The influence of hypertension management on frailty prevention among older persons aged 65 and over

Gerontopole Brussels Study group; Qipo, Orgesa; Debain, Aziz; Bautmans, Ivan; Scafoglieri, Aldo

Published in:
Aging Clinical and Experimental Research

DOI:
10.1007/s40520-022-02247-0

Publication date:
2022

License:
Unspecified

Document Version:
Accepted author manuscript

The influence of hypertension management on frailty prevention among older persons aged 65 and over: a systematic review

*Orgesa Qipo[a], *Aziz Debain[a,b], Ivan Bautmans[a,b,c,1], on behalf of the Gerontopole Brussels Study Group[d].

[a]Gerontology department, Vrije Universiteit Brussel (VUB), Laarbeeklaan 103, B-1090 Brussels, Belgium

[b] Frailty in Ageing (FRIA) Research department, Vrije Universiteit Brussel (VUB), Laarbeeklaan 103, B-1090 Brussels, Belgium

[c]Department of Geriatrics, Universitair Ziekenhuis Brussels (UZBrussels), Laarbeeklaan 101, B-1090 Brussels, Belgium

[d] Members of the Gerontopole Brussels Study group: Ivan Bautmans (FRIA, VUB) ivan.bautmans@vub.be; Dominque Verté (Belgian Ageing Studies BAST, VUB) dominique.verte@vub.be; Ingo Beyer (Geriatric Medicine department, UZ Brussel) ingo.beyer@uzbrussel.be; Mirko Petrovic (ReFrail, UGent) mirko.petrovic@ugent.be; Nico De Witte (Belgian Ageing Studies BAST, VUB) nico.de.witte@vub.be; Tinie Kardol (Leerstoel Bevordering Active Ageing, VUB) mjmkardol@hotmail.com; Gina Rossi (Clinical and Lifespan Psychology KLEP, VUB) grossi@vub.be; Peter Clarys (Physical Activity and Nutrition PANU, VUB) pclarys@vub.be; Aldo Scafoglieri (Experimental Anatomy EXAN, VUB) aldo.scafoglieri@vub.be; Erik Cattrysse (Experimental Anatomy EXAN, VUB) ecattrys@vub.be; Paul de Hert (Fundamental Rights and Constitutionalism Research group FRC, VUB) paul.de.hert@vub.be; Bart Jansen (Department of Electronics and Informatics ETRO, VUB) bart.jansen@vub.be

*** joint first author (contributed equally)**

Corresponding author & contact details

[1]Corresponding author: Ivan Bautmans, PhD, Gerontology (GERO) and Frailty in Ageing Research (FRIA) Departments, Vrije Universiteit Brussel (VUB), Laarbeeklaan 103, B-1090 Brussels, Belgium. E-mail address: ivan.bautmans@vub.be (I. Bautmans)

ABSTRACT

Background: Frailty and hypertension are interrelated, but it remains unclear whether this relationship is modified by antihypertensive drugs.

Methods & results: A systematic review of PubMed and Web of Science databases was performed to review the influence of hypertension management on preventing the occurrence or progression of frailty in older people aged 65 and over. Studies providing information on this association regardless of the study setting, or definition of hypertension and frailty were included. Among the initial 2298 articles identified, 7 were included in the review. Three observational studies assessed the association between frailty and hypertension. Two of them reported no relationship between Aldosterone Antagonists use and frailty prevention. No relationship between BP and incidence frailty after adjustment for hypertension treatment was observed in two other articles. An indirect relationship was reported in the RCTs included. Higher AT11RaAb levels (control group), can lead to a generalized weakness/ frailty risk shown by a decrease in grip strength (r=–0.57, p<0.005) and walking speed (r=–0.47, p<0.005). No significant differences between int--hypertensive intervention and control were observed in frailty status after 12-weeks follow-up after applying three different frailty measurement tools in the other RCT.

Conclusions: Based on the results of this systematic review we conclude that BP and frailty occur together but whether the treatment with anti-hypertensive drugs modifies this relationship remains unclear and needs to be further investigated.

Keywords

Hypertension; Antihypertensive agent; Aged; Frail; Systematic review

1. BACKGROUND

The world's population is aging rapidly driven by increasing levels of life expectancy and decreasing levels of fertility [1]. The most problematic expression of population ageing is the clinical condition of frailty [2]. This condition has a high prevalence, ranging from 8% to 16% in community-dwelling older adults aged 65 and over [3]. Frailty may be conceptually defined as a clinically recognizable state in older people who have increased vulnerability, resulting from age-associated declines in physiological reserve and function across multiple organ systems, such that the ability to cope with acute or everyday stressors, is compromised. It is characterized by multisystem dysregulations, leading to a loss of dynamic homeostasis and physiological reserve and an increased vulnerability for subsequent morbidity and mortality. Frequent components of the biological substratum underlying frailty include a pro-inflammatory state, sarcopenia, anemia, relative deficiencies in anabolic hormones (androgens and growth hormone) and excessive exposure to catabolic ones (cortisol), insulin resistance, compromised or altered immune function, micronutrient deficiencies and oxidative stress [4]. These manifestations emphasize the importance and need for frailty intervention and prevention in older adults. Since frailty is at least partially reversible [2, 5], interventions to reduce the severity or prevalence of frailty can have important benefits in this population of older persons.

Several studies [3, 6-10] have assessed the association of frailty with hypertension, a chronic condition in which the blood vessels show persistently raised pressure which can increase the risk of heart, brain, kidney and other diseases [11]. Arterial stiffness is the major cause of elevated systolic blood pressure (SBP) and pulse pressure (PP = SBP minus diastolic blood pressure [DBP]), as well as lower DBP in older adults. Moreover, these age-related alterations in blood pressure are powerful determinants of major cardiovascular disease (CVD) events and all-cause mortality [12]. Reaching old age in optimal cardiovascular health, as represented by a higher number of ideal cardiovascular metrics, is also associated with lower risk of frailty. The main contributors to cardiovascular health are physical activity and body weight [13].

In a study conducted in Brazil [7] it was found that hypertension was more prevalent in the pre-frail (72.5%) and frail (83%) groups than among controls (51.7%), and significantly associated with frailty. The hypertension clinical practice guidelines released in 2017 [14] advocate that blood pressure lowering therapy is one of the interventions that can reduce mortality risk in frail older individuals. Moreover, hypertension is related to poorer cognitive performance in adults and hypertension-related changes in the brain are well-documented [15-18]. SBP and DBP levels have been inversely related to cognitive performance level [19]. Hypertension leads to chronic endothelial dysfunction which is a risk factor for cognitive decline, disrupting the integrity of endothelial cells (ECs) and contributing to oxidative stress, inflammation, and atherosclerosis [16, 20]. (See figure 1)

Nevertheless, there are relatively few studies focusing on the effects of antihypertensive treatment on frailty and the benefits of the various therapeutic strategies [21]. The benefit to risk ratio of treating patients with hypertension aged 80 or older has not yet been established. One of the largest studies conducted in hypertensive subjects aged 80 or older, the HYVET study [9], concluded that both the frailer and the fitter older adults with hypertension may benefit from treatment. However, further work is needed to explore whether antihypertensive treatment modifies frailty as measured by the Frailty Index (FI) [22]. Better insights regarding the impact of hypertension therapy on frailty could potentially help in treatment optimization in frail older persons. Furthermore, the best target values and choice of antihypertensive treatment for frail older adults are still under debate.

The aim of this study is to systematically review the literature and provide pooled estimations of evidence regarding the influence of hypertension management on preventing the occurrence or progression of frailty.

2. METHODS

2.1. Data sources and search

We reviewed studies providing information on the association between frailty and treatment of hypertension in older people (i.e., 65 years or older), regardless of the study setting or definition of hypertension and frailty. The protocol of the present study was registered in the international prospective register of systematic reviews (registration number: CRD42021256855). This systematic review was carried out in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses recommendations [23].

We searched two databases on 20 December 2020 for relevant articles: (1) PubMed electronic database of the National Library of Medicine and (2) Web of Science. The detailed search queries are reported below:

[("Aged"[MeSH] OR "Aged, 80 and over"[Mesh] OR elderly OR old) AND ("Antihypertensive Agents"[Mesh] OR antihypertens* OR blood pressure OR hypertens*) AND ("Frailty"[Mesh] OR Frail*)] in PubMed and

[(elderly OR aged OR old) AND (hypertension treatment OR hypertension OR blood pressure OR antihypertens*) AND (frail* OR frailty*)] in Web of Science.

2.2 Study selection

EndNote Desktop version X9 was used to remove duplicates from PubMed and Web of Science search results, and the Rayyan web application [24] was used for eligibility screening and in/exclusion. Two researchers independently screened records for inclusion. The researchers were blinded to each other's decisions. Conflicts were resolved based on consensus. Final inclusion was based on full-text screening.

Inclusion criteria were defined as: 1) articles that provided information on the association between hypertension management and frailty among older people aged 65 years and over; 2) articles in English; 3) study design: cohort, cross-sectional, randomized and non-randomized studies
Exclusion criteria were defined as: 1) articles not investigating the aims of the review; 2) including middle aged adults or older people aged 65 or over without hypertension; 3) articles not in English.

2.3 Study quality assessment

The methodological quality of the studies was evaluated independently by two assessors using the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies [25] and the RoB 2 tool for randomized control trials [26].

2.4. Data extraction

The full text of the articles selected by the assessors were retrieved for evaluation. Two assessors read the full texts and independently extracted the information from the selected studies. In each included article, hazard ratios or odd ratios were extracted when available. We reported on existing comorbidity in the patients' population and settings (community dwelling, hospitalized or institutionalized older adults). Other confounders such as as duration of intervention and the age of the participants were also extracted.

3. RESULTS

3.1. Search results

A total of 2298 articles were identified by the literature search. 675 duplicates were removed and the other 1627 articles were screened based on the title and abstract. 1613 articles were excluded, leaving 14 potentially eligible articles. After reviewing the full text of these articles, another 7 articles were excluded. Reasons for exclusion were no treatment intervention and wrong study outcome (e.g. no frailty measurements). The remaining 7 articles were included in this systematic review (Figure 1).

3.2. Study quality

Overall, the quality of the articles was good. The article of Sanders et al. [27]was rated as fair (Table 2), because it was a post-hoc analysis of the TOPCAT trial and the frailty classes were not pre-specified nor directly measured. From the randomized controlled trials, the article of Abadir et al. [28] showed a high risk of bias (Table 3) because of a relatively small sample size of the validation group (60 participants), impeding robust analyses of drug (ARBs) effects on frailty. Also, the authors did not assess at-risk status in subjects using the complete Fried criteria for frailty.

3.3. Study and participants' characteristics

The included studies were published between February 2009 and January 2020. Five studies were observational studies and the other two were randomized controlled trials. The majority of the studies included community-dwelling older persons. The number of participants per study ranged between 60 and 27378. The total number of included participants (n=34589) can be categorized as community dwelling (n=32606), hospitalized (n=1923) and living in a long term facility (n=60). The average age ranged from 63 to 85 years old across the studies. The studies were carried out in the United States of America (n=4), Europe (n=2) and in Asia (China, n=1). Hypertension was measured either through a 24-hours monitoring of BP or ambulatory BP monitoring. Different frailty scales were used, of which the physical frailty phenotype as described by Fried et al. [29] was the most common (Table 1).

3.4. Study Results

Table 1 provides an overview of the included articles. Five observational studies[27, 30-33] and two randomised control trials [28, 34] assessed the association between hypertension treatment and frailty occurrence or progression. Results were different across studies. The study of Anker et al. [30] revealed that BP and frailty occur together in older adults, but after adjustment for antihypertensive treatment, the associations between frailty status and BP did not change substantially. A higher odds ratio was found for women (OR [95% CI] =2.45 [1.22-4.92], p=0.0115) compared to men (OR =1.45 [0.54-3.98], p=0.457).

A similar conclusion was derived from the article of Ghazi et al. [31], where no significant association between BP and incident frailty was found after multivariable adjustment (age, race, sex, marital status, income, smoking, alcohol use, illicit drug use, body mass index, use of antihypertensive medications, history of hypertension, diabetes mellitus, hyperlipidaemia, anaemia, C-reactive protein, urine protein-creatinine ratio, depression, stroke, and GFR at time of ambulatory BP). Hazard Ratio (HR [95% CI]) for incident frailty by BP patterns adjusted for antihypertensive treatment were HR=0.62 [0.37-1.0] for white-coat hypertension, HR=1.07 [0.85-1.36] for masked hypertension and HR=0.99 [0.76-1.30] for sustained hypertension. Although, participants with masked hypertension had 0.41 (95% CI [−0.78- −0.05]) points lower short physical performance battery scores (SPBB) compared with those with controlled hypertension in the fully adjusted model. The incidence of frailty was found to be very high in this population, namely 529 of the 1189 participants (44.5%) developed frailty.

Gray et al. [32] investigate the incidence of frailty in women aged 65 and over, and no differences were noticed between current ACE inhibitor users and non-users OR=0.96 [0.82-1.13] (p=0.88).

In the study of Sanders et al. [27], a post-hoc analysis of data obtained in the TOPCAT trial was performed. Although they observed a significant difference of SBP between different frailty groups, no interaction between frailty class (Class 1; Class2; Class 3; Class 4) and treatment with spironolactone was found (test of interaction p=0.35).

The observational study of Ze-Bing Wu et al. [33] investigated the association of frailty with morning BP and BP variability in elderly patients with hypertension. Frailty was also closely related to morning SBP ($p<0.01$)), but not associated with BP variability ($p>0.05$). There were no significant differences in gender, age, history of smoking, hypertension duration, antihypertensive drug usage, triglycerides, total cholesterol, low density lipoprotein cholesterol, high density lipoprotein cholesterol, fasting glucose and uric acid among the three groups (non-frail, pre-frail and frail group). Greater odds for frailty incidence were found for those subjects using Calcium Channel Blockers OR_1=5.91 [3.63-9.64] ($p<0.0001$); ACEI OR_2=3.21 [1.76-5.84] (p= 0.0001); ARBs OR_3=3.73 [2.17-6.39] ($p<0.0001$); Diuretics OR_4=3.87 [1.62-9.27] ($p<0.0024$) and Beta-blockers OR_5=4.14; [2.08-8.25] (p=0.0001). Treatment with Aldosterone Antagonists was not associated with frailty incidence OR_6=2.6 [0.8-8.48] (p=0.1126).

The most recent study that investigated the relationship between the use of anti-hypertensive medications and frailty was the randomised control trial of Sheppard et al. [34]. No significant differences in frailty status after 12-weeks follow-up were observed between the intervention group (medication reduction) and the control group (usual care) after applying three different frailty scales (the Frailty Index [22], the Electronic Frailty Index [35], the FRAIL scale [36]).

The study of Abadir et al. [28] including 60 participants from residential care facilities, found that ARB treatment was associated with a blunting of the harm seen in patients with high levels of agonistic autoantibodies to AT1R, indicating that the use of ARBs may attenuate the association between levels of AT1RaAb and decline in grip strength. An increase of AT11RaAb levels can lead to a generalized weakness or frailty risk shown by a decrease in grip strength (r=–0.57, $p<0.005$) and walking speed (r=–0.47, $p<0.005$). The levels of AT1RaAb were lower, albeit not statistically significantly, in the intervention group (ARB use 8.1±8.8 µg/mL IgG), than in the control group (no ARB 9.8±10.7 µg/mL IgG).

4. DISCUSSION

This systematic review shows that the incidence of frailty in hypertensive patients aged 65 and over is very high (44.49%) [31] but whether the treatment of hypertension can prevent frailty occurrence or progression is still uncertain. Ninety-four percent of the participants of the TOPCAT trial [27] were frail at baseline but despite the high prevalence, few observational studies have assessed this relationship and even fewer randomized control trials (only 2 RCTs included). Frail patients aged 65 and over are almost always excluded from RCTs assessing the effects of treatments of cardiovascular diseases, including hypertension. Frailty has become a high-priority theme in cardiovascular medicine due to the ageing and the complex nature of patients suffering from cardiovascular conditions and might indeed influence the therapeutic choices for many cardiovascular diseases [37]. Three studies [27, 30, 33] reassessed the relationship between frailty and hypertension.

Frailty status was associated with a higher risk of cardiovascular outcomes and mortality in the post-hoc analyses of the data obtained from the TOPCAT trial [27]. They found a significant difference of SBP

between different frailty groups. All of them were heart failure patients with a preserved ejection fraction (HFpEF). A greater percentage of subjects were using heart failure medications (diuretics, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, and beta-blockers) at baseline as frailty severity increased, but there was no interaction between frailty class and treatment effect of spironolactone. The same result was found after calculating ORs for different treatment options in the study of Ze-Bing Wu et al. [33]. No association between treatment with Aldosterone Antagonists and frailty prevention was observed, OR_6 95% 2.6 [0.8-8.48] (p=0.1126). The aldosterone antagonists were prescribed not according to frailty status but in function of hypertension status. This emphasizes the need for larger studies with sufficient follow-up period to really understand if anti-hypertensive treatment has a preventive effect on frailty. On the other hand, greater odds of frailty incidence were found for the use of other antihypertensive drugs used, but we have to take into consideration (as confounding factors) the small number of participants included in the study and also the presence of other antihypertensive drugs used at the same time. Frailty was also closely related to morning SBP, but not associated with blood pressure variability. The study of Ze-Bing Wu et al. [33] showed that if the BP of the older patients was under control, their morning BP was significantly lower than the non-frail patients, and the patients' morning BP decreased with a lower progression of frailty no matter if they were pre-frail or frail patients.

Another large prospective study [32] of generally healthy older women showed no association between current ACE inhibitor use and the development of frailty over three years follow-up (OR=0.96). They didn't correct for Heart Failure (HF) and this might have been a limitation of this study. A lot of ACE-I patients were also using diuretics and beta blockers, suggesting that a lot of the participants might have been HF patients too, but we did not know how many of them were using ACE-I for HF. An overlap between the two syndromes might have been present.

The article of Ghazi et al. [31] showed the association of 24-Hour ambulatory BP patterns with cognitive function and physical functioning in CKD patients. They used logistic regression models to investigate the cross-sectional association between BP patterns and clinically significant cognitive impairment and frailty as a binary variable. They assessed incidence of frailty in participants who were not frail or pre-frail at baseline (time of ambulatory BP monitoring) and did 3 adjustments: for age, race, sex, education, marital status, and income in the first model; for smoking, alcohol use, and illicit drug use and the last model adjusted for model 2 plus body mass index, use of antihypertensive medications, history of hypertension, diabetes mellitus, hyperlipidaemia, anaemia, C-reactive protein, urine protein-creatinine ratio, depression, stroke, and GFR at time of ambulatory BP. By comparing the reference model and the last one, it is clear that treatment diminishes the HR suggesting a smaller risk of developing frailty after treatment. But we have to be very careful when interpreting this result.

The study of Anker et al. [30] after adjustment for age and sex (Model 1), for socio-economic characteristics (education, Swiss citizenship, financial difficulties, living alone), CVD risk factors (hypercholesterolemia, diabetes, history of CVD, smoking), and body mass index (BMI) (Model 2) and also for antihypertensive medication use (Model 3), observed no change in the relationship between frailty status and BP. There was a trend but not a statistical significance for men, meanwhile an association was found between treatment and frailty prevention in female participants (p=0.0115).

No relevant changes in frailty status between the intervention group and the controls were found in the study of Sheppard et al. [34] after removing antihypertensive drugs from those who were over-treated, but since it was a 12 week follow up study, further research is needed to better understand long-term clinical outcomes.

There was a lot of heterogeneity between the articles included in the review which can be explained by the different types of interventions and treatments used and demographic differences (including illnesses)

across studies. Another limitation might be that frailty was described solely on physical attributes, while more recent approaches describe the phenomenon in broader, multidimensional terms by incorporating the concept of cognitive frailty [38]. Taking into consideration both cognitive and physical factors may improve the ability to explore the relationship between blood pressure and frailty among older people over physical factors alone. Furthermore, the relationship between hypertension management and frailty was indirectly defined.

This is to our knowledge, the first review to define the possible preventive effect of anti-hypertensive treatment on the frailty outcome in the elderly. As the HYVET study [9] suggested in 2015, more prospective research is needed to evaluate this association but since then less is done to fill this gap. There has been a recent call [39, 40] to increase the number of studies incorporating the frailty syndrome and identifying new frailty/healthy aging markers to prevent frailty occurrence or progression is extremely important.

5. CONCLUSIONS

Based on the results of the systematic review of the literature we can conclude that BP and frailty occur together but whether the treatment with anti-hypertensive drugs modifies this relationship remains unclear and needs to be further investigated in studies with a relevant treatment duration. Yet, a definitive conclusion cannot be drawn.

6. DECLARATIONS

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Funding

This study was funded by an “Interdisciplinary Research Program” grant from the research council of the Vrije Universiteit Brussel (VUB).

Authors' contributions

Ivan BAUTMANS conceived the review idea, acquired the funding and contribute to the review protocol, selection of the articles, interpretation of the data, and writing and editing of the manuscript. Orgesa QIPO and Aziz DEBAIN performed the literature search, article selection, quality assessment, data-extraction and prepared the original draft of the manuscript.

Acknowledgements

Members of the Gerontopole Brussels Study group:

Ivan Bautmans (FRIA, VUB) ivan.bautmans@vub.be;
Dominque Verté (Belgian Ageing Studies BAST, VUB) dominique.verte@vub.be;
Ingo Beyer (Geriatric Medicine department, UZ Brussel) ingo.beyer@uzbrussel.be;
Mirko Petrovic (ReFrail, UGent) mirko.petrovic@ugent.be;
Nico De Witte (Belgian Ageing Studies BAST, VUB) nico.de.witte@vub.be;
Tinie Kardol (Leerstoel Bevordering Active Ageing, VUB) mjmkardol@hotmail.com;
Gina Rossi (Clinical and Lifespan Psychology KLEP, VUB) grossi@vub.be;
Peter Clarys (Physical Activity and Nutrition PANU, VUB) pclarys@vub.be;
Aldo Scafoglieri (Experimental Anatomy EXAN, VUB) aldo.scafoglieri@vub.be;
Erik Cattrysse (Experimental Anatomy EXAN, VUB) ecattrys@vub.be;
Paul de Hert (Fundamental Rights and Constitutionalism Research group FRC, VUB) paul.de.hert@vub.be;
Bart Jansen (Department of Electronics and Informatics ETRO, VUB) bart.jansen@vub.be

7. REFERENCES

1. United Nations Department of Economic and Social Affairs PD. World Population Ageing 2020 Highlights: Living arrangements of older persons: United Nations; 2020.
2. Clegg A YJ, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. Elsevier Ltd. 2013:381(9868), 752-762.
3. Vetrano DL PK, Galluzzo L, Giampaoli S, Marengoni A, Bernabei R, Onder G, group. JAAW. Hypertension and frailty: a systematic review and meta-analysis. BMJ. 2018;8:e024406.
4. World Health Organization Clinical Consortium on Healthy Ageing. Report of consortium meeting 1–2 December 2016. Geneva: World Health Organization; 2017.
5. Cesari M, Prince, M., Thiyagarajan, J.A., De Carvalho, I.A., Bernabei, R., Chan, P., Gutierrez-Robledo, L.M., Michel, J.P., Morley, J.E., Ong, P., Rodriguez Manas, L., Sinclair, A., Won, C.W., Beard, J., Vellas, B. Frailty: An Emerging Public Health. Journal of the American Medical Directors Association 17. 2016:17(3), 188-92.
6. Ma L ZL, Sun F, Li Y, Tang Z. Frailty in Chinese older adults with hypertension: Prevalence, associated factors, and prediction for long-term mortality. Journal of clinical hypertension (Greenwich, Conn). 2018:20(11), 1595–602.
7. Aprahamian I SE, Dos Santos MF, Izbicki R, Pulgrossi RC, Biella MM, Borges ACN, Sassaki MM, Torres LM, Fernandez ÍS, Pião OA, Castro PLM, Fontenele PA, Yassuda MS. Hypertension and frailty in older adults. J Clin Hypertens (Greenwich). 2017:186-92.
8. Jankowska-Polańska B DK, Szymanska-Chabowska A, Uchmanowicz I. The influence of frailty syndrome on medication adherence among elderly patients with hypertension. Clinical Interventions in Aging. 2016:11, 1781-90.
9. Warwick J FE, Rockwood K, Mitnitski A, Thijs L, Beckett N, Bulpitt C, Peters R. No evidence that frailty modifies the positive impact of antihypertensive treatment in very elderly people: an investigation of the impact of frailty upon treatment effect in the HYpertension in the Very Elderly Trial (HYVET) study, a double-blind, placeb. BMC Medicine. 2015:13, 78.
10. Fattori A SM, Alves RM, Guariento ME, Neri AL. Influence of blood pressure profile on frailty phenotype in community-dwelling elders in Brazil - FIBRA study. Archives of gerontology and geriatrics. 2013:56(2), 343–9.
11. World Health Organization. Hypertension. [cited 2022 August 12]; Available from: https://www.who.int/health-topics/hypertension/#tab=tab_1
12. Benetos A PM, Strandberg T. Hypertension Management in Older and Frail Older Patients. Circ Res. 2020:124(7), 1045-60.
13. Graciani A G-EE, López-García E, Banegas JR, Rodríguez-Artalejo F. Ideal Cardiovascular Health and Risk of Frailty in Older Adults. Circulation Cardiovascular quality and outcomes. 2020:9(3), 239–45.
14. Whelton PK CR, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, DePalma SM, Gidding S, Jamerson KA, Jones DW, MacLaughlin EJ, Muntner P, Ovbiagele B, Smith SC Jr, Spencer CC, Stafford RS, Taler SJ, Thomas RJ, Williams KA Sr, Williamson JD. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task F. Hypertension. 2017:71(6), 1269–324.
15. Iadecola C, Duering M, Hachinski V, Joutel A, Pendlebury ST, Schneider JA, et al. Vascular Cognitive Impairment and Dementia: JACC Scientific Expert Panel. J Am Coll Cardiol. 2019 Jul 2;73(25):3326-44.
16. Mone P, Gambardella J, Pansini A, de Donato A, Martinelli G, Boccalone E, et al. Cognitive Impairment in Frail Hypertensive Elderly Patients: Role of Hyperglycemia. Cells. 2021 Aug 17;10(8).

17. Satizabal C, Beiser AS, Seshadri S. Incidence of Dementia over Three Decades in the Framingham Heart Study. N Engl J Med. 2016 Jul 7;375(1):93-4.
18. Panza F, Seripa D, Solfrizzi V, Tortelli R, Greco A, Pilotto A, et al. Targeting Cognitive Frailty: Clinical and Neurobiological Roadmap for a Single Complex Phenotype. J Alzheimers Dis. 2015;47(4):793-813.
19. Elias PK, Elias MF, Robbins MA, Budge MM. Blood pressure-related cognitive decline: does age make a difference? Hypertension. 2004 Nov;44(5):631-6.
20. Ma L, Chan P. Understanding the Physiological Links Between Physical Frailty and Cognitive Decline. Aging Dis. 2020 Apr;11(2):405-18.
21. Paul M Ridker M, MPH, Nancy Cook S. Clinical Usefulness of Very High and Very Low Levels of C-Reactive Protein Across the Full Range of Framingham Risk Scores. Circulation. 2004:109(16), 1955–9.
22. Rockwood K SX, MacKnight C, Bergman H, Hogan DB, McDowell I, Mitnitski A. A global clinical measure of fitness and frailty in elderly people. CMAJ. 2005:173(5), 489–95.
23. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021:n71.
24. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan-a web and mobile app for systematic reviews. Syst Rev. 2016 Dec 5;5(1):210.
25. National Heart Lung and Blood Institute. Study Quality Assessment Tools. July 2021 [cited 2022 August 12]; Available from: https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools
26. Sterne JAC, Savovic J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019 Aug 28;366:l4898.
27. Sanders NA SM, Lewis EF, Liu J, Claggett B, Pfeffer MA, Desai AS, Sweitzer NK, Solomon SD, Fang JC. The frailty syndrome and outcomes in the TOPCAT trial. European journal of heart failure. 2018:20(11), 1570–7.
28. Abadir PM JA, Powell LJ, Xue QL, Tian J, Hamilton RG, Bennett DA, Finucane T, Walston JD, Fedarko NS. Discovery and Validation of Agonistic Angiotensin Receptor Autoantibodies as Biomarkers of Adverse Outcomes. Circulation. 2017:135(5), 449-59.
29. Fried LP TC, Walston J, Newman AB, Hirsch C, Gottdiener J, Seeman T, Tracy R, Kop WJ, Burke G, McBurnie MA, Group. CHSCR. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci. 2001:56(3), M146–M56.
30. Anker D S-EB, Zwahlen M, Santschi V, Rodondi N, Wolfson C, Chiolero A. Blood pressure in relation to frailty in older adults: A population-based study. J Clin Hypertens (Greenwich). 2019:21(12), 1895-904.
31. Ghazi L YK, Tamura MK, Rahman M, Hsu CY, Anderson AH, Cohen JB, Fischer MJ, Miller ER 3rd, Navaneethan SD, He J, Weir MR, Townsend RR, Cohen DL, Feldman HI, Drawz PE, Investigators. CS. Association of 24-Hour Ambulatory Blood Pressure Patterns with Cognitive Function and Physical Functioning in CKD. Clinical journal of the American Society of Nephrology : CJASN. 2020:15(4), 455–64.
32. Gray SL LA, Aragaki AK, McDermott M, Cochrane BB, Kooperberg CL, Murray AM, Rodriguez B, Black H, Woods NF, Study. WsHIO. Angiotensin-converting enzyme inhibitor use and incident frailty in women aged 65 and older: prospective findings from the Women's Health Initiative Observational Study. Journal of the American Geriatrics Society. 2009:57(2), 297–303.
33. Wu Z, Zhang Y, Yu Q, Shen G, Hu S. Association of frailty with morning blood pressure and blood pressure variability in elderly patients with hypertension. International Journal of Clinical and Experimental Medicine. 2017:10(7):11172-8.
34. Sheppard JP BJ, Lown M, Temple E, Lowe R, Fraser R, Allen J, Ford GA, Heneghan C, Hobbs FDR, Jowett S, Kodabuckus S, Little P, Mant J, Mollison J, Payne RA, Williams M, Yu LM, McManus RJ. Effect of Antihypertensive Medication Reduction vs Usual Care on Short-term Blood Pressure Control in Patients

With Hypertension Aged 80 Years and Older: The OPTIMISE Randomized Clinical Trial. JAMA. 2020:323(20), 2039–51.
35. Boyd PJ NM, Ford JA, Khondoker M, Cross JL, Fox C. The electronic frailty index as an indicator of community healthcare service utilisation in the older population. Age and Ageing. 2019:48(2), 273-7.
36. Morley JE MT, Miller DK. A simple frailty questionnaire (FRAIL) predicts outcomes in middle aged African Americans. The journal of nutrition, health & aging. 2012:16(7), 601–8.
37. Vetrano DL PK, Galluzzo L on behalf of the Joint Action ADVANTAGE WP4 group. Hypertension and frailty: a systematic review and meta-analysis. BMJ Open. 2018;8:e024406.
38. Vella Azzopardi R, Beyer I, Vermeiren S, Petrovic M, Van Den Noortgate N, Bautmans I, et al. Increasing use of cognitive measures in the operational definition of frailty-A systematic review. Ageing Res Rev. 2018 Feb 7;43:10-6.
39. Aprahamian I, Xue, QL. Shaping the next steps of research on frailty: challenges and opportunities. BMC Geriatr. 2021:21, 432.
40. Kojima G, Liljas, A., & Iliffe, S. Frailty syndrome: implications and challenges for health care policy. Risk management and healthcare policy. Risk Management and Healthcare Policy. 2019:12, 23–30.

FIGURES

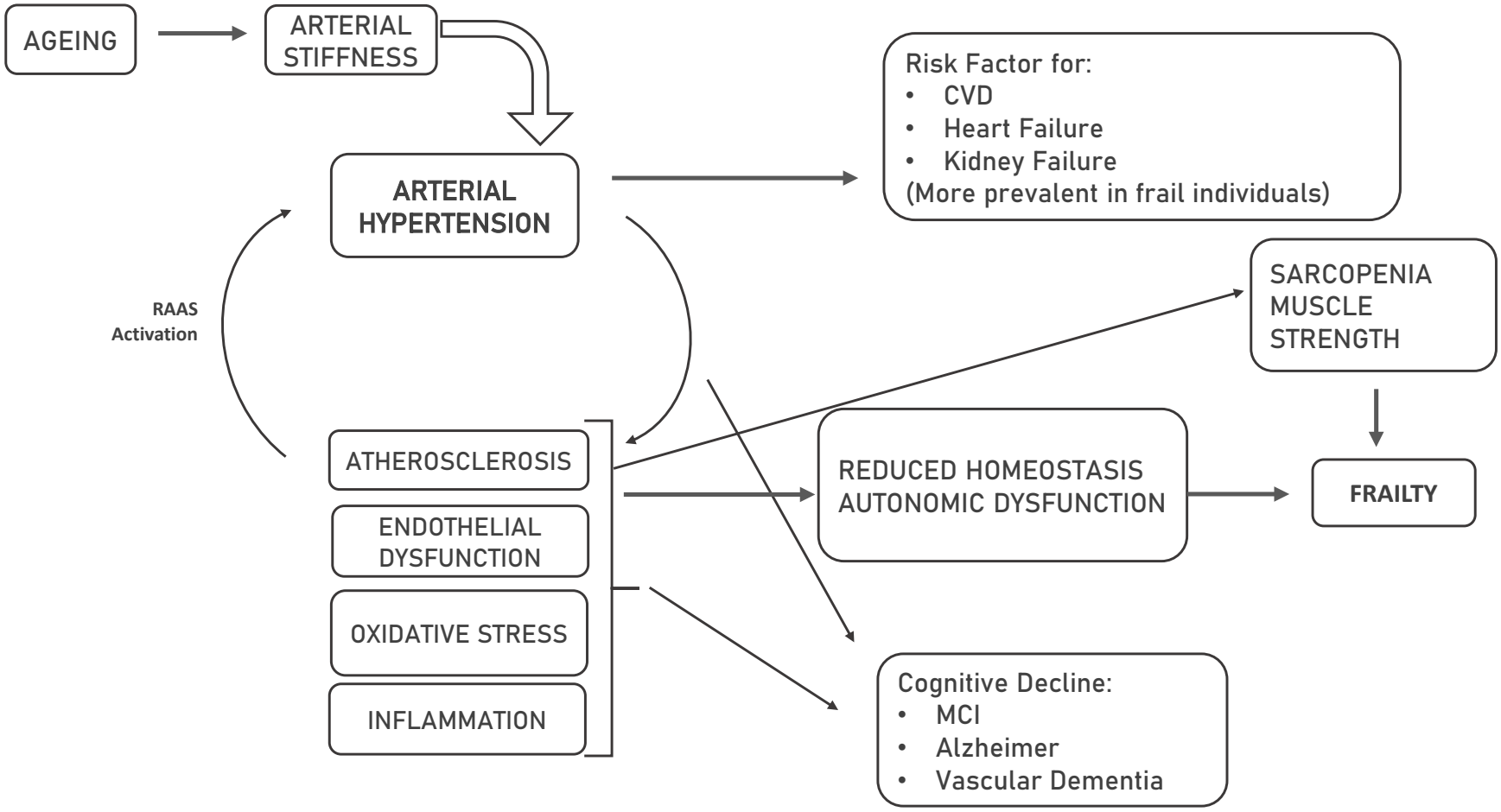

Figure 1. Hypertension, cognitive decline and frailty
Ageing promotes arterial stiffness which is the major cause of elevated systolic BP. Age-related BP alterations are powerful determinants of major cardiovascular disease events and all-cause mortality. Hypertension leads to chronic endothelial dysfunction which is a risk factor for cognitive decline (MCI, Alzheimer, Vascular dementia), disrupting the integrity of endothelial cells and contributing to oxidative stress, inflammation, and atherosclerosis. Furthermore, inflammation reduces homeostasis and promotes autonomic dysfunction, leading to cognitive impairments as well as sarcopenia and reduced muscle strength which contribute to frailty.
RAAS= Renin-Angiotensin-Aldosterone-System; CVD= Cardiovascular Disease; MCI= Mild Cognitive Impairment

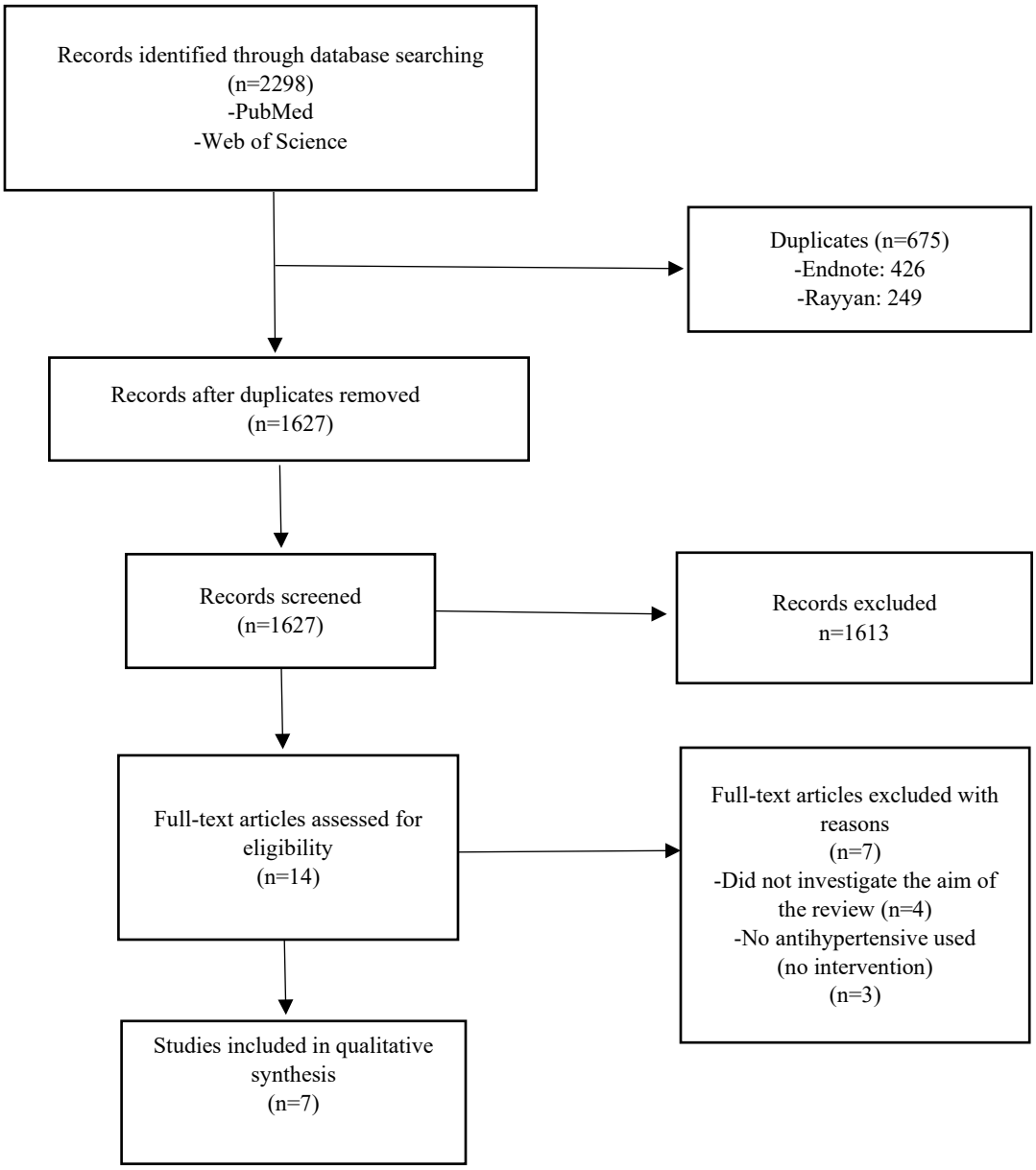

Figure 2. Flowchart: selection process.

TABLES

Table 1. Summary of findings

Author, Year	Study design	Country/ setting	Duration	N	Characteristics of the participants	Hypertension measurements	Antihypertensive used as intervention	Frailty Measurement	Study outcome & OR
Abadir et al. 2017	RCT	Second part of the study (validation group) Chicago, Older people living in residential care facilities	Until death	60	**Age**: 84±7 Comorbidities, n: 1.3 ± 1.3	Ambulatory BP monitoring	**Intervention group:** ARBs (n=30) **Control group:** No ARBs (n=30)	Fried frailty criteria: (only walking speed and grip strength measurements)	↑ AT11RaAb → ↑ Generalised weakness/Frailty risk [↓Grip strength (r=–0.57, P<0.005) ↓Walking speed (r=–0.47, P<0.005)] **AT1RaAb, µg/mL IgG`:** **No ARBs: 9.8 (10.7)** **ARBs: 8.1 (8.8)**
Anker et al. 2019	Cross-sectional analysis of a cohort study	Switzerland Community-dwelling residents	2 years	3157 With hypertension **1867** (51.1 %)	**Age**: 73.3 ± 4.1 Not institutionalized and no dementia present	Ambulatory BP measurements, a mean of 3 readings with 5-10 min interval, sitting position	Non-specified	Fried's phenotype model, **Non-frail** →2226 (61.0%) **Pre-frail**→ 1243 (34.1%) **Frail** → 121 (3.3%)	OR* men = 1.45 (0.54: 3.98) P = 0.4578 OR* women = 2.45 (1.22: 4.92) P = 0.0115
Ghazi et al. 2020	Observational, cohort	*Minnesota*	4 years	1502 Participants from seven clinical	Patients with non-dialysis-dependent CKD Mean Age: 63 ±10	24-hour ambulatory BP measurements	ACE-I/ARB Diuretic Calcium channel blocker Beta blocker Vasodilator	Fried's Frailty criteria (At baseline and then annually) The short physical performance	Hazard Ratio (95% CI) for incident frailty by BP patterns adjusted for antihypertensive treatment:

				centres (1189 non frail patients)				battery (SPPB) score (0-12) At baseline For physical performance	White-coat hypertension: HR= 0.62 (0.37 to 1.0) Masked hypertension: HR= 1.07 (0.85 to 1.36) Sustained hypertension: HR= 0.99 (0.76 to 1.30) 529 of 1189 participants developed frailty (44.5%)
Gray et al. 2009	Observational, cohort	40 clinical centres, United States	3 years	27378	Non frail women **Age:** 65-79 Comorbidities reported: hypertension, arthritis, treated diabetes, cancer	Ambulatory BP monitor	ACE inhibitors → 2192 (8%) and Other anti-hypertensive drugs: Calcium channel blockers, Beta-blockers, Diuretics, and Statins (dose used) the cut-off point	Fried's criteria: 3950 (14.54%) women developed frailty	OR = 0.96 (0.82, 1.13) P =0.88
Sheppard et al. 2020	Interventional, RCT	69 primary care sites in England	12 weeks	569 (n_{CT} = 287 n_{IT} = 282)	Patients of primary care with baseline systolic blood pressure lower than 150 mm Hg, receiving at least 2 antihypertensive medications Comorbidities, mean (SD): 5.7 ±2.7	Ambulatory BP measurement, seated, mean of 3 readings	**Intervention group, It** (reduction in antihypertensive drugs used) **Control, Ct** (usual care) Antihypertensive drugs used: **ACE-I/ARB→** n_{It} = 238 n_{Ct} = 243 **Calcium channel blocker→** n_{It} = 199	The Frailty index The Electronic Frailty Index The Morley FRAIL scale	No significant differences between groups in frailty status after follow-up

					6.0 ± 2.9 **Mean age:** It: 84.6 ± 3.3 Ct: 85.0 ± 3.5		n_{Ct}= 191 **ß-blocker→** n_{It} = 112 n_{Ct} = 116 **Thiazide and related diuretics→** n_{It} = 109 n_{Ct} = 111		
Sander et al. 2018	Cohort Study A post-hoc analysis of data obtained in the TOPCAT trial	United States, Canada, Brazil, Argentina	Median follow up: 26.6 months in PARADIGM-HF 36.7 months in ATMOSPHERE	1767	HF patients with preserved injection fracture, with at least a history of hospitalization within the previous 12 months **Mean age**: 71.5 years	Ambulatory BP monitoring	**Aldosterone Antagonist** **Active group**: spironolactone 15–45 mg daily **Diuretics→** n1=402 n2= 538 n3=415 n4=218 **ACEI/ARB→** n1=355 n2=473 n3=369 n4=198 **Beta-blocker→** n1=366 n2=460: n3=370 n4=191	Frailty Index (FI) based on a deficit accumulation approach (CFS-Rockwood) Class 1 (score: < 0.3) Class 2 (score: 0.3–0.4) Class 3 (score: 0.4–0.5) Class 4 (score: ≥ 0.5) **Frail: 94%** **(FI > 0.21)**	No evidence that the effect of spironolactone relative to placebo was different across frailty classes Test of interaction =0.35
Ze-Bing Wu et al. 2017	Observational, cohort	China, Anhui Participants recruited from the Third Affiliated Hospital of Anhui Medical University.	16 months	156	Diagnosed Hypertensive patients (3 times measuring SBP > 160 mmHg,] DBP > 100 mmHg)	24-hour-monitoring of BP	**1-Calcium channel blocker:** $n_{control}$ = 48 $n_{pre\text{-}frail}$ = 60 n_{frail} = 43 **2-ACEI:** $n_{control}$ 19 $n_{pre\text{-}frail}$ = 7 n_{frail} = 18 **3-ARB:** $n_{control}$ = 30 $n_{pre\text{-}frail}$ = 33 n_{frail} = 24 **4-Diuretics**: $n_{control}$ 10 $n_{pre\text{-}frail}$ = 14 n_{frail} = 7 **5-Beta blocker:**	The frail scale from International Society for nutrition and aging **Non-frail** : 50 (32.05%) (Control) **Pre-frail :** 62 (39.74%) **Frail:** 44 (28.20%)	OR_1 *=5.91 (3.63-9.64) P < 0.0001 OR_2 *= 3.21 (1.76-5.84) P = 0.0001 OR_3 *=3.73 (2.17-6.39) P < 0.0001 OR_4 *= 3.87 (1.62-9.27) P = 0.0024

							$n_{control}$ = 18 $n_{pre\text{-}frail}$ = 22 n_{frail} = 12 **6-Aldosterone antagonists:** $n_{control}$ = 4 $n_{pre\text{-}frail}$ = 6 n_{frail} = 4		OR_5 *= 4.14 (2.08-8.25) P = 0.0001 OR_6 *= 2.6 (0.8-8.48) P = 0.1126

*Self-Calculation of OR

Table 2. Quality assessment for cross-sectional and cohort studies (NIH 2019)

Reference		Questions*														Quality Rating**
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	
1.	Anker et al. 2019	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Good
2.	Ghazi et al. 2020	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	No	Yes	NR	CD	Yes	Good
3.	Gray et al. 2009	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	NR	No	Yes	Good
4.	Sanders et al. 2018	Yes	NA	CD	No	No	Yes	NA	Yes	Yes	NA	Yes	NA	NA	Yes	Fair***
5.	Ze-Bing Wu et al. 2017	Yes	Yes	Yes	Yes	Yes	Yes	CD	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good

*Yes / No / Other: CD (cannot determine), NR (not reported), NA (not applicable)

** Good / Fair / Poor

*** Not pre-specified nor directly measurements of frailty classes

Table 3. Quality assessment for cluster-randomized trials (RoB 2 CRT, 2021)

Reference / Ratings*	Abadir et al. 2017	Sheppard et al. 2020
Domain 1a: Risk of bias arising from the randomization process		
1a.1	Partly No	Partly yes
1a.2	Partly No	Yes
1a.3	No	No
Risk-of-bias judgement	Some Concerns	Low
Domain 1b: Risk of bias arising from the timing of identification or recruitment of participants in a cluster-randomized trial		
1b.1	No	Yes
1b.2	Partly Yes	Yes
1b.3	No	Partly No
Risk-of-bias judgement	Some Concerns	Low
Domain 2: Risk of bias due to deviations from the intended interventions (*effect of assignment to intervention*)		
2.1a	Yes	Yes
2.1b	Yes	Yes
2.2	No Information	Yes
2.3	No	Partly No
2.4	Not Applicable	Partly No
2.5	Not Applicable	Partly Yes
2.6	Partly No	Yes
2.7	Partly Yes	Not Applicable
Risk-of-bias judgement	High	Low
Domain 2: Risk of bias due to deviations from the intended interventions (*effect of adhering to intervention*)		
2.1	Partly Yes	Yes
2.2	No Information	Yes
2.3	No Information	Not Applicable
2.4	Partly Yes	Not Applicable
2.5	No	Partly No
2.6	Partly No	Not Applicable
Risk-of-bias judgement	High	Some concerns
Domain 3: Risk of bias due to missing outcome data		
3.1a	No	Partly Yes
3.1b	Yes	Partly Yes
3.2	Partly No	Not Applicable
3.3	Partly Yes	Not Applicable
3.4	Partly Yes	Not Applicable
Risk-of-bias judgement	High	Low
Domain 4: Risk of bias in measurement of the outcome		
4.1	No	No
4.2	No	Partly No
4.3a	No Information	Yes
4.3b	No Information	Partly Yes
4.4	Partly No	Partly No
4.5	Partly No	Partly No
Risk-of-bias judgement	Low	Low
Domain 5: Risk of bias in selection of the reported result		
5.1	Yes	Partly No
5.2	Partly No	Partly Yes
5.3	Partly No	Partly No
Risk-of-bias judgement	Low	Some Concerns
Overall risk of bias	**High****	**Low**

*Low/Some concerns/ High

**A relatively small validation group sample size (60 participants) and not having at-risk status assessed using the complete Fried criteria for frailty