

30. Nguyen HL, Gore JM, Saczynski JS, Yarzebski J, Reed G, Spencer FA, et al. Age and Sex Differences and 20-Year Trends (1986 to 2005) in Prehospital Delay in Patients Hospitalized With Acute Myocardial Infarction. Circulation-Cardiovascular Quality and Outcomes. 2010;3(6):590-U70.

31. Izadnegahdar M, Norris C, Kaul P, Pilote L, Humphries KH. Basis for Sex-Dependent Outcomes in Acute Coronary Syndrome. Canadian Journal of Cardiology. 2014;30(7):713-20.

32. Sadowski M, Gasior M, Gierlotka M, Janion M, Polonski L. Gender-related differences in mortality after ST-segment elevation myocardial infarction: a large multicentre national registry. Eurointervention. 2011;6(9):1068-72.

33. Hvelplund A, Galatius S, Madsen M, Rasmussen JN, Rasmussen S, Madsen JK, et al. Women with acute coronary syndrome are less invasively examined and subsequently less treated than men. European Heart Journal. 2010;31(6):684-90.

34. Halvorsen S, Eritsland J, Abdelnoor M, Hansen CH, Risoe C, Midtbo K, et al. Gender Differences in Management and Outcome of Acute Myocardial Infarctions Treated in 2006-2007. Cardiology. 2009;114(2):83-8.

35. Zhang BC. A Meta-Analysis of Early Percutaneous Coronary Intervention within 24 Hours of Thrombolysis in Acute ST-Elevation Myocardial Infarction. American Journal of Cardiology. 2012;109(7):6S-7S.

36. Udell JA, Steg PG, Scirica BM, Smith SC, Ohman EM, Eagle KA, et al. Living Alone and Cardiovascular Risk in Outpatients at Risk of or With Atherothrombosis. Archives of Internal Medicine. 2012;172(14):1086-95.

37. Lammintausta A, Airaksinen JKE, Immonen-Raiha P, Torppa J, Kesaniemi AY, Ketonen M, et al. Prognosis of acute coronary events is worse in patients living alone: the FINAMI myocardial infarction register. European Journal of Preventive Cardiology. 2014;21(8):989-96.

38. Kulkarni SP, Alexander KP, Lytle B, Heiss G, Peterson ED. Long-term adherence with cardiovascular drug regimens. American Heart Journal. 2006;151(1):185-+.

39. Patel MR, Calhoon JH, Dehmer GJ, Grantham JA, Maddox TM, Maron DJ, et al. ACC/AATS/AHA/ASE/ASNC/SCAI/SCCT/STS 2016 Appropriate Use Criteria for Coronary Revascularization in Patients With Acute Coronary Syndromes. Journal of the American College of Cardiology. 2017;69(5):570-91.

40. Dai XM, Busby-Whitehead J, Alexander KP. Acute coronary syndrome in the older adults. Journal of Geriatric Cardiology. 2016;13(2):101-8.