Association Between Antihypertensive Medication Use and Non-cardiovascular Outcomes in Older Men

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BACKGROUND: Antihypertensive drugs are prescribed commonly in older adults for their beneficial cardiovascular and cerebrovascular effects, but few studies have assessed antihypertensive drugs' adverse effects on non-cardiovascular outcomes in routine clinical practice.

OBJECTIVE: To evaluate, among older adults, the association between antihypertensive medication use and physical performance, cognition, and mood.

DESIGN AND SETTING: Prospective cohort study in a Veterans Affairs primary care clinic, with patients enrolled in 2000–2001 and assessed for medication use, comorbidities, health behaviors, and other characteristics; and followed-up 1 year later.

PARTICIPANTS: 544 community-dwelling hypertensive men over age 65 years.

MEASUREMENTS: Timed chair stands; Trail Making Test part B; and Centers for Epidemiologic Studies Depression (CES-D) scores.

RESULTS: Participants had a mean age of 74.4± 5.2 years and took a mean of 2.3±1.2 antihypertensive medications at baseline. After adjustment for age, comorbidities, level of blood pressure, and other confounders, each 1-unit increase in antihypertensive medication "intensity" was associated with a 0.11-second (95% confidence interval, 0.05–0.16) increase in the time required to complete the timed chair stands. No significant relationship was found between antihypertensive medication intensity and outcomes for Trail Making B or CES-D scores.

CONCLUSIONS: A higher cumulative exposure to antihypertensive medications in community-living older men was associated with adverse effects on physical performance, but not on the cognitive or depression measures available in this study. Clinicians should consider non-cardiovascular related adverse effects when treating older males taking multiple antihypertensive medications.

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BACKGROUND

More than half of adults over 65 years have hypertension,[1] and antihypertensive medications are widely prescribed. Compelling evidence of the benefit of these medications in decreasing cardiovascular events has been demonstrated in randomized controlled trials. Accordingly, current clinical guidelines suggest the use of 1, or often several, medications to control hypertension.[2,3] As the number of medications older adults take increases, however, medication non-adherence,[4] adverse drug effects,[5] and drug interactions[6] also increase. Treatment of hypertension with multiple medications to achieve cardiovascular benefits must therefore be balanced against potential harms.

Previous studies have shown that antihypertensive medications are associated with potential drug effects apart from their intended cardiovascular outcomes, including changes in the domains of muscle function,[7–9] energy level and fatigue,[10,11] and cognition.[12] Although data from the Systolic Hypertension in the Elderly Program Trial[13] did not provide evidence of an impact of antihypertensive drug use on several measures of cognition, physical function, and mood,[14] few data are available regarding whether older adults who routinely take these drugs in usual practice are at increased risk for adverse noncardiovascular outcomes. In addition, extrapolating medication safety from clinical trials data alone is problematic, because patients enrolled in large-scale efficacy trials often differ from community-living adults in terms of their age, comorbidity profile, and other health factors; and follow-up data on non-cardiovascular outcomes are often not systematically collected.

The aim of the current study was to determine whether medications used to treat hypertension in routine clinical practice are associated with changes in 3 outcome domains important in terms of older adults' ability to remain independent—physical performance, cognition, and depressive symptoms.

METHODS

Population. The *Connecticut Veterans Longitudinal Cohort* was a prospective cohort of patients at the Veterans Administration (VA) Healthcare System in West Haven, Connecticut.[15] The cohort enrolled a consecutive series of veterans attending VA primary care clinics from July 2000–August 2001. Inclusion criteria were age 65 years or older, English speaking, ability to ambulate independently within the clinic either with or without an assistive device, and ability to give informed consent. Among a total of 935 veterans screened, 767 (82%) agreed to participate. The final study sample included 544 male participants with hypertension who had completed the required medical interviews at baseline. Participants were interviewed and examined in person at baseline and at 1-year follow-up. The study protocol was approved by VA Connecticut.

Health Status and Comorbidities. Sociodemographic data (age, sex, race/ethnicity, and years of education) were recorded from patient interviews. The Cumulative Illness Rating Scale for geriatrics (CIRS-G), a validated scale that rates all health conditions by category and severity, was used to measure comorbidity.[16] We recorded the number of disease categories for each participant from the medical record. Health behaviors, including alcohol use (in the previous month) and history of tobacco use (current, former, never smoker), were recorded from patient self-report. Instrumental activities of daily living (IADLs),[17] representing higher-level tasks necessary for independent living (e.g., meal preparation), were obtained from patient self-report during the baseline interview and coded as the number of tasks for which participants were dependent or required assistance. Blood pressure was measured in millimeters of mercury with a standard sphygmomanometer while the participant was seated at rest. Four hypertension severity levels were defined using Joint National Committee guidelines, ranging from <130/85 mmHg to the highest level of ≥160 for systolic or ≥100 for diastolic blood pressure.[3]

Medication Use. Prescription and over-the-counter medications used regularly by participants were recorded at baseline and at 1 year. Data were gathered from participants' self-report and inspection of medication bottles (during the baseline interview) and verified by reviewing the electronic pharmacy record. Prescribed antihypertensive drugs were subsequently abstracted from electronic records at 3-month intervals over the course of the follow-up period. Information on medication use in pharmacy records and medical records were merged; discrepancies were resolved by clinical consensus. Medications were coded[18] and classified using the American Hospital Formulary System.[19] Antihypertensives were classified according to the 5 commonly prescribed classes, as defined by Joint National Committee guidelines[3]: angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers; beta-blockers; calcium-channel blockers; diuretics; and centrally acting agents. Duration of medication use before enrollment and dosage were not available for the current analyses; non-VA medications were not recorded at follow-up.

Antihypertensive medication intensity was defined in 2 ways. First, to provide a quantitative measure of the "intensity" of exposure, the sum of the number of antihypertensive classes prescribed across all four 3-month intervals was determined, yielding an integer score from 0 (no antihypertensive drug use) to 20 (use of 5 antihypertensive classes over all 4 quarters). (For example, a participant taking a beta-blocker and an ACE-inhibitor for 1 full year would have a score 2×4=8.) Multiple antihypertensive agents within the same class, taken during the same 3-month interval, were counted only once toward the exposure intensity score. This method accounted for several clinical scenarios, including participants who: a) stopped taking an antihypertensive during the follow-up period; b) switched to another antihypertensive class; or c) added an antihypertensive to an existing regimen. Adherence at each interval was determined by VA records, not participant interviews.

A second approach to measure antihypertensive medication use was used to enhance clinical interpretation of the study results. Antihypertensive medication exposure was defined using a categorical approach based on the number of medication classes a patient was exposed to, involving a time frame of at least 2 of the 3-month intervals. The categories for this approach were none, minimal (i.e., used an antihypertensive drug in only one 3-month interval), 1, 2, and 3 or more antihypertensive medication classes. (Because 12.9% [70 of 544 participants] took an antihypertensive drug for only one 3-month interval, they were classified in the shortest-term user group ["minimal"], providing an assessment whether their outcomes were different from patients who were exposed to an antihypertensive drug class for at least 2 or more intervals.)

Outcome Measures. Three primary outcomes—physical performance, cognition, and depressive symptoms—were measured by a trained research nurse at baseline during a face-to-face interview and again at follow-up after 1 year. These outcomes were chosen because they represent domains that have been reported to be affected by antihypertensive medication use, although uncertainty still remains.[7,14,20,21] Timed chair stands, a measure of physical performance associated with functional decline and disability,[22] is defined as the amount of time needed to complete 3 sit-to-stand maneuvers from a chair. The Trail Making Test Part B (Trail Making B) is a timed measure of cognitive flexibility that requires attention, visuo-spatial ability, and immediate memory skills.[23] Participants were given up to 300 seconds to connect a series of numbers and letters in an alternating pattern. The 11-item Center for Epidemiologic Studies-Depression (CES-D) scale is a self-reported measure of depressive symptoms, which was transformed to the 20-item score.[24]

For the first analysis focusing on a quantitative assessment of drug-outcome associations, each measure of performance at 1 year was analyzed as a (continuous) dependent variable. A second analysis, given the absence of well-established cut-points to define clinically significant impairment in performance, was conducted by redefining the outcomes as dichotomous based on the predicted values of each outcome from the primary regression models, as described below.

Statistical analysis. Baseline characteristics of the population were reported using descriptive statistics.

In the first analytic approach, a separate multiple linear regression model was used to analyze the association between

Table 1. Baseline Characteristics of Participants

Characteristic	*N*=544
Demographics	
Age, years	74.4±5.2
Non-white	61 (11.2)
Education, years	12.0±2.8
Comorbidity	
Cumulative Illness rating scale (CIRS-G), no. categories	5.0±1.9
CIRS-G, mean score	10.4±4.3
Selected comorbidities	
Diabetes mellitus without end-organ damage	145 (26.7)
Chronic pulmonary disease	87 (16.0)
Myocardial infarction	72 (13.2)
Cerebrovascular disease	56 (10.3)
Congestive heart failure	46 (8.5)
Other health factors	
Number of IADL impairments	0.6±1.0
Alcohol use, past 30 d	277 (50.5)
Current smoker	63 (11.6)
Clinical characteristics	
Timed chair stands, seconds	7.6±2.8
Trail Making B, seconds	156.0±76.0
CES-D depressive symptoms	3.9±3.7
Systolic blood pressure, mmHg	138.8±18.7
Diastolic blood pressure, mmHg	76.8±10.3

IADL=Instrumental activities of daily living; CES-D=Center for Epidemiologic Studies-Depression

Table 2. Medication Use Among the 544 Participants

Medications	*N* (%)*
No. total medications taken at baseline	
Mean±SD	7.3±3.3
Median (interquartile range)	7 (5–10)
No. antihypertensive medications taken at baseline	
Mean±SD	2.3±1.2
Median (interquartile range)	2 (1.5–3)
Taking 1 antihypertensive drug†	119 (21.9)
ACE inhibitor use alone	45 (8.3)
Beta-blocker use alone	29 (5.3)
Calcium-channel blocker use alone	26 (4.8)
Central-acting agents alone	11 (2.0)
Diuretic use alone	8 (1.5)
Taking 2 antihypertensive drugs†	181 (33.3)
ACEI + Diuretics	29 (5.3)
ACEI + Beta blockers	27 (5.0)
Beta blockers + Calcium channel blockers	23 (4.2)
Calcium channel blockers + Central acting agents	20 (3.7)
ACEI + Central acting agents	18 (3.3)
Taking ≥3 antihypertensive drugs†	227 (41.7)
ACEI + Beta blockers + Diuretics	37 (6.8)
ACEI + Diuretics + Calcium channel blockers	26 (4.8)
ACEI + Beta blockers + Diuretics + Calcium channel blockers	20 (3.7)
ACEI + Beta blockers + Central acting agents	14 (2.6)
ACEI + Beta blockers + Calcium channel blockers	13 (2.4)
Antihypertensive intensity score during the study year‡	
Mean±SD	6.2±4.1
Median (interquartile range)	6, 3–9

**Unless otherwise indicated.*
†*The 5 most common drug(s) are listed.*
‡*See Methods section for calculation of antihypertensive intensity score (range 0–20), which is calculated for the entire 1-year follow-up period.*

the antihypertensive medication intensity score as a continuous predictor and each of the outcome measures (Timed chair stands; Trail Making B; CES-D score). Each model was adjusted first for the baseline value of the corresponding outcome and then for potential confounders, including sociodemographic factors (age, race, education level), other health behaviors (alcohol and tobacco use), hypertension (blood pressure) severity level, and comorbidity (CIRS-G score). To test for potential departure from the assumed linear effects of the antihypertensive medication intensity, a quadratic term for this score was included in the model. The model fit was assessed by examining residuals and other diagnostic statistics.[25]

In the second analytic approach, the adjusted multiple regression models described above were refitted by removing the antihypertensive medication intensity score. The predicted value of each outcome from these models was used to classify individuals as either having or not having an impaired performance based on the upper ("worst") quartile value of the population. That is, patients whose scores were among the worst 25% of the population values were classified as having an impaired performance. The relationship between levels of antihypertensive exposure (i.e., none, minimal, 1, 2, or ≥3) and the proportion of participants falling within the worst quartile for each outcome was assessed using the Cochrane–Armitage trend test.[26]

Because of missing data for the outcomes or covariates in 3–11% of patients, multiple imputation techniques were used to replace the missing values and refit the fully adjusted models using SAS MI and MIANALYZE procedures to assess the potential impact of the missing data on the results.[25,27]

All models were analyzed using SAS Version 9.1 (Cary, NC); a *P* value of <0.05 was considered to be statistically significant.

RESULTS

The mean age of participants was 74.4±5.2 years (Table 1). The majority of patients were white, high school educated, and had substantial comorbidity. At baseline, participants had mean systolic blood pressure of 138.8±18.7 mmHg, and took a mean of 7.3±3.3 medications, including 2.3±1.2 antihypertensive medications, with ACE inhibitors and beta-blockers being the most commonly prescribed medications (Table 2).

Table 3 displays the results of the linear regression models evaluating the association between antihypertensive medication intensity and each outcome, with and without adjusting for potential confounders. For each 1-unit increase in antihypertensive medication intensity score, the adjusted time required to complete the chair stands test was 0.11 seconds (95% CI 0.05–0.16) longer. Assessment of a quadratic relationship between antihypertensive medication intensity and the chair stands test approached statistical significance (beta for quadratic term=0.01; p=0.066). A statistically significant association was not found between antihypertensive medication use and performance in the Trail Making B or the CES-D score.

Table 4 displays the association between level of exposure to antihypertensive medications classes and the worst quartile of performance for each outcome, based on its predicted values using multiple linear regression models. A significant linear relationship was found between the number of antihypertensive classes and chair stand performance (p<0.001). For Trail

Table 3. Multiple Linear Regression Models of the Effects of Antihypertensive Drug Exposure* on Primary Outcomes in 544 Older Hypertensive Patients

	Chair Stands		Trail Making B		CES-D	
Model†	β (95% CI)‡	*P* value	β (95% CI)	*P* value	β (95% CI)	*P* value
Baseline§	0.13 (0.07–0.18)	<0.001	0.34 (−0.68–1.37)	0.51	0.004 (−0.06–0.05)	0.90
Adjusted//	0.11 (0.05–0.16)	<0.001	0.18 (−0.92–1.28)	0.75	–0.03 (−0.09–0.04)	0.41

*Defined by a composite measure of number of antihypertensive drug classes exposed across 4 follow-up intervals over the study year (range 0–20; see "Methods" section for details).

† Chair stands, Trail Making B, and CES-D score were measured at 1-year follow-up; each is a dependent variable.

‡ β is the regression coefficient for the effect of a 1 unit increase in the antihypertensive intensity score on the primary outcome at 1 year.

§Baseline models included the antihypertensive intensity score and the baseline value of the corresponding outcome. N used in each model was 488, 495, 507, respectively.

//Adjusted models included the antihypertensive intensity score and the baseline value of the corresponding outcome, plus the following covariates: age, race, education, alcohol use, smoking status, Cumulative Illness Rating Scale-Geriatrics score and hypertension (blood pressure) severity level. N used in each model was 482, 492, and 506, respectively.

Making B (p=0.325) and CES-D depression score (p=0.127), no significant relationships were found.

Patients who were missing an outcome measure at follow-up tended to have worse baseline IADL function (p=0.008), lower education (p=0.03), and slower Trail Making B performance (p=0.001) compared to those without missing data, but were comparable in terms of baseline antihypertensive drug use (p=0.11), number of comorbidities (p=0.22) and total number of medications used (p=0.12). Multiple imputation analyses of the data shown in Table 3, however, yielded consistent results (data not shown).

DISCUSSION

This study provides evidence of an association between antihypertensive medication intensity and the risk of non-cardiovascular outcomes in older males with hypertension. Our data suggest that an increase in the overall exposure to antihypertensive medications was associated with decreased physical performance as measured by chair stands. In contrast, no evidence was found of a potential adverse effect on cognitive or mood outcomes. The results were similar using a worst-quartile cutpoint approach, suggesting the relationship is robust and is not an artifact of a particular measurement or analytic method.

In comparison to participants in other clinical trials,[28] participants in this sample included a greater proportion of older adults with multiple comorbidities. In addition, previous large efficacy trials have focused largely on selected cardiovascular endpoints as the primary or secondary outcomes. Consequently, our study has several important implications for interpreting the data on prescription of blood pressure lowering drugs in older males. For example, although clinical trials can provide estimates of the cardiovascular benefits of antihypertensive drugs, they overlook a range of other relevant outcomes that may be highly valued by older adults,[29] such as mood, cognition, sleep, and physical performance. Use of observational data and surveillance of commonly prescribed drugs, as described in the Institute of Medicine's report on drug safety,[30] are increasingly promoted as means to enhance the detection of adverse drug-related effects in real-world patients. Prescription of antihypertensive medications in older adults requires ongoing attention to balance the long-term

Table 4. Number and Percent of Participants in the Worst Quartile of the Predicted Outcome* by Number of Antihypertensive Drug Classes Exposed

No. Antihypertensive Classes Exposed†	*N*‡	Chair Stands§		Trail Making B§		CES-D Score§	
		n	%	*n*	%	*n*	%
3+	190	58	31.4	50	26.7	52	27.4
2	142	40	28.6	37	26.1	37	26.1
1	111	22	20.0	27	24.3	31	27.9
Minimal	70	11	15.7	14	20.3	8	11.4
None	31	3	10.3	7	23.3	8	26.7
Overall	**544**	**134**	**[24.6]**	**135**	**[24.8]**	**136**	**[25.0]**
P for linear trend//			<0.001		0.325		0.127

*Estimated using the adjusted multiple linear regression models shown in Table 3, except that the antihypertensive intensity score was removed. (If no association existed, a proportion of 25% would be expected regardless of drug class.)

†Exposure to an antihypertensive drug class was defined by prescription of a drug for 2 or more 3-month intervals during the study year, except the short-term users ("minimal"), who used antihypertensive drug(s) in only 1 interval.

‡Represents number of participants among each antihypertensive exposure group at baseline. Actual N used as the denominator of the row percentages was smaller across outcomes because of missing observations.

§Thresholds for worst quartile were 8.8 sec for chair stands, 188.6 sec for trail making B; and 5.3 for CES-D score.

//Cochran–Armitage test of linear trend on the association between proportions of participants within the worst performance and the number of antihypertensive classes exposed.

disease-specific cardiac and stroke-risk benefits, against the potential for deleterious, non-cardiac clinical outcomes that can occur in the short-term, such as potential for impaired physical performance.

The observed association between increasing intensity of antihypertensive medication use and poor physical performance deserves careful evaluation. An exploratory analysis found evidence consistent with, but not conclusive of, a non-linear (quadratic) relationship between antihypertensive medication use and performance on the chair stands test; additional research in other (e.g., larger) populations may help to clarify the pattern of a possible association. Based on our model, each 1-unit increase in antihypertensive medication "intensity" was associated with a modest overall change (0.11 second) in timed chair stands across the entire study population, but: a) participants at the highest intensity score (20) would incur a 2.2-second slower performance, compared to those in the lowest exposure category; b) changes in certain participants are much greater than the "average" value of the coefficient (as represented by the quartile analysis); and c) a similar situation exists in other contexts, such as a modest lowering of cholesterol on a population basis resulting in significant lowering in certain patients and an overall impact on group outcomes.

No accepted definitions exist for clinically significant changes in completing 3 timed chair stands, and investigators have used different numbers of repetitions of chair stands in their work. A summary performance measure incorporating 5 repetitions of chair stands, in conjunction with other tests of lower extremity function, demonstrated that a gradient of performance is related to self-reported disability, mortality, and nursing home admission.[31] Timed chair stands alone as a distinct physical performance measure has been linked to an important clinical outcome, falls, in older adults.[32,33] Analyzing chair stands using the worst quartile approach (similar to our second approach) has been shown a potent independent predictor of falls and fall injuries.[32]

The observed association lacks a confirmed mechanism at this time, but a physiological explanation is supported by previous research suggesting that users of beta-blockers, thiazide diuretics, and calcium channel blockers have lower cross-sectional measures of muscle mass compared to users of ACE-inhibitors.[34] ACE-inhibitor use, in contrast, has been reported to be associated with prevention of physical disability and maintenance of muscle strength in older patients.[7,35] Because we do not have sufficient power to distinguish the effects of 1 antihypertensive medication from another in the same or different class, a larger study comparing different antihypertensive drugs in relation to changes in muscle strength is needed. In addition, because muscle weakness predicts disability and mortality in older adults,[36–38] antihypertensive regimens that potentially impact physical performance are important to study, along with effects on related outcomes such as balance and endurance. Finally, studies suggest that older persons experiencing an adverse drug effect may value their overall quality of life more than the primary prevention of cardiac or cerebrovascular disease.[39,40]

The relationship between antihypertensive medication use and cognitive and depression outcomes has been explored in previous studies using clinical trials data. Muldoon et al.[41] have shown no prominent neuropsychological changes in older patients taking antihypertensives when analyzing data from multiple clinical trials. Prince et al.,[12] using Medical Research Council data, found no prominent cognitive changes when older patients began initial treatment for hypertension. Taken together with the results of this cohort study, no clear evidence exists that treatment for hypertension is associated with short-term cognitive changes, although trials have reported a reduced incidence of dementia.[42,43] Similarly, evidence for neuropsychiatric changes, such as depression or depressive symptoms, was not found, supporting recent work[14,44] that refutes earlier reports of associations between beta-blocker[21,45] and calcium channel blocker[46,47] use and depression. The instruments used in the current study, however, could not capture all facets of cognitive or mood states in older persons, so future research is warranted.

Unmeasured confounding may provide an alternative explanation for our findings, although we minimized potential confounding by adjusting for variables—sociodemographic, comorbidity, hypertension severity, and baseline values of the main outcome measures—that were measurable and relevant to the outcome measures studied. Increased medication use could reflect increased comorbidity, and some antihypertensive medications may be used for indications other than hypertension. In a secondary analysis, however, we removed participants with heart failure or renal disease (other prominent indications for antihypertensive medications) from the analyses and found no substantive difference in results.

All participants were diagnosed with hypertension before enrollment, and thus the study design is not an inception cohort. Participants' tolerance to the effects of different antihypertensive drugs may differ from patients who are new users. For any individual participant, drugs having an unacceptable adverse effect profile may have been discontinued before the study entry, resulting in a bias toward observing the potential effects of drugs deemed most "optimal" or tolerable for an individual. The observational cohort design may therefore underestimate the true potential for adverse drug effects.

Enrolling participants in the VA limits the generalizability of the study to women, and these findings should be confirmed in diverse populations. The VA clinics have the advantage, however, of electronic records for data abstraction. In addition, VA patients have low-cost prescription drug coverage that may minimize non-adherence because of cost.

In summary, greater intensity of antihypertensive medication was associated with worse performance on a measure of physical performance, but not with measures of cognition and mood, in older men. Given the number and diversity of drugs prescribed for aging adults, continued attention to the potential harms and benefits of commonly used drugs should be part of regular, comprehensive drug regimen reviews to inform ongoing prescribing decisions.

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Conflict of Interest: *Dr. Foody has received speaker honoraria from Merck and Pfizer. There are no other potential conflicts of interest to disclose.*

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REFERENCES

1. **Wolf-Maier K, Cooper RS, Banegas JR, et al.** Hypertension prevalence and blood pressure levels in 6 European countries, Canada, and the United States. JAMA. 2003;289:2363–9.
2. **Brown MJ, Cruickshank JK, Dominiczak AF, et al.** Better blood pressure control: how to combine drugs. J Hum Hypertens. 2003;17:81–6.
3. **Anonymous.** The sixth report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure. Arch Intern Med. 1997;157:2413–46.
4. **Schroeder K, Fahey T, Ebrahim S.** How can we improve adherence to blood pressure-lowering medication in ambulatory care? Systematic review of randomized controlled trials. Arch Intern Med. 2004;164:722–32.
5. **Agostini JV, Han L, Tinetti ME.** The relationship between number of medications and weight loss or impaired balance in older adults. J Am Geriatr Soc. 2004;52:1719–23.
6. **Huang SM, Lesko LJ.** Drug-drug, drug-dietary supplement, and drug-citrus fruit and other food interactions: what have we learned? J Clin Pharmacol. 2004;44:559–69.
7. **Onder G, Penninx BW, Balkrishnan R, et al.** Relation between use of angiotensin-converting enzyme inhibitors and muscle strength and physical function in older women: an observational study. Lancet. 2002;359:926–30.
8. **Imai Y, Watanabe N, Hashimoto J, et al.** Muscle cramps and elevated serum creatine phosphokinase levels induced by beta-adrenoceptor blockers. Eur J Clin Pharmacol. 1995;48:29–34.
9. **Mosenkis A, Townsend RR.** Muscle cramps and diuretic therapy. J Clin Hypertens (Greenwich). 2005;7:134–5.
10. **Chen K, Chiou CF, Plauschinat CA, et al.** Patient satisfaction with antihypertensive therapy. J Hum Hypertens. 2005;19:793–9.
11. **Cheung BM, Wong YL, Lau CP.** Queen Mary utilization of antihypertensive drugs study: side-effects of antihypertensive drugs. J Clin Pharm Ther. 2005;30:391–9.
12. **Prince MJ, Bird AS, Blizard RA, et al.** Is the cognitive function of older patients affected by antihypertensive treatment? Results from 54 months of the Medical Research Council's trial of hypertension in older adults. BMJ. 1996;312:801–5.
13. **Anonymous.** Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). SHEP Cooperative Research Group. JAMA. 1991;265:3255–64.
14. **Applegate WB, Pressel S, Wittes J, et al.** Impact of the treatment of isolated systolic hypertension on behavioral variables. Results from the systolic hypertension in the elderly program. Arch Intern Med. 1994;154:2154–60.
15. **Reid MC, Boutros NN, O'Connor PG, et al.** The health-related effects of alcohol use in older persons: a systematic review. Subst Abuse. 2002;23:149–64.
16. **Miller MD, Paradis CF, Houck PR, et al.** Rating chronic medical illness burden in geropsychiatric practice and research: application of the Cumulative Illness Rating Scale. Psychiatry Res. 1992;41:237–48.
17. **Fillenbaum GG.** Multidimensional Functional Assessment of Older Adults: The Duke Older Americans Resources and Services Procedures. Hillsdale, NJ: Erlbaum; 1988.
18. **Pahor M, Chrischilles EA, Guralnik JM, et al.** Drug data coding and analysis in epidemiologic studies. Eur J Epidemiol. 1994;10:405–11.
19. American Hospital Formulary Service. Drug Information. Bethesda, MD: American Society of Hospital Pharmacists; 1994.
20. **Birns J, Kalra L.** Blood pressure and vascular cognitive impairment: the debate continues. J Hum Hypertens. 2006;20:1–3.
21. **Thiessen BQ, Wallace SM, Blackburn JL, et al.** Increased prescribing of antidepressants subsequent to beta-blocker therapy. Arch Intern Med. 1990;150:2286–90.
22. **Guralnik JM, Ferrucci L, Simonsick EM, et al.** Lower-extremity function in persons over the age of 70 years as a predictor of subsequent disability. N Engl J Med. 1995;332:556–61.
23. **Vickers D, Vincent N, Medvedev A.** The geometric structure, construction, and interpretation of path-following (trail-making) tests. J Clin Psychol. 1996;52:651–61.
24. **Kohout FJ, Berkman LF, Evans DA, et al.** Two shorter forms of the CES-D (Center for Epidemiological Studies Depression) depression symptoms index. J Aging Health. 1993;5:179–93.
25. SAS. SAS Version 9.1. Cary, NC: SAS Institute Inc.; 2003.
26. **Fleiss J.** The comparison of proportions from several independent samples. In: Statistical Methods for Rates and Proportions, 2nd ed. New York, NY: Wiley; 1981:143–6.
27. **Allison PD.** Missing Data. Sage University Papers on Quantitative Applications in the Social Sciences, 07-136. Thousand Oaks, CA: Sage; 2001:27–87.
28. **Lee PY, Alexander KP, Hammill BG, et al.** Representation of elderly persons and women in published randomized trials of acute coronary syndromes. JAMA. 2001;286:708–13.
29. **Fried TR, Bradley EH, Towle VR, et al.** Understanding the treatment preferences of seriously ill patients. N Engl J Med. 2002;346:1061–6.
30. Committee on the Assessment of the US Drug Safety System, Baciu A, Stratton K, Burke SPa, eds. The Future of Drug Safety: Promoting and Protecting the Health of the Public. Washington, D.C.: The National Academies Press; 2006.
31. **Guralnik JM, Simonsick EM, Ferrucci L, et al.** A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. J Gerontol. 1994;49:M85–94.
32. **Davis JW, Ross PD, Nevitt MC, et al.** Risk factors for falls and for serious injuries on falling among older Japanese women in Hawaii. J Am Geriatr Soc. 1999;47:792–8.
33. **de Rekeneire N, Visser M, Peila R, et al.** Is a fall just a fall: correlates of falling in healthy older persons. The Health, Aging and Body Composition Study. J Am Geriatr Soc. 2003;51:841–6.
34. **Di Bari M, van de Poll-Franse LV, Onder G, et al.** Antihypertensive medications and differences in muscle mass in older persons: the Health, Aging and Body Composition Study. J Am Geriatr Soc. 2004;52:961–6.
35. **Gambassi G, Lapane KL, Sgadari A, et al.** Effects of angiotensin-converting enzyme inhibitors and digoxin on health outcomes of very old patients with heart failure. SAGE Study Group. Systematic Assessment of Geriatric drug use via Epidemiology. Arch Intern Med. 2000;160:53–60.
36. **Rantanen T, Avlund K, Suominen H, et al.** Muscle strength as a predictor of onset of ADL dependence in people aged 75 years. Aging Clin Exp Res. 2002;14:10–5.
37. **Rantanen T, Guralnik JM, Sakari-Rantala R, et al.** Disability, physical activity, and muscle strength in older women: the Women's Health and Aging Study. Arch Phys Med Rehabil. 1999;80:130–5.
38. **Laukkanen P, Heikkinen E, Kauppinen M.** Muscle strength and mobility as predictors of survival in 75–84-year-old people. Age Ageing. 1995;24:468–73.
39. **Weir MR, Prisant LM, Papademetriou V, et al.** Antihypertensive therapy and quality of life. Influence of blood pressure reduction, adverse events, and prior antihypertensive therapy. Am J Hypertens. 1996;9:854–9.
40. **Lewis DK, Robinson J, Wilkinson E.** Factors involved in deciding to start preventive treatment: qualitative study of clinicians' and lay people's attitudes. BMJ. 2003;327:841.
41. **Muldoon MF, Waldstein SR, Jennings JR.** Neuropsychological consequences of antihypertensive medication use. Exp Aging Res. 1995;21:353–68.
42. **Forette F, Seux ML, Staessen JA, et al.** The prevention of dementia with antihypertensive treatment: new evidence from the Systolic Hypertension in Europe (Syst-Eur) study. Arch Intern Med. 2002;162:2046–52.

43. **Tzourio C, Anderson C, Chapman N, et al.** Effects of blood pressure lowering with perindopril and indapamide therapy on dementia and cognitive decline in patients with cerebrovascular disease. Arch Intern Med. 2003;163:1069–75.
44. **Ko DT, Hebert PR, Coffey CS, et al.** Beta-blocker therapy and symptoms of depression, fatigue, and sexual dysfunction. JAMA. 2002;288:351–7.
45. **Avorn J, Everitt DE, Weiss S.** Increased antidepressant use in patients prescribed beta-blockers. JAMA. 1986;255:357–60.
46. **Hullett FJ, Potkin SG, Levy AB, et al.** Depression associated with nifedipine-induced calcium channel blockade. Am J Psychiatry. 1988;145:1277–9.
47. **Eccleston D, Cole AJ.** Calcium-channel blockade and depressive illness. Br J Psychiatry. 1990;156:889–91.