Safety and efficacy of exercise training in patients with abdominal aortic aneurysm: A meta-analysis of randomized controlled trials

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ABSTRACT

Objective: Low exercise capacity preoperatively leads to increased postoperative complications, perioperative mortality, length of stay, and inpatient costs among patients going through elective abdominal aortic aneurysm (AAA) surgery. Therefore, exercise training may be extremely important for reducing perioperative adverse events in AAA patients. This paper aimed to perform a meta-analysis of randomized controlled trials to evaluate the safety of exercise training and its effects on exercise capacity in AAA patients.

Methods: We searched for randomized controlled trials published up to December 2017 that compared exercise training vs usual care without exercise training in AAA patients. The primary outcome was safety, specifically the occurrence of cardiovascular adverse events during the study. Secondary outcomes were changes in AAA diameter, inflammation markers, and exercise capacity based on peak oxygen consumption (peak $\dot{V}O_2$) and anaerobic threshold (AT).

Results: We identified 341 trials, and after an assessment of relevance, 7 trials with a combined total of 489 participants were analyzed. There were a total of two cardiovascular adverse events during the exercise test and training, and the cardiovascular event rate and its 95% confidence interval (CI) were 0.8% and 0.2% to 3.1%. Exercise training did not tend to increase AAA diameter, and it also tended to decrease high-sensitivity C-reactive protein level in patients with AAA. All studies that evaluated the changes in AAA diameter or high-sensitivity C-reactive protein level involved patients with AAA diameter <55 mm at baseline; there was no study involving participants with AAA diameter ≥55 mm at baseline. Exercise training significantly increased peak $\dot{V}O_2$ (pooled mean difference, 1.67 mL/kg/min; 95% CI, 0.69-2.65; $P < .001$) and AT (pooled mean difference, 1.98 mL/kg/min; 95% CI, 0.77-3.19; $P < .001$) in AAA patients. The result of meta-regression suggested that the effects of exercise training on peak $\dot{V}O_2$ and AT were not modulated by the exercise duration.

Conclusions: Our analyses suggested that exercise training among AAA patients is generally safe, although future research should be carried out to further clarify the safety among patients with large AAAs. Exercise training improved peak $\dot{V}O_2$ and AT in AAA patients. More data are required to identify the optimal exercise duration for improving exercise capacity in patients with AAA. (J Vasc Surg 2018;■:1-11.)

Keywords: Abdominal aortic aneurysm; Exercise training; Safety; Exercise capacity

Abdominal aortic aneurysm (AAA) is a degenerative condition of the abdominal aorta and is frequently lethal if it ruptures.[1] The incidence of AAA is high in Japan in comparison with other countries because of the high prevalence of hypertension, a large proportion of elderly in the population, and the high availability of computed tomography, which facilitates the diagnosis of aortic diseases.[2] More than 13,000 open or endovascular AAA repairs are performed in Japan each year.[3]

AAA typically develops in elderly persons with arteriosclerosis. AAA is found in 5% to 7.5% of men and 1.5% to 3% of women older than 65 years.[1] In elderly AAA patients, exercise capacity is often poor as a consequence of comorbid diseases, sedentary lifestyle, and age.[4] Exercise capacity is known to be associated with AAA repair outcomes; low exercise capacity preoperatively leads to increased postoperative complications, perioperative mortality, length of stay, and inpatient costs.[5-7] Therefore, to reduce perioperative adverse events, exercise training may be extremely important for AAA patients. However, exercise training in AAA patients has received little attention in the literature. Some small randomized controlled trials (RCTs) have reported that exercise training is safe and leads to increased exercise capacity in AAA patients, but no systematic review or meta-analysis has been carried out to date. Given the limited evidence, physicians and other health care providers may hesitate to recommend

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exercise training to AAA patients. Therefore, it is necessary to determine the safety of exercise training and its effects on exercise capacity among AAA patients.

This paper aimed to perform a meta-analysis of RCTs on the safety of exercise training and its effects on exercise capacity in AAA patients.

METHODS

Search strategy. Medline, Embase, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Cumulative Index to Nursing and Allied Health Literature, Web of Science, PEDro, and abstracts from major cardiology conferences up to December 2017 were queried to identify published and unpublished trials. The following search string was used in PubMed: ("abdominal" AND ("aorta" OR "aortic") AND ("aneurysm" OR "aneurysms") AND ("exercise" OR "interval training" OR "resistance training" OR "weight training" OR "physical fitness" OR "rehabilitation") AND ("randomized" OR "randomly" OR "randomization" OR "randomized controlled trial"). The search was limited to human studies in English. We used reference lists from retrieved manuscripts and PubMed's related article search feature to ensure that the search was comprehensive. When data were insufficient, investigators of each trial were contacted as needed.

There was no ethical approval because this study did not include confidential personal data and did not involve patient intervention.

Inclusion and exclusion criteria. The inclusion criteria for our analysis were as follows: AAA managed nonoperatively or AAA scheduled for an elective operation; AAA with aortic diameter ≥30 mm[8]; RCT; exercise intervention group received exercise training; control group received usual care without exercise training; and outcome includes safety and exercise capacity. The exclusion criteria were as follows: >85 years old; morbid obesity (body mass index ≥39 kg/m^2); deterioration in cardiac function (left ventricular ejection fraction <20% or New York Heart Association class III or IV); and inability to perform the exercise. Three reviewers (M.K., H.T., and A.K.) each reviewed all eligible trials and determined whether they fulfilled the selection criteria. Disagreements were resolved by discussion.

The manuscript was prepared in accordance with the standards set forth by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[9]

Study variables and outcome. The following data were extracted from each report: study design, number of patients assigned to each group, baseline characteristics of the participants, and details of the exercise intervention (mode, intensity, time, frequency, and duration).

The primary outcome was the occurrence of cardiovascular adverse events during the study. Cardiovascular adverse events included myocardial infarction, unstable angina, serious adverse arrhythmia, aortic rupture, and other AAA-related events. The secondary outcomes were change in AAA diameter, inflammation markers, and exercise capacity. The change in AAA diameter was assessed using transabdominal ultrasound and was determined by the maximal anterior-posterior diameter obtained in the sagittal imaging plane. For inflammation markers, we analyzed the level of high-sensitivity C-reactive protein (hs-CRP) because hs-CRP is known as a parameter of aortic aneurysm progression and rate of expansion.[10] For exercise capacity, peak oxygen capacity (peak $\dot{V}O_2$) was measured using a treadmill or an ergometer with a respiratory gas analyzer, and anaerobic threshold (AT) was determined using the V-slope method. Data were extracted in duplicate by two investigators (A.K. and M.K.) and verified independently by a third (H.T.). Some data were calculated by the authors using the *Cochrane Handbook for Systematic Reviews of Interventions* methods.[11]

Assessment of risk of bias and quality in the studies included. The risk of bias for each study was assessed by two investigators (M.K. and A.K.) using the risk of bias tool in the *Cochrane Handbook for Systematic Reviews of Interventions*.[12] Furthermore, we assessed quality of the studies included using the Tool for the assEssment of Study qualiTy and reporting in EXercise (TESTEX), which consists of 15 different items and has been shown to be a reliable tool for performing a comprehensive review of exercise training trials.[13] Disagreements were resolved by discussion.

Statistical analysis. Dichotomous variables were analyzed using risk ratio with 95% confidence interval (CI). Continuous outcome measures were expressed as a change in the mean ± standard deviation (SD) from baseline to follow-up and were pooled as the mean difference (MD) with 95% CI. When the values of SD for each group were not available, they were reconstructed from the *P* value of the difference in the means between groups using the RevMan calculator (The Cochrane Collaboration, London, United Kingdom). Statistical heterogeneity was evaluated according to Higgins I^2 statistic. I^2 values of 0% to 24.9%, 25% to 49.9%, 50% to 74.9%, and 75% to 100% were considered no, low, moderate, and high statistical heterogeneity, respectively.[14] To consider for statistical heterogeneity, we used random-effects model based on DerSimonian and Laird's methods.[15] Random-effects metaregression was performed to determine whether the effects of exercise training on peak $\dot{V}O_2$ and AT were modulated by the exercise duration.

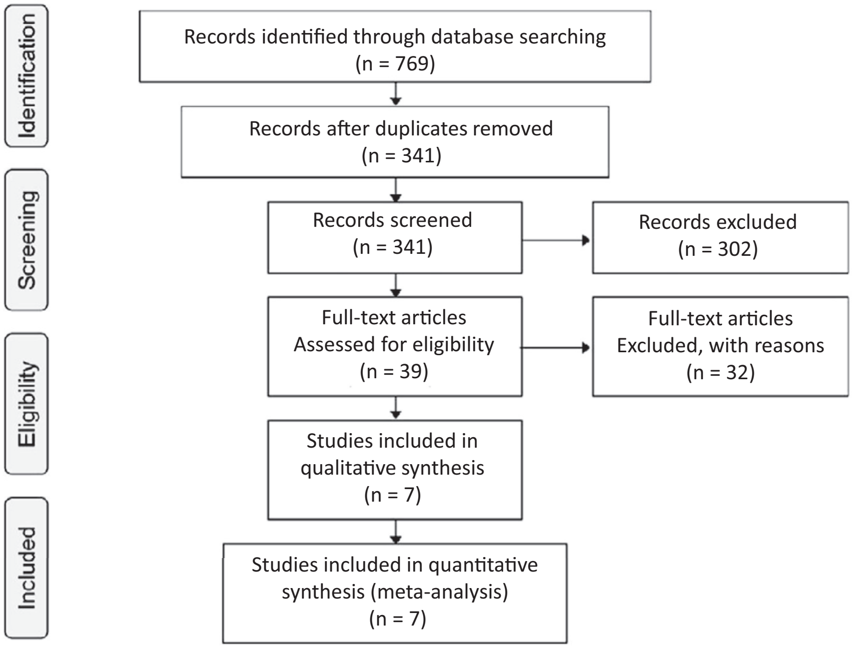

Fig 1. Flow chart of the systematic literature research for the meta-analysis.

It is well known that when the diameter of the aneurysm exceeds 55 mm, the risk of rupture is markedly increased.[2] The enlargement rate of an aneurysm is also influenced by aneurysm diameter.[16] Therefore, we categorized patients into large (AAA diameter ≥55 mm) or small (AAA diameter <55 mm) AAA and performed subgroup analyses regarding cardiovascular adverse events, AAA diameter, and hs-CRP level.

P value of <.05 was considered statistically significant. Analyses were carried out using Review Manager (version 5.3; The Cochrane Collaboration) and ProMeta version 3.0 (available from https://idostatistics.com/prometa3/).

RESULTS

Eligible studies. Of the total of 769 references that were initially screened, there were 341 unique studies. After review of the titles and abstract, 302 were rejected. We conducted a full-text review of these 39 studies for potential inclusion (Fig 1). Ultimately, seven studies with a combined total of 489 patients were included in the analyses.[4,17-22] No additional studies were found when we manually searched the references of the selected articles, relevant reviews, and meta-analyses. All the studies included were designed to compare exercise training with continuation of the patient's lifestyle or usual care without exercise training (the control) in AAA patients.

Study and patient characteristics. The baseline characteristics of the patients of the included studies are presented in Table I. The sample sizes ranged from 25 to 140, and the mean age, body mass index, and AAA diameter ranged from 70 to 75 years, 26.6 to 28.1 kg/m^2, and 30 to 62 mm, respectively. The proportion of men ranged from 80% to 100%. At baseline, mean peak $\dot{V}O_2$ and AT ranged from 16.1 to 20.2 mL/kg/min and 10.5 to 14.6 mL/kg/min, respectively. Two studies included patients with large (≥55 mm) AAA who were scheduled for surgery, and patients of these studies underwent surgery after the exercise intervention. The remaining studies included patients with small (<55 mm) AAA who were not scheduled for surgery.

Exercise intervention in included studies. Table I also presents the details of exercise interventions of the included studies. The training types were endurance and resistance training in four studies, endurance training alone in two studies, and high-intensity interval training alone in one study. The training intensities were moderate (6%-80% of heart rate reserve, 12-14 on the Borg 6-20 scale) in six studies and moderate to high (5-7 on the Borg 0-10 scale) in one study. Training time, frequency, and duration of exercise training ranged from 40 to 60 min/session, 2 or 3 times/wk, and 4 to 48 weeks, respectively.

Risk of bias and quality in the studies included. The risk of bias is summarized in Table II. There was a lack of blinding of participants and personnel (performance bias) because personnel had to teach and supervise patients during exercise training. The mean ± SD of the

Table I. Characteristics of included studies

Author	Total No. (Ex/Uc)	Patients' characteristics					
		Age, years	Male, %	BMI, kg/m^2	AAA diameter, mm	Peak $\dot{V}O_2$, mL/kg/min	AT, mL/kg/min
Kothmann, 2009	25 (17/8)	70 (61-79)	80	N/A	40 (30-51)	N/A	10.5 ± 2.0
Myers, 2010	57 (26/31)	71 ± 8	93	27.5 ± 3.9	30-50	20.2 ± 7.2	N/A
Tew, 2012	25 (11/14)	73 ± 7	84	28.1 ± 3.2	40 ± 7	18.5 ± 5.1	12.5 ± 3.0
Myers, 2014	140 (72/68)	72 ± 7	92	28.1 ± 3.7	34 ± 5	19.7 ± 6.1	14.6 ± 4.7
Barakat, 2016	124 (62/62)	73 ± 7	90	27.0 ± 3.9	62 ±8	17.5 ± 4.5	12.5 ± 3.9
Lima, 2018	65 (33/32)	72 ± 7	100	28.0 ± 3.3	37 ± 5	19.2 ± 5.2	14.4 ± 4.2
Tew, 2017	53 (27/26)	75 ± 6	94	26.6 ± 3.8	59 ± 4	16.1 ± 3.4	11.0 ± 2.4

AAA, Abdominal aortic aneurysm; *AT,* anaerobic threshold; *BMI,* body mass index; *ET,* endurance training; *Ex,* exercise training; *HIT,* high-intensity interval training; *HR,* heart rate; *N/A,* not applicable; *RT,* resistance training; $\dot{V}O_2$, oxygen consumption; *Uc,* usual care.
Data are shown as mean ± standard deviation or as mean (range) for continuous variables.

Table II. Risk of bias and assessment of study quality and reporting

Studies	The Cochrane Collaboration Tool					
	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting
Kothmann, 2009	Low	Unclear	High	Low	Low	Low
Myers, 2010	High	High	High	Low	Low	Unclear
Tew, 2012	Low	Low	High	Low	High	Unclear
Myers, 2014	High	High	High	Low	Low	Unclear
Barakat, 2016	Low	Low	High	Unclear	High	Low
Lima, 2018	High	High	High	Low	Low	High
Tew, 2017	Low	Low	High	Low	Unclear	Low
Low risk of bias, %	57	43	0	86	57	43
High risk of bias, %	43	43	100	0	29	14
Unclear, %	0	14	0	14	14	43

Low, Low risk; *High,* high risk.

total TESTEX score, study quality score, and reporting score of the studies included were 9.0 ± 0.8, 3.7 ± 0.8, and 5.3 ± 1.1, respectively (Table II).

Primary outcomes. All seven studies evaluated cardiovascular adverse events, but only during the exercise test and training, not during the entire study duration. We could not compare the rate of cardiovascular events during the exercise test and training between the exercise and the control groups because the control group, who did not receive the exercise test and training, is essentially defined to have zero events. A total of 2 cardiovascular adverse events were reported during the exercise test and training in 248 patients of the intervention group: cardiac arrest and short-lived angina. There were no AAA ruptures during exercise training. The cardiovascular event rate during the exercise test and training and its 95% CI were 0.8% and 0.2% to 3.1%.

Secondary outcome. Two trials included measurement of AAA diameter before and after the exercise training.[18,19] However, the meta-analysis for AAA diameter was not performed because there were only two studies and one of the two studies had a very high weight. Tew et al[18] reported that the MD of AAA diameter in exercise training compared with usual care was −0.2 mm (95% CI, −5.42 to 5.02) per 12 weeks, indicating that the exercise did not increase AAA diameter compared with the control (AAA growth rates per year for exercise and control groups: 2.0 mm and 2.8 mm, respectively). In addition, Myers et al[19] showed that the MD of AAA diameter in exercise training

Table I. Continued.

Exercise intervention				
Mode	Time, min/session	Frequency, times/wk	Duration, weeks	Intensity
ET	40	2	7	Moderate (range of 12-14 on the Borg 6-20 scale)
ET + RT	55	3	48	Moderate (target HR: 60%-80% of HR reserve, range of 12-14 on the Borg 6-20 scale)
ET	45	3	12	Moderate (range of 12-14 on the Borg 6-20 scale)
ET + RT	55	3	48	Moderate (target HR: 60%-80% of HR reserve, range of 12-14 on the Borg 6-20 scale)
ET + RT	60	3	6	Moderate
ET + RT	55	3	12	Moderate (target HR: 60%-80% of HR reserve, range of 12-14 on the Borg 6-20 scale)
HIT	47	3	4	Moderate to high (high-intensity cycling interspersed with 2-minute rest)

Table II. Continued.

The Tool for the assEssment of Study qualiTy and reporting in Exercise (TESTEX)		
Total score (/15)	Study quality score (/5)	Study reporting score (/10)
8	5	3
9	3	6
10	4	6
9	3	6
9	4	5
8	3	5
10	4	6

compared with usual care was −0.3 mm (95% CI, −2.08 to 1.48) per 48 weeks (AAA growth rates per year for exercise and control groups: 1.5 mm and 1.8 mm, respectively). Both of these studies involved patients with AAA diameter <55 mm at baseline; there was no study involving patients with AAA diameter ≥55 mm at baseline (Table III).

Two trials included measurement of hs-CRP level.[17,18] The meta-analysis for hs-CRP level was not performed because there were only two studies and one of the two studies had a very high weight. Myers et al[17] reported that the MD of hs-CRP level in exercise training compared with usual care was −0.3 mg/dL (95% CI, −0.54 to −0.06), indicating decrease in the exercise group. Tew et al[18] showed that the MD of hs-CRP level in exercise training compared with usual care was −0.8 mg/dL (95% CI, −1.81 to 0.21). Both of these studies involved patients with AAA diameter <55 mm at baseline; there was no study involving patients with AAA diameter ≥55 mm at baseline (Table III).

Six trials assessed peak $\dot{V}O_2$ with a total of 231 patients in the intervention group and 233 patients in the control group.[17-22] Exercise training significantly increased peak $\dot{V}O_2$ compared with the usual care among AAA patients (pooled MD, 1.67 mL/kg/min; 95% CI, 0.69-2.65; $P < .001$; Fig 2; Table IV). There was low heterogeneity across studies for peak $\dot{V}O_2$ ($I^2 = 28\%$). The metaregression coefficient (slope of the metaregression line) was not statistically significant (1.378; $P = .158$; Fig 3).

Six trials assessed AT with a total of 187 patients in the intervention group and 174 patients in the control group.[4,18-22] Exercise training significantly increased AT in AAA patients, with pooled MD of 1.98 mL/kg/min (95% CI, 0.77-3.19; $P < .001$; Fig 4; Table IV). However, there was a high degree of statistical heterogeneity across studies for AT ($I^2 = 81\%$). Subanalysis was performed

Table III. Cardiovascular adverse events and changes in abdominal aortic aneurysm (*AAA*) diameter and high-sensitivity C-reactive protein (*hs-CRP*) level

	Cardiovascular adverse events		AAA diameter, mm					
			Baseline		Follow-up		Absolute change	
Author	Ex	Uc	Ex	Uc	Ex	Uc	Ex	Uc
Kothmann, 2009	1 (cardiac arrest)	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Myers, 2010	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Tew, 2012	0	N/A	40.9 ± 7.0	39.3 ± 6.4	41.4 ± 7.0	40.0 ± 5.7	0.5 ± 7.0	0.7 ± 6.1
Myers, 2014	0	N/A	34.7 ± 5.1	33.7 ± 5.1	36.2 ± 5.6	35.5 ± 5.6	1.5 ± 5.4	1.8 ± 5.4
Barakat, 2016	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Lima, 2018	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Tew, 2017	1 (angina)	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Ex, Exercise training; *N/A*, not applicable; *Uc*, usual care.
Data are shown as mean ± standard deviation.

using only five studies with exercise training >4 weeks because increase in exercise capacity is greatly affected by exercise duration and most previous studies define short-term exercise training as ≤4 weeks. In the results, exercise training of >4 weeks significantly increased AT among AAA patients and the degree of statistical heterogeneity became low (MD, 2.40 mL/kg/min; 95% CI, 1.55-3.24; $P < .001$, $I^2 = 32\%$; Fig 5). The metaregression analysis was performed with all six studies and the coefficient was not statistically significant (1.058; $P = .152$; Fig 6).

DISCUSSION

Main findings. This meta-analysis, which included 489 patients, aimed to evaluate the safety of exercise training and its effects on exercise capacity in AAA patients. Although included studies did not report the rate of cardiovascular adverse events during the study, all seven studies reported the rate of cardiovascular adverse events during the exercise test and training. Our results suggested that there were only a few cardiovascular adverse events with the exercise test and training (event rate, 0.8%) in AAA patients. Exercise training also tended not to increase AAA diameter and to decrease hs-CRP level in patients with AAA diameter <55 mm. Furthermore, exercise training significantly improved peak $\dot{V}O_2$ and AT in AAA patients. To our knowledge, this is the first meta-analysis to assess the safety and potential benefits of exercise training in AAA patients.

Safety. This study showed that the cardiovascular event rate and its 95% CI were 0.8% and 0.2% to 3.1% in patients of the exercise training group. There were no AAA ruptures. Similar to our findings, the incidence of cardiovascular adverse events with exercise training among AAA patients was very low in some observational studies. One study evaluated the safety of treadmill exercise stress testing in 262 patients who had AAA diameter ≥40 mm, and the rate of aneurysm rupture was 0.4%.[23] Another observational study evaluated the incidence of cardiovascular adverse events during exercise training among 27 AAA patients and reported only one cardiovascular adverse event (event rate, 3.7%).[24] Furthermore, two studies with a total of 40 AAA patients reported no cardiovascular events with the exercise program.[25,26] Consistent with our results, these four studies, which were not included in our meta-analysis, reported only a few cardiovascular adverse events with the exercise test and training. Therefore, it seems that it is generally safe for AAA patients to participate in exercise training programs.

There is a possibility that exercise training expands AAA diameter because it increases blood pressure and heart rate temporarily during exercise, resulting in increased aortic wall tension.[18] In addition, a study showed that hs-CRP is released from aneurysmal arteries with degenerating elastic lamina during AAA formation.[27] Therefore, we also analyzed changes in AAA diameter and hs-CRP level as a parameter of safety. As a result, the AAA diameter tended not to increase in the exercise group compared with the usual care group when the baseline AAA diameter was <55 mm. A previous long-term study also observed 140 patients with small AAAs and reported no significant differences in the need for surgical AAA repairs between exercise and no-exercise groups.[28] Moreover, Tew et al[22] evaluated changes in AAA diameter before and after exercise training in AAA patients with a diameter of 55 to 70 mm. The results showed that the mean ± SD for AAA diameter was 60 ± 0.4 mm and 59 ± 0.4 mm at baseline and 5 weeks after exercise training, respectively. This study also demonstrated that hs-CRP level tended to decrease in the exercise group compared with the usual care group when the baseline AAA diameter is <55 mm. This finding is consistent with previous studies that suggested lower

Table III. Continued.

hs-CRP level, mg/dL					
Baseline		Follow-up		Absolute change	
Ex	Uc	Ex	Uc	Ex	Uc
N/A	N/A	N/A	N/A	N/A	N/A
0.43 ± 0.34	0.39 ± 0.23	0.32 ± 0.05	0.58 ± 0.67	−0.1 ± 0.3	0.2 ± 0.6
1.4 ± 1.1	2.3 ± 1.5	0.9 ± 0.9	2.6 ± 1.6	−0.5 ± 1.0	0.3 ± 1.6
N/A	N/A	N/A	N/A	N/A	N/A
N/A	N/A	N/A	N/A	N/A	N/A
N/A	N/A	N/A	N/A	N/A	N/A
N/A	N/A	N/A	N/A	N/A	N/A

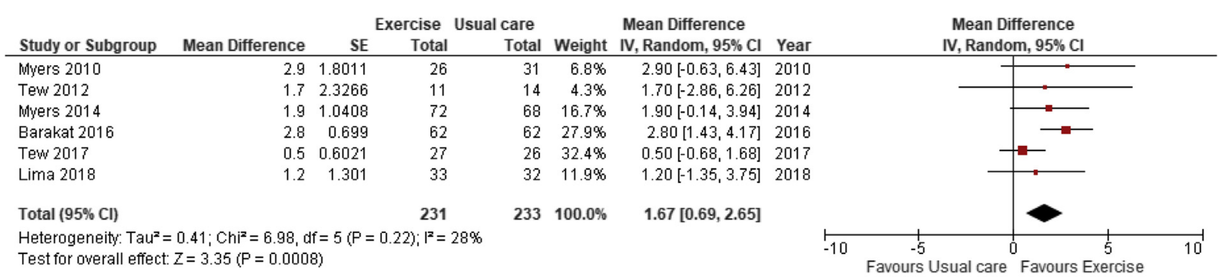

Fig 2. Forest plot comparing exercise training and usual care in terms of peak oxygen consumption ($\dot{V}O_2$; mL/kg/min) changes in abdominal aortic aneurysm (AAA) patients. *CI*, Confidence interval; *IV*, inverse variance; *SE*, standard error. If the mean difference (MD) is positive, it means that peak $\dot{V}O_2$ increased more in the exercise training group from baseline to follow-up compared to the control group.

inflammation with exercise training among AAA patients. Windsor et al[29] reported that tumor necrosis factor α, one of the inflammation markers, significantly decreased after a bout of exercise training in patients with AAA. In addition, regular exercise training is also associated with lower systemic markers of inflammation relevant to AAA.[30] However, there was no study involving participants with AAA diameter ≥55 mm regarding changes in AAA diameter and inflammation markers. More data are required to further evaluate the safety of exercise training in patients with large AAA.

Exercise capacity. Exercise capacity measurements such as peak $\dot{V}O_2$ and AT are independent predictors of short- and long-term survival after elective AAA repair.[6,31] Therefore, the cardiopulmonary exercise test could become an increasingly important tool in determining the risk, and preoperative exercise training may be extremely important for reducing postoperative adverse events for AAA patients.[32] This study showed that exercise training significantly improved peak $\dot{V}O_2$ and AT compared with the usual care with a pooled MD of 1.67 and 1.98 mL/kg/min, respectively. A previous study also showed that a 6-week supervised exercise program improved peak $\dot{V}O_2$ and AT with an MD of 1.8 and 2.2 mL/kg/min, respectively, in 20 patients awaiting AAA repair.[25] In addition, a systematic review of five RCTs reported that preoperative exercise training among AAA patients had beneficial effects on various physical fitness variables.[7] These published studies are consistent with the results of our quantitative analyses showing that exercise training improved exercise capacity in AAA patients.

In this study, there was a high degree of statistical heterogeneity across studies ($I^2 = 81\%$) for the analysis of AT, and thus we conducted a subanalysis with exercise training of ≤4 weeks and >4 weeks. Whereas the five studies with exercise training of >4 weeks significantly increased AT, one study by Tew et al reported that exercise training of ≤4 weeks did not significantly increase peak $\dot{V}O_2$ and AT among AAA patients (MD, 0.50 mL/kg/min [95% CI, −0.68 to 1.68; $P = .40$]; MD, 0.30 mL/kg/min [95% CI, −0.29 to 0.89; $P = .32$], respectively). Previous studies reported that endurance training of five times per week for 4 weeks could improve exercise capacity such as peak $\dot{V}O_2$ and AT in patients with cardiovascular disease and healthy patients.[33,34] A possible

Table IV. Changes in peak oxygen consumption ($\dot{V}O_2$) and anaerobic threshold (*AT*)

Author	Peak $\dot{V}O_2$, mL/kg/min					
	Baseline		Follow-up		Absolute change	
	Ex	Uc	Ex	Uc	Ex	Uc
Kothmann, 2009	N/A	N/A	N/A	N/A	N/A	N/A
Myers, 2010	18.5 ± 5.9	21.6 ± 7.8	20 ± 5.5	20.2 ± 7.9	1.5 ± 5.7	−1.4 ± 7.9
Tew, 2012	19.3 ± 4.5	17.9 ± 5.4	21.1 ± 6.7	18.0 ± 5.7	1.8 ± 5.9	0.1 ± 5.6
Myers, 2014	19.6 ± 6.0	20.2 ± 6.5	20.9 ± 5.9	19.6 ± 6.1	1.3 ± 6.0	−0.6 ± 6.3
Barakat, 2016	18.4 ± 4.4	19.6 ± 4.4	20 ± 3.3	18.4 ± 3.6	1.6 ± 4.0	−1.2 ± 4.1
Lima, 2018	18.8 ± 4.8	19.7 ± 5.5	19.9 ± 4.5	19.6 ± 6.0	1.1 ± 4.7	−0.1 ± 5.8
Tew, 2017	N/A	N/A	16.8	16.3	MD of absolute change, 0.5 (95% CI, −0.68 to 1.68)	

CI, Confidence interval; *Ex,* exercise training; *MD,* mean difference; *N/A,* not applicable; *Uc,* usual care.
Data are shown as mean ± standard deviation.

explanation for the discrepancy might be that there was a difference in exercise frequency. All studies included in our meta-analysis prescribed exercise training for two or three times a week. Therefore, when the frequency of exercise training is lower at two or three times a week, exercise duration of >4 weeks may be necessary to sufficiently improve exercise capacity in AAA patients.

We performed metaregression to determine whether the effects of exercise training on peak $\dot{V}O_2$ and AT were modulated by the exercise duration. However, the metaregression coefficients were not statistically significant, which suggested that the effects of exercise training on peak $\dot{V}O_2$ and AT were not modulated by the exercise duration. More studies and investigation are required to identify the optimal exercise duration for improving exercise capacity in patients with AAA.

Furthermore, previous studies showed that peak $\dot{V}O_2$ ≥15 mL/kg/min and AT ≥10 mL/kg/min preoperatively are associated with decreased risk of early death after AAA repair.[6,35] Some of the patients included in our meta-analysis had $\dot{V}O_2$ and AT values above these thresholds, whereas others did not. Targeting patients with peak $\dot{V}O_2$ <15 mL/kg/min and AT <10 mL/kg/min may be the priority for exercise training in patients awaiting AAA repair.

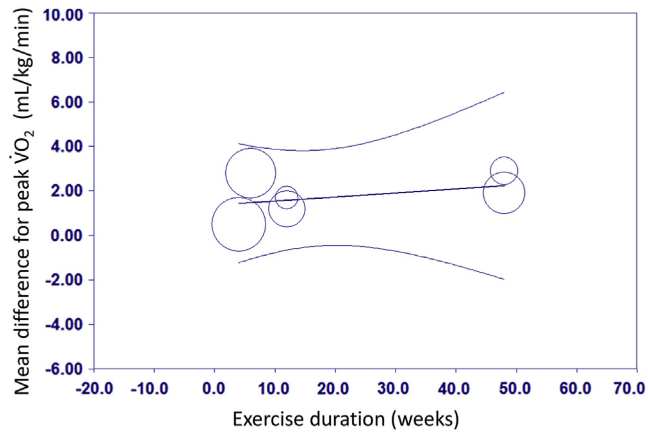

Fig 3. Metaregression analysis of the exercise duration (weeks) on the mean difference (MD) for the peak oxygen consumption ($\dot{V}O_2$).

Limitations. This meta-analysis has several limitations. First, the numbers of included studies and patients were relatively small with only 7 RCTs and 489 patients, which may not be sufficient for a valuable meta-analysis. Furthermore, some of the outcomes were reported in only a few of these seven studies. Second, although our primary goal was to compare the occurrence of cardiovascular adverse events between the exercise and control groups, this was not possible because of insufficient data in the included studies. Instead, we were able to report the occurrence of cardiovascular adverse events during the exercise test and training only in the intervention group. Third, as several studies had missing SDs for the changes from baseline to follow-up, we needed to reconstruct these data from the *P* value for differences in means between groups. Fourth, the size of AAA that becomes high risk for rupture is reported to be different between men and women.[36] However, the patients were not divided by sex because it was difficult to analyze men and women separately in this meta-analysis. Fifth, we stated that exercise duration of >4 weeks may be necessary when the frequency of exercise training is two or three times a week to improve exercise capacity in the discussion. However, it is unknown whether exercise training >4 weeks is safe in patients with AAA ≥55 mm. Therefore, exercise training to patients with large AAA may need additional supervision or regular examination, such as transabdominal ultrasound by a physician, to detect AAA expansion. Finally, the study focused on the safety of exercise

Table IV. Continued.

AT, mL/kg/min					
Baseline		Follow-up		Absolute change	
Ex	Uc	Ex	Uc	Ex	Uc
10.6 ± 2.0	10.4 ± 2.0	12.1 ± 2.2	10.8 ± 1.6	1.5 ± 2.1	0.4 ± 1.8
N/A	N/A	N/A	N/A	N/A	N/A
12.8 ± 2.4	12.2 ± 3.3	15.3 ± 3.9	12.2 ± 3.1	2.5 ± 3.4	0.0 ± 3.2
13.7 ± 4.7	16 ± 5	15 ± 3.5	13.7 ± 4.3	1.3 ± 4.2	−2.3 ± 4.7
12 ± 3	12.3 ± 2.7	13.9 ± 3.3	12.1 ± 3.0	1.9 ± 3.2	−0.2 ± 2.9
13.3 ± 3.3	15.6 ± 4.7	15.0 ± 3.4	14.3 ± 3.8	1.7 ± 3.4	−1.3 ± 4.3
N/A	N/A	11.7	11.4	MD of absolute change, 0.3 (95% CI, −0.29 to 0.89)	

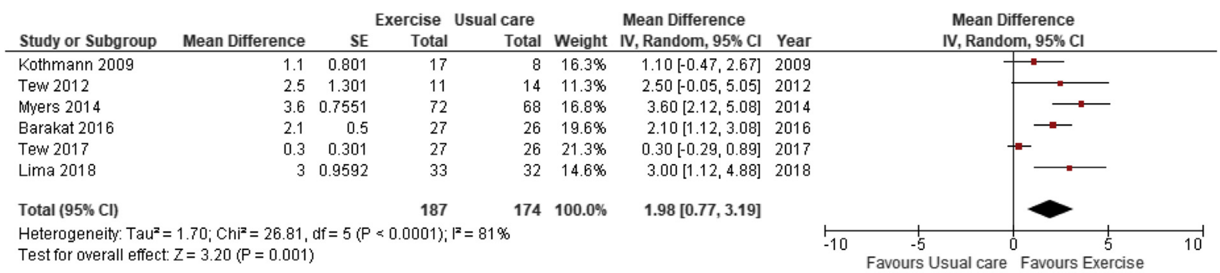

Fig 4. Forest plot comparing exercise training and usual care in terms of anaerobic threshold (AT; mL/kg/min) changes in abdominal aortic aneurysm (AAA) patients. *CI,* Confidence interval; *IV,* inverse variance; *SE,* standard error. If the mean difference (MD) is positive, it means that AT increased more in the exercise training group from baseline to follow-up compared to the control group.

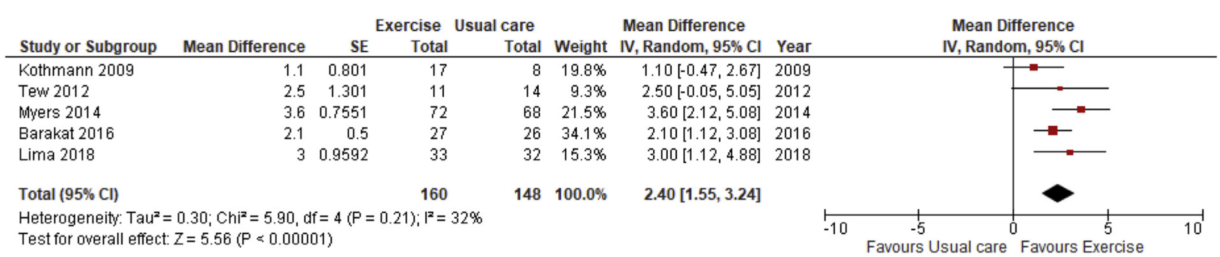

Fig 5. Subanalysis forest plot comparing exercise training and usual care in terms of anaerobic threshold (AT; mL/kg/min) changes in abdominal aortic aneurysm (AAA) patients. *CI,* Confidence interval; *IV,* inverse variance; *SE,* standard error. If the mean difference (MD) is positive, it means that AT increased more in the exercise training group from baseline to follow-up compared to the control group.

training and its effect on exercise capacity but did not evaluate the rate of postoperative complications or duration of hospital stays. Two of the studies included in our meta-analysis evaluated these outcomes but had contradictory results. Barakat et al[20] reported that preoperative exercise training reduced the incidence of postoperative cardiac, pulmonary, and renal complications and duration of hospital stay compared with the no-exercise group. On the other hand, another study suggested that preoperative exercise training did not decrease postoperative organ-specific morbidity score.[22] Therefore, further studies will be needed to compare the effects on postoperative complications or duration of hospital stay in this population of patients.

CONCLUSIONS

Our analyses suggested that exercise training among AAA patients is generally safe, although future research should be carried out to further clarify the safety among patients with large AAAs. Exercise training improved

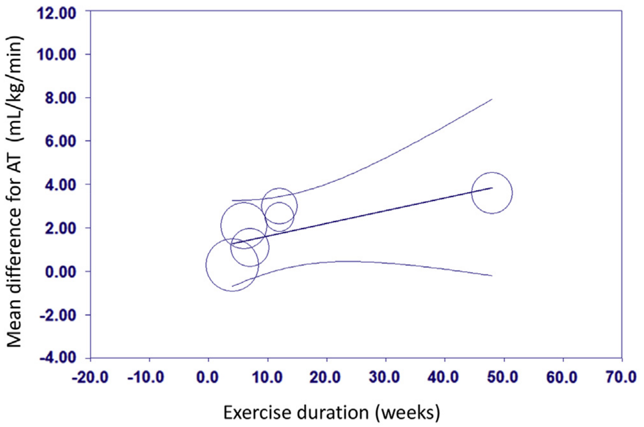

Fig 6. Metaregression analysis of the exercise duration (weeks) on the mean difference (MD) for the anaerobic threshold (*AT*).

peak $\dot{V}O_2$ and AT in AAA patients. More data are required to identify the optimal exercise duration for improving exercise capacity in patients with AAA.

AUTHOR CONTRIBUTIONS

Conception and design: MK, HT
Analysis and interpretation: MK, AK, FG, HT
Data collection: MK, AK, HT
Writing the article: MK, FG
Critical revision of the article: MK, AK, FG, HT
Final approval of the article: MK, AK, FG, HT
Statistical analysis: MK, HT
Obtained funding: Not applicable
Overall responsibility: MK

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