Original Article

The Pharmacological Treatment of Arterial Hypertension in Frail, Older Patients

A Systematic Review

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Summary

Background: It is debated whether the treatment goals and decision-making algorithms for elderly patients with hypertension should be the same as those for younger patients. The American and European guidelines leave decisions about antihypertensive treatment in frail, institutionalized patients up to the treating physician. We therefore systematically searched the literature for publications on the phamacotherapy of arterial hypertension in frail patients.

Methods: The MEDLINE, Embase, and Central databases were systematically searched for randomized, controlled trials (RCTs) and non-randomized studies, including observational studies, on the pharmacotherapy of arterial hypertension in elderly patients since the introduction of the concept of frailty, published over the period 1992–2017.

Results: Out of 19 282 citations for randomized, controlled trials and 5659 for non-randomized trials and observational studies, four RCTs and three observational studies were included in the further analysis. The included RCTs showed a trend towards a benefit from pharmacotherapy of hypertension in frail patients with respect to mortality, cardiovascular disease, functional status, and quality of life. On the other hand, some of the observational studies indicated a lower rate of falls and lower mortality among patients who received no antihypertensive treatment.

Conclusion: In view of the conflicting findings of RCTs and non-randomized studies, the lower representation of frail subjects in RCTs, and the high risk of bias in non-randomized studies, the findings of the studies included in this review do not enable the formulation of any strictly evidence-based treatment recommendations. As a rule of thumb, the authors propose that a target systolic blood pressure of <150 mmHg should be aimed at in patients whose gait speed is less than 0.8 m/s, while a target range of 130–139 mmHg can be set for patients over age 80 who are no more than mildly frail.

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The current recommendations for blood pressure target values and pharmacological treatment of arterial hypertension in older people are heterogeneous (1, 2). The 2017 guideline of the American College of Cardiology recommends a new target value of systolic blood pressure <130 mmHg for persons ≥ 65 years living at home (3). For the same age group, the recently published guidelines of the European Society of Cardiology (ESC), state a target range of 130 to 139 mmHg for systolic pressure (level of evidence A) (4). The German Hypertension League and the German College of General Practitioners and Family Physicians (DEGAM) also recommend that the blood pressure should be <140/90 mmHg in the elderly (5–7). However, the DEGAM describes the research data on antihypertensive treatment in older patients as inadequate (6). Management of high blood pressure is particularly challenging in frail, elderly persons owing to the potential complications and the problem of tolerance. The above-mentioned American guideline (3) differentiates older patients primarily by morbidity, age, and institutionalization, but not by degree of frailty. In contrast, the current ESC guideline distinguishes between fit, independent patients and frail patients (4). While it can be assumed that older hypertensive patients who are not frail can be treated analogously to younger age groups, one has to question whether frail elderly patients benefit from such a therapy (8).

But what is "frailty"? The term has never been clearly defined since its introduction in 1992 and remains controversial. While the explanatory model proposed by Fried et al. (9) defines frailty mainly in physical terms such as measurements of grip strength, undesired weight loss, physical activity, and gait speed, the Frailty Index (FI) of Rockwood et al. (10) also embraces cognitive parameters, comorbidity, and malnutrition. In order to achieve comparable characterization of older participants in randomized controlled trials (RCTs), in 2015 the European Medicines Agency (EMA) suggested measuring walking speed and carrying out the Short Physical Performance Battery (11).

At present, both the American and European guidelines leave the decision on antihypertensive treatment of frail, older adults to the treating physician (3, 4). Although frailty already plays a role in guideline recommendations, the existing systematic reviews

The clinical perspective

- Before the commencement of treatment, older patients should be screened for physical frailty in terms of gait speed or Short Physical Performance Battery (SPPB) score.
- The evidence is insufficient for patients with severe physical frailty. Based on current knowledge, for patients with a gait speed of <0.8 m/s we recommend a target systolic blood pressure of <150 mmHg. Adverse effects, particularly orthostatic hypotension, should be avoided if at all possible.
- In patients >80 years of age who are not or only slightly frail, the target systolic blood pressure should be 130–139 mmHg. It goes without saying that the patient's tolerance of the treatment should be taken into account in each individual case.
- The greater the frailty and functional limitations of the patients, the more closely they should be monitored after any change in treatment.

have only considered age. For this reason, we took frailty into account in a systematic assessment of the evidence regarding the pharmacological treatment of arterial hypertension.

Method

The MEDLINE, Embase, and Central databases were searched for relevant records in the period 1 January 1992 to 31 December 2017 (PROSPERO CRD42017067253) (12). Two reviewers (VM, SB) independently carried out the following steps:

- Selection of studies
- Data extraction
- Assessment of the risk of bias in the primary studies

Any disagreements between the reviewers were resolved by discussion or by a third person (MD, DD). Included for analysis were RCTs that investigated the effects of pharmacological treatment of hypertension on the endpoints functionality, mortality, morbidity, or quality of life in relation to physical frailty. Non-randomized controlled trials (non-RCTs) were also included if they analyzed physical frailty as effect modifier of antihypertensive treatment for the above-mentioned endpoints (for further details, please refer to the *eMethods* supplement). Physical frailty was evaluated systematically on the basis of the functional assessments (e.g., of mobility or activities of daily living [ADL]) that had been performed (13).

Results

The survey revealed 19 282 records for RCTs based on the titles and abstracts, of which 39 were identified as potentially relevant. For non-RCTs and observational studies, 41 of 5659 records were judged potentially relevant. After full-text screening, four RCTs (14–19) and three prospective longitudinal cohort studies (20–22) were included for analysis. One re-analysis of an RCT (23) was identified and included after an additional search for the first and last authors of these seven studies. Details of the studies included and their results are presented in *Table 1* and *eTable 1*, and the risk of bias for the RCTs is shown in *eTable 2*.

Randomized controlled trials

Four RCTs were identified *(Table 1, eTable 1)*:

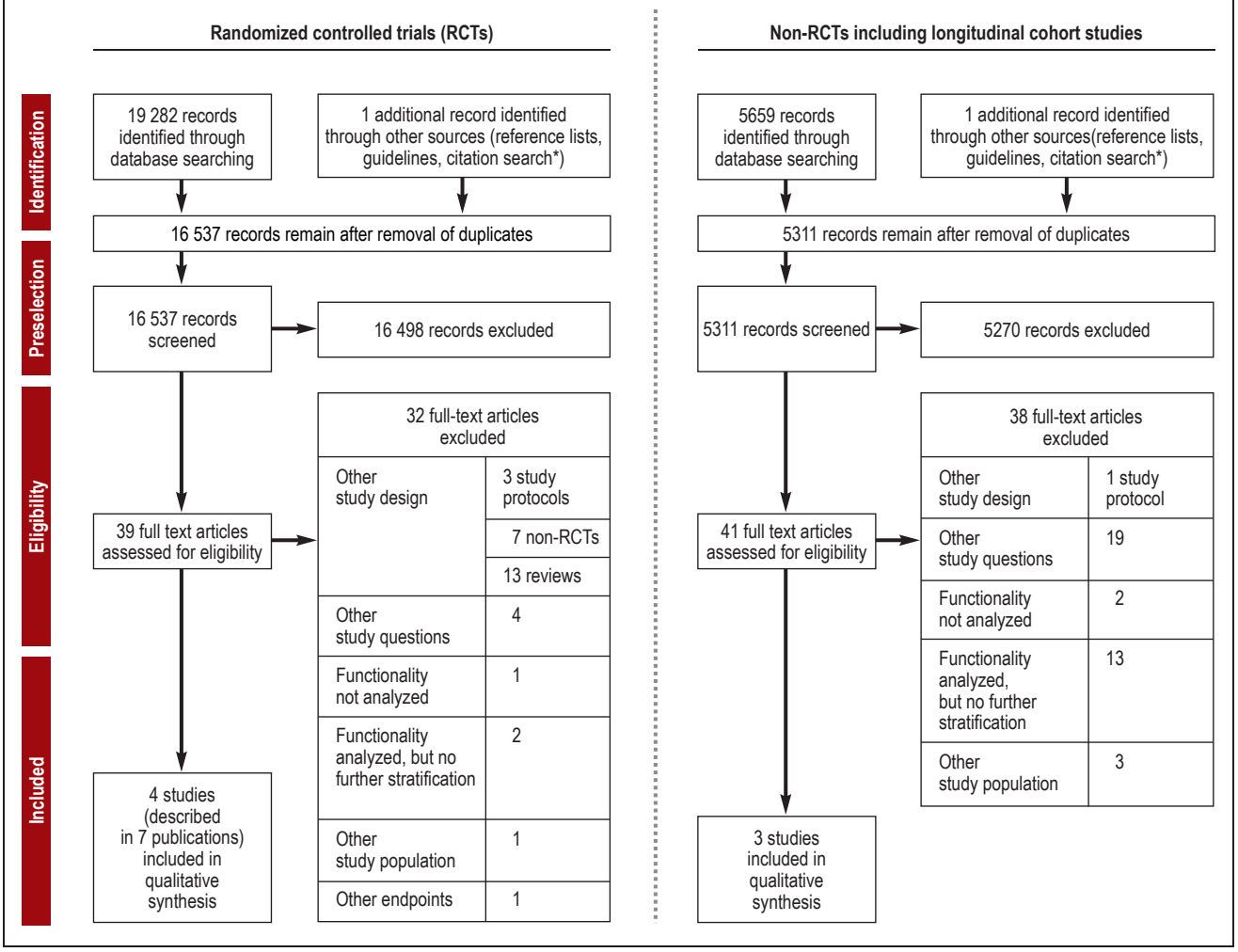
- HYVET (HYpertension in the Very Elderly Trial) (16, 17)
- DANTE (Discontinuation of Antihypertensive Treatment in Elderly People) (18)
- SHEP (Systolic Hypertension in the Elderly Program) (19)
- SPRINT (Systolic Blood Pressure Intervention Trial) (14, 15, 23)

HYVET investigated the interaction between drug treatment (a combination of slow-release indapamide 1.5 mg ± perindopril 2–4 mg) and frailty in patients 80 years of age or older with a systolic blood pressure >160 mmHg (16). In this context the available data suggest that the protective effect of antihypertensive treatment—with regard to the incidence of strokes and of fatal or non-fatal cardiovascular events—could be greater with increasing frailty. Further analysis of the HYVET data with the change in frailty during the first 24 months as endpoint showed no significant difference, but the outcome tended to be better in the intervention group (17). The risk of bias for HYVET was found to be predominantly low. However, the description of random sequence generation was insufficient *(eTable 2)*.

In DANTE, short-term discontinuation of antihypertensive treatment in patients ≥ 75 years of age with mild cognitive deficits (Mini-Mental State Examination [MMSE] score 21–27) did not improve cognition or functionality (ADL) after 16 weeks (18). The treatment for hypertension also showed no differences in effect on cognition between groups with and without restricted ADL. The risk of bias was predominantly low, but there was no blinding of participants or study personnel (18) *(eTable 2)*.

SHEP, published in 1991, was the first American RCT to show the protective effect of antihypertensive treatment (chlorthalidone ± atenolol) against fatal and nonfatal stroke compared with placebo (25). A post-hoc analysis 25 years after the end of the study demonstrated no modification of the effect by self-reported functional limitations (19). There were

FIGURE 1



PRISMA flow chart of the various phases of the literature survey

* Citation search = search for citations of the first and last authors of the studies included

Non-RCTs, non-randomized studies

signs that the treatment increased the risk of occurrence of the secondary endpoints overall mortality, cardiovascular mortality, myocardial infarction, and stroke in functionally impaired patients. The risk of bias was predominantly low; however, the risk was unclear for random sequence generation and high for incomplete outcome data *(eTable 2)*.

SPRINT examined, in a subanalysis, the effects on the primary endpoints mortality and cardiovascular disease of intensive treatment for high blood pressure (<120 mmHg) compared with standard treatment (<140 mmHg) in patients aged 75 years and over (14). Intense lowering of blood pressure protected against cardiovascular events regardless of gait speed. Further analyses of the SPRINT data showed no differences between the groups for decrease in gait speed over the following 3 years (15). For intensive treatment the risk of death was lower in patients without restricted mobility. However, the protective effect did not attain significance in those with restricted mobility. Patients who reported worse physical quality of life at the beginning of the study showed a more rapid decrease in gait speed than those whose self-assessment was better (15). After stratification by frailty, no significant difference in subjective quality of life was observed between the two groups (23). The risk of bias was predominantly unclear due to inadequacies in the description of random sequence generation and in blinding *(eTable 2)* (26, 27).

Non-randomized controlled trials

The three non-RTCs included for analysis were the Health, Aging, and Body Composition Study (Health ABC) (21), the Medicare Current Beneficiary Survey (20), and the Jerusalem Longitudinal Study (22) *(Table 1, eTable 1)*. (For information on study quality, please refer to the *eMethods* supplement.)

TABLE 1a

Characteristics of the randomized trials included for analysis

Study question/Population/Endpoints	Parameters of functionality	Results					
HYpertension in the Very Elderly Trial (HYVET), 2000–2008, Europe, China, Australasia, Tunisia → slow-release indapamide ± perindopril compared to placebo (hazard ratio [95% CI])							
Endpoints: Stroke, total mortality, cardiovascular events (stroke, myocardial infarction, and heart failure) Patients: ≥ 80 years systolic blood pressure >160 mmHg (n = 2656) (16)	Median FI (Rockwood): Placebo group 0.17 95% CI: [0.11; 0.24] Intervention group 0.16 95% CI: [0.11; 0.24]	FI	Stroke		Cardiovascular events		Overall mortality
		0.1	0.75 [0.40; 1.38]		0.62 [0.42; 0.92]		0.89 [0.63; 1.25]
		0.2	0.66 [0.43; 1.01]		0.60 [0.45; 0.78]		0.84 [0.66; 1.07]
		0.3	0.59 [0.36; 0.96]		0.57 [0.42; 0.79]		0.80 [0.61; 1.04]
		0.4	0.52 [0.25; 1.09]		0.55 [0.34; 0.89]		0.76 [0.50; 1.14]
		0.5	0.47 [0.16; 1.33]		0.53 [0.26; 1.06]		0.72 [0.40; 1.29]
		0.6	0.41 [0.10; 1.65]		0.50 [0.20; 1.27]		0.68 [0.32; 1.48]
Endpoints: Changes in FI over 24 months (n = 1665) (17)	FI (Rockwood)	No significant difference in average increase of FI over 24 months (p = 0.06): Intervention group HR 0.79; 95 % CI [0.26; 1.32] versus placebo group HR 1.53; 95% CI [0.97; 2.10]					
Discontinuation of Antihypertensive Treatment in Elderly People (DANTE), 2011–2013, Netherlands → short-term discontinuation of antihypertensive treatment (hazard ratio [95% CI])							
Endpoints: cognitive, psychological and general functionality Patients: ≥ 75 years, mild cognitive deficit (n = 385) (18)	Groningen Activity Restriction Scale (GARS): intervention group: 23 (IQR 18–28); control group 22 (IQR 19–29)		Change in overall cognitive compound score [95% CI]				
		GARS-Score ≤ 22	–0.07 [–0.36; 0.22]				
		GARS-Score >22	0.09 [–0.21; 0.40]				
Systolic Hypertension in the Elderly Program (SHEP), 1984–1996, USA → antihypertensive treatment (chlorthalidone ± atenolol) compared to placebo (hazard ratio [95% CI])							
Endpoints: all-cause death, cardiovascular death, myocardial infarction, stroke, falls, symptomatic hypotension Patients: > 60 years (n = 4593) (19)	Self-reporting of limited physical function: 545 patients (11.9%) functionally limited	Endpoint	No limited physical function		Limited physical function		P value for interaction
		Mortality	0.82 [0.66; 1.00]		1.22 [0.79; 1.88]		0.10
		Cardiovascular death	0.71 [0.51; 0.98]		1.27 [0.71; 2.28]		0.08
		Myocardial infarction	0.57 [0.40; 0.81]		1.25 [0.54; 2.89]		0.08
		Falls	0.81 [0.66; 0.99]		1.32 [0.87; 2.00]		0.04
		Stroke	0.64 [0.49; 0.85]		0.80 [0.44; 1.46]		0.48
		Symptomatic hypotension	No effect, regardless of functionality				
Systolic Blood Pressure Intervention Trial (SPRINT), 2010–2016, USA → intensive treatment (<120 mmHg) versus standard treatment (<140 mmHg) (hazard ratio [95 % CI)							
Endpoint: Myocardial infarction, coronary syndrome, stroke, decompensated heart failure, death from cardiovascular events Patients: ≥ 75 years (n = 2636) (14)	Gait speed: <0.8 m/s, 740 patients (28.1%) FI (Rockwood): >0.21, 815 patients (30.9%)	<0.8 m/s	0.63 [0.40; 0.99]	P value for interaction 0.85	Fit: FI ≤ 0.10	0.68 [0.45; 1.01]	P value for interaction 0.84
		≥ 0.8 m/s	0.67 [0.47; 0.94]		Less fit: (0.10<FI ≤ 0.21)	0.63 [0.43; 0.91]	
					Frail: FI >0.21	0.47 [0.13; 1.39]	
Endpoint: Gait speed and mobility Patients: ≥ 75 years with data on mobility (n = 2629) (15)	Gait speed and self-reported mobility: limitations in 464 patients (18%)		Based on gait speed and self-reporting		Based on gait speed		
		No limitation of mobility → death	0.62 [0.43; 0.90]		0.74 [0.54; 1.04]		
		Limitation of mobility → death	0.82 [0.52; 1.28]		0.56 [0.29; 1.07]		
Endpoint: Physical (PCS) and mental (MCS) health-related quality of life as measured by the Veterans RAND 12-Item Health Survey Patients: ≥ 50 years (n = 9361) (23)	FI (Rockwood): 2560 patients (27.3%) characterized as frail		PCS difference		MCS difference		
		Fit (FI ≤ 0.10)	−0.166 [−0.357; 0.024]	P value for interaction 0.49	0.077 [−0.122; 0.276]	P value for interaction 0.91	
		Less fit (0.10<FI≤ 0.21)	0.011 [−0.137; 0.160]		−0.002 [−0.160; 0.156]		
		Frail (FI>0.21)	−0.028 [−0.275; 0.219]		−0.001 [−0.281; 0.279]		

95% CI, 95% confidence interval; FI, frailty index; IQR, interquartile range; MCS, Mental Component Summary Score; PCS, Physical Component Score; RAND, Research and Development

TABLE 1b

Characteristics of the non-randomized controlled trials included for analysis

Study question/Population/Endpoints	Parameters of functionality	Results		
Jerusalem Longitudinal Study, since 1990 (survey period 2010–2011), Israel → association of groups below with 5-year mortality independent of functionality (hazard ratio [95 % CI])				
Endpoint: 5-year mortality Participants: 90 years old (n = 480) (22)	Reduced grip strength (men <26 kg, women <16 kg) n = 149 (31.0%) Dependence in ≥ 1 ADL, n = 194 (40.4%)		Low grip strength*	Dependent in ≥ 1 ADL*
		Normotensive	Reference	Reference
		Untreated hypertension	0.90 [0.31; 2.67]	0.93 [0.35; 2.42]
		Treated hypertension	1.75 [0.78; 3.92]	1.37 [0.67; 2.80]
Health, Aging, and Body Composition Study, since 1997 (survey period 1997–2014), USA → association of consumption of antihypertensive medication with recurrent falls (hazard ratio [95 % CI])				
Endpoint: recurrent falls Participants: no functional limitations (n = 2948) (21)	Gait speed compared with median at baseline, 1.17 m/s		Gait speed	Risk of recurrent falls over 7-year period*
		<1.17 m/s		0.61 [0.35; 1.06]
		≥ 1.17 m/s		0.99 [0.56; 1.74]
Medicare Current Beneficiary Survey, 2004–2009, USA → association of groups below with risk of severe injuries from falls (hazard ratio [95 % CI])				
Endpoint: severe fall injuries Participants: Medicare patients ≥ 70 years with hypertension and data available on medication (n = 4961) (20)	Falls in previous year: n = 503 (10.1%) n = 1919 (38.7%) restricted in at least one BADL, n = 2791 (56.3%) in at least one IADL		Fall in previous year	Risk of severe injuries over 3-year period*
			Moderate blood pressure-lowering treatment	Intensive blood pressure-lowering treatment
		No (n = 4621)	1.24 [0.89; 1.73]	1.10 [0.76; 1.59]
		Yes (n = 503)	2.17 [0.98; 4.80]	2.31 [1.01; 5.29]

*Adjusted (see *eTable 1b*); ADL, activities of daily living; BADL, basic activities of daily living; IADL, instrumental activities of daily living; 95 % CI, 95 % confidence interval

Health ABC investigated the association between consumption of antihypertensive medications and recurrent falls over a period of 7 years in 2948 community-dwelling, initially well-functioning older adults (21). A sensitivity analysis showed no effect modification by gait speed. The risk of bias was assessed as moderate.

One of the analyses in the Medicare Current Beneficiary Survey showed that administration of intensive drug treatment for high blood pressure was associated with an increased risk of serious fall injuries in 4961 Medicare patients ≥ 70 years of age. The risk was significantly higher in patients who were physically frail (as defined by falls in the foregoing year); however, there was no essential difference in risk between the groups with moderate and high decreases in blood pressure (20). The risk of bias was assessed as serious.

The Jerusalem Longitudinal Study examined the association between medicinal treatment of arterial hypertension and overall mortality in patients over 90 years of age depending on frailty, assessed in terms of ADL and grip strength (22). There were trends towards slightly lower mortality in untreated persons with hypertension and higher mortality in those who received treatment for hypertension compared with normotensive persons who did not receive treatment. The protective effect without treatment was greater among the participants with better physical functionality (22). The risk of bias was assessed as moderate

Discussion

Although the term "frailty" was introduced as long ago as 1992 (28), our literature search for this review found only a small number of studies that characterized their participants in this respect. The findings of the RCTs we identified show that even patients with pronounced physical frailty may benefit from treatment of hypertension in terms of mortality, cardiovascular disease, functionality, and quality of life. However, because the risk of bias was often unclear, the proportion of participants with marked functional limitations mostly low, and the heterogeneity of the studies analyzed high, the quality of the evidence does not permit derivation of treatment recommendations. The quality of the non-RCTs we identified is also too low to evaluate whether physical frailty can be considered an effect modifier.

HYVET and SPRINT can be described as landmark RCTs for our study question, as they were the first to characterize the participants precisely in terms of frailty *(eTable 3)*. The results show that antihypertensive treatment has a protective effect even in physically frail older patients. However, the subgroup analyses lacked the necessary statistical power for robust conclusions. Furthermore, it is questionable to what extent the RCTs' selected patient populations reflect the the reality of prescription practice. For instance, SPRINT excluded patients with diabetes, symptomatic heart failure, orthostatic hypotension, or

dementia and nursing home residents (29, 30). Dementia and the need for 24-h care were also exclusion criteria in HYVET (16).

The risk of bias in SPRINT was predominantly unclear, with inadequacies in the description of random sequence generation and in blinding of study personnel (26, 27). Gait speed and mobility restriction were not considered endpoints at the beginning of the study according to the registered study protocol (ClinicalTrials.gov identifier: NCT01206062). Since all the study results display wide confidence intervals, the precision of the estimate of effect is low. Both HYVET and SPRINT were terminated prematurely, so the effect of the intervention may be overestimated (31). Moreover, in HYVET the FI, used to classify functionality, was also calculated for participants in whom not all, or not at least half, of the items were present (16). Therefore, the classification of the participants may be erroneous in this respect.

In addition, a higher risk of bias must be assumed for the non-RCTs. The results presented are of little assistance in deciding on differential treatment depending on physical frailty. Here too, many of the study participants had only slight functional limitations or none at all (21). While the known risk of a higher rate of falls with more intensive treatment for high blood pressure was confirmed, functional limitation seems to increase the risk (20). Many non-RCTs had to be excluded from our analysis either because they merely used the measured blood pressure as a surrogate for antihypertensive treatment or because they investigated neither greater functional limitation nor physical frailty as effect modifier. Only the PARTAGE study looked at the interaction between systolic blood pressure and the number of antihypertensive medications in residents of nursing homes. The results showed that patients with systolic blood pressure <130 mmHg who were taking at least two antihypertensive medications had the highest risk of death (32). Unfortunately there was no stratification of participants according to physical frailty, so this study had to be excluded.

The PARTAGE findings are in accordance with those of other epidemiological studies that postulate a J-shaped association between blood pressure and mortality. However, there is a distinct danger of reverse causation. For example, persons over 80 years old in Great Britain were found to be at greater risk of death with systolic blood pressure <120 mmHg (33). On examination of the blood pressure over time, however, a sharp drop in pressure was found particularly in the last 2 years of life, independent of antihypertensive treatment. The association may thus be explained by an as yet pathophysiologically unexplained blood pressure decrease up to 2 years before death, rather than by treatment for hypertension or by the blood pressure at the beginning of the study (33, 34). In the absence of sensitivity analyses to exclude reverse causation, results should therefore always be viewed critically. However, these analyses point to a basic problem: in the months before death, treatments may be no longer indicated or required but are nevertheless continued (33).

The target systolic blood pressure of 130–139 mmHg in the new ESC guideline for persons over 80 years of age may need critical re-evaluation for patients with severe or very severe physical limitations (4). In HYVET, for instance, there was a reduction in mortality for target pressures <150 mmHg (16). More research is needed to ascertain to what extent a further reduction of the target to <140 mmHg would provide further protection. The ongoing INFINITY study ("Intensive Versus Standard Blood Pressure Lowering to Prevent Functional Decline in Older People"; ClinicalTrials.gov NCT01650402) will also achieve little with regard to persons with severe to very severe limitations, because it excluded patients with signs of physical frailty (Short Physical Performance Battery score <10 points).

Strengths and limitations

The strength of this systematic review is that for the first time the available literature—both RCTs and non-RCTs, including observational studies—on the treatment of hypertension has been evaluated taking into account physical frailty. We strove to ensure identification of all relevant publications by hand-searching the reference lists of systematic reviews on antihypertensive treatment in older patients (35–37) and further landmark studies *(eTable 3)*. However a small risk remains that single subgroup-analyses were not considered. Another critical point is the method used to identify physically frail, functionally impaired patients. The heterogeneity of the definitions of frailty highlighted the considerable differences between function-oriented assessments, cognition-oriented assessments, and deficit models such as Rockwood's cumulative FI (used in SPRINT and HYVET). For instance, the FI in SPRINT features hardly any aspects of physical function. Moreover, post-hoc subgroup analyses limit the robustness of the results. In most non-RCTs not all confounding factors can be taken into account. Assessment of publication bias was not feasible owing to the small number of studies identified.

Summary

Even after a systematic analysis of the published data with regard to physical frailty, questions remain open. The SPRINT and HYVET findings seem to show that antihypertensive treatment as recommended in the prevailing guidelines may also be indicated in this group of patients. Whether patients with severe physical frailty were included in these studies is uncertain because of the deficit-oriented FI they used. Furthermore, these two studies are not representative due to their exclusion criteria. Among the non-RCTs only a small number of studies have analyzed both drug treatment and physical function in detail. To ensure reliable characterization and facilitate comparability among studies, not only

should older members of the population be included in future research, as stated so often before, but systematically evaluated geriatric assessment instruments should be used. This is the only way in which modification of effects by physical frailty can be evaluated. Moreover, in order to fill the gaps in evidence, not only classical clinical studies but also deprescribing RCTs and new methodological approaches including prospective meta-analyses should be carried out in established research networks.

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Conflict of interest statement
The authors declare that no conflict of interest exists.

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Translated from the original German by David Roseveare

Key messages

- Although the term "frailty" was introduced as early as 1992, the physical function and/or frailty of older study participants is hardly ever documented in randomized controlled trials (RCTs) or non-RCTs.
- The lower target blood pressures in the current guidelines must be critically reconsidered and, as the guidelines state, the target must be decided on an individual basis for each patient.
- When interpreting the results with regard to a possible J-shaped association between blood pressure and mortality in observational studies, one should, even in the presence of conceivable pathophysiology, take the methodological limitations (reverse causation) into account.
- To improve the characterization of older persons in clinical studies and observational studies with regard to their functionality, validated instruments for functional assessment should be used. We agree with the European Medicines Agency that at least gait speed and the Short Physical Performance Battery should be included.

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► **Supplementary material**

For eReferences please refer to:
www.aerzteblatt-international.de/ref0319

eMethods, eBoxes, eTables:
www.aerzteblatt-international.de/19m0023

Supplementary material to:

The Pharmacological Treatment of Arterial Hypertension in Frail, Older Patients

A Systematic Review

by Viktoria Mühlbauer, Dhayana Dallmeier, Simone Brefka, Claudia Bollig, Sebastian Voigt-Radloff, and Michael Denkinger

Dtsch Arztebl Int 2019; 116: 23–30. DOI: 10.3238/arztebl.2019.0023

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eMETHODS

The search strategy was based on a validated filter for geriatric patients (e2) and established search filters for randomized controlled trials (RCTs) (e3) and non-RCTs including observational studies (e4), supplemented with further search terms related to functionality and hypertension *(eBox 2)*. The search was carried out with no language restrictions of publication. In addition, the reference lists of national and international guidelines were handsearched. Finally, a search was conducted for citations of the first and last author of all studies included for analysis over the whole period. The permitted comparisons were antihypertensive treatment versus placebo, no treatment, or other drug treatment. Comparisons of different target blood pressures were also included. Observational studies that exclusively investigated the measured blood pressure values as the exposure of interest were excluded.

To optimize comparability of the estimation of functionality across various studies/indications, we analyzed all of the functionality scores (including a frailty index) used in studies and arranged them into a comparative system (13). The references were selected with the aid of Covidence, which is a screening software from the Cochrane Collaboration with various functions that accelerate the selection process.

The studies chosen for full-text screening were those on pharmacological treatment of hypertension that referred to assessment of functionality in the abstract. The risk of bias was assessed by means of the Cochrane Risk of Bias Tool (e3) for RCTs. The non-RCTs were assessed for risk of bias according to ROBINS-I (e5) *(eTable 4)* and reported according to STROBE (e6) *(eTable 5)*.

eBOX 1

Effect modification

Effect modification is present when the influence of a factor (in our case the drug treatment of arterial hypertension) on an endpoint is modified by the presence of another factor, the so-called effect modifier (in our case physical frailty). One can also talk of an interaction between the exposure of interest and the effect modifier (e1). A question increasingly being asked in the field of clinical epidemiology is whether the effects of a treatment on various endpoints in elderly populations could be modified by frailty.

There are several ways of investigating an interaction. First, one can test, in the statistical model, whether an interaction term, made up of the variable of interest and the possible effect modifier (interaction term = variable*effect modifier), is relevant. If the interaction is significant, the statistical model must contain the interaction term; this, however, complicates interpretation of the effects of the variable. Another way of investigating a possible interaction is to conduct stratified analyses—stratified by the effect modifier (e.g., frail versus not frail). By this means the effects of the variable of interest on the various strata are calculated and contrasted. However, stratification reduces the number of observations per group (stratum), so the statistical power may be affected.

eBOX 2a

Search strategies

MEDLINE search strategy RCTs

1. elder*.ti,ab,kf.
2. (community adj1 dwelling).ti,ab,kf.
3. geriatric.ti,ab,kf.
4. „mini-mental state“.ti,ab,kf.
5. alzheimer*.ti,ab,kf.
6. mmse.ti,ab,kf.
7. caregiver*.ti,ab,kf.
8. falls.ti,ab,kf.
9. adl.ti,ab,kf.
10. frail*.ti,ab,kf.
11. Gds.ti,ab,kf.
12. Ag?ing.ti,ab,kf.
13. Mci.ti,ab,kf.
14. dement*.ti,ab,kf.
15. (psycho-geriatric* or psychogeriatric*).ti,ab,kf.
16. „cognitive impairment“.ti,ab,kf.
17. „postmenopausal women“.ti,ab,kf.
18. comorbid*.ti,ab,kf.
19. exp Nursing Homes/
20. exp Geriatric Assessment/
21. exp Frail Elderly/
22. Alzheimer Disease/ep
23. Cognition Disorders/di
24. Cognition disorders/ep
25. exp Homes for the Aged/
26. disability.ti,ab,kf.
27. „functional decline“.ti,ab,kf.
28. (gerontopsychiatry or geronto-psychiatry).ti,ab,kf.
29. „activities of daily living“.ti,ab,kf.
30. immobility.ti,ab,kf.
31. „Activities of daily living“/
32. exp dementia/
33. immobilization.ti,ab,kf.
34. disabled persons/ or persons with hearing impairments/ or visually impaired persons/
35. or/1–34
36. exp Hypertension/
37. hypertens*.ti,ab,kf.
38. (essential adj3 hypertension).ti,ab,kf.
39. (isolat* adj3 hypertension).ti,ab,kf.
40. (elevat* adj3 blood adj pressur*).ti,ab,kf.
41. (high adj3 blood adj pressur*).ti,ab,kf.
42. (increase* adj3 blood pressur*).ti,ab,kf.
43. ((systolic or diastolic or arterial) adj3 pressur*).ti,ab,kf.
44. or/36–43
45. exp pregnancy/
46. exp Hypertension, Pregnancy-Induced/
47. (pre-eclampsia or preeclampsia).ti,ab,kf.
48. exp Hypertension, Malignant/
49. exp Hypertension, Portal/
50. exp Hypertension, Pulmonary/
51. exp Hypertension, Renal/
52. exp Intracranial Hypertension/
53. exp Ocular Hypertension/
54. exp diabetes mellitus/
55. or/45–54
56. 44 not 55
57. drug therapy/ or drug administration routes/ or drug administration schedule/ or drug delivery systems/ or drug dosage calculations/ or drug prescriptions/ or drug therapy, combination/ or drug therapy, computer-assisted/ or inappropriate prescribing/ or medication errors/ or polypharmacy/ or self administration/ or self medication/
58. „drug therap*“.ti,ab,kf,fs.
59. (pharmacotherap* or pharmaco-therap*).ti,ab,kf.
60. exp „antihypertensive agents“/
61. („antihypertensive agent*“ or „anti-hypertensive agent*“).ti,ab,kf.
62. drugs.ti,ab,kf.
63. medication.ti,ab,kf.
64. 57 or 58 or 59 or 60 or 61 or 62 or 63
65. 56 and 64
66. exp thiazides/
67. exp sodium chloride symporter inhibitors/
68. exp sodium potassium chloride symporter inhibitors/
69. ((ceiling or loop) adj diuretic?).ti,ab,kf,nm.
70. (amiloride or benzothiadiazine or bendroflumethiazide or bumetanide or chlorothiazide or cyclopenthiazide or furosemide or hydrochlorothiazide or hydroflumethiazide or methyclothiazide or metolazone or polythiazide or trichlormethiazide or veratide or quinethazone or clopamide or mefruside or meticrane or clorexolon or fenquizone or thiazide?).ti,ab,kf,nm.
71. (chlorthalidone or chlortalidone or phthalamudine or chlorphthalidolone or oxodoline or thalitone or hygroton or indapamide or metindamide or azosemide ortriamterene or torasemide or xipamide or piretanide).ti,ab,kf,nm.
72. or/66–71 [THZ]
73. exp angiotensin-converting enzyme inhibitors/
74. angiotensin converting enzyme inhibit$.ti,ab,kf,nm.
75. (ace adj3 inhibit$).ti,ab,kf,nm.
76. acei.ti,ab,kf,nm.
77. (alacepril or altiopril or ancovenin or benazepril or captopril or ceranapril or ceronapril or cilazapril or deacetylalacepril or delapril or derapril or enalapril or epicaptopril or fasidotril or fosinopril or foroxymithine or gemopatrilat or idapril or imidapril or indolapril or libenzapril or lisinopril or moexipril or moveltipril or omapatrilat or pentopril$ or perindopril$ or pivopril or quinapril$ or ramipril$ or rentiapril or saralasin or s nitrosocaptopril or spirapril$ or temocapril$ or teprotide or trandolapril$ or utibapril$ or zabicipril$ or zofenopril$ or Aceon or Accupril or Altace or Capoten or Lotensin or Mavik or Monopril or Prinivil or Univas or Vasotec or Zestril).ti,ab,kf,nm.
78. or/73–77 [ACEI]
79. exp Angiotensin Receptor Antagonists/
80. (angiotensin adj3 (receptor antagon$ or receptor block$)).ti,ab,kf,nm.
81. arb?.ti,ab,kf,nm.

82. (abitesartan or azilsartan or candesartan or elisartan or embusartan or eprosartan or forasartan or irbesartan or losartan or milfasartan or olmesartan or saprisartan or tasosartan or telmisartan or valsartan or zolasartan or aliskiren or Atacand or Avapro or Benicar or Cozaar or Diovan or Micardis or Teveten).ti,ab,kf,nm.
83. or/79–82 [ARB]
84. exp calcium channel blockers/
85. (amlodipine or aranidipine or barnidipine or bencyclane or benidipine or bepridil or cilnidipine or cinnarizine or clentiazem or clevidipine or darodipine or diltiazem or efonidipine or elgodipine or etafenone or fantofarone or felodipine or fendiline or flunarizine or gallopamil or isradipine or lacidipine or lercanidipine or lidoflazine or lomerizine or manidipine or mibefradil or nicardipine or nifedipine or niguldipine or nilvadipine or nimodipine or nisoldipine or nitrendipine or perhexiline or prenylamine or semotiadil or terodiline or tiapamil or verapamil or Cardizem CD or Dilacor XR or Tiazac or Cardizem Calan or Isoptin or Calan SR or Isoptin SR Coer or Covera HS or Verelan PM).ti,ab,kf,nm.
86. (calcium adj2 (antagonist? or block$ or inhibit$)).ti,ab,kf,nm.
87. or/84–86 [CCB]
88. (methyldopa or alphamethyldopa or amodopa or dopamet or dopegyt or dopegit or dopegite or emdopa or hyperpax or hyperpaxa or methylpropionic acid or dopergit or meldopa or methyldopate or medopa or medomet or sembrina or aldomet or aldometil or aldomin or hydopa or methyldihydroxyphenylalanine or methyl dopa or mulfasin or presinol or presolisin or sedometil or sembrina or taquinil or dihydroxyphenylalanine or methylphenylalanine or methylalanine or alpha methyl dopa).ti,ab,kf,nm.
89. sympatholytics/ or bethanidine/ or butoxamine/ or clonidine/ or debrisoquin/ or dibenzylchlorethamine/ or guanethidine/ or methyldopa/ or moxisylyte/ or oxidopamine/
90. (reserpine or serpentina or rauwolfia or serpasil).ti,ab,kf,nm.
91. (clonidine or adesipress or arkamin or caprysin or catapres$ or catasan or chlofazolin or chlophazolin or clinidine or clofelin$ or clofenil or clomidine or clondine or clonistada or clonnirit or clophelin$ or dichlorophenylaminoimidazoline or dixarit or duraclon or gemiton or haemiton or hemiton or imidazoline or isoglaucon or klofelin or klofenil or m-5041t or normopresan or paracefan or st-155 or st 155 or tesno timelets).ti,ab,kf,nm.
92. exp hydralazine/
93. or/88–92 [CNS]
94. exp adrenergic beta-antagonists/
95. (acebutolol or adimolol or afurolol or alprenolol or amosulalol or arotinolol or atenolol or befunolol or betaxolol or bevantolol or bisoprolol or bopindolol or bornaprolol or brefonalol or bucindolol or bucumolol or bufetolol or bufuralol or bunitrolol or bunolol or bupranolol or butofilolol or butoxamine or carazolol or carteolol or carvedilol or celiprolol or cetamolol or chlortalidone cloranolol or cyanoiodopindolol or cyanopindolol or deacetylmetipranolol or diacetolol or dihydroalprenolol or dilevalol or epanolol or esmolol or exaprolol or falintolol or flestolol or flusoxolol or hydroxybenzylpinodolol or hydroxycarteolol or hydroxymetoprolol or indenolol or iodocyanopindolol or iodopindolol or iprocrolol or isoxaprolol or labetalol or landiolol or levobunolol or levomoprolol or medroxalol or mepindolol or methylthiopropranolol or metipranolol or metoprolol or moprolol or nadolol or nebivolol or oxprenolol or penbutolol or pindolol or nadolol or nebivolol or nifenalol or nipradilol or oxprenolol or pafenolol or pamatolol or penbutolol or pindolol or practolol or primidolol or prizidilol or procinolol or pronetalol or propranolol or proxodolol or ridazolol or salcardolol or soquinolol or sotalol or spirendolol or talinolol or tertatolol or tienoxolol or tilisolol or timolol or tolamolol or toliprolol or tribendilol or xibenolol).ti,ab,kf,nm.
96. (beta adj2 (adrenergic? or antagonist? or block$ or receptor?)).ti,ab,kf,nm.
97. or/94–96 [BB]
98. exp adrenergic alpha antagonists/
99. (alfuzosin or bunazosin or doxazosin or metazosin or neldazosin or prazosin or silodosin or tamsulosin or terazosin or tiodazosin or trimazosin).ti,ab,kf,nm.
100. (adrenergic adj2 (alpha or antagonist?)).ti,ab,kf,nm.
101. ((adrenergic or alpha or receptor?) adj2 block$).ti,ab,kf,nm.
102. or/98–101 [AB]
103. 72 or 78 or 83 or 87 or 93 or 97 or 102
104. 65 or 103
105. randomized controlled trial.pt.
106. controlled clinical trial.pt.
107. randomi#ed.ab.
108. placebo.ab.
109. drug therapy.fs.
110. randomly.ab.
111. groups.ab.
112. trial.ab.
113. exp animals/ not humans.sh.
114. 105 or 106 or 107 or 108 or 109 or 110 or 111 or 112
115. 114 not 113
116. 35 and 104 and 115

eBOX 2b

Search strategies

MEDLINE search strategy non-RCTs

1. elder*.ti,ab,kf.
2. (community adj1 dwelling).ti,ab,kf.
3. geriatric.ti,ab,kf.
4. „mini-mental state“.ti,ab,kf.
5. alzheimer*.ti,ab,kf.
6. mmse.ti,ab,kf.
7. caregiver*.ti,ab,kf.
8. falls.ti,ab,kf.
9. adl.ti,ab,kf.
10. frail*.ti,ab,kf.
11. Gds.ti,ab,kf.
12. Ag?ing.ti,ab,kf.
13. Mci.ti,ab,kf.
14. dement*.ti,ab,kf.
15. (psycho-geriatric* or psychogeriatric*).ti,ab,kf.
16. „cognitive impairment“.ti,ab,kf.
17. „postmenopausal women“.ti,ab,kf.
18. comorbid*.ti,ab,kf.
19. exp Nursing Homes/
20. exp Geriatric Assessment/
21. exp Frail Elderly/
22. Alzheimer Disease/ep
23. Cognition Disorders/di
24. Cognition disorders/ep
25. exp Homes for the Aged/
26. disability.ti,ab,kf.
27. „functional decline“.ti,ab,kf.
28. (gerontopsychiatry or geronto-psychiatry).ti,ab,kf.
29. „activities of daily living“.ti,ab,kf.
30. immobility.ti,ab,kf.
31. „Activities of daily living“/
32. exp dementia/
33. immobilization.ti,ab,kf.
34. disabled persons/ or persons with hearing impairments/ or visually impaired persons/
35. or/1–34
36. exp Hypertension/
37. hypertens*.ti,ab,kf.
38. (essential adj3 hypertension).ti,ab,kf.
39. (isolat* adj3 hypertension).ti,ab,kf.
40. (elevat* adj3 blood adj pressur*).ti,ab,kf.
41. (high adj3 blood adj pressur*).ti,ab,kf.
42. (increase* adj3 blood pressur*).ti,ab,kf.
43. ((systolic or diastolic or arterial) adj3 pressur*).ti,ab,kf.
44. or/36–43
45. exp pregnancy/
46. exp Hypertension, Pregnancy-Induced/
47. (pre-eclampsia or preeclampsia).ti,ab,kf.
48. exp Hypertension, Malignant/
49. exp Hypertension, Portal/
50. exp Hypertension, Pulmonary/
51. exp Hypertension, Renal/
52. exp Intracranial Hypertension/
53. exp Ocular Hypertension/
54. exp diabetes mellitus/
55. or/45–54
56. 44 not 55
57. drug therapy/ or drug administration routes/ or drug administration schedule/ or drug delivery systems/ or drug dosage calculations/ or drug prescriptions/ or drug therapy, combination/ or drug therapy, computer-assisted/ or inappropriate prescribing/ or medication errors/ or polypharmacy/ or self administration/ or self medication/
58. „drug therap*“.ti,ab,kf,fs.
59. (pharmacotherap* or pharmaco-therap*).ti,ab,kf.
60. exp „antihypertensive agents“/
61. („antihypertensive agent*“ or „anti-hypertensive agent*“).ti,ab,kf.
62. drugs.ti,ab,kf.
63. medication.ti,ab,kf.
64. 57 or 58 or 59 or 60 or 61 or 62 or 63
65. 56 and 64
66. exp thiazides/
67. exp sodium chloride symporter inhibitors/
68. exp sodium potassium chloride symporter inhibitors/
69. ((ceiling or loop) adj diuretic?).ti,ab,kf,nm.
70. (amiloride or benzothiadiazine or bendroflumethiazide or bumetanide or chlorothiazide or cyclopenthiazide or furosemide or hydrochlorothiazide or hydroflumethiazide or methyclothiazide or metolazone or polythiazide or trichlormethiazide or veratide or quinethazone or clopamide or mefruside or meticrane or clorexolon or fenquizone or thiazide?).ti,ab,kf,nm.
71. (chlorthalidone or chlortalidone or phthalamudine or chlorphthalidolone or oxodoline or thalitone or hygroton or indapamide or metindamide or azosemide ortriamterene or torasemide or xipamide or piretanide).ti,ab,kf,nm.
72. or/66–71 [THZ]
73. exp angiotensin-converting enzyme inhibitors/
74. angiotensin converting enzyme inhibit$.ti,ab,kf,nm.
75. (ace adj3 inhibit$).ti,ab,kf,nm.
76. acei.ti,ab,kf,nm.
77. (alacepril or altiopril or ancovenin or benazepril or captopril or ceranapril or ceronapril or cilazapril or deacetylalacepril or delapril or derapril or enalapril or epicaptopril or fasidotril or fosinopril or foroxymithine or gemopatrilat or idapril or imidapril or indolapril or libenzapril or lisinopril or moexipril or moveltipril or omapatrilat or pentopril$ or perindopril$ or pivopril or quinapril$ or ramipril$ or rentiapril or saralasin or s nitrosocaptopril or spirapril$ or temocapril$ or teprotide or trandolapril$ or utibapril$ or zabicipril$ or zofenopril$ or Aceon or Accupril or Altace or Capoten or Lotensin or Mavik or Monopril or Prinivil or Univas or Vasotec or Zestril).ti,ab,kf,nm.
78. or/73–77 [ACEI]
79. exp Angiotensin Receptor Antagonists/
80. (angiotensin adj3 (receptor antagon$ or receptor block$)).ti,ab,kf,nm.
81. arb?.ti,ab,kf,nm.
82. (abitesartan or azilsartan or candesartan or elisartan or

embusartan or eprosartan or forasartan or irbesartan or losartan or milfasartan or olmesartan or saprisartan or tasosartan or telmisartan or valsartan or zolasartan or aliskiren or Atacand or Avapro or Benicar or Cozaar or Diovan or Micardis or Teveten).ti,ab,kf,nm.
83. or/79–82 [ARB]
84. exp calcium channel blockers/
85. (amlodipine or aranidipine or barnidipine or bencyclane or benidipine or bepridil or cilnidipine or cinnarizine or clentiazem or clevidipine or darodipine or diltiazem or efonidipine or elgodipine or etafenone or fantofarone or felodipine or fendiline or flunarizine or gallopamil or isradipine or lacidipine or lercanidipine or lidoflazine or lomerizine or manidipine or mibefradil or nicardipine or nifedipine or niguldipine or nilvadipine or nimodipine or nisoldipine or nitrendipine or perhexiline or prenylamine or semotiadil or terodiline or tiapamil or verapamil or Cardizem CD or Dilacor XR or Tiazac or Cardizem Calan or Isoptin or Calan SR or Isoptin SR Coer or Covera HS or Verelan PM).ti,ab,kf,nm.
86. (calcium adj2 (antagonist? or block$ or inhibit$)).ti,ab,kf,nm.
87. or/84–86 [CCB]
88. (methyldopa or alphamethyldopa or amodopa or dopamet or dopegyt or dopegit or dopegite or emdopa or hyperpax or hyperpaxa or methylpropionic acid or dopergit or meldopa or methyldopate or medopa or medomet or sembrina or aldomet or aldometil or aldomin or hydopa or methyldihydroxyphenylalanine or methyl dopa or mulfasin or presinol or presolisin or sedometil or sembrina or taquinil or dihydroxyphenylalanine or methylphenylalanine or methylalanine or alpha methyl dopa).ti,ab,kf,nm.
89. sympatholytics/ or bethanidine/ or butoxamine/ or clonidine/ or debrisoquin/ or dibenzylchlorethamine/ or guanethidine/ or methyldopa/ or moxisylyte/ or oxidopamine/
90. (reserpine or serpentina or rauwolfia or serpasil).ti,ab,kf,nm.
91. (clonidine or adesipress or arkamin or caprysin or catapres$ or catasan or chlofazolin or chlophazolin or clinidine or clofelin$ or clofenil or clomidine or clondine or clonistada or clonnirit or clophelin$ or dichlorophenylaminoimidazoline or dixarit or duraclon or gemiton or haemiton or hemiton or imidazoline or isoglaucon or klofelin or klofenil or m-5041t or normopresan or paracefan or st-155 or st 155 or tesno timelets).ti,ab,kf,nm.
92. exp hydralazine/
93. or/88–92 [CNS]
94. exp adrenergic beta-antagonists/
95. (acebutolol or adimolol or afurolol or alprenolol or amosulalol or arotinolol or atenolol or befunolol or betaxolol or bevantolol or bisoprolol or bopindolol or bornaprolol or brefonalol or bucindolol or bucumolol or bufetolol or bufuralol or bunitrolol or bunolol or bupranolol or butofilolol or butoxamine or carazolol or carteolol or carvedilol or celiprolol or cetamolol or chlortalidone cloranolol or cyanoiodopindolol or cyanopindolol or deacetylmetipranolol or diacetolol or dihydroalprenolol or dilevalol or epanolol or esmolol or exaprolol or falintolol or flestolol or flusoxolol or hydroxybenzylpinodolol or hydroxycarteolol or hydroxymetoprolol or indenolol or iodocyanopindolol or iodopindolol or iprocrolol or isoxaprolol or labetalol or landiolol or levobunolol or levomoprolol or medroxalol or mepindolol or methylthiopropranolol or metipranolol or metoprolol or moprolol or nadolol or nebivolol or oxprenolol or penbutolol or pindolol or nadolol or nebivolol or nifenalol or nipradilol or oxprenolol or pafenolol or pamatolol or penbutolol or pindolol or practolol or primidolol or prizidilol or procinolol or pronetalol or propranolol or proxodolol or ridazolol or salcardolol or soquinolol or sotalol or spirendolol or talinolol or tertatolol or tienoxolol or tilisolol or timolol or tolamolol or toliprolol or tribendilol or xibenolol).ti,ab,kf,nm.
96. (beta adj2 (adrenergic? or antagonist? or block$ or receptor?)).ti,ab,kf,nm.
97. or/94–96 [BB]
98. exp adrenergic alpha antagonists/
99. (alfuzosin or bunazosin or doxazosin or metazosin or neldazosin or prazosin or silodosin or tamsulosin or terazosin or tiodazosin or trimazosin).ti,ab,kf,nm.
100. (adrenergic adj2 (alpha or antagonist?)).ti,ab,kf,nm.
101. ((adrenergic or alpha or receptor?) adj2 block$).ti,ab,kf,nm.
102. or/98–101 [AB]
103. 72 or 78 or 83 or 87 or 93 or 97 or 102
104. 65 or 103
105. exp cohort studies/
106. cohort$.tw.
107. controlled clinical trial.pt.
108. epidemiologic methods/
109. limit 108 to yr=1971–1988
110. or/105–107,109
111. 35 and 104 and 110

eTABLE 1a

Characteristics of the randomized trials included for analysis

Study question/Population/Endpoints	Parameters of functionality	Results			
HYpertension in the Very Elderly Trial (HYVET), 2000–2008, Europa, China, Australasia, Tunisia (hazard ratio [95% CI])					
Effect of the combination of slow-release indapamide 1.5 mg ± perindopril 2–4 mg or placebo in patients ≥ 80 years with systolic blood pressure of 160 mmHg or more on the endpoints stroke, total mortality, and cardiovascular events (stroke, myocardial infarction, and heart failure) (n = 2656) (16)	Median FI (Rockwood): Placebo group 0.17 [0.11; 0.24] Intervention group 0.16 [0.11; 0.24]	Effect of treatment with perindopril compared with placebo			
		FI	Stroke	Cardiovascular events	Overall mortality
		0.1	0.75 [0.40; 1.38]	0.62 [0.42; 0.92]	0.89 [0.63; 1.25]
		0.2	0.66 [0.43; 1.01]	0.60 [0.45; 0.78]	0.84 [0.66; 1.07]
		0.3	0.59 [0.36; 0.96]	0.57 [0.42; 0.79]	0.80 [0.61; 1.04]
		0.4	0.52 [0.25; 1.09]	0.55 [0.34; 0.89]	0.76 [0.50; 1.14]
		0.5	0.47 [0.16; 1.33]	0.53l [0.26; 1.06]	0.72 [0.40; 1.29]
		0.6	0.41 [0.10; 1.65]	0.50 [0.20; 1.27]	0.68 [0.32; 1.48]
Effect of the above treatment on "frailty" (change in FI over period of 24 months) (n = 1665) (17)	FI (Rockwood)	No significant difference in average increase of FI over 24 months (p = 0.06): intervention group HR 0.79; 95% CI [0.26; 1.32] versus placebo group HR 1.53; 95% CI [0.97; 2.10]			
Discontinuation of Antihypertensive Treatment in Elderly People (DANTE), 2011–2013, Netherlands (hazard ratio [95% CI])					
Effect of short-term discontinuation of antihypertensive treatment on cognitive, psychological and general functionality in participants ≥ 75 years with mild cognitive deficits (n = 385) (18)	Groningen Activity Restriction Scale (GARS): intervention group 23 (IQR 18–28) ; control group 22 (IQR 19–29)		Change in overall cognitive compound score		
		GARS score ≤ 22	–0.07 [–0.36; 0.22]		
		GARS score >22	0.09 [–0.21; 0.40]		
Systolic Hypertension in the Elderly Program (SHEP), 1984–1996, USA (hazard ratio [95% CI])					
Influence of functional status on the efficacy of antihypertensive treatment (chlorthalidone ± atenolol) in patients ≥ 60 years on the endpoints all-cause mortality, cardiovascular death, myocardial infarction, stroke, falls, and symptomatic hypotension (n = 4593) (19)	Self-reporting of limited physical function (response "no" to at least one question: "Can you, without assistance: [a] do heavy work around the house? [b] walk up two flights of stairs? [c] walk half a mile?"). Limited physical function in 545 patients (11.9%)	Endpoint	No limited physical function*	Limited physical function*	P value for interaction
		Mortality	0.82 [0.66; 1.00]	1.22 [0.79; 1.88]	0.10
		Cardiovascular death	0.71 [0.51; 0.98]	1.27 [0.71; 2.28]	0.08
		Myocardial infarction	0.57 [0.40; 0.81]	1.25 [0.54; 2.89]	0.08
		Falls	0.81 [0.66; 0.99]	1.32 [0.87; 2.00]	0.04
		Stroke	0.64 [0.49; 0.85]	0.80 [0.44; 1.46]	0.48
		Symptomatic hypotension	No effect, regardless of functionality		
		*Adjusted for age, sex, ethnicity, baseline SBP and DBP			

Study question/Population/Endpoints	Parameters of functionality	Results

Systolic Blood Pressure Intervention Trial (SPRINT), 2010–2016, USA (hazard ratio [95% CI])

Effect of intensive blood pressure-lowering treatment (<120 mmHg) compared with standard treatment (<140 mmHg) on the primary endpoint (myocardial infarction, coronary syndrome, stroke, decompensated heart failure, death from cardiovascular events) in patients ≥ 75 years (n = 2636) (14)

Gait speed: <0.8 m/s, 740 patients (28.1%)

FI (Rockwood): >0.21, 815 patients (30.9%)

Intensive treatment versus standard treatment for primary endpoint

<0.8 m/s	0.63 [0.40; 0.99]	P value for interaction 0.85	Fit: FI ≤ 0.10	0.68 [0.45; 1.01]	P value for interaction 0.84
≥ 0.8 m/s	0.67 [CI 0.47; 0.94]		Less fit: (0.10< FI ≤ 0.21)	0.63 [0.43; 0.91]	
			Frail: FI >0.21	0.47 [0.13; 1.39]	

Effect of blood pressure-lowering treatment (see above) on gait speed and mobility in patients ≥ 75 years with data on mobility (n = 2629) (15)

Gait speed and self-reported mobility: limitations in 464 patients (18%)

Intensive treatment versus standard treatment

	Based on gait speed and self-reporting	Based on gait speed
No mobility limitation → death	0.62 [0.43; 0.90]	0.74 [0.54; 1.04]
Mobility limitation → death	0.82 [0.52; 1.28]	0.56 [0.29; 1.07]

Effect of blood pressure-lowering treatment (see above) on physical (PCS) and mental health-relevant quality of life as measured by the Veterans RAND 12-Item Health Survey in patients ≥ 50 years (n = 9361) (23)

FI (Rockwood): 2560 patients (27.3%) characterized as frail

Intensive treatment versus standard treatment (difference)

FI	PCS score	P value for interaction	MCS score	P value for interaction
Fit (FI ≤ 0.10)	−0.166 [–0.357; 0.024]	0.49	0.077 [–0.122; 0.276]	0.91
Less fit (0.10< FI≤0.21)	0.011 [–0.137; 0.160]		−0.002 –[0.160; 0.156]	
Frail (FI>0.21)	−0.028 [–0.275; 0.219]		−0.001 [–0.281; 0.279]	

FI, Frailty index; HR, hazard ratio; 95% CI, 95% confidence interval; IQR, interquartile range; SBP, systolic blood pressure; DBP, diastolic blood pressure; RAND, Research and Development

eTABLE 1b

Characteristics of the non-randomized controlled trials included for analysis

Study question/Population/Endpoints	Parameters of functionality	Results		
Jerusalem Longitudinal Study, since 1990 (survey period 2010–2011), Israel (hazard ratio [95% CI])				
Correlation of normotensive participants and treated or untreated hypertension with activities of daily living (ADL), grip strength, and 5-year mortality in participants ≥ 90 years (n = 480) (22)	Reduced grip strength (men <26 kg, women <16 kg) in 149 participants (31.0%). Dependence in ≥ 1 ADL in 194 participants (40.4%)		Low grip strength*1	Dependence in ≥1 ADL*2
		Normotensive	Reference	Reference
		Untreated hypertension	HR 0.90; 95 % CI [0.31; 2.67]	HR 0.93; 95% CI [0.35; 2.42]
		Treated hypertension	HR 1.75; 95% CI [0.78; 3.92]	HR 1.37; 95% CI [0.67; 2.80]
		*1 Adjusted for sex, education, self-rated health, ischemic heart disease, diabetes, chronic kidney disease, depression, ADL difficulty *2 Adjusted for sex, education, self-rated health, ischemic heart disease, diabetes, chronic kidney disease, depression, ADL difficulty, grip strength.		
Health, Aging, and Body Composition Study, since 1997 (survey period 1997–2014), USA (hazard ratio [95% CI])				
Association of antihypertensive medication use with recurrent falls in patients >70 years who had no functional limitations at baseline (n = 2948) (21)	Gait speed compared with median at baseline 1.17 m/s	Gait speed	Risk of repeated falls*1	
		< 1.17 m/s	HR 0.61; 95% CI [0.35; 1.06]	
		≥ 1.17 m/s	HR 0.99; 95% CI[0.56; 1.74]	
		*1 Adjusted for study site, heart failure, benign prostatic hyperplasia, cognitive impairment, depressive symptoms, self-reported hypertension, drugs that increase risk of falls, education, age, marital status, alcohol use, cerebrovascular disease, diabetes, pulmonary disease, arthritis, urinary problems, vision problems, total number of prescription medications, syncope.		
Medicare Current Beneficiary Survey, 2004–2009, USA (hazard ratio [95% CI])				
Association of antihypertensive medication with severe injury from falls in Medicare patients ≥ 70 years with hypertension and data available on medication in previous 3 years (n = 4961) (20)	Falls in previous year in 503 participants (10.1%). Basic and instrumental ADLs: 1919 (38.7%) restricted in at least one BADL, 2791 (56.3%) in at least one IADL	Fall in previous year	Risk of severe injuries over 3-year period*1	
			Moderate blood pressure-lowering treatment	Intensive blood pressure-lowering treatment
		No (n = 4621)	HR 1.2;4 95% CI [0.89; 1.73]	HR 1.10; 95% CI [0.76; 1.59]
		Yes (n = 503)	HR 2.17; 95% CI [0.98; 4.80]	HR 2.31; 95% CI [1.01; 5.29]
		*1 Adjusted for year of study entry, propensity score, age, sex, fall injury in past year, use of an assistive device, difficulty walking, obesity, osteoporosis, Parkinson disease, depression, cognitive impairment, severe vision impairment, physical function score, prior myocardial infarction, prior stroke, heart failure, diabetes, psychosis, statin use, number of non-antihypertensive medications, self-perceived health, and blood pressure measured within the past 6 months.		

ADL, Activities of daily life; BADL, basic activities of daily life; IADL, instrumental activities of daily life; HR, hazard ratio 95% CI, 95% confidence interval

eTABLE 2

Assessment of bias in the randomized controlled trials included for analysis

Trial	Authors	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reports
HYVET	Warwick et al. 2015 (16)	●	●	●	●	●	●
	Beckett et al. 2015 (17)	●	●	●	●	●	●
DANTE	Moonen et al. 2015 (18)	●	●	●	●	●	●
SHEP	Charlesworth et al. 2016 (19)	●	●	●	●	●	●
SPRINT	Williamson et al. 2016 (14)	●	●	●	●	●	●
	Odden et al. 2017 (15)	●	●	●	●	●	●
	Berlowitz et al. 2017 (23)	●	●	●	●	●	●

● Low risk of bias. ● Unclear risk of bias. ● High risk of bias.

eTABLE 3

Overview of availability of functional parameters in large randomized controlled trials on arterial hypertension in old age

Name of RCT, beginning of study	Study question	Functionality documented/addressed?
EWPHE (European Working Party on High Blood Pressure in the Elderly) 1972	What is the effect of antihypertensive treatment in older persons aged 60 years and over?	No
HEP (Trial of Hypertension in Elderly Patients in Primary Care) 1978	Does antihypertensive treatment in patients aged 60 to 79 years influence the rates of stroke, coronary heart disease, and mortality?	No
MRC (Medical Research Council Trial of Treatment of Hypertension in Older Adults) 1981	Can treatment with a diuretic or beta-blocker reduce the risk of stroke, coronary heart disease, and death in older patients with hypertension?	No
SHEP (Systolic Hypertension in the Elderly Program) 1984	Does antihypertensive treatment lower the risk of fatal and non-fatal stroke in patients with isolated systolic hypertension?	Yes
STOP (Swedish Trial in Old Patients with Hypertension) 1985	Are beta-blockers and diuretics better than placebo for decreasing the rates of stroke, myocardial infarction, and other cardiovascular endpoints in patients aged 70–84 years?	No
HOT (Hypertension Optimal Treatment) 1992	This trial investigated the relationships between three diastolic blood pressure levels (≤ 90, ≤ 85, ≤ 80 mmHg) and cardiovascular morbidity and mortality as well as the effect of low-dose ASS (75 mg/d) on morbidity and mortality.	No
ALLHAT (Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial) 1993	Are drugs such as amlodipine, lisinopril, and doxazosine better than chlorthalidone for reducing the rate and speed of progression of coronary heart disease?	No
Syst-China (Systolic Hypertension in China) 1988	Does antihypertensive treatment lower the risk of stroke and other cardiovascular complications in patients with isolated systolic hypertension?	No
Syst-Eur (Systolic Hypertension in Europe) 1989	Does antihypertensive treatment lower the risk of stroke and other cardiovascular complications in patients with isolated systolic hypertension?	No
PROGRESS (Perindopril Protection Against Recurrent Stroke Study) 1995	What is the effect of long-term treatment with an ACE inhibitor on the rate of stroke in patients who have already had a stroke or a TIA?	No
INVEST (International Verapamil/ Trandolapril Study) 1997	The influence of treatment with verapamil or atenolol on mortality, myocardial infarction, and stroke in patients with coronary heart disease and hypertension	No
SCOPE (Study on Cognition and Prognosis in the Elderly) 1997	Does treatment with candesartan decrease the rate of cardiovascular events, cognitive deficit, or dementia in older patients with mild or moderate hypertension?	No
ASCOT–BPLA (Anglo-Scandinavian Cardiac Outcomes Trial–Blood Pressure Lowering Arm) 1998	What is the effect of atenolol + thiazide compared with amlodipine + perindopril on the rates von myocardial infarction and coronary heart disease?	No
FEVER (Felodipine Event Reduction Study) 1998	What is the effect of a combination of a low-dose diuretic and a low-dose calcium antagonist compared with monotherapy with a a low-dose diuretic on the rates of stroke and other cardiovascular events in Chinese patients?	No
ACCORD (Action to Control Cardiovascular Risk in Diabetes Blood Pressure) 1999	Comparison of intensive blood pressure-lowering treatment (<120 mmHg) and standard treatment (<140 mmHg) in diabetics	No
HYVET (Hypertension in the Very Elderly Trial) 2000	Effect of treatment with indapamide ± perindopril or placebo on the endpoints stroke, cardiovascular events, and mortality in patients aged 80 years and over with systolic blood pressure of 160 mmHg or higher	Yes
JATOS (Japanese Trial to Assess Optimal Systolic Blood Pressure in the Elderly) 2001	Comparison of intensive treatment (systolic blood pressure <140 mmHg) and moderate treatment (systolic blood pressure 140 to 160 mmHg) on the endpoints stroke, cardiovascular events, and renal failure	No
ADVANCE (Action in Diabetes and Vascular Disease: preterAx and DiamicroN-MR Controlled Evaluation) 2001	Efficacy and safety of a fixed combination of perindopril and indapamide for lowering the blood pressure of patients with diabetes mellitus type 2 in in the age groups below 65, 65 to 74, and 75 years or older	No
VALISH (Valsartan in Elderly Isolated Systolic Hypertension) 2003	Is intensive treatment (systolic blood pressure <140 mmHg) superior to moderate treatment (systolic blood pressure 140–<150 mmHg) for reducing cardiovascular mortality in older patients with isolated systolic hypertension?	No
Cardio-Sis (Italian Study on the Cardiovascular Effects of Systolic Blood Pressure Control) 2005	Comparison of intensive treatment (systolic blood pressure <130 mmHg)and standard treatment (systolic blood pressure <140 mmHg) on left ventricular hypertrophy in non-diabetics	No
SPRINT (Systolic Blood Pressure Intervention Trial) 2010	Effect of intensive blood pressure-lowering treatment (<120 mmHg) compared with standard treatment (<140 mmHg) on the endpoints myocardial infarction, cardiovascular events, and mortality	Yes

eTABLE 4a

Risk of bias assessment (systematic errors) by ROBINS-I

Stessman et al. 2017, Jerusalem Longitudinal Study (22)	
Bias due to confounding	Moderate
Bias in selection of participants into the study	Low
Bias due to the classification of interventions	Low
Bias due to deviations from intended interventions	Low
Bias due to missing data	Moderate
Bias in measurement of outcomes	Low
Bias due selection in reporting of the result	Low
Overall bias	Moderate

eTABLE 4b

Risk of bias assessment (systematic errors) by ROBINS-I

Marcum et al. 2015, Health, Aging and Body Composition Study (Health ABC) (21)	
Bias due to confounding	Moderate
Bias in selection of participants into the study	Low
Bias due to the classification of interventions	Low
Bias due to deviations from intended interventions	Moderate
Bias due to missing data	Moderate
Bias in measurement of outcomes	Low
Bias due selection in reporting of the result	Low
Overall bias	Moderate

eTABLE 4c

Risk of bias assessment (systematic errors) by ROBINS-I

Tinetti et al. 2014, Medicare Current Beneficiary Survey (20)	
Bias due to confounding	High
Bias in selection of participants into the study	Low
Bias due to the classification of interventions	Low
Bias due to deviations from intended interventions	Not specified
Bias due to missing data	Low
Bias in measurement of outcomes	Low
Bias due selection in reporting of the result	Low
Overall bias	High

eTABLE 5a

STROBE Statement—checklist of items for reports of observational studies

Stessman et al. 2017, Jerusalem Longitudinal Study (22)	
STROBE checklist	Page (p.) in Stessman et al. 2017 **(22)**
Title and abstract	
Title and abstract	p. 277.e13 Abstract
Introduction	
Background/rationale	p. 277.e14
Objectives	p. 277.e14
Methods	
Study design	p. 277.e14 Study population
Setting	p. 277.e14 Study population
Participants	p. 277.e14 Study population
Variables	p. 277.e14 Measurements
Data sources/measurement	p. 277.e14 Blood pressure measurement and hypertension diagnosis
Bias	p. 277.e14 Study population
Study size	Stessman 1995: The Jerusalem seventy year olds longitudinal study; p. 677
Quantitative variables	p. 277.e14 Measurements p. 277.e14 Blood pressure measurement and hypertension diagnosis
Statistical methods	p. 277.e14–p. 277.e15 Statistical analyses
Results	
Participants	Phase I-III: Jacobs et al. 2009 **(e7)**, p. 1464 Phase IV: p. 277 e15 Study population
Descriptive data	p. 277.e15 Table 1 p. 277.e18 Table 3
Outcome data	p. 277.e16 Figure 1
Main results	p. 277.e16 Table 2
Other analyses	p. 277.e16 Table 2
Discussion	
Key results	p. 277.e15–p. 277.e16
Limitations	p. 277.e16 Strengths and weaknesses of this study
Interpretation	p. 277.e18 Comparison with other studies
Generalizability	p. 277.e19 Conclusions and implications
Other information	
Funding	Jacobs 2009 **(e7)**, p. 1468 Stessman 1995 **(e8)**, p. 683

The references in **bold type** can be found in the reference lists of this article; the remaining citations refer to page numbers in the article by Stessman, where e14 is the first page and e19 the last page of the article.

eTABLE 5b

STROBE Statement—checklist of items for reports of observational studies

Marcum et al. 2015, Health, Aging and Body Composition Study (Health ABC) (21)	
STROBE checklist	Page (p.) in Marcum et al. 2015 **(21)**
Title and abstract	
Title and abstract	p.1562 Abstract
Introduction	
Background/rationale	p.1563
Objectives	p.1563
Methods	
Study design	p.1563 Study design, data source, and sample
Setting	p.1563 Study design, data source, and sample
Participants	p.1563 Study design, data source, and sample, p.1565 Table 1
Variables	p.1563 Methods
Data sources/measurement	p.1563 Methods
Bias	p.1563 Control variables, p.1564 Statistical analysis
Study size	p.1563 Study design, data source, and sample
Quantitative variables	p.1563 Primary independent variables, Control variables
Statistical methods	p.1563 Statistical analysis
Results	
Participants	p.1564 Results, p.1565 Table 1
Descriptive data	p.1565 Table 1
Outcome data	p.1566 Tables 2–4
Main results	p.1566 Table 4
Other analyses	p.1564 Results
Discussion	
Key results	p.1564–1565 Discussion
Limitations	p.1567
Interpretation	p.1564–1567
Generalizability	p.1566–1567
Other information	
Funding	National Institute on Aging, Intramural Research Program of the National Institutes of Health, National Institute of Nursing

The references in **bold type** can be found in the reference lists of this article; the remaining citations refer to page numbers in the article by Marcum et al.

eTABLE 5c

STROBE Statement—checklist of items for reports of observational studies

Tinetti et al. 2014, Medicare Current Beneficiary Survey (20)	
STROBE checklist	Page (p.) in Tinetti et al. 2014 **(20)**
Title and abstract	
Title and abstract	p. 588 Abstract
Introduction	
Background/rationale	p. 589
Objectives	p. 589
Methods	
Study design	p. 588 Design, participants, and setting
Setting	p. 589 Study design and sample
Participants	p. 589 Study design and sample, p. 591
Variables	p. 590 Statistical analysis
Data sources/measurement	p. 589 Methods
Bias	p. 590 Statistical analysis
Study size	p. 589 Study design and sample
Quantitative variables	p. 589 Medication data
Statistical methods	p. 590 Statistical analysis
Results	
Participants	p. 590 Results
Descriptive data	p. 591 Table 1
Outcome data	p. 592, Table 2, p. 593 Figure
Main results	p. 592 Table 2
Other analyses	p. 593 Figure
Discussion	
Key results	p. 592 Table 2
Limitations	p. 593–594
Interpretation	p. 592–594
Generalizability	p. 594
Other information	
Funding	Unclear

The references in **bold type** can be found in the reference lists of this article; the remaining citations refer to page numbers in the article by Tinetti et al.