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ORIGINAL ARTICLE

Trends in antihypertensive drugs in the elderly: the decline of thiazides

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The last decade has seen the publication of different editions of guidelines for the pharmacological treatment of hypertension that were based on the results of large, randomised trials. Since these guidelines were meant to inform practitioners, we analysed the pattern of prescription of antihypertensive agents between 1988 and 1997 among older hospitalised adults. Because of the wealth of data supporting the use of thiazides diuretics, we focused on diuretic prescription, to identify independent predictors of their utilisation. To this end, we used the GIFA database that includes patients admitted to academic medical centres throughout Italy between 1988 and 1997. We studied 5061 patients over 65 years of age selected among a population of 28 411, based on the diagnosis of arterial hypertension at discharge. The use of ACE-inhibitors has been raising steadily through the years, and they are the agents most commonly used since 1996. Calcium channel blockers showed a similar trend and were the top prescribing drug until 1995; afterwards, the documentation of potentially severe side effects has resulted in a nearly 20% reduction of their use. Beta-blockers have remained unpopular throughout the decade. Instead, the prescription of diuretics as a class showed a biphasic trend; an initial decrease with a prolonged steady state and a more recent raise. However, at a separate analysis, it was a evident that a progressive increase of the use of loop diuretics since 1988 has been paralleled by a nearly 50% reduction of thiazides prescriptions. Loop diuretics were more likely to be prescribed to older individuals, those with cardiac heart failure, coronary heart disease and high creatinine level. In contrast, independent predictors of thiazides use were female gender, good functional status, preserved renal function, and absence of cardiovascular comorbidity. In conclusion, despite continued recommendations to use thiazides diuretics for the treatment of hypertension among older individuals, their use has been declining steadily between 1988 and 1997. A possible explanation is that the choice to prescribe a thiazides diuretic is influenced by age, functional status and comorbidity.
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Introduction

The prevalence of hypertension progressively increases with age, and pharmacological therapy is a mainstay of its treatment.[1,2] Meta-analyses of the randomised trials available so far have suggested that the absolute benefits of pharmacological treatment are even more pronounced among older adults.[3,4] Nonetheless, there is evidence that increased age is associated with undertreatment.[5] Diuretics and beta-blocker use has been associated with a clear benefit in terms of cardiovascular morbidity and mortality.[6–10] Despite abundant literature documenting their ability to lower blood pressure levels in hypertensive patients,[11] there is no evidence for a positive effect of calcium channel blockers (CCB) and angiotensin converting enzyme (ACE) inhibitors on hard outcomes. In addition, some retrospective studies have found a possible association between CCB use and serious adverse effects among elderly hypertensives.[12–14]

Guidelines for treatment of hypertension have changed significantly in the last decade, especially regarding the role of ACE-inhibitors and CCB as first-line agents. In 1988 the JNC IV[15] recommended them, but subsequently JNC V[16] did not endorse their use any longer. Current guidelines (JNC VI)[17] have renewed emphasis on the use of CCB and ACE-inhibitors as first-line agents for specific indications. In the case of thiazides diuretics, there has been an unchanged consensus through the years, and their use as first-line agents has constantly been recommended along with that of beta-blockers.

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Adherence to these guidelines is recommended based upon pharmacoeconomic considerations. In fact, the costs for antihypertensive medications, which account for up to 80% of the total expenditure for the treatment of hypertension,[16,18] ranges between 5 US $ per year in the case of thiazides diuretics to over 1400 US $ per year in the case of ACE-inhibitors.[19]

Thus, the aim of our study was to examine to what extent antihypertensive drug prescribing patterns conformed to these guidelines during the past decade at academic medical centres throughout Italy. Furthermore, we analysed the prescription patterns of different forms of diuretics to identify independent predictors of their use.

Materials and methods

We used the GIFA database which has been described in detail elsewhere.[20] Briefly, a group of trained physicians collected information on all the patients admitted to 81 academic medical centres throughout Italy from 1 May to 30 June and 1 September to 31 December, 1988, from 15 May to 15 June, 1991, and from 1 May to 30 June and 1 September to 31 October, in 1993, 1995, and 1997. For each patient a questionnaire was completed on admission and updated daily. Among other variables, the form included demographic characteristics, tests describing functional status, biochemical parameters, admission and discharge diagnoses, drugs taken prior to admission, during hospital stay and at discharge, in addition to any eventual adverse reaction.

Physical function was measured with the activities of daily living (ADL) scale, while cognitive performance was assessed immediately prior to discharge using the Hodkinson Abbreviated Mental Test (AMT).[21] Clinical diagnoses were coded according to the International Classification of Diseases, Ninth Edition, Clinical Modification codes,[22] while drugs were automatically labelled with the Anatomical Therapeutic and Chemical codes.[23]

Study population

From an initial population of 28 411 subjects, we initially excluded those younger than 65 years ($n = 8145$), and those who died during a hospital stay ($n = 1587$). Among the remaining 18 679 patients, we identified 5061 (27%) with a diagnosis of hypertension on the discharge record. The clinical diagnosis of hypertension was made exclusively by physicians, according to blood pressure repeated measurements, previous history, and based upon the use of drugs such as antihypertensives. Blood pressure values were not a mandatory item in the collection form.

Patients included in the study sample were equally distributed across the years: 1411 in 1988, 543 in 1991, 1050 in 1993, 1089 in 1995 and 968 in 1997.

We evaluated age differences by stratifying the sample in three categories: 65 to 74 years ($n = 1952$), 75 to 84 years ($n = 2407$), and 85 years and older ($n = 702$). We considered exclusively four classes of antihypertensive medication (diuretics, beta-blockers, CCB, and ACE-inhibitors) as they were prescribed during hospital stay and at discharge.

Data analysis

Data are expressed as mean ± sd. Analysis of variance for normally distributed variables was performed by ANOVA comparisons; otherwise, the nonparametric Kruskal–Wallis H test was adopted. Chi-square analysis was used for dichotomous variables.

The significance of the trend across the years of survey was assessed using the Mantel–Haenszel test for linear trend.

To determine the independent predictors of receiving a diuretic, we ran a multivariate analysis. Initially, candidate predictors at bivariate comparisons, ($P < 0.1$), were selected and entered into separate, logistic regressions models, age and sex-adjusted as appropriate. A value of P below 0.05 was considered statistically significant.

All analyses were performed using SPSS for Windows version 9.0.

Results

Mean age of the 5061 patients was 77.1 ± 6.8 years, 61% were females, and in approximately two out of three of cases they were admitted to a geriatric ward. Nearly 75% of patients had at least one antihypertensive drug prescribed out of all the possible medications available. Interestingly, the proportion of patients being treated has been progressively increasing through the years: 69% in 1988, 70% in 1991, 76% in 1993, 77% in 1995, and 83% in 1997 ($P < 0.001$ for trend). Table 1 shows the principal characteristics of the population stratified according to diuretic use. Non-diuretic users were slightly younger, with fewer comorbid conditions, especially congestive heart failure, but they were characterised by a more prevalent impairment of physical and cognitive function.

Trend in the prescription of antihypertensive drugs is shown in Figure 1. Beta-blockers were used in a minority of patients (<3%) despite a significant rising trend ($P < 0.01$). ACE-inhibitors instead have been used at a progressively increasing rate, becoming the class most commonly used by year 1997 (50%). The pattern of prescriptions in the case of CCB was bimodal. Prior to 1995, CCB were the most common drugs (40% in 1988, 47% in 1991, 49% in 1993, 49% in 1995), but following the CCB controversy prescriptions fell to 43% ($P = 0.01$ *vs* 1995).

An opposite trend was evident for diuretics (Figure 2). Their prescription fell precipitously between 1988 and 1991 following JNC IV publication (from 41% to 34%; $P < 0.01$, while there were

Table 1 Characteristics of the study population according to diuretic use

	Diuretics users (n = 1938) %	*Non-diuretic users (n = 3123) %*	*P*
Age, y (mean ± SD)	77.44 ± 6.83	76.87 ± 6.79	<0.01
Sex (F)	61.8	60.2	0.277
Functional status (1 or more impaired ADL)	28.9	33.0	<0.01
Cognitive impairment (AMT<7)	19.3	23.5	<0.01
Number of coexisting conditions			
0–3	38.2	42.0	
4–5	42.8	41.0	0.022
⩾6	18.9	17.0	
Congestive heart failure	20.0	4.8	<0.001
Coronary heart disease	28.7	22.4	<0.001
Diabetes mellitus	24.7	23.1	0.190
Serum creatinine levels (mg/dl)			
<1.5	72.8	83.4	
1.5–2.0	15.8	10.8	<0.001
>2.0	11.4	5.8	
Serum cholesterol (mg/dl) (mean ± s.d.)	200.0 ± 51.2	201.9 ± 50.7	0.266
Type of ward			
Geriatric	62.4	62.5	
Internal medicine	34.0	34.5	0.544
Cardiology	3.6	3.1	
Year of survey			
1988	41.1	58.9	0.708
1991	34.3	65.7	
1993	34.7	65.3	
1995	35.0	65.0	
1997	44.1	55.9	

AMT, Abbreviated Mental Test; ADLs, activities of daily living.

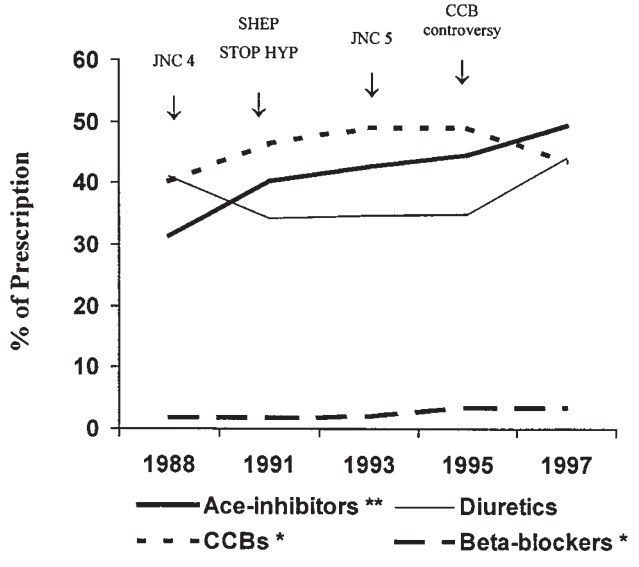

Figure 1 Trends in the prescription of antihypertensive drugs among patients above 65 years of age. The arrows above identify the relation to the release of guidelines (JNC: Joint National Committee), or to the publication of clinical trials (SHEP: Systolic Hypertension in Elderly Trial; STOP: Swedish Trial in Old Patients). $*P < 0.01$, $**P < 0.001$ for trend.

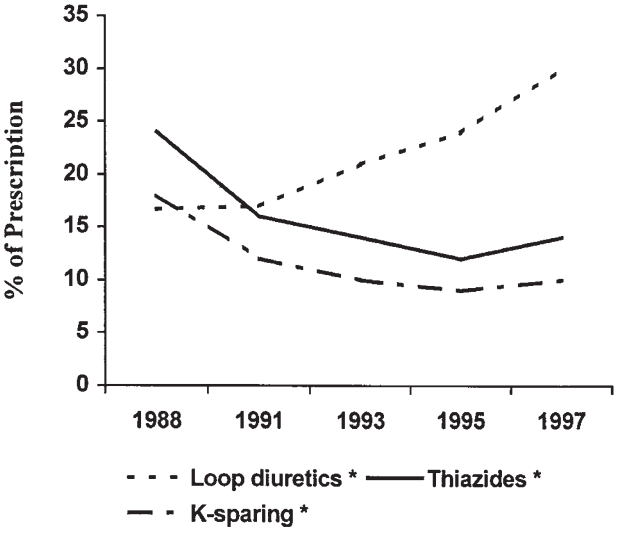

Figure 2 Trends in the prescription of diuretics by different classes. For the relation to the release of guidelines and publication of trials refer to Figure 1. $*P < 0.01$ for trend.

only minor variations in 1993 and 1995. In more recent years, diuretics prescription has shown the most definite rise reaching values above those registered a decade earlier (44% in 1997 ($P < 0.001$) *vs* 1995), and they have become the most commonly used antihypertensive agents, second only to ACE-inhibitors.

However, if analysed separately, there were divergent trends for the three main classes of diuretics. While the prescriptions of loop diuretics increased progressively through the years and more decisively after 1991 (17% in 1988, 18% in 1991, 21% in 1993, 24% in 1995, 30% in 1997; $P < 0.001$ for trend), there was a parallel decline of thiazides whose prescriptions almost halved in the same period (24% in 1988, 16% in 1991, 14% in 1993, 12% in 1995, 14% in 1997; $P < 0.001$ for trend). The fate of potassium sparring agents was similar (18% in 1988, 12% in 1991, 10% in 1993, 9% in 1995, 10% in 1997; $P < 0.001$ for trend).

We also analysed the trend for thiazides across different age-categories. There was a significant decline independently of age, although more pronounced among patients aged 85+ years, until the years 1991–1993. Since then, the prevalence of thiazides prescriptions remained steady at level around 10%.

At a multivariate analysis (Table 2), loop diuretics were more likely to be prescribed to older individuals (28% increment for each 10 years), those with heart failure, coronary heart disease and high creatinine level. In contrast, independent predictors of thiazides use were female gender, good functional status, preserved renal function, and absence of cardiovascular comorbidity.

Potassium sparing diuretics were prescribed primarily (98%) in association with loop diuretics, and preferentially to patients with heart failure (OR 2.8;

Table 2 Factors independently associated with any diuretic, loop diuretic and thiazides prescription

	Any diuretic (n = 1938)	*Loop diuretics (n = 1094)*	*Thiazides (n = 841)*
Age (for each decade increment)	1.11 (1.01–1.21)	1.28 (1.14–1.43)	0.95 (0.83–1.10)
Male gender	0.88 (0.79–1.00)	1.09 (0.93–1.26)	0.75 (0.56–0.98)
1 or more impaired ADLs	0.88 (0.73–1.05)	1.03 (0.83–1.26)	0.61 (0.50–0.74)
Cognitive impairment (AMT <7)	0.76 (0.62–0.92)	0.82 (0.65–1.03)	0.82 (0.63–1.07)
Congestive heart failure	4.68 (3.82–5.73)	6.68 (5.49–8.13)	0.74 (0.56–0.98)
Coronary heart disease	1.31 (1.14–1.50)	1.53 (1.30–1.80)	0.94 (0.78–1.12)
Creatinine, mg/dl (*vs* <1.4)			
1.5–2.0	1.51 (1.51–1.98)	1.89 (1.41–2.55)	0.81 (0.55–1.20)
>2.0	2.13 (1.53–2.98)	3.39 (2.39–4.79)	0.55 (0.33–0.96)
Year of survey (*vs* 1988)			
1991	0.41 (0.22–0.77)	0.44 (0.18–1.08)	0.47 (0.21–1.07)
1993	0.36 (0.20–0.68)	0.45 (1.18–1.09)	0.41 (0.18–0.94)
1995	0.36 (0.19–0.67)	0.50 (0.21–1.22)	0.35 (0.15–0.80)
1997	0.52 (0.28–0.98)	0.67 (0.27–1.63)	0.47 (0.20–1.06)

AMT, Abbreviated Mental Test; ADLs, activities of daily living.

95% CI 2.1–3.8), and normal renal function (OR 0.7; 95% CI 0.5–0.9 for each mg/dl increase).

Discussion

The present study documents that in the past decade the number of elderly hypertensive patients receiving pharmacological treatment has been increasing progressively, but that the pattern of prescription does not concur with widely accepted guidelines. In particular, the use of thiazides diuretics is limited to less than 15% of patients, and their use is greatly influenced by functional status and comorbidity, mainly cardiovascular.

While it is reassuring that in 10 years the proportion of patients diagnosed with hypertension who receive no drug treatment is reduced by more than 50% (from 31% in 1988 to 17% in 1997), it remains uncertain why nearly one out of five patients still do not receive antihypertensive medications, a finding consistent with previous reports in other settings.[24,25] Because of the limitations of our data, no inferences can be made regarding quality or appropriateness of treatment. For instance, patients on no antihypertensive medications could have been classified as having a form of hypertension requiring exclusively lifestyle modification (ie, the equivalent of stage I hypertension based on the JNC-VI classification). However, it cannot be conclusively excluded that the fact that one in five patients does not receive an antihypertensive medication reflects simply malpractice. In this respect, previous studies have suggested that age *per se* was associated with an increased likelihood of not being treated.[5] On the other hand, the possibility that the benefit of antihypertensive treatment does not extend to patients beyond a certain age threshold needs to be carefully evaluated.

The pattern of drug prescription that we have documented suggest that evidence-based guidelines have little, if any, informed practice of physicians at academic centres in Italy. Regardless of the fact that, based on the evidence available, the Joint National Committee has continuously recommended the use of diuretics and beta-blockers as the preferred first-line agents, CCB and ACE-inhibitors were the most commonly prescribed agents in our study. These findings are in agreement with several recent reports describing the progressive decline of diuretic use and the parallel increase in use of ACE-inhibitors and CCB that have occurred in other settings.[26,27] The choice of antihypertensive agent does go beyond individual physician's preference because only diuretics and beta-blockers can reduce the incidence of heart failure, as well as stroke, coronary disease, and overall cardiovascular mortality.[6–10] The Systolic Hypertension in Europe trial,[28] the only one to show that a CCB can reduce stroke rate and the incidence of all cardiac events relative to placebo, was published in late 1997 and could not have influenced the prescription pattern in our study.

While beta-blockers continue to be used very rarely, but with an upward trend in more recent years, the present study also testifies to a progressive, inexorable decline of the prescription of thiazides diuretics, whose benefit is proven based on the only trials available among elderly patients. Whereas there may be a reluctance to use beta-blockers as a class because there seems to be no apparent reason why barely 5% of antihypertensive patients across a decade should receive them, it is more complex to try to disentangle the issue of thiazides. In fact, there is both an overall under-prescription, but at the same time there is also a constant decline irrespective of repeated recalls invoking their utilisation. Besides, in the same period, the prescriptions of loop diuretics have almost doubled and that the trend does not seem to level out.

Several reasons can possibly explain the apparent non adherence to widely accepted guidelines. First of all, physicians might have preferred not to use diuretics and beta-blockers based on the misconception of possible but unproven medical problems

related to these drugs, such as adverse change in lipid and glucose metabolism and increased risk of hypokalaemia and consequent arrhythmia.[29]

Consequently, physicians could have considered satisfactory the ACE-inhibitors and CCB ability to reduced blood pressure, and to improve surrogate end-points, and could have overvalued the possibility that these agents may also be better tolerated than beta-blockers and diuretics.[30,31] Secondly, some authors have suggested that the results of trials in which blood pressure reduction has yielded less benefit on coronary artery disease outcomes might have discouraged physicians from following rigid guidelines. Such consideration implies a widespread dissemination of the latter which has been shown not to occur in different settings.[32,33] Instead, it is likely that advertisements in scientific journals and the effectiveness of pharmaceutical promotions, or simply the attractiveness of using newer agents, could have influenced the prescribing patterns of physicians, even at academic medical centres.[34,35]

Alternatively, the present findings on a population of frail, elderly individuals, may reflect the difficult application of guidelines recommendations to patients with multiple comorbid conditions and concomitant, complex pharmacological regimens. Indeed, the patients in our sample are really different from those 'eligible' for clinical trials, on which treatment efficacy is based, who are usually younger and healthier, and present with less functional impairment and better cognitive function.[36] For example, the Systolic Hypertension in the Elderly Program Trial[6] included only 2% demented, and 7% physically disabled patients, while in our study these conditions are reported much more frequently. The frail elderly have never been adequately studied, and a physicians' decision could then rely more appropriately on other contingent factors such as severity of symptoms, illness, comorbidity, and other clinical nuances.

In our opinion the result about diuretics prescription is a clear demonstration of the latter possibility. Loop diuretics, that have never been considered a first choice therapy for hypertension, are used more frequently than thiazides, probably because they are co-prescribed with ACE-inhibitors in patients with heart failure,[37] and because they are considered to be more effective if it coexists with renal impairment.[38] On the other hand, thiazides are used more frequently in patients with a relatively good functional status, and without important cardiovascular comorbid conditions, who resembles those eligible for clinical trials.

Yet, if the difficult applicability of trials' results explain the low use of thiazides, less immediate is the reason why their rate should be constantly declining. In fact, while the trend for loop diuretics seems to parallel the net increase in the incidence and prevalence of heart failure, thiazides trend should reflect the admission of antihypertensive patients who are progressively more fragile. Indeed, this seems to be true. Using the GIFA database, we have documented that the patients aged 85 or older have increased from 9 to 19%, those with ADL impairment from 25 to 32%, and the proportion of those with six or more comorbid conditions has increased almost five times from 6 to 28%.

As such, the results of the present study raise an issue of generalisability. Our sample, in fact, was comprised exclusively of hospitalised patients and they are clearly dissimilar from those living in the community, and even more so from those included in clinical trials. Yet, the issue is who is representative of whom, and until proven differently, guidelines should generally be considered applicable across the different spectrum of patients.

Some limitations of our study need to be acknowledged. First, we did not have available blood pressure measurements, thus, we could not correlate the use of any specific agent to the attainment of optimal values. However, our population refers to patients admitted to academic medical centres and although hypertension was not the primary diagnosis in most cases, it is hypothesised that antihypertensive drugs were used toward the goal of optimal pressure values. Yet optimal blood pressure control is a moving target and is infrequently attained.[39] Second, we studied the overall prescription of each drug class without discriminating whether or not they were chosen as single antihypertensive agent or as add-on therapy. This may be relevant since it is possible that some physicians tend to use certain agents (ie, diuretics) preferably as add-on therapy. Nonetheless, the focus of our study was on the overall choice of antihypertensives since also on a stepwise approach, one should always start with diuretics and beta-blockers. In addition, the high prevalence of cardiovascular comorbidity might have rendered it difficult to recognise the specific indication for which the given drug was prescribed. Third, the translation of guidelines into clinical practice is not a straightforward process, and it has been shown to be controversial and to require some time.[38] In that respect, our attempt to relate changes in the trend of prescription to specific events (ie, publication of guidelines, trials' results, recommendations) should be considered only indicative. Even more so, should be in the case of the sixth report of the Joint National Committee released reported in the late 1997.[17] Finally, our results reflect on the prescribing attitudes of physicians in Italy and these may differ from those in other countries. These cannot be refuted completely although the evidence available suggests that Italy is by no means different from other countries with regard to hypertension treatment.[40]

In conclusion, among elderly hypertensive patients admitted to academic medical centres in Italy in the past decade, drug prescription patterns did not concur with widely approved guidelines. Physicians seemed to prefer newer agents based on theoretical advantages and lower side effects, rather

than those whose efficacy has been proven in clinical trials. This phenomenon is not limited to Italy and explanations are probably multi-factorial. However, especially in the case of diuretics, the prescription may reflect the distance between the ideal patient of a trial and that in the real world. Future studies on antihypertensive drugs are warranted but these need to include elderly frail patients.

References

1 Dannenberg AL, Garrison RJ, Kannel WB. Incidence of hypertension in the Framingham Study. *Am J Public Health* 1988; **78**: 676–679.
2 National High Blood Pressure Education Program Working Group. National High Blood Pressure Education Program Working Group report on hypertension in the elderly. *Hypertension* 1994; **23**: 275–285.
3 Psaty BM *et al*. Health outcomes associated with antihypertensive therapy used as first line agents: a systematic review and meta-analysis. *JAMA* 1997; **277**: 739–745.
4 Gueyffier F *et al*. Effect of antihypertensive drug treatment on cardiovascular outcomes in women and men: a meta-analysis of individual patient data from randomized controlled trials. *Ann Intern Med* 1997; **126**: 761–767.
5 Gambassi G *et al*. Prevalence, clinical correlates and treatment of hypertension in elderly nursing home residents. *Arch Intern Med* 1998; **158**: 2377–2385.
6 SHEP Cooperative Research Group. Prevention on stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the systolic Hypertension in the Elderly Program (SHEP). *JAMA* 1991; **265**: 3255–3264.
7 Kostis JB *et al*, for the SHEP Cooperative Research Group. Prevention of hearth failure by antihypertensive drug treatment in older persons with isolated systolic hypertension. *JAMA* 1997; **278**: 212–216.
8 Dalhof B *et al*. Morbidity and mortality in the Swedish Trial in Old Patients with Hypertension (STOP-Hypertension). *Lancet* 1991; **338**: 1281–1285.
9 MRC Working Party. Medical Research Council trial of treatment of hypertension in older adults: principal results. *BMJ* 1992; **304**: 405–412.
10 Murlow C *et al*. Pharmacotherapy for hypertension in the elderly. *Cochrane Database Syst Rev* 2000; **2**: CD000028.
11 Psaty BM *et al*. Health outcomes associated with antihypertensive therapies used as first-line agents. A systematic review and meta-analysis. *JAMA* 1997; **277**: 739–745.
12 Pahor M *et al*. Calcium-channel blockade and incidence of cancer in aged populations. *Lancet* 1996; **348**: 493–497.
13 Zuccala G *et al*. Use of calcium antagonists and need for perioperative transfusion in older patients with hip fracture: an observational study. *Br Med J* 1997; **314**: 643–664.
14 Psaty BM *et al*. The risk of myocardial infarction associated with antihypertensive drug therapies. *JAMA* 1995; **274**: 620–625.
15 Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure. The 1988 Report of the Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure. *Arch Intern Med* 1988; **148**: 1023–1038.
16 Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure. The Fifth Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC V). *Arch Intern Med* 1993; **153**: 154–183.
17 Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure. The sixth report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure. *Arch Intern Med* 1997; **157**: 2413–2446.
18 Task Force on the Availability of Cardiovascular Drugs to the Medically Indigent. Report of the Task Force on the Availability of Cardiovascular Drugs to the Medically Indigent. *Circulation* 1992; **85**: 849–860.
19 Drugs for hypertension. *Med Lett Drugs Ther* 1993; **35**: 55–60.
20 Pahor M *et al*. Age and severe adverse drug reactions caused by nifedipine and verapamil. *J Clin Epidemiol* 1996; **49**: 921–928.
21 Hodkinson HM. Evaluation of a mental test score for assessment of mental impairment in the elderly. *Age Ageing* 1972; **1**: 233–238.
22 PHS-HCFA. International Classification of Diseases, 9th rev. Public Health Service-Health Care Financing Administration, Washington DC, 1980.
23 Pahor M *et al*. Drug data coding and analysis in epidemiologic studies. *Eur J Clin Epidemiol* 1994; **10**: 405–411.
24 Siegel D *et al*. Trends in antihypertensive drug use in the United States: do the JNC V recommendations affect prescribing? *JAMA* 1997; **278**: 1745–1748.
25 Manolio TA *et al*. Trends in pharmacologic management of hypertension in the United States. *Arch Intern Med* 1995; **155**: 1855–1860.
26 Fishkind D, Paris BE, Aronow WS. Use of digoxin, diuretics, beta blockers, angiotensin-converting enzyme inhibitors, and calcium channel blockers in older patients in an academic hospital-based geriatrics practice. *J Am Geriatr Soc* 1997; **45**: 809–812.
27 Nelson CR, Knapp DA. Trends in antihypertensive drug therapy of ambulatory patients by US office-based physicians. *Hypertension* 2000; **36**: 600–603.
28 Staessen JA *et al*. Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. The Systolic Hypertension in Europe (Syst-Eur) Trial Investigators. *Lancet* 1997; **350**: 757–764.
29 Moser M. Why are physicians not prescribing Diuretics more frequently in the management of hypertension? *JAMA* 1998; **279**: 1813–1816.
30 Monane M *et al*. The effects of initial drug choice and comorbidity on antihypertensive therapy compliance: results from a population based study in the elderly. *Am J Hypertens* 1997; **10**: 697–704.
31 Phillip T *et al*. Randomised, double blind, multicentre comparison of hydroclorothiazide, atenol, nitredipine, and enalapril in antihypertensive treatment: results of the HANE study. *Br Med J* 1997; **315**: 154–159.
32 Alderman MH, Madhavan S, Cohen H. Antihypertensive drug therapy: the effect of JNC criteria on prescribing pattern and patient status through the first year. *Am J Hypertens* 1996; **9**: 413–418.
33 Pogue VA *et al*. New staging of fifth Joint National Commettee on the Detection, Evaluation and Treatment of High Blood Pressure alters assessment of the

severity and treatment of hypertension. *Hypertension* 1996; **28**: 713–718.
34 Wang TJ, Ausiello JC, Stafford RS. Tends in antihypertensive drug advertising, 1985–1996. *Circulation* 1999; **99**: 2055–2057.
35 Moser M *et al*. Who really determines your patients' prescriptions? *JAMA* 1991; **265**: 498–500.
36 West E, Newton J. Clinical guidelines: an ambitious national strategy. *Br Med J* 1997; **315**: 324.
37 van Kraaij DJ, Jansen RW, Gribnau FW, Hoefnagels WH. Loop diuretics in patients aged 75 years or older: general practitioners' assessment of indications and possibilities for withdrawal. *Eur J Clin Pharmacol* 1998; **54**: 323–327.
38 Allison ME, Shilliday I. Loop diuretic therapy in acute and chronic renal failure. *J Cardiovasc Pharmacol* 1993; **22** (Suppl 3): S59–S70.
39 Berlowitz DR *et al*. Inadequate management of blood pressure in a hypertensive population. *N Engl Med J* 1998; **339**: 1957–1963.
40 Di Bari *et al*. Undertreatment of hypertension in community-dwelling older adults: a drug utilization study in Dicomano, Italy. *J Hypertens* 1999; **17**: 1633–1640.