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Published in:
Drugs & Aging

DOI:
10.1007/s40266-020-00831-5

Publication date:
2021

License:
Other

Document Version:
Accepted author manuscript

Effect of antihypertensive and statins medication use on muscle performance in community-dwelling older adults performing strength training

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Word count:

Abstract: 296 words

Main text: 2997 words

Impact statement

We certify that this work is novel. Strength training programs have shown to prevent sarcopenia and physical decline in older adults. However, many medications such as antihypertensive drugs (AHTD) and statins drugs that older adults often use for the treatment of their chronic conditions might have an impact on or interfere with their exercise progression or ability and commitment. It is unclear whether this interferes with the expected benefits of the exercise program. In fact, the interactions between the aforementioned drugs and exercise training are not well-documented in the literature. This study reports on the interference of AHTD and statins use with muscle adaptations and physical performance following different modalities of strength training in older adults.

Abstract

OBJECTIVES:

Antihypertensive drugs (AHTD) and statins have shown to have effects beyond their primarily designed purpose; here we investigate their possible effect on muscle performance and strength in older adults following a physical exercise program.

DESIGN:

The SENIOR PROJECT INTENSIVE TRAINING (SPRINT) study is a randomized, controlled clinical trial, designed to evaluate the effects of physical exercise on the immune system and muscle performance in older adults.

PARTICIPANTS:

In this secondary analysis, we included 179 independent participants (aged 65 years and above). We applied further categorization based on medication use: AHTD (including, angiotensin-converting-enzyme-inhibitors (ACEI), angiotensin II receptor blockers (ARB), β-blockers, other-AHTD), and statins.

INTERVENTION:

Participants were allocated randomly to one of the three exercise protocols: intensive strength training 3 times/weekly (3 × 10 repetitions at 80% of one-repetition maximum), strength endurance training (2 × 30 repetitions at 40% of one-repetition maximum), or control (passive stretching exercise) for 6 weeks.

MEASUREMENTS:

The change in maximal handgrip strength (GS), muscle fatigue resistance (FR), muscle strength index (MSI), the 6-Minute Walk Test (6MWT), and Timed Up and Go Test (TUG) were assessed before and after 6 weeks of training.

RESULTS:

After six weeks, muscle strength (MSI and TUG) improved significantly in all training groups compared to baseline, independently of AHTD use. Moreover, AHTD had no effect on exercise improvements showing no significant differences between medication groups, except for TUG in ARB-

users, which exhibited a significantly lower performance. On the other hand, statin-users, presented a significant longer FR time indicating better performance compared to non-users. Finally, medication did not affect the participants' commitment to the training program

CONCLUSION:

Our study showed that statins and ARB usage might affect participant's response to strength training. Nevertheless, six weeks of training significantly improved muscle strength and performance irrespective of AHTD or statins use. .

Keywords

exercise; Antihypertensive drugs (AHTD); statins; physical performance; older adults

77 ***Declarations***

78 **Funding** This study was partly funded by the Wetenschappelijk Fonds Willy Gepts of the Universitair
79 Ziekenhuis Brussel and Strategic Growth Funding by the Research Council of the Vrije Universiteit
80 Brussel. M Alturki was supported by the Custodian of 'The Two Holy Mosques' Overseas Scholarship
81 Program (no funding ID available).

82 **Conflicts of interest/Competing interests** The authors have declared no other conflicts of interest for
83 this article. The sponsors had no role in the design, methods, subject recruitment, data collections,
84 analysis, or preparation of the article.

85 **Ethics approval** The study protocol is in accordance with the Declaration of Helsinki and was approved
86 from the local Ethics Committee (IRB 2011/257).

87 **Consent to participate** All participants gave written informed consent to participate.

88 **Consent for publication** All participants gave written informed consent for publication.

89 **Availability of data and material** All data and material are available.

90 **Code availability** Not applicable.

91 **Authors' contributions** I Bautmans and T Mets designed the study. All authors contributed to the data
92 collection. M Alturki and I Bautmans analyzed and interpreted the data. M Alturki wrote the first draft
93 of the manuscript and structured the figures and table. All the authors reviewed the draft, contributed to
94 the revision of the manuscript, and approved the final version of the manuscript.

95

1. INTRODUCTION

Ageing results in a gradual decrease in muscle mass and strength referred to as sarcopenia [1,2]. Nowadays, sarcopenia is considered a critical public health issue due to its association with low physical performance, frailty, poor health, falls, fractures, and increased utilisation of health care services, hospital admissions, institutionalisation, and higher mortality [3]. Health care systems are expected to face major challenges in the upcoming years, as the increase in human life expectancy related to increased longevity and improved living conditions will require solid plans to promote independence, healthy ageing, and decreased frailty in older adults. Several ageing-related factors are associated with the development of sarcopenia, including genetic and epigenetic influences, immobility, malnutrition, hormone deficiencies, chronic inflammation, and increased levels of inhibitors of tissue regeneration[4]. These factors can lead to a disrupt in the anabolic and catabolic pathways that regulate muscle mass and also reduce the ability to generate the energy necessary for muscles to function properly.

A large proportion of older adults have one or more chronic conditions that prompt the need for long-term treatment. A number of antihypertensive drugs (AHTD) have potential effects beyond their primarily designed purpose. For example, drugs such as angiotensin-converting enzyme inhibitors (ACEI) and angiotensin II receptor blockers (ARB), through their effects on angiotensin II activity, have been shown to influence the inflammatory pathway and functional capacity in older adults [5,6]. Also, statins are now widely accepted as having anti-inflammatory and immunomodulatory effects by reducing circulating C-reactive protein (CRP) and pro-inflammatory cytokine levels through the inhibition of mevalonate synthesis via the HMG-CoA reductase pathway [7,8].

To date, progressive exercise training has gained a fundamental place in not only helping older adults become stronger for preserving their intrinsic capacity, but also in management of sarcopenia, increasing muscle function and to suppressing systemic inflammation; as exercise has been shown to produce anti-inflammatory effects [1,9,10]. The interactions between the aforementioned drugs and exercise training are not well-documented. In our previous systematic review, only one study was found that illustrates the possible effect of ACEI on inflammation and muscle performance; that study,

however, did not include an exercise intervention. The ACEI fosinopril failed to show any significant differences in inflammatory cytokines or physical performance when compared to placebo users [11–13]. Our previous review revealed a gap in our knowledge on the effect of AHTD and statins interaction with training on muscle adaptation, physical performance and inflammation[11]; therefore, in this study we investigated the effect of chronic AHTD and statins use on the effects on muscle adaptation and physical performance in a prospective, controlled study of community-dwelling older persons.

2. PARTICIPANTS AND METHODS

2.1. The SPRINT study trial design

The present analyses were conducted (as a sub-analysis) using data from participants enrolled in the SENIOR PROJECT INTENSIVE TRAINING (SPRINT) study, registered at ClinicalTrials.gov n° NCT04534049. The SPRINT study is an ongoing prospective, randomized, controlled trial conducted by the Frailty in Ageing research department (FRIA) of the Vrije Universiteit Brussel (VUB). Overall aim of the SPRINT project is to evaluate the effect of physical exercise at different modalities and intensities on the immune system of older people and concurrent changes in their muscle performance. The study protocol is in accordance with the Declaration of Helsinki and was approved from the local Ethics Committee (IRB 2011/257). All participants gave written informed consent.

2.2. Participants

The eligibility criteria of the SPRINT study have been previously described in detail [14,15]. Briefly, the participants were community dwelling older adults (male or female, aged >65yrs). Exclusion criteria were: (1) physical exercise performance at higher intensities than habitual daily activity within the past 6 months, (2) contraindication to exercise based on the medical screening, (3) corticosteroids or nonsteroidal anti-inflammatory drugs (NSAID) usage, (4) cognitive impairment (Mini-Mental State Examination (MMSE) <24/30), or (5) physical disability that affects understanding the exercise instructions. We did not exclude comorbidity except acute, uncontrolled conditions and/or acute inflammation (C-reactive protein (CRP) ≥10mg/L). Participants were recruited through advertisements

in the form of flyers distributed in day centres, health insurance companies, senior associations, general practitioner offices, municipalities, and other public places.

2.4. Training intervention

The SPRINT study takes place in the exercise facilities of the Brussels Health Campus of the Vrije Universiteit Brussel on Technogym™ (Technogym, Gambettola, Italy) and Matrix® (Matrix, Wisconsin, USA) single station cable-type devices. In this study, there are three training groups, as previously explained [14]: (1) Intensive strength training (IST); three sets of 10 repetitions at 80% of one-repetition maximum (1RM) (i.e., the maximum weight that can be moved once over the whole range of movement), three times per week. (2) Strength-endurance training (SET); two sets of 30 repetitions at 40% of 1RM, three times per week. IST and SET exercise protocols were designed to be equal in volume (%1RM multiplied by the number of sets and repetitions). Every two weeks, the participants' 1RM was measured, and exercise loads were adapted accordingly. (3) Control group (CON) which did flexibility training; three sets of 10 to 12 sustained (30-sec) passive, static stretching exercises of the large muscle groups by applying mechanical tension to the muscles and tendons, three times per week. Regardless of the training group, participants performed a warm-up of 10 exercises without external resistance for 5-10 minutes before the start of each training session. All sessions were supervised by trained instructors to minimise the risk of injury and ensure that participants used the proper technique and weights to perform the exercise. Training adherence was calculated based on the percentage of training, considering that the ideal participant would come three times per week using the following formulas:

Expected number of training sessions= (the number of weeks trained x 3 sessions per week)

Training adherence= (the number of actual performed training / the number of expected training)

2.5. Medical screening

A physician performed a comprehensive medical screening and all necessary tests to confirm eligibility and ability to perform the exercise program.

2.6. Chronic medication use

Chronic medication was defined as any drug that is prescribed to treat any disease or other condition which is determined to be permanent, persistent or lasting indefinitely. Usage of chronic medication was assessed during baseline medical screening. Prescribed and over the counter (OTC) drugs, were identified by checking the participants' electronic medical files and inquiring. All current medications were coded to reflect their function and drug class, according to The Belgian Centre for Pharmacotherapeutic Information (BCFI) (www.bcfi.be) and the classification of the World Health Organization Anatomical Therapeutic Chemical code/Defined Daily Dose (ATC/DDD)[16]. Subsequently, we analysed the variables for AHTD and statins use with expected effects on muscle performance. This included the use of statins (ATC Code: C10AA), ACEI (ATC Code: C09A and C09B), ARB (ATC Code: C09C and C09D) and β-blockers (ATC Code: C07); while calcium-channel blockers (ATC Code: C08), thiazides (ATC Code: C03A), central and peripheral α-blockers were grouped in one variable as other-AHTD (ATC Code: C02).

After the participant is included in the study, the change in medication use is reviewed every 2 weeks and recorded through self-report.

2.7. Measurement of variables and outcomes

2.7.1. Inflammatory biomarker

At baseline, participants' venous blood specimens were collected, and the CRP levels were quantified by immunonephelometry using a high-sensitivity CRP (hsCRP) kit obtained from Dade Behring (Marburg GmbH, Germany).

2.7.2 Muscle strength and performance

Participants were assessed at baseline and after six weeks of training for: (1) maximum grip strength (GS) and (2) fatigue resistance (FR), using the Martin vigorimeter (Elmed, Addison, I11, USA), as described previously [17]. Cut-off values of less than 71 kilopascal (kPa) for men and less than 42 kPa for women indicated low muscle strength. [18]. To measure FR, the participant was asked to maintain maximal pressure as long as possible, under standardized verbal stimulation by the

investigator; the time (in seconds) until the GS dropped to 50% of its maximum value was recorded; (3) six-minute walking test (6MWT)[19]; and (4) timed up and go test (TUG)[20]. Muscle strength was measured using the one-repetition maximum (1RM). For each training device (leg press, hip adduction, hip abduction, low-row, chest press & vertical traction), the 1RM value was determined and the average 1RM for the 6 devices was defined as Muscle Strength Index (MSI).

2.8. Health categories and randomisation

Based on a modified SENIEUR's protocol and the risk for complications during physical training [21], participants were classified into health categories as described previously. In brief, the system grades each participant according to risk of complications during the training sessions, and allows the physical therapists to adapt the scheduled training program according to the health-condition of the participant[22] (Table S1). Randomisation was stratified for sex (male/female) age (65–74 / ≥75 years) and health category (Table S1) by a researcher who was blind to the study outcomes and allocation sequence.

2.9. Statistical analysis

Statistical analyses were carried out on April 2018 using the software package IBM Statistics SPSS version 25. We categorised participants according to the use of AHTD/statins as "users" and "non-users". The baseline participant's descriptive characteristics are presented according to medication groups showing mean and standard deviation (SD). The normality of distribution and homoscedastic variance of the continuous variables were tested by Kolmogorov-Smirnov and Levene's tests. Multicollinearity among the independent variables was assessed using the variance inflation factor (VIF). Only low VIF values were observed between the independent factors (VIF <10). Medication groups at baseline were compared using a one-way analysis of variance (ANOVA) test with pairwise comparison and one-way ANCOVA tests for body mass index (BMI), GS, FR, MSI, 6MWT, and TUG, adjusted for health categories, age (as the use of AHTD and statins may increase with age) and gender (as there were more females than males in our cohort), followed by post-hoc tests to verify between-groups differences. Factorial ANOVA tests were performed to explore the overall difference between

training groups after six weeks of training for GS, FR, MSI, 6MWT, and TUG, followed by a post-hoc test to verify between which groups there was a time by group interaction. As there were no significant differences between the intervention training groups (IST and SET) for GS, FR, TUG, and 6MWT, both groups were pooled in our analysis (no significant difference in the number of participants between training groups, chi-square p-value >0.05). Differences in improvement according to medication use were analysed using ANCOVA tests, adjusted for health categories, baseline score values, age, gender and use of other medication (AHTD/statin). When significant interactions between the group of medication and training interventions were observed, pairwise comparisons were performed. Statistical significance was set at $p<0.05$.

3. RESULTS

3.1. Baseline general characteristics

Our study represents 179 participants; mean age 71.6 (±4.8) years; 63.1% of them were female. Two participants withdrew before the randomisation, 11 others withdrew after training allocation but before the start of training whereas an additional 11 participants dropped-out during the study (Fig.S1). Reasons for drop-out were back pain (n=2), health problems (n=2), an old surgery scar reopened (n=1), decision to stop exercise (n=3), participant's partner dropout (n=1), death (n=1), or not reported (n=1). None of the illnesses or death were related to the study intervention.

The sample population showed 30.3% and 15.9% with low muscle strength for males and females respectively, there was no difference according to AHTD or statins use (see table 1 & 2).

AHTD group: at baseline, 49.1% took at least one AHTD: ACEI (18.4%), ARB (11.7%), β-blockers (13.4%), or any other AHTD (5.6%). Females were noticed to be significantly more in the non-AHTD-users (p=0.044). After adjustments for statin use, health categories, age and gender, no significant differences with respect to AHTD-use were observed for BMI, and hsCRP levels (Table 1).

Statins group: this represents 35.5% of our cohort. Herewith, more females were in the non-statin-users group (p=0.008). After adjustment for age and gender, no significant differences between statin users and non-users were observed at baseline for BMI and hsCRP levels (Table 2).

3.2. Baseline characteristics in muscle strength and performance

As shown in Table 1, there were no significant differences between non-AHTD-users and users for GS and FR. Overall, a significant difference in baseline performance on the 6MWT and TUG tests was observed (p=0.003 and 0.034, respectively). After applying the post-hoc test to show the medication impact on 6MWT and TUG tests this revealed, compared to non-AHTD-users, significantly lower results in ARB-users (p=0.033 and 0.03, respectively), β-blockers-users (p=0.001 and 0.004, respectively), and other AHTD-users (p=0.008 for 6MWT but was not significant for TUG). ACEI-users showed tendency for lower performance in 6MWT compared to non-AHTD-users (p=0.08). Moreover, there was no statistically significant difference between the four AHTD groups at baseline in performance, both the 6MWT and TUG had a tendency for lower performance in β-blockers-users as compared to ACEI-users (p=0.079 and 0.052, respectively). As presented in Table 2, the baseline physical performances of statin-users did not differ significantly from those of non-users.

3.3. Effects of training interventions

After six weeks of training, significant improvement was observed for MSI ($p<0.001$). Overall, there was a significant time*training group interaction (p=0.001), with the control group showing significantly lower MSI gain compared to the two training interventions. Moreover, the two training groups did not differ significantly in the observed MSI improvement. Additionally, an overall improvement in TUG scores was observed ($p<0.001$); however, no significant difference between groups was found. The 6MWT did not show a significant difference over time between groups (Table 3).

3.4. Exercise-induced changes in muscle strength and performance according to medication use

During the two weekly medical screenings, none of the included participants reported changes in health status or medication of interest over the six-week training program. After six weeks of training AHTD users showed lower adherence to the exercise program (IST+SET) than non-AHTD users (p=0.031),

both β-blockers and other-AHTD users were significantly lower in adherence compared to non-AHTD users (p=0.005 and 0.024, respectively). Statins use did not reveal any difference in adherence to the exercise intervention: no significant difference between users and non-users was observed (Table S2).

Both exercise protocols were approximately equal in volume and showed no significant difference in improvement after training (Table 3). Therefore, the two intervention groups (IST and SET) were pooled and the results after six weeks of training were adjusted for baseline scores, age, and gender.

Between AHTD-users and non-users, no overall differences were found for change in GS, FR, MSI, and 6MWT after six weeks of training (Table 4). When compared to baseline scores, the statistically significant difference that had previously been observed between AHTD-users and non-users for 6MWT had attenuated after six weeks of training. There was a significant overall effect of exercise on TUG (p=0.03). However, ARB-users improved the least compared to non-AHTD-users, ACEI-users, and other-AHTD-users (p=0.01, 0.01, and 0.02, respectively), but not to β-blockers-users. On the other hand, when ACEI- and ARB-users were grouped together (Table S3), results showed that there were no statistical significant differences in scores between the AHTD-users and non-users for GS, FR, MSI, TUG and 6MWT after six weeks of training.

Statin-users, as compared to non-users improved significantly more for FR (p=0.03). No other significant differences were observed between groups in either physical performance or muscle strength (Table 5).

4. DISCUSSION

Chronic medication use is common among older adults and can be expected to interfere with exercise in several ways, including influencing skeletal muscle performance and training effects, or interfering with training schedules and creating training barriers. The novelty of our study is that, six weeks of

training improved muscle strength and widely prescribed AHTD and statins did not impair exercise improvements, nor did they affect participants' commitment to the training program. In contrary, this rapid response can motivate older adults to adhere to exercise programs. With respect to AHTD, and after controlling for baseline values, those participants receiving ARB did not show improvement in the TUG test as compared to non-users of AHTD. Thus, the gap in performance that was observed at baseline was not overcome after six weeks of intervention, suggesting that chronic ARB use might have a negative effect on older adult's mobility performance. Participants taking statins improved more on the FR test than did non-users.

Recent literature reviews showed that several drugs that target the renin-angiotensin system have shown beneficial effects on inflammation, skeletal muscle metabolism and oxygen delivery improvement [6,23–26]. However, other studies presented contradicting findings [27–36]. This discrepancy could relate to the studies design (with or without exercise), the type of drug, the participants' characteristics and health status, the study duration, and the outcome measures. Mixed findings were obtained with respect to the effect of ACEI without exercise, showing either no or favourable effects [13,27–31,37,38]. Two of the three studies examining the effect of ACEI combined with exercise clearly showed beneficial effects on performance [32–34]. These two studies compared ACEI-users to other AHTD-users and had longer exercise programs (12 and 24 months) [32,33]. In our cohort, six weeks of training might not have been enough to show a similar effect.

After six weeks of exercise training, SPRINT participants showed improvements in muscle strength and physical performance (MSI and TUG test), despite AHTD or statins use. The AHTD-users did not perform differently from non-users except that ARB-users showed significantly slightly more time to do the TUG test than did non-users. Other studies of ARB-users who had left ventricle hypertrophy or right ventricle dysfunction suggested no beneficial effects on exercise capacity [35,36]. Some indicated a protective association between ARB use and functional decline [39] while others showed its favourable interaction with exercise, reporting better functional exercise capacity [5]. These findings contrast with those of our study, in which, at baseline, ARB users performed less well on 6MWT and

TUG compared to non-AHTD users. On the other hand, β-blockers users showed a tendency for lower performance on 6MWT and TUG as compared to ACEI-users, which might have been due to the negative chronotropic and inotropic properties of β-blockers and their side-effects [40]. Another explanation could be the lower adherence to the exercise program something that has been observed in our data during the first 6 weeks of follow up, thus, special consideration should be given to these type of patients in order to motivate them to adhere to a regular exercise program which can significantly impact not only their muscle performance but also provide a cardiovascular protective effect.

When ACEI- and ARB-users were grouped, outcomes showed no difference in performance compared to non-users, this was different from what we have observed when they were ungrouped. A possible explanation is that those two drugs might have a different protective pathway.

Statins are feared for provoking myopathy, a common side effect that can be linked to muscle weakness and that can promote sedentary behaviour [41]. However, the literature is inconsistent, as several studies could not confirm a decrease in functional performance or any difference in muscle strength and exercise capacity [30,42]. Still, others presented favourable effects [43–45]. In longitudinal studies, statin use was not associated with more pronounced declines in physical function; in fact, better self-perceived physical function was observed [46,47]. Several studies suggested that statin use and exercise training had a positive interaction with respect to muscular response, performance, functional status, and proximal muscle strength [33,48,49], while, on the other hand, other studies reported that statins may increase the incidence of exercise-related complaints, reduce aerobic exercise tolerance, and result in greater declines in strength and impaired exercise capacity in older males [50–53]. These inconsistencies in outcomes could be related to the heterogeneity of the included participants and the different outcome-measures. Moreover, these discrepancies could be also related to the different intensities of statins which can depend on the molecule or the dose strength and their impact on hsCRP.[54]. However, in other studies, this impact on hsCRP was not observed [55,56]. In general, our study was consistent with those that showed a positive effect of statins on exercise training with respect FR. There might be a connection with the effect of statins on endothelial function and vascular reactivity; nevertheless, the anti-inflammatory action of statins cannot be neglected[7].

Preventive care and regular muscle-strengthening exercises should be considered by clinicians and care providers for promoting and maintaining healthy ageing. Preserving or even enhancing functional ability and intrinsic capacity of older adults have been emphasized by the WHO recommendations, enabling older people to remain a resource to their families, communities and economies. Despite the small improvement in muscle performance that have been observed in our study, medication use was not a barrier for these improvements and these results should provide confidence to health care providers to promote the importance of exercise even in those using chronic medication as it doesn't show inhibition or negate benefits.

Our work has some limitations. As the SPRINT project was not designed to test the effect of chronic medication use on training performance, the study design did not allow us to claim a cause-effect relationship. Also, because many of the participants used more than one medication, it was not possible to conduct a head-to-head drug comparison of our chosen outcomes. Furthermore, the SPRINT study participants are representing a sample of well-functioning older adults who are willing to join a training program. Although this could have induced a selection bias, our participants, however, can be considered as a representative group of older people who would engage in this type of exercises. Unlike in randomised trials, confounding factors in observational studies could influence the outcome measures, even though we applied the recommended statistical methods such as stratification and adjustment to control them in our models. We also could not include the dose of medication in our analysis and length of time participants had been on the medications of interest; although the adherence on medication during the 6 weeks of training was assessed every 2 weeks. Moreover, due to the short term of follow up we observed small average improvements in strength and performance which may not give a clinically meaningful change. Finally, due to the small sample size in each medication group, other factors could have influenced the results, such as drug-drug and drug-disease interactions, duration of treatment, type of drug, and dosage. Future results from the SPRINT trial will verify the shape of improvement in further time points in our cohort .

5. CONCLUSIONS

Although the literature suggested that many chronic medications effects older adults' gains from exercise, our study provides evidence that widely prescribed AHTD and statins did not affect participants' commitment to the training program, nor did it hinder exercise improvements, except in the case of ARB-users who showed significantly lower improvement in TUG. Our results support the notion that the beneficial outcome of exercise is not limited to healthy older individuals but, rather, also extends to those with chronic conditions that require chronic medication use. Future longitudinal studies are necessary to confirm our observations and advance our understanding of their mechanistic anti-inflammatory pathways.

6. ACKNOWLEDGEMENTS

The authors acknowledge and greatly appreciate all participants for their contribution to science by participating in the SPRINT study.

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567

	Non-AHTD-users (n=92)	ACEI-users (n=34)	ARB-users (n=21)	β blockers-users (n=24)	Other-AHTD-users (n= 8)	p value
Age (mean ± SD, years)	71.17 ± 4.4	72.26 ± 5.58	73.33 ± 5.21	70.07 ± 3.55	72.72 ± 5.54	0.15
Age Category, years N (%)						0.26¤
<75	69 (52.67%)	22 (16.79%)	14 (10.69%)	19 (14.50%)	7 (2.98%)	
≥75	22 (45.83%)	11 (22.91%)	7 (14.58%)	5 (10.42%)	3 (6.25%)	
Gender N (%)						**0.04¤**
Male	31 (46.97%)	17 (25.76%)	8 (12.12%)	4 (6.06%)	6 (9.09%)	
Female	60 (53.10%)	16 (14.16%)	13 (11.50%)	20 (17.70%)	4 (3.54%)	
Health Category [(1)]						**<0.001°**
A1	9	0	0	0	0	
A2	13	0	0	0	0	
B1	44	0	0	0	0	
B2	12	21	14	19	7	
C	14	13	7	5	1	
BMI ($mean_{Adj}$ ± SE, kg/m^2)	26.16 ± 0.55	28.64 ± 0.85	28.08 ± 1.03	28.51 ± 1.01	26.93 ± 1.41	0.14
hsCRP ($mean_{Adj}$ ± SE, mg/l)	1.40 ± 0.21	2.37 ± 0.32	2.15 ± 0.38	2.12 ± 0.37	1.63 ± 0.54	0.16
GS ($mean_{Adj}$ ± SE, kPa)	65.03 ± 1.69	61.65 ± 2.62	61.34 ± 3.15	58.09 ± 3.02	61.61 ± 4.33	0.42
Prevalence of muscle weakness according to GS[(2)] (%)	15.9%	29.0%	35.0%	27.3%	30.0%	0.20¤

FR (mean$_{Adj}$ ± SE, sec)	69.76 ± 4.13	63.87 ± 6.39	56.28 ± 7.70	70.46 ± 7.38	73.18 ± 10.58	0.55
MSI (mean$_{Adj}$ ± SE, kg)	42.96±1.33	40.18± 2.00	41.27±2.52	38.17±2.33	36.46±3.27	0.27
TUG (mean$_{Adj}$ ± SE, sec)	6.47 ± 0.15	6.74 ± 0.24	7.22 ± 0.29 *	7.43 ± 0.27 *	6.78 ± 0.39	**0.034**
6MWT (mean$_{Adj}$ ± SE, m)	589.41 ± 7.52	563.18 ± 11.67 *	553.04 ± 14.21 *	532.84 ± 13.29 *	532.98 ± 19.05 *	**0.003**
Training						0.91¤
IST	31	10	5	10	4	
SET	30	12	7	7	3	
CON	29	12	9	7	1	

Table 1: Participants characteristics at baseline according to AHTD use. BMI, body mass index; hsCRP, C-reactive protein; GS, grip strength; FR, fatigue resistance; 6MWT, 6-minute walk test; TUG, time up and go; MSI, muscle strength index; sec, seconds; kPa, kilopascal; m, meters, IST, intensive strength training; SET, strength endurance training; CON, control. Values are number unless otherwise indicated. (1) For details, see table S1. (2) a cut-off value of less than 71 kilopascal (kPa) for men and less than 42 kPa for women to indicate low muscle strength[18]. Significance: $p < 0.05$. P-values were derived using univariate analysis (continuous) or ¤ chi-square tests (categorical) or ° fisher's exact test for each characteristic. * Significantly different from non-AHTD-users (One-way ANOVA and One-way ANCOVA [BMI, hsCRP, GS, FR, MSI, 6MWT and TUG], adjusted for statin use, health categories, age and gender).

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	Non-users (N=115)	Users (N=64)	p value
Age (mean ± SD, years)	71.13 ± 4.32	72.41 ± 5.42	0.10
Age Category, years N (%)			0.18¤
<75	87 (66.41%)	44 (33.59%)	
≥75	29 (60.42%)	19 (39.58%)	
Gender N (%)			**0.008¤**
Male	35 (53.03%)	31 (46.97%)	
Female	81 (71.68%)	32 (28.32%)	
Health Category (1)			**<0.001°**
A1	8	0	
A2	11	3	
B1	35	11	
B2	44	26	
C	17	24	
BMI ($mean_{Adj}$ ± SE, kg/m^2)	27.16 ± 0.44	27.31 ± 0.62	0.85
hsCRP ($mean_{Adj}$ ± SE, mg/l)	1.83 ± 0.17	1.72 ± 0.23	0.71
GS ($mean_{Adj}$ ± SE, kPa)	63.17 ± 1.34	62.16 ± 1.86	0.67
Prevalence of muscle weakness according to GS(2) (%)	29%	32.2%	0.61¤

FR (mean$_{Adj}$ ± SE, sec)	64.66 ± 3.28	72.21 ± 4.55	0.19
MSI (mean$_{Adj}$ ± SE, kg)	40.40±1.04	42.52±1.44	0.25
TUG (mean$_{Adj}$ ± SE, sec)	6.75 ± 0.12	6.78 ± 0.17	0.88
6MWT (mean$_{Adj}$ ± SE, m)	565.69 ± 5.91	575.20 ± 8.28	0.37
Training			0.29¤
IST	33	27	
SET	42	17	
CON	38	20	

Table 2: Participants characteristics at baseline according to statins use. BMI, body mass index; hsCRP, C-reactive protein; GS, grip strength; FR, fatigue resistance; 6MWT, 6 minutes walking test; TUG, time up and go; MSI, muscle strength index; sec, seconds; kPa, kilopascal; m, meters; IST, Intensive Strength Training; SET, Strength Endurance Training; CON, control. Values are number unless otherwise indicated. (1) For details see Table S1. (2) a cut-off value of less than 71 kilopascal (kPa) for men and less than 42 kPa for women to indicate low muscle strength. Significance: $p < 0.05$. P-values were derived using univariate analysis (continuous) or ¤ chi-square tests (categorical) or ° fisher's exact test for each characteristic. * Significantly different from non-users (One-way ANOVA and One-way ANCOVA [BMI, hsCRP, GS, FR, MSI, 6MWT and TUG], adjusted for AHTD use, health categories, age and gender).

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							Time	**Time x group effect**
	IST		SET		CON			
	Baseline	6 weeks	Baseline	6 weeks	Baseline	6 weeks		
GS (mean ± SD, kPa)	63.87±16.27	63.00±14.92	62.26±17.78	62.06±16.90	63.17±22.40	64.00±21.93	0.88	0.42
FR (mean ± SD, sec)	61.84±28.48	63.05± 27.97	67.18± 34.57	63.41± 33.52	74.09± 36.28	66.50± 37.11	0.23	0.45
MSI (mean ± SD, kg)	42.71±17.06	52.51±22.44	40.58±16.83	47.51±17.38	39.80±15.71	42.49±14.74*****	**<0.001**	**0.001**
TUG (mean ± SD, sec)	6.55±1.11	6.32± 1.05	6.85± 1.45	6.48± 1.17	6.93± 1.44	6.55± 1.24	**<0.001**	0.66
6MWT (mean ± SD, m)	576.72±79.36	585.59±75.29	572.59± 68.66	571.95± 60.59	564.31± 81.96	568.67± 86.49	0.21	0.52

587 **Table 3.** Effect of training on muscle strength and performance (mean ± SD). IST, Intensive Strength Training; SET, Strength Endurance Training; CON,
588 control; FR, fatigue resistance; GS, grip strength; 6MWT, 6 minutes walking test; TUG, time up and go; MSI, muscle strength index; sec, seconds; kPa,
589 kilopascal; m, meters. Repeated measures ANOVA, Significance: $p < 0.05$, * Significant difference from IST and SET training groups.

Parameter	AHTD	N	6 weeks	p value
			$Mean_{Adj}$ (SE)	
GS				0.06
	Non-AHTD user	52	61.75(0.91)	
	ACEI	15	62.71(1.62)	
	ARB	10	67.95(1.88)	
	β Blocker	13	61.64(1.70)	
	Other-AHTD	7	61.59(2.18)	
FR				0.09
	Non-AHTD user	52	67.54(4.46)	
	ACEI	15	47.78(7.95)	
	ARB	10	51.09(9.07)	
	β Blocker	13	64.58(8.29)	
	Other-AHTD	7	79.20(10.79)	
MSI				0.77
	Non-AHTD user	50	50.2749.70(1.68)	
	ACEI	15	48.62(2.89)	
	ARB	10	53.09(3.43)	
	β Blocker	13	49.75(3.05)	
	Other-AHTD	7	46.89(4.02)	
TUG				**0.03**
	Non-AHTD user	51	6.29(0.12)	
	ACEI	15	6.24(0.21)	
	ARB	10	7.05(0.25) **ǂ§**	
	β Blocker	13	6.70(0.22)	
	Other-AHTD	7	6.22(0.28)	
6MWT				0.24
	Non-AHTD user	50	588.27(6.15)	
	ACEI	14	571.08(10.99)	
	ARB	8	559.99(14.17)	
	β Blocker	13	560.73(11.29)	
	Other-AHTD	7	579.58(14.85)	

Table 4. Effect of AHTD use with training intervention (IST+SET) on muscle strength and performance. ANCOVA, adjusted for baseline scores, health categorises, age, gender and statins use. GS, grip strength; FR, fatigue resistance; 6MWT, 6 minutes walking test; TUG, time up and go; MSI, muscle strength index. * Significantly different from non-AHTD users; ǂ Significantly different from ACEI users; § Significantly different from Other-AHTD-users, Significance: $p < 0.05$.

	Statins use	N	6 weeks	p value
			$Mean_{Adj}$ (SE)	
GS				0.21
	No	64	63.12(0.76)	
	Yes	33	61.35(1.10)	
FR				**0.03**
	No	64	58.08(3.71)	
	Yes	33	73.22(5.38) *****	
MSI				0.75
	No	63	49.73(1.32)	
	Yes	32	50.50(1.91)	
TUG				0.86
	No	63	6.40(0.10)	
	Yes	33	6.43(0.14)	
6MWT				0.32
	No	61	581.72(4.95)	
	Yes	31	572.52(7.21)	

Table 5. Effect of statins use with training intervention (IST+SET) on muscle strength and performance. Repeated measures ANCOVA, adjusted for baseline scores, health categorises , age, gender and AHTD-use. GS, grip strength; FR, fatigue resistance; 6MWT, 6 minutes walking test; TUG, time up and go; MSI, muscle strength index. * Significant difference from non-users, Significance: $p < 0.05$.

Health Category		Description *	Clinical examples
A	**A1**	Completely healthy; no medication	
	A2	Completely healthy; using only preventive medication	Hormonal replacement therapy, aspirin, …
B	**B1**	Functioning normally; presence of stabilised, non cardiovascular disease; absence of cardiovascular abnormalities	treated hypothyroidism, stable diabetes, …
	B2	functioning normally; using medication with cardiovascular effect, no overt cardiovascular disease other than normalized arterial hypertension	Arterial hypertension; β blocking agent, …
C		(history of) cardio-vascular pathology or abnormal ECG.	Bundle branch block; angina, CABG; …
D		presenting signs of acute or active disease at the moment of examination.	bronchospasm, swollen joints, influenza, …

Table S1: Health categories for risk stratification of complications during physical exercise in elderly persons. Table adapted from Bautmans et al [22], * Status after questioning, physical examination, ECG, and laboratory examination of blood, serum & urine according to the SENIEUR protocol [21]. CABG: coronary artery bypass graft

Medication	N	6 weeks	p value
		$Mean_{Adj}$ (SE)	
			0.031
Non-AHTD user	52	87.81(4.79)	
ACEI	19	74.53(7.49)	
ARB	10	67.63(9.70)	
β Blocker	15	59.17(8.14)*	
Other-AHTD	8	60.22(10.65)*	
			0.28
Non-statin users	66	79.81(3.72)	
Statin users	38	72.64(5.07)	

Table S2. The percentage of adherence to training interventions (IST+SET) according to AHTD and statins use. ANCOVA adjusted for medication use (statin/AHTD), health categories age, and gender, * Significant difference from non-users, Significance: $p < 0.05$.

Parameter	AHTD	N	6 weeks	p value
			$Mean_{Adj}$ (SE)	
GS				0.26
	Non-AHTD user	52	61.70(0.93)	
	ACEI+ARB	25	64.87(1.34)	
	β Blocker	13	61.71(1.74)	
	Other-AHTD	7	61.66(2.23)	
FR				0.05
	Non-AHTD user	52	67.52(4.44)	
	ACEI+ARB	25	49.12(6.42)	
	β Blocker	13	64.60(8.24)	
	Other-AHTD	7	79.22(10.73)	
MSI				0.88
	Non-AHTD user	50	50.25(1.68)	
	ACEI+ARB	25	50.42(2.36)	
	β Blocker	13	49.79(3.05)	
	Other-AHTD	7	46.94(4.03)	
TUG				0.34
	Non-AHTD user	51	6.29(0.12)	
	ACEI+ARB	25	6.56(0.18)	
	β Blocker	13	6.70(0.22)	
	Other-AHTD	7	6.22(0.29)	
6MWT				0.17
	Non-AHTD user	50	588.15(6.13)	
	ACEI+ARB	22	567.09(9.14)	
	β Blocker	13	560.70(11.26)	
	Other-AHTD	7	580.06(14.78)	

Table S3. Effect of AHTD use with training intervention (IST+SET) on muscle strength and performance. ANCOVA, adjusted for baseline scores, health categorises, age, gender and statin use. GS, grip strength; FR, fatigue resistance; 6MWT, 6 minutes walking test; TUG, time up and go; MSI, muscle strength index. Significance: $p < 0.5$.