Contents lists available at ScienceDirect

International Journal of Cardiology Cardiovascular Risk and Prevention

journal homepage: www.journals.elsevier.com/international-journal-of-cardiology-cardiovascular-risk-and-prevention

Efficacy of exercise training-based cardiac rehabilitation programmes after transcatheter aortic valve implantation: A systematic review and meta-analysis☆

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ARTICLE INFO

Handling Editor: Dr D Levy

Keywords:
Exercise training
Cardiac rehabilitation
Transcatheter aortic valve implantation
6-Min walk test
Barthel index

ABSTRACT

Background: The beneficial effects of exercise training-based cardiac rehabilitation (CR) in different cardiac conditions have been previously studied. In this meta-analysis, we focused on the potential impact of CR on patients undergoing transcatheter aortic valve implantation (TAVI).

Methods: Multiple databases were searched in a systematic approach to find the eligible studies. All the studies investigating the potential impact of exercise training-based CR programmes on exercise capacity and health-related quality of life in patients undergoing TAVI were retrieved. The primary endpoint of interest was 6-min walk test (6MWT). The pooled standardized mean difference (SMD) and 95 % confidence interval (CI) were measured to compare the improvement or worsening the endpoints using a random- or fixed-effects model, as appropriate.

Results: A total of eleven studies (685 patients) were considered eligible for quantitative synthesis. The results showed that performing exercise training-based CR after TAVI is associated with significant improvement in 6MWT (SMD 0.59, 95 % CI (0.48; 0.71), $p < 0.01$), Barthel index (SMD 0.73, 95 % CI (0.57; 0.89), $p < 0.01$), 12-item Short Form (SF-12) physical (SMD 0.30, 95 % CI (0.08; 0.52), $p < 0.01$) and mental (SMD 0.27, 95 % CI (0.05; 0.49), $p = 0.02$) survey scores, and hospital anxiety and depression scale – depression (HADS-D) score (SMD -0.26, 95 % CI (−0.42; −0.10), $p < 0.01$).

Conclusion: Performing exercise training-based CR following TAVI has significant benefits regarding physical capacity and health-related quality of life irrespective of the programme duration.

1. Introduction

Exercise training is a valuable element of cardiac rehabilitation (CR) which offers a wide variety of advantages in patients with different cardiovascular diseases including coronary artery diseases, heart failure, and valvular heart diseases [1]. Most of the exercise-based CR programmes include aerobic endurance training with or without resistance training and also inspiratory muscle training (IMT) [2,3]. Accumulating evidence suggests that training programs offered in CR provide multiple health benefits including improvements in peak oxygen consumption (VO_2 Max), myocardial flow reserve, and quality of life [1]. These health benefits may be associated with reduced rates of mortality and hospitalization in patients with coronary artery diseases [4].

Aortic stenosis (AS) is the narrowing of the aortic valve which its prevalence increases in an age dependent manner. The consistent left ventricular pressure overload secondary to AS can consequently lead to ventricular hypertrophy and heart failure. Transcatheter aortic valve implantation (TAVI) promotes substantial therapeutic impacts for the treatment of AS and is preferred over surgical replacement in many patients with severe symptomatic AS [5,6]. As the population

☆ 1)This paper is not under consideration elsewhere; 2) None of the paper's contents have been previously published 3) All authors have read and approved the manuscript; and 4) All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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https://doi.org/10.1016/j.ijcrp.2024.200238
Received 31 October 2023; Accepted 18 January 2024
Available online 26 January 2024

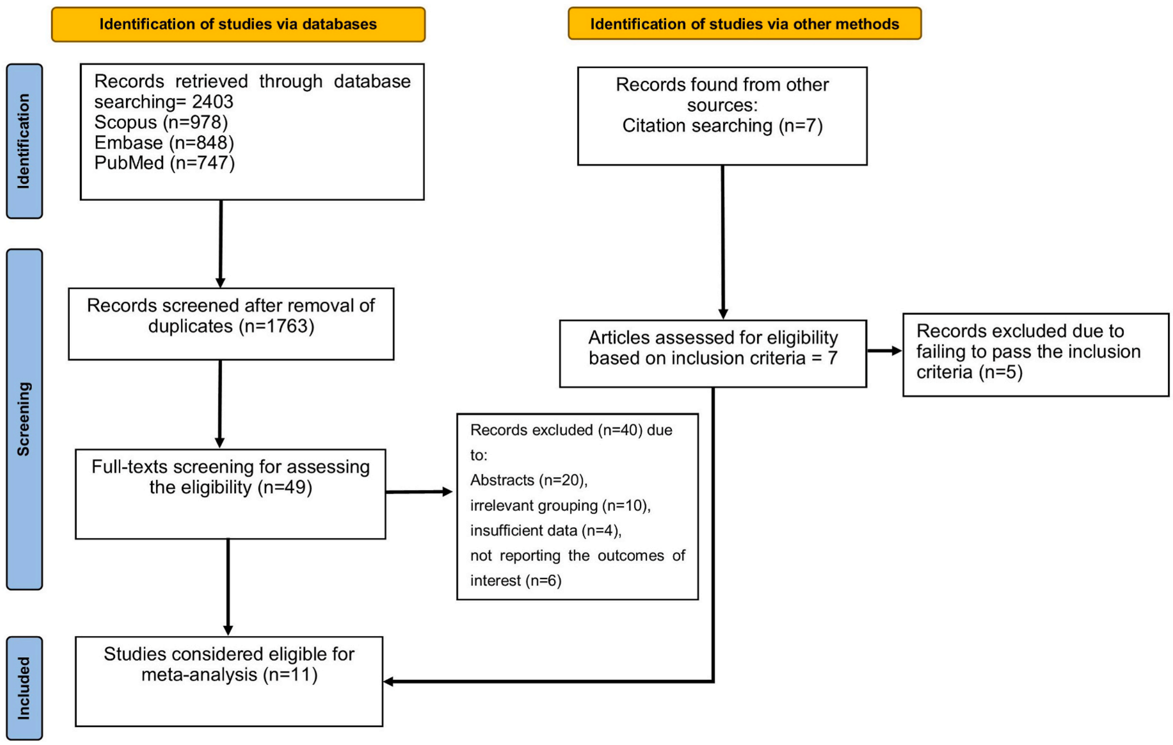

Fig. 1. Study Flowchart of the inclusion process.

undergoing TAVI are among the older adults with high level of disability and frailty, adaptation of CR programs is highly suggested as it is concomitant with better survival and quality of life [7]. Although the contemporary studies have shown promising results, there is paucity of data with most of the studies having relatively small sample sizes. Also, the recently published meta-analyses may not be comprehensive enough to show reliable results [8,9]. Since the majority of the effect of CR is based on exercise training programs [1], in the present meta-analysis, we investigated if performing exercise training-based CR in patients undergoing TAVI is associated with improved exercise capacity and quality of life-associated parameters.

2. Methods

We implemented this systematic review and meta-analysis using the recommendations provided by Preferred Reporting Items for Systematic review and Meta-analysis (PRISMA) [10]. The protocol for conducting the present systematic review is registered on the International Prospective Register of Systematic Reviews (PROSPERO) (CRD42023456492).

Search strategy: We sought for potentially eligible studies indexed in three online databases (PubMed, Scopus, and Embase) from the time of inception up to 25 August 2023. No filters were used for restriction of the results based on language, study design, and time frame. The details regarding the keywords used for searching the databases are presented at Supplementary Material – Table S1. Potentially eligible records were transferred to Rayyan web-based application [11] and screening of titles and abstracts was performed there independently by two reviewers (AA and HH). Citation searching of eligible articles and previous meta-analyses was also done for additional records.

Selection criteria and study population: The studies practicing any kind of exercise training associated with a cardiac rehabilitation programme in patients with AS who underwent TAVI irrespective of the study design were considered potentially eligible for quantitative synthesis. The studies were required to report outcomes before and after the rehabilitation program. The outcomes of interest were either compared before and after the training programs in a single group or compared between an intervention group receiving the training programs and a group receiving the usual care. The studies were excluded if: (1) they were animal studies, (2) irrelevant training programs were used, (3) the data on before and after the program were not provided, (4) abstract articles with no published full-length articles, and (5) studies with suspected overlapping population (the study with the smaller sample size was excluded).

Data extraction and quality appraisal: The primary endpoint for the present study was the 6-min walk test (6MWT). Secondary outcome of interest was Barthel Index (BI). Other endpoints were extracted for meta-analysis if three or more studies reported the data on the outcomes. Using a pre-specified Excel Spreadsheet, general data including the name of the first author, country where the study was conducted, study design, detailed information regarding the exercise training programme and duration of the programme, mean age, body mass index (BMI), data on gender, New York Heart Association (NYHA) functional class, left ventricular ejection fraction (LVEF), and baseline comorbidities including diabetes, hypertension, and coronary artery disease were extracted. Specific data regarding outcomes of interest including sample size, and baseline, final and change in the endpoints were extracted for analysis. In case of incomplete reporting of the endpoints, corresponding authors were contacted for further information.

For qualitative assessment of the included studies, we used the Newcastle-Ottawa Scale, a tool for quality appraisal of nonrandomized studies assessing the quality in three main domains of selection, comparability, and outcome. The overall score for each study is ranged from 0 to 9 and the scores 6–9, 3–5, and 0–2 were used to rate each study as high, fair, and poor quality. For randomized trials, the Cochrane Collaboration's tool for risk of bias assessment was used [12].

Statistical analysis: Two sets of analyses were conducted. First, we included the studies reporting the outcomes of interest before and after the training programmes. Also, we performed an analysis comparing changes in primary outcome of interest (6MWT) between the groups undergoing the rehabilitation program versus the control group receiving usual care. If the values of change in outcomes in the follow-up

Table 1
General characteristics and baseline demographics of the included studies.

Study	Country	Study design	Type of THV used	Sample size	Mean age	Gender (male)	BMI	DM	HTN	CAD	Smoking	NYHA (≥III)
Eichler 2016	Germany	Prospective cohort	Edwards Sapien XT 30 (22.1 %) CoreValve 93 (68.4 %) Other 13 (9.5 %)	136	80.6 ± 5.0	65 (47.8 %)	27.7 ± 4.2	54 (39.7 %)	ND	91 (66.9 %)	ND	51 (37.5 %)
Fauchère 2014	Switzerland	Retrospective cohort	Medtronic CoreValve Edwards Sapien XT	34	82 ± 5	13 (38 %)	28.2 ± 5.4	11 (32 %)	26 (76 %)	50 (45 %)	3 (9 %)	2.9 ± 0.8 (mean ± SD)
Hu 2023	China	Prospective, randomized controlled trial	ND	MICT 33 Control 33	MICT 70.36 ± 6.93 Control 70.94 ± 6.35	MICT 18 (54.5 %) Control 18 (54.5 %)	MICT 23.96 ± 3.78 Control 24.29 ± 3.31	MICT 5 (15.2 %) Control 5 (15.2 %)	MICT 17 (51.5 %) Control 13 (39.4 %)	MICT 13 (39.4 %) Control 11 (33.3 %)	MICT 9 (27.3 %) Control 7 (21.2 %)	MICT 0 (0.00 %) Control 1 (3.1 %)
Kleczynski 2021	Poland	Retrospective cohort	Edwards Sapien 3 41 (39 %) Evolut R 64 (61 %)	CR 52 DH 53	CR 81 ± 4.9 DH 80 ± 5.5	CR 22 (42 %) DH 20 (38 %)	CR 23.9 (22.4–27.9) DH 24.2 (23.0–28.3)	CR 22 (42 %) DH 25 (47 %)	CR 22 (42 %) DH 25 (47 %)	CR 19 (37 %) DH 20 (43 %)	ND	105 (100 %)
Pressler 2016	Germany	Prospective pilot study	Edwards Sapien 6 Sapien XT 14 Sapien 3 (n = 3), Medtronic CoreValve (=3), Symetis Acurate (n = 1)	Training group 13 Usual care 14	TG 81 ± 7 UC 81 ± 5	TG 7 (54 %) UC 8 (57 %)	TG 26.9 ± 3.1 UC 26.9 ± 3.7	TG 1 (8 %) UC 4 (29 %)	TG 9 (69 %) UC 10 (71 %)	TG 9 (69 %) UC 10 (71 %)	ND	TG 2 (15 %) UC 4 (29 %)
Russo 2014	Italy	Observational study	TAVI (balloon-expandable Edwards Sapien, self-expanding Medtronic CoreValve) Edwards *trans*-apical 16 (20 %) Edwards *trans*-femoral 47 (60 %), Corevalve 15 (20 %)	78	83.3 ± 3.6	31.7 %	24.7 ± 3.7	24.4 %	95.1 %	65.1 %	ND	2.93 ± 0.26 (mean ± SD)
Tarro Genta 2019	Italy	Prospective observational study	Edwards Sapiens valve: 28 Edwards Sapiens XT: 12 Edwards Sapiens 3: 5 Medtronic CoreValve: 50	95	82.7 ± 4.9	33 (35 %)	24.8 ± 4.8	25 (26 %)	74 (78 %)	42 (45 %)	ND	ND
Völler 2014	Germany	Retrospective observational, nonrandomized study	ND	76	83.3 ± 3.6	32 (42.1 %)	26.10 ± 4.44	27 (35.5 %)	ND	49 (64.5 %)	ND	30 (39.4 %)

(*continued on next page*)

Table 1 (*continued*)

Study	Country	Study design	Type of THV used	Sample size	Mean age	Gender (male)	BMI	DM	HTN	CAD	Smoking	NYHA (≥III)
Yu 2021	China	Retrospective observational study	ND	90	74.7 ± 8.1	54 (60 %)	23.3 ± 4.2	27 (30 %)	64 (71 %)	46 (51 %)	30 (33 %)	73 (81 %)
Xu 2023	China	Randomized clinical trial	ND	48	72.01 ± 5.56	25 (52.08 %)	22.72 ± 3.72	9 (18.75 %)	17 (35.42 %)	14 (29.17 %)	1 (2.08 %)	26 (54.16 %)
Zanettini 2014	Italy	Prospective cohort	Medtronic CoreValve 55 (91 %) Direct Flow valve 4 (6 %) Edwards sapien valve 1 (0.01 %)	60	83.5 ± 5.0	28 (46 %)	25.2 ± 4.5	8 (13 %)	ND	31 (52 %)	ND	1.8 ± 0.4 (mean ± SD)

Numerical data are presented as either mean ± SD or number (%) (THV: transcatheter heart valve, BMI: body mass index, DM: diabetes mellitus, HTN: hypertension, CAD: coronary artery disease, ND: no data, SD: standard deviation, MICT: moderate intensity continuous training, CR: cardiac rehabilitation, TG: training group, DH: discharged home, UC: usual care, TAVI: transcatheter aortic valve implantation).

period were not available, we calculated the mean change and standard deviation (SD) of change using the method explained in the study by Yagiz and colleagues [13]. If only median and quartiles were reported for an outcome, we calculated mean and SD by the method proposed by Wan and colleagues [14]. The analyses were generated using a random-effects or fix-effects model based on the level of heterogeneity. In case of significant heterogeneity, the results of the random-effects model were taken into account. The main results were depicted using forest plots reporting standardized mean difference (SMD) (Cohen's *d*) and the associated 95 % confidence interval (CI) as the effect size. For interpreting the magnitude of the effect size (SMD), we used cut-off values of 0.2, 0.5, and 0.8 for small, medium, and large zone of effect, respectively [15]. A subgroup analysis was performed for the primary endpoint based on the duration of the training programmes (≤3 weeks or > 3 weeks). The SMDs were pooled using inverse variance method which uses inverse variance of each of the included studies as weights. Publication bias was assessed using Egger's test and visual inspection of funnel plot in case of 10 or more studies present for an analysis. We assessed heterogeneity based on I^2 statistics and an $I^2 \geq 50$ % was considered as a significant level of heterogeneity. Sensitivity analysis was performed using "leave-one-out" method which omits each study at a time to detect if excluding each of the studies has a significant impact on the results. The test for overall effect was considered to be statistically significant if the associated *p*-value ≤0.05 or the effect size did not overlap with 0. All of the reported results were conducted in R Software version 4.1.3 using "meta" and "metafor" packages.

3. Results

Search results and description of the included studies: Of the 2403 records identified through database searching, a total of 1763 articles were screened after removal of duplicates. Full-text screening was performed for 49 articles and the reasons for exclusion are presented at Fig. 1. The search process yielded a total of 11 studies [16–26] eligible for meta-analysis. General characteristics and baseline comorbidities of individual studies are presented at Table 1. Four potentially eligible studies [20,26–28] were found to have overlapping population and the ones [20,26] with larger sample size were included for analysis. The majority of the studies were from Germany, Italy, and China. Three studies [18,20,25] were randomized controlled trials but the majority of the included studies were among cohorts. The duration of the training programmes lasted from two weeks to two months. One trial used IMT in addition to the usual rehabilitation program [25]. The training programmes performed in the majority of the studies were aerobic and strength exercises. The participants in one trial underwent moderate intensity continuous training (MICT) [18] (Table 2). The sample sizes ranged from 13 to 112 participants reporting outcomes before and after rehabilitation. A total of 685 patients undergoing CR were included for the before and after analysis. The mean (95 % CI) age of the whole studied population was 78.89 (76.25; 81.54) years. None of the study populations had reduced LVEF with the baseline measures ranging between 50 and 61.5 %. Three studies were considered eligible for comparing the group with training exercises and another group receiving the usual care [18–20]. A study compared the group undergoing IRT and usual CR and another group with only usual CR [25]. Since the control group received an active treatment (usual CR), this study was not included for comparison of training and usual care groups analysis. Quality assessment of the studies showed that all of the included studies had an either fair or high quality **(Table S2)**.

Six-minute walk test: Eleven studies reported data on 6MWT before and after undergoing exercise-based CR. Performing exercise training programmes resulted in a significant improvement in 6MWT (SMD 0.82, 95 % CI (0.24; 1.40), $p = 0.01$) but a significant level of heterogeneity was noted ($I^2 = 89$ %) (Figure S1). After removing the potential outlier [19] from the analysis, the level of association decreased (SMD 0.59, 95 % CI (0.48; 0.71), $p < 0.01$) but heterogeneity became insignificant ($I^2 = 12$ %). Subgroup analysis stratified studies based on programme duration (≤3 versus >3 weeks) and the results showed that both groups had significant improvement in 6MWT (≤3 weeks: SMD 0.59, 95 % CI (0.46; 0.72), $p < 0.01$; >3 weeks: SMD: 0.59 (0.35; 0.83), $p < 0.01$) (Fig. 2A). In a separate analysis, change in 6MWT was compared between patients undergoing exercise training-based CR and the ones receiving usual care. After inclusion of three studies, performing exercise training programmes were associated with better improvement in 6MWT compared to the control group (SMD 0.33, 95 % CI (0.05; 0.61), $p = 0.02$, $I^2 = 0$ %) (Fig. 2B).

Secondary endpoints: For assessing the functional independence, we compared BI before and after training programmes and the results from four study including 318 participants showed that performing CR is associated with improvement in BI (SMD 0.73, 95 % CI (0.57; 0.89), $p < 0.01$, $I^2 = 42$ %) (Fig. 3A). Depression and anxiety were compared pre and post training using hospital anxiety and depression score (HADS) scale. Four studies reported on HADS anxiety and depression (HADS-A and HADS-D). Pooled analysis showed no significant change in HADS-A score (SMD -0.54, 95 % CI (−1.17; 0.09), $p = 0.07$, $I^2 = 76$ %) with a high level of heterogeneity but a significant decrease in HADS-D score (SMD -0.26, 95 % CI (−0.42; −0.10), $p < 0.01$, $I^2 = 10$ %) following exercise training programmes (Fig. 3B and C). 12-item short form survey (SF-12) scores were compared before and after training programmes to assess physical and mental health. Data pooled from three available

Table 2
Details of the exercise training programs.

Study	Programme description	Programme duration	Study main findings
Eichler 2016	Ergometer endurance training, (outdoor walking, gymnastics, aqua gymnastics and spinal gymnastics in groups were added as further elements of physical therapy in some patients)	3 weeks- 5 times per week- 30 min per session	TAVI-treated aortic stenosis patients benefited from a 3-week cardiac rehab, improving physical capacity, quality of life, anxiety, and frailty, with outcomes influenced by preexisting factors like nutrition and cognition.
Fauchère 2014	Supervised gymnastics, aerobic and respiratory workout sessions	3 weeks- 2–3 sessions per day- 6 days per week	Despite the TAVI group being older and sicker than sAVR patients, both groups equally benefited from a post-acute in-patient rehabilitation program, as shown by improvements in 6-Minute Walking Tests and FIM scores.
Hu 2023	The warm-up begins below 50 % of the target intensity for 2 min, then gradually increases to reach 100 % within 5–10 min. The exercise phase begins at 100 % of the target intensity and lasts for an initial 20 min, gradually extending to 45 min over one month or maintaining that duration for the following two months. Finally, the cool-down phase includes a gradual reduction in load within a 3-min period.	3 months- 3 times per week- 30–60 min per session	MICT positively impacted cardiopulmonary function and physical capacity in patients following TAVI
Kleczynski 2021	Cardiovascular and resistance training using: Treadmill (walk), cycloergometer (with no resistance), functional exercise such as “sit to stand to sit”.	14-night stay with 6 days a week- 15–30 min per session	Patients undergoing TAVI tended to experience better clinical performance and a higher quality of life. Improved daily activity performance post-TAVI may be the primary patient concern, but this improvement diminished after one year.
Pressler 2016	Endurance training (cycle ergometers) Resistance training (bench press, rowing, shoulder press, pull down, leg press)	8 weeks- 2 or 3 supervised sessions per week - 20 to 45 min per session	After TAVI, exercise training was a safe and highly effective approach for enhancing exercise capacity, muscular strength, and quality of life in patients.
Russo 2014	Morning: respiratory workout, followed by an aerobic session on a cyclette (or on an arm ergometer in those patients who were not able to cycle) Afternoon: callisthenic exercises.	2 weeks- 6 days per week- 3 sets per day- 30 min of respiratory workout- 45 min of aerobic session- 30 min of callisthenic exercises	Cardiac rehabilitation benefited patients after transcatheter aortic valve implantation as well as after traditional surgery, enhancing their independence, mobility and functional capacity.
Tarro Genta 2019	Intensive, supervised, tailored aerobic incremental exercise training program consisting of two daily sessions of cycling or treadmill exercise (one in the morning and one in the afternoon except for Saturday when the exercise training took place only in the morning). Temporarily contraindicated treadmill or cycling exercise: a daily session of walking along the 6MWT route and pedal exerciser sessions. A 40-min daily session of respiratory exercise for all patients. Bedridden, markedly disabled or with a high risk of falls at admission patients: individualized physical therapy interventions for early mobilization. Psychological education and dietary counseling.	3 weeks Length of CR stay (days): All 24.4 ± 10.2 .5 Survivors 21.6 ± 7 Non-survivors 29.5 ± 12.3 Aerobic incremental exercise: two daily 30-min sessions- 6 days per week. Walking along the 6MWT route daily session of up to 30 min, pedal exerciser sessions up to 30 min twice a day. Respiratory exercise: a 40-min daily session of	In TAVI patients undergoing cardiac rehabilitation, lower exercise tolerance, higher Barthel Index, and elevated serum creatinine levels at discharge may serve as predictors of 3-year mortality.
Völler 2014	Aerobic exercise: bicycle ergometer, outdoor walking, gymnastics in groups or single, and resistance training of the lower extremities. Psychological education: stress management, Tai Chi, and progressive muscle relaxation	TAVI 19.17 ± 4.54 days	Cardiac rehabilitation benefited TAVI patients, regardless of age and comorbidities, by preserving independence in daily activities and social engagement.
Yu 2021	Phase I, 1–3 days before TAVI: Patient education, nutrition and psychological support, systematic respiration training. Phase II, Immediately after TAVI: Within 24 h after TAVI: in-bed	1 month Phase I: 2 times per day, 5–10 min per time- Phase II: Within 24 h after TAVI: 2 times per day, 5–10 min per time, after 24 h and before discharge: 2 times	CGA-based cardiac rehab improved functional status in TAVI patients, with BMI, frailty, and malnutrition influencing its impact on exercise capacity. CGA played a pivotal role in evaluating and

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Table 2 (*continued*)

Study	Programme description	Programme duration	Study main findings
	passive/active incremental exercises, respiration training, calf muscle pump function and ankle movement After 24 h and before discharge: in-bed passive/ active cycling, sitting upright, bed-chair transfer, standing and walking, low intensity of resistance training, 6MWT (when clinically feasible). Phase III, 1-month after discharge, respiration training, resistance training, walking (according to the 6 MWD before discharge), gymnastics, and other aerobic exercise (traditional Chinese medicine therapy: Tai chi, and Baduanjin)	per day, 10–15 min per time- Phase III:10–25 min per time, 5–6 times per week	planning CR strategies.
Xu 2023	CR plus IMT group: mobilization training in bed, 'sit to stand' transferring training, and aerobic walking training (and patient assessment, disease education, physical activity counseling, prescription of exercise training, dietary advice, and psycho management)	CR: 30 min at a time, once a day, 3–5 days a week throughout the hospital stay [12.50 (10.00–14.00) days] IMT: 20 min, once a day, 3–5 days a week throughout the hospital stay [11.00 (10.00–12.00) days] Hospital stay, all patients: 12.00 (10.00–13.75) days	IMT combined with CR proved to be effective in enhancing exercise endurance, pulmonary ventilation function, and inspiratory muscle strength in post-TAVI patients. Additionally, this combined approach led to shorter hospital stays compared to standard CR alone.
Zanettini 2014	Personalized exercise program: Patients unable to perform 6MWT and/or with dependence: bed exercises, sitting calisthenics and ambulatory training, Patients with mild disability and/or moderate reduction of functional capacity during the 6MWT: interval or steady-state aerobic training with cycloergometer or treadmill and calisthenics. Psychological support and antidepressants therapy- Nutritional support	6 days a week- 18.3 ± 5.6 days	In rehabilitation with multidimensional assessment and intervention, most patients saw significant improvements in function, quality of life, and autonomy, which remained stable in the majority during mid-term follow-up.

TAVI: transcatheter aortic valve implantation, sAVR: surgical aortic valve replacement, FIM: functional independence measure, MICT: Moderate-Intensity Continuous Training, CGA: Comprehensive Geriatric Assessment, BMI: body mass index, CR: cardiac rehabilitation, 6MWT: 6-min walk test, 6 MWD: 6-min walk distance, IMT: inspiratory muscle training.

studies showed that exercise-based CR led to improvements in both physical (SMD 0.30, 95 % CI (0.08; 0.52), $p < 0.01$, $I^2 = 0$ %) and mental (SMD 0.27, 95 % CI (0.05; 0.49), $p = 0.02$, $I^2 = 0$ %) components of SF-12 questionnaire (Fig. 3D and E).

Sensitivity analysis and publication bias: Results of the leave-one-out analysis showed that for 6MWT, BI, and HADS scale excluding studies at a time would not change the effect size significantly. For SF-12, omitting one of the three studies would change the pooled estimate to non-significant zone (Figure S2-7). Only for one of the analyses we had more than 10 studies included and Egger's test was not significant ($p = 0.22$) and funnel plot was relatively symmetrical with only one outlier study (Figure S8).

4. Discussion

Herein, we reported a meta-analysis of eleven studies investigating the potential impact of exercise-based CR in patients undergoing TAVI. We compared the endpoints on cardiopulmonary function and physical independence before and after performing training programmes. Two recently published meta-analyses investigated on the similar topic. One of them has only included seven studies for quantitative synthesis and the only compared endpoints were 6MWT and BI [9]. Another similar meta-analysis with 11 studies included for the primary endpoint (6MWT) had five studies from two teams with potential overlapping population [8]. Thus, their findings may have not yielded the most reliable results. In this regard, we conducted the present meta-analysis comprising of 685 patients for the primary endpoint. For the first time, we included studies exploring the impact of MICT and IMT in addition to the usual CR. We also sought to explore the potential effect of exercise training on the scores of two well-known questionnaires (HADS and SF-12) which assess the person's condition on anxiety and depression and also individual's well-being in everyday life.

Our results showed that performing exercise-based CR irrespective of the programme duration has a significant improvement in 6MWT. Exercise training programmes were considered to have moderate positive impact on the 6MWT (SMD = 0.59). This beneficiary effect was observed in the programmes with both shorter (≤3 weeks) and longer (3–8 weeks) duration. The positive impact of CR on 6MWT after TAVI should be emphasized since 6MWT has been established as a prognostic marker of adverse clinical outcomes in patients following TAVI. It has been demonstrated that a baseline 6MWT before TAVI is associated with lower survival along with male sex and presence of chronic obstructive pulmonary disease (COPD) as a baseline comorbidity. Moreover, each 10 m decrease in 6MWT was considered as an important predictor of death [29]. In another study, a baseline 6MWT of lower than 178 m was correlated with a significantly higher plasma B-type natriuretic peptide. A 6MWT <178 m was associated with a higher cumulative incidence of all-cause mortality and readmission. Also, a cut-off value of 178 6-min walk distance could predict mortality and readmission with 67 % sensitivity [30]. Previously, it was shown that CR programmes could drastically reduce the occurrence of cardiovascular mortality, hospitalization, and myocardial infarction in patients with coronary heart disease [4]. However, the potential effect of CR programmes on outcomes

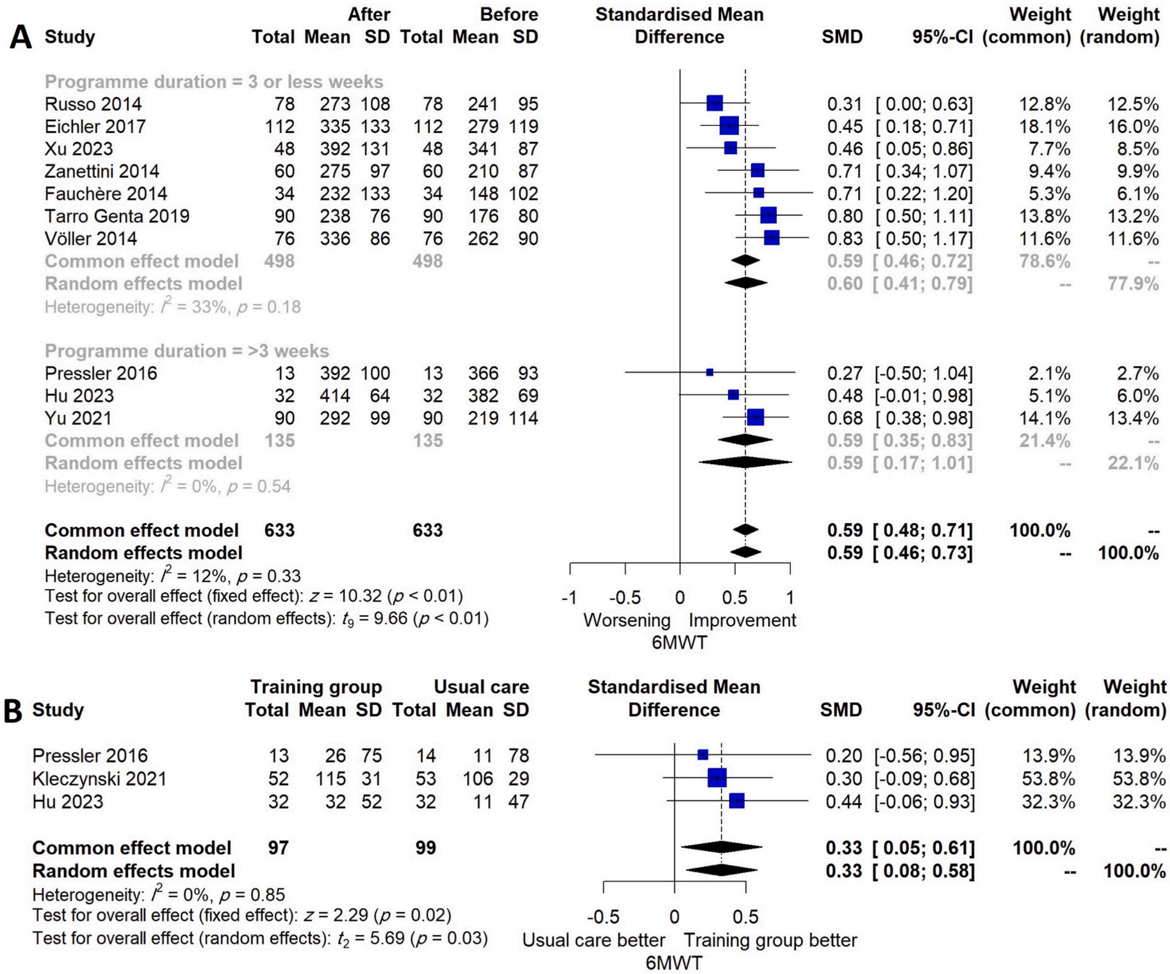

Fig. 2. Forest plot of the standardized mean difference on A: 6MWT before and after performing CR (after exclusion of the outlier) and B: 6MWT change compared between training group and usual care group (6MWT: 6-min walk test, CR: cardiac rehabilitation, SMD: standardized mean difference, SD: standard deviation).

of TAVI is less studied. Performing IMT in addition to CR may be associated with shorter hospital stay and lower post-operative complications compared to the group receiving only usual CR [25]. Overall, one may conclude that since 6MWT is among the important prognostic factors in patients undergoing TAVI, improvement in 6MWT may be translated into better clinical outcomes in long-term follow-up. Future prospective studies investigating the long-term impact of CR programmes on clinical outcomes following TAVI are warranted to confirm this hypothesis.

Multiple scales and questionnaires have been developed for assessing the patient's state on depression, anxiety, and physical independence. An index for assessing the activities of everyday life compared before and after performing training programmes was BI. The Barthel Index is a 10-item scale assessing the person's capability to perform every day's activities [31]. Our results showed that CR has a medium effect (SMD = 0.73) on improving BI following TAVI. For assessment of anxiety and depression, we compared HADS scores, a 14-item questionnaire for screening of anxiety and depression, before and after CR in patients who had undergone TAVI [32]. On the other hand, it was revealed that exercise training programmes may not result in decreasing the level of anxiety following TAVI measured by HADS-A scores although small positive improvement (SMD = −0.26) in depression state was noted in the participants after training programmes. Moreover, SF-12, a 12-item questionnaire which assesses quality of life in both physical and mental domains [33], showed some improvements after CR. Our results provided evidence that exercise-based CR appears to have positive impacts on health-related questionnaires and surveys implying and overall upgrade in person's quality of life although this effect was considered small and the sample size was limited.

Our results should be interpreted in the context of several limitations. First, conducting pre-post effect sizes of a single group in a meta-analysis may be introduced to some level of bias [34]. In this regard, we conducted a supplementrary analysis comparing changes of 6MWT in two independent groups and the significance of the results did not change although the level of association diminished. We could not perform a subgroup analysis based on the type of exercise training practiced in each study to explore the superior training programmes since most of the studies used a mixture of exercises. The follow-up time to record the post-programme tests especially for the primary endpoint (6MWT) was immediately after discharge from CR programme and the long-term effects of CR on 6MWT were not available for the majority of the studies. Several endpoints to explore the cardiopulmonary function of the participants including peak oxygen consumption (VO_2 peak), metabolic equivalent of task (MET), respiratory exchange ratio (RER), and anaerobic threshold (AT) were not reported in sufficient amount of studies to be included for meta-analysis. For the secondary endpoints, data were limited and many studies did not report their data on the mentioned markers. Thus, future studies are needed to confirm the results of this meta-analysis. Next, there were limited data regarding the reporting of long-term clinical outcomes following CR after TAVI. As a result, we could not synthesize the data on clinical outcomes. Future prospective studies are warranted to assess if performing exercise-based CR can lead to better clinical outcomes.

In conclusion, we showed that performing exercise training-based CR in patients after TAVI can result in a significant improvement in exercise

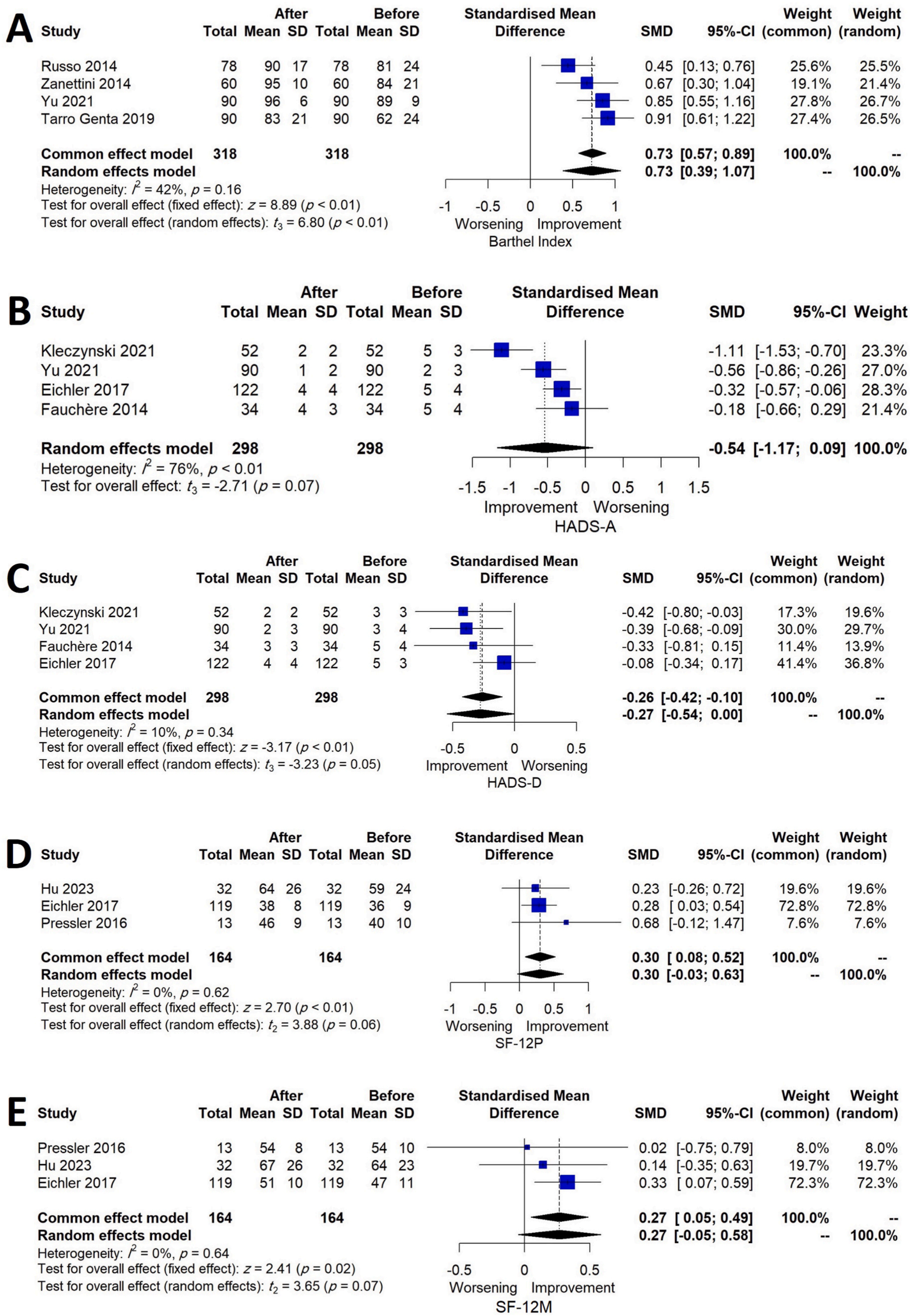

Fig. 3. Forest plot of the standardized mean difference on A: Barthel index, B: HADS-A, C: HADS-D, D: SF-12P, and E: SF-12 M before and after performing CR (HADS-A&D: hospital anxiety and depression scale-anxiety and depression, SF-12P&M: 12-item short form survey-physical and mental CR: cardiac rehabilitation, SMD: standardized mean difference, SD: standard deviation).

capacity and health-related quality of life as demonstrated in BI, SF-12, and HADS-D irrespective of the programme duration. Also, there was a significantly better improvement in 6MWT in patients undergoing training programmes compared to the ones receiving usual care. In this regard, widespread adoption of all kinds of exercise-based CR including aerobic, strength, and IMT exercises after TAVI seems reasonable. Future prospective studies are needed to confirm the findings of the present meta-analysis.

Author contributions

AH contributed to the conceptualization. Primary draft was provided by AH, PA, and HH. AH, AA, and MKJ reviewed the draft and edited the manuscript. All the listed authors have contributed to the manuscript substantially and have agreed to the final submitted version.

Funding

This study received no funding.

Data availability statement

The data underlying this article will be shared on reasonable request from the corresponding author.

Ethical approval

Not applicable.

Declaration of competing interest

The authors declare no conflict of interests.

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