Supplement

Appendix A

Search strategy for MEDLINE

Database: Ovid MEDLINE(R) <1946 to October Week 2 2017>
Search Strategy:
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1 (transcatheter adj2 implantation).tw. (344)
2 percutaneous aortic valve replacement.tw. (172)
3 percutaneous aortic valve implantation.tw. (105)
4 exp heart valve prosthesis implantation/ (21728)
5 exp transcatheter aortic valve implantation/ (2327)
6 exp transcatheter aortic valve replacement/ (2327)
7 TAVI.mp. (2547)
8 transcatheter aortic valve implant.mp. (5)
9 transfemoral aortic valve implantation.mp. (107)
10 transapical aortic valve implant.mp. (2)
11 transapical aortic valve implantation.mp. (223)
12 direct aortic valve implantation.mp. (3)
13 exp heart valve disease/ (115948)
14 exp heart valve prosthesis/ (34457)
15 (cardiac adj2 prosthesis).tw. (241)
16 (heart adj2 prosthesis).tw. (562)
17 (heart adj2 replacement).tw. (1381)
18 (aortic valve adj1 replacement).tw. (12504)
19 (valve adj2 (disease* or stenos* or insufficien*)).mp. (98815)
20 (valve adj2 (surg* or replace* or repair* or prosthe*)).mp. (63419)
21 AVR.mp. (3891)
22 SAVR.mp. (373)
23 "surgical aortic valve replacement".mp. (960)
24 "surgical aortic valve implantation".mp. (11)
25 aortic valve replacement.mp. (13931)
26 aortic valve implant.mp. (14)
27 aortic valve implantation.mp. (3697)
28 exp cardiac catheterization/ (51637)
29 cardiac catheterisation.mp. (1381)
30 exp exercise therapy/ (43801)
31 sports/ (29378)
32 physical exertion/ (60305)
33 rehabilitat*.mp. (152208)
34 (physical* adj5 (fit* or train* or therap* or activit*)).mp. (172329)
35 exp exercise/ (169423)
36 (train* adj5 (strength* or aerobic* or exercise*)).tw. (28930)
37 ((exercise* or fitness) adj3 (treatment or intervent* or program*)).tw. (21067)
38 exp rehabilitation/ (281574)
39 kinesiotherapy*.tw. (122)
40 "physical education and training"/ (14224)
41 exercise tolerance/ (11266)
42 exercis*.tw. (238392)
43 sport*.tw. (52748)

44 physical fitness/ (26962)
45 (fitness or fitter or fit).tw. (140062)
46 (muscle* adj3 (train* or activ*)).tw. (45396)
47 ((aerobic or resistance) adj3 (train* or activ*)).tw. (19551)
48 rehabilitation/ (17992)
49 rehabilitation centers/ (7982)
50 rehabilitat*.tw. (126804)
51 dance therapy/ (289)
52 danc*.tw. (5077)
53 (("lifestyle" or life-style) adj5 activ$).tw. (4275)
54 (("lifestyle" or life-style) adj5 physical$).tw. (3659)
55 walk*.tw. (87591)
56 run*.tw. (146440)
57 jog*.tw. (1920)
58 randomized controlled trial.pt. (496594)
59 controlled clinical trial.pt. (99232)
60 randomized.ab. (383424)
61 placebo.ab. (186698)
62 drug therapy.fs. (2114290)
63 randomly.ab. (260369)
64 trial.ab. (403052)
65 groups.ab. (1622146)
66 exp animals/ not humans.sh. (4677262)
67 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 (4066863)
68 67 not 66 (3476794)
69 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 (22014)
70 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 (187422)
71 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 (1095334)
72 68 and 69 and 70 and 71 (162)
73 69 and 70 and 71 (693)
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Appendix B
Summary of findings tables

Exercise compared to no exercise for patients following open surgical aortic valve replacement and transcatheter aortic valve implant (TAVI): a systematic review						
Patient or population: patients following open surgical aortic valve replacement and transcatheter aortic valve implant (TAVI): a systematic review **Setting:** **Intervention:** Exercise **Comparison:** no exercise						
Outcomes	**Anticipated absolute effects*** **(95% CI)**		**Relative effect (95% CI)**	**№ of participants (studies)**	**Certainty of the evidence (GRADE)**	**Comments**
	Risk with no exercise	**Risk with Exercise**				
Serious adverse events follow up: range 2 months to 8 months	Study population		RR 1.65 (0.44 to 6.18)	221 (3 RCTs)	⨁⨁⊖⊖ LOW [1] [2]	
	3 per 100	4 per 100 (1 to 16)				
Drop outs due to adverse events follow up: range 2 months to 8 months	Study population		RR 1.05 (0.05 to 22.62)	74 (2 RCTs)	⨁⨁⊖⊖ LOW [1] [2]	
	5 per 100	6 per 100 (0 to 100)				
Exercise capacity at maximum follow up - RCTs assessed with: V02 max follow up: range 2 months to 12 months	The mean exercise capacity at maximum follow up - RCTs was 14-91	SMD 0.41 higher (0.11 higher to 0.7 higher)	-	186 (3 RCTs)	⨁⨁⨁⊖ MODERATE [3]	
Exercise capacity at maximum follow up - Non-RCTs assessed with:	The mean exercise capacity at maximum follow up - Non-RCTs was 21-27	SMD 0.76 higher (0.26 lesser to	-	55 (2 observational studies)	⨁⊖⊖⊖ [4] [5] [6] VERY LOW	

VO2 max follow up: range 2 months to 4 months		1.79 higher)				
Exercise capacity assessed with: 6MWT follow up: range 2 months to 6 months	The mean exercise capacity ranged from 330-594 meters	MD 22.9 meters higher (31.64 lower to 77.43 higher)	-	140 (2 RCTs)	⨁⨁⨁⊖ MODERATE [3]	
HRQoL mental component assessed with: SF-12 and SF-36 follow up: range 2 months to 6 months	The mean hRQoL mental component ranged from 51-55	MD 0.44 lower (3.43 lower to 2.56 higher)	-	149 (2 RCTs)	⨁⨁⨁⊖ MODERATE [3]	
HRQoL physical component assessed with: SF-12 and SF-36 follow up: range 2 months to 6 months	The mean hRQoL physical component ranged from 38-52	MD 2.81 higher (5.82 lower to 11.44 higher)	-	149 (2 RCTs)	⨁⨁⨁⊖ MODERATE [3]	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio;

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

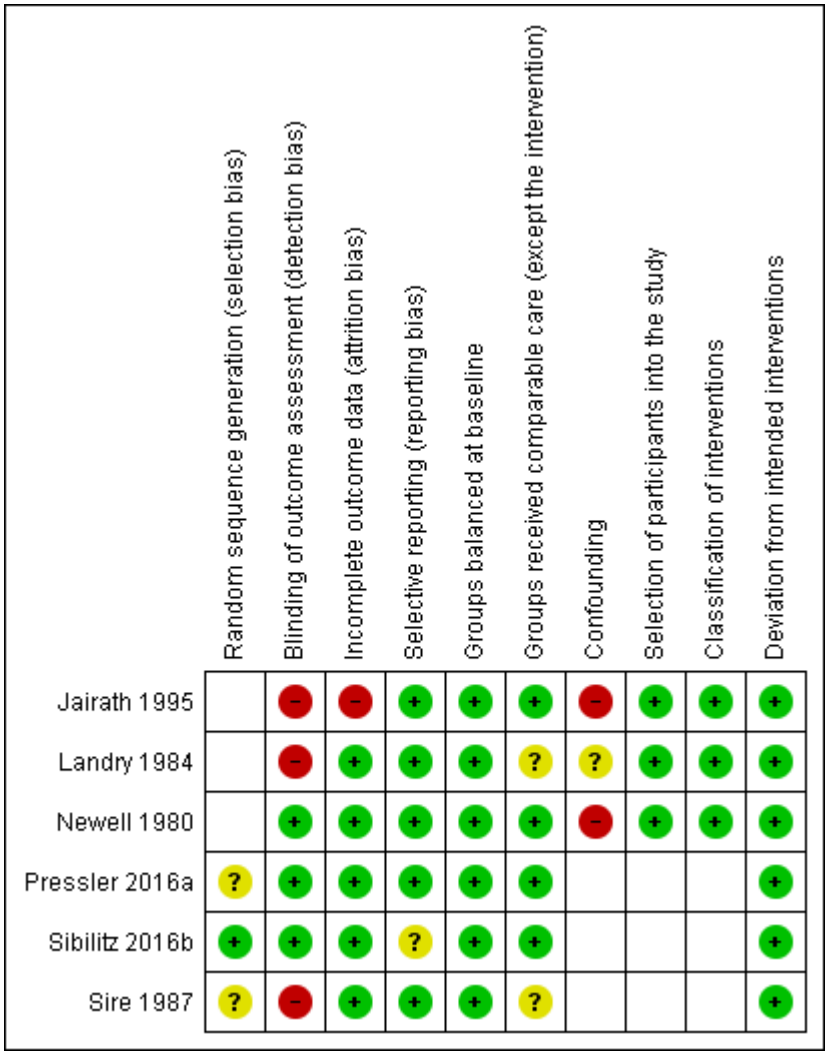
Footnotes

[1] High risk of bias for blinding of outcome assessment, and some concerns for random sequence generation (especially in the Sire study), therefore quality of evidence downgraded by one level. [2]

Imprecise due to small number of participants (<300), therefore quality of evidence downgraded by one level. [3] Imprecise due to small number of participants (<400), therefore quality of evidence downgraded by one level. [4] High risk of bias for confounding for Jairath and some concerns for the Landry study, therefore quality of evidence downgraded by one level. [5] High risk of bias for blinding of outcome assessment for both studies, therefore quality of evidence downgraded by one level. [6] imprecise due to very small number of studies and very few participants, therefore quality of evidence downgraded by one level.

Appendix C

Risk of bias of included studies

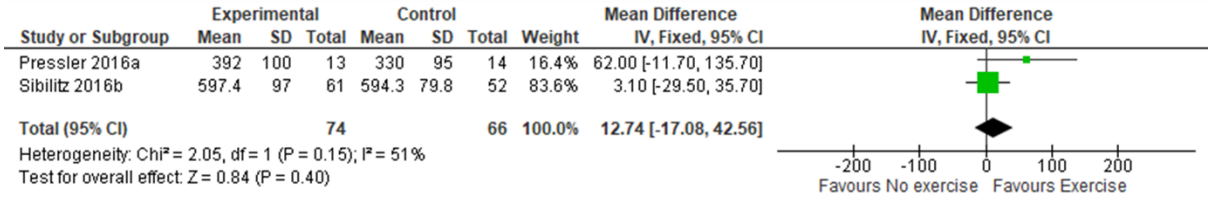


Risk of bias summary. Review authors' judgements about each risk of bias item in included studies. + = low risk, - = high risk, ? =some concerns, and empty space represents where the item was non-applicable for some of the studies. Some items are not applicable to randomised controlled trials (RCTs) while others are not applicable to non-RCTs.

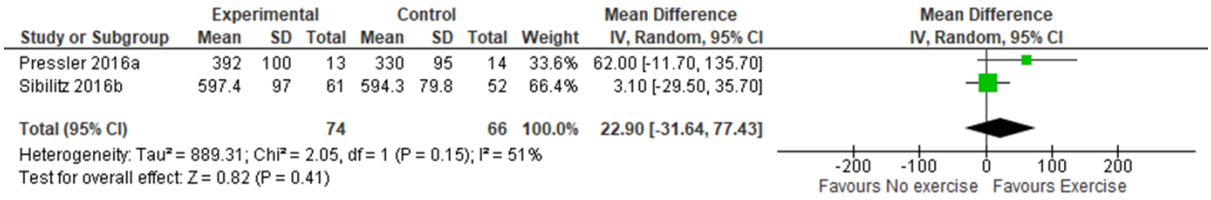
Appendix D

Exercise capacity measured using the six minute walk test

a)



b)



Forest plot of comparison: Exercise versus no exercise, outcome: Exercise capacity (6MWT) at maximum follow up, a) using a fixed-effects model and b) using a random-effects model. Only two studies reported exercise capacity measured using the 6-minute walk test. Overall, the effect estimate was not statistically significant between the exercise and the control groups (Fixed effects: MD 12.74, 95% CI -17.08 to 42.56, Random effects: MD 22.90, 95% CI -31.64 to 77.43), but it favoured the exercise group. According to the results, exercise-based CR does not seem to have a significant effect on the exercise capacity measured by the 6MWT.

Appendix E

Health-related quality of life results

Study	Measure	Result at final follow up (Mean ± SD)		P-value (95% CI)	Results favour intervention or not
		Exercise Group	Control group		
Pressler 2016	KCCQ Overall Summary	81.9 ± 18.3 (n=13)	66.1 ± 20.1 (n=14)	0.044 (0.2 to 14.4)	Favours intervention
	KCCQ Clinical summary	83.9 ± 13.9 (n=13)	64.1 ± 21.9 (n=14)	0.009 (3.4 to 21.4)	Favours intervention
	SF-12 Physical component	45.9 ± 8.9 (n=13)	38 ± 10.1 (n=14)	0.090 (-0.6 to 7.6)	Favours intervention
	SF-12 Mental component	54.3 ± 8.4 (n=13)	51.3 ± 7.9 (n=14)	0.857 (-6.3 to 5.3)	Neutral

Sibilitz 2016	SF-36 Mental component	53.6 ± 10.5 (n=64)	55.1 ± 8.8 (n=58)	0.40	Neutral
	SF-36 Physical component	51.2 ± 8.3 (n=64)	52.2 ± 7.4 (n=58)	0.71	Neutral

Health related quality of life (HRQoL) in exercise versus control groups after completion of the intervention (exercise-based cardiac rehabilitation). HRQoL was measured using the Kansas City Cardiomyopathy Questionnaire (KCCQ), the 12-Item Short-Form survey (SF-12) and the Short-Form 36 survey (SF-36). Only two studies reported the HRQoL outcome. Results given as mean ± standard deviation. P-values are accompanied by 95% confidence interval values. Statistical significance: $P < 0.05$. n is the number of patients in each group. Three of the HRQoL measures favour the intervention while three are neutral. “Vote counting” therefore favours the intervention.

Appendix F

Functional capacity results

Study	NYHA class	Results		P-value	Result favours intervention or not
		Exercise group (N=63)	Control group (N=52)		
Sibilitz 2016	I	46	46	0.59	Neutral
	II	12	6	-	-
	III	1	0	-	-
	IV	0	0	-	-
Overall	Functional capacity				Neutral

Functional capacity of exercise versus control group at 4 months after randomisation. Measured using the New York Heart Association (NYHA) class. The lower the class, the better the functional capacity of the patient. N is the total number of patients per group. From the results, exercise-based cardiac rehabilitation did not influence the functional capacity of the patients.

Appendix G

Return to work results

Study	Status	Results		Statistical significance
		Exercise group (n=21)	Control group (n=23)	
Sire 1987	Working after operation	17	15	NS

Return to work of patients in the exercise versus control group following exercise-based cardiac rehabilitation. After the intervention, 17 of 21 patients in the intervention group had returned to work while this was 15 of 23 patients in the control group. No statistically significant difference was seen between the exercise and the control groups.

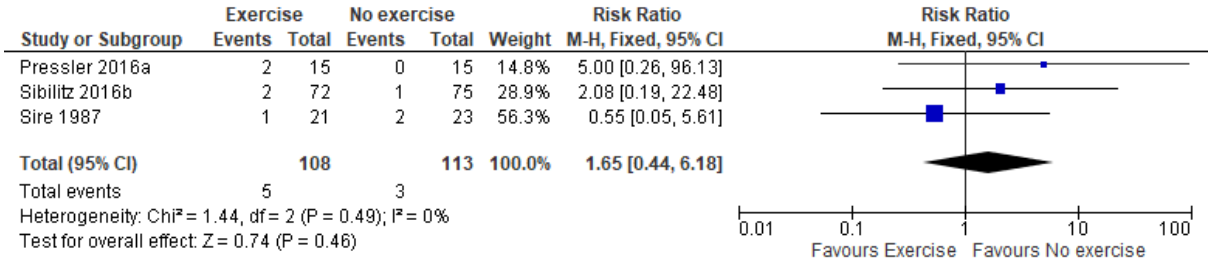
Appendix H

H.1 Adverse effects results

Study	Adverse events		Results	
			Exercise group (n= 72)	Control group (n= 75)
Sibilitz 2016	Total		11 patients	3 patients
	Breakdown of events	Repetitive pericardial effusion	1	-
		Palpitations/heavy heart beat several days after training	1	-
		Dyspnoea after training	1	-
		Symptoms of thromboembolism	1	1
		Chest pain	2	1
		Musculoskeletal injuries	7	1

Self-reported adverse events in the exercise versus control group. In the exercise group, 11 of the 72 patients reported 13 adverse effects while 3 of the 75 patients reported 3 adverse effects in the control group. Table also shows the breakdown of the adverse events, and the number of patients per adverse event reported.

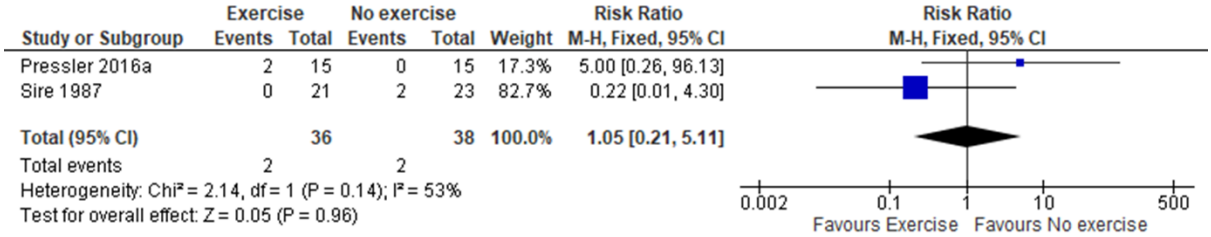
H.2 Serious adverse events results



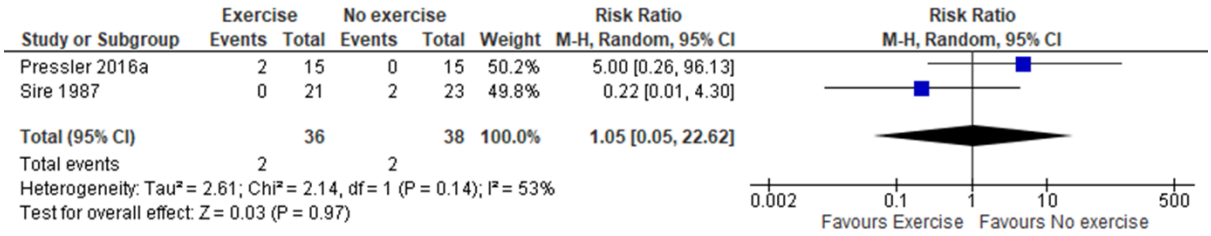
Forest plot of comparison: Exercise versus no exercise, outcome: Serious adverse events. Three studies reported serious adverse events. A fixed-effects meta-analysis was carried out using risk ratios in the Review Manager 5 software. Overall, 5/108 events were seen in the exercise group compared to 3/113 in the control group (risk ratio 1.65, 95% confidence interval 0.44 to 6.18). There was no statistically significant difference seen between the exercise and no exercise groups, but the effect estimate favours the control (no exercise) group.

H.3 Drop out due to adverse events

a)



b)



Forest plot of comparison: Exercise versus no exercise, outcome: Drop outs due to adverse events, a) using a fixed-effects model and b) using a random-effects model. Two studies reported drop out due to adverse events. Meta-analysis was carried out using risk ratios in the Review Manager 5 software. Overall, 2/36 events were seen in the exercise group compared to 2/38 in the control group (Fixed effects risk ratio 1.05, 95% confidence interval 0.21 to 5.11, Random effects risk ratio 1.05, 95% confidence interval 0.05 to 22.62). The effect estimate was not statistically significant between both groups.

Appendix I

Total societal cost results

Study	Type of cost	Result through 6 months of follow up (Mean)		Group difference (95% CI)	Statistical significance	Results favour intervention or not
		Exercise group	Control group			
Sibilitz 2016	Total societal cost	14185	17448	-1609 (-6162 to 2942)	ns	Favours intervention

Total societal cost (in Euros) of healthcare expenses for exercise versus control groups from heart valve surgery to 6 months follow up. Only one study reported this outcome. Cost given per patient as mean only. The calculated group difference between the exercise and control group is also shown with 95% confidence interval value. There was no statistically significant difference in the cost between both groups.