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Generalizability of guidelines and physicians' adherence. Case study on the Sixth Joint National Commitee's guidelines on hypertension

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Abstract

Background: Clinical practice guidelines (CPG) are thought to be an effective tool in improving efficiency and outcomes of clinical practice. Physicians' adherence to guidelines is reported to be poor. We evaluated the relationship between generalizability of guidelines on hypertension and physicians' adherence to guidelines' recommendations for pharmacological treatment.

Methods: We used the Sixth Joint National Committee's (JNC VI) guidelines on hypertension to evaluate our hypothesis. We evaluated the evidence from controlled clinical trials on which the JNC VI bases its recommendation, and compared the population enrolled in those trials with the American hypertensive population. Data on this population came from the National Health and Nutritional Examination Survey III.

Results: Twenty-three percent of the NHANES population had a diagnosis of hypertension, 11% had hypertension requiring drug treatment according to the JNC VI. Only half of the population requiring treatment would have been enrolled in at least two trials. Rate of adherence to CPG was 69%. We found a weak association between generalizability and physicians' adherence to guidelines. Baseline risk was the major determinant of the decision to treat.

Conclusion: JNC VI guidelines may not be generalizable to their target population. We found a relatively poor adherence rate to these guidelines. Failing of completely taking into account the clinical characteristics of the patients may be partly responsible for this lack of adherence.

Background

Guidelines are "systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances".[1] Guidelines seem to be effective in improving the processes and outcomes of care, [2] and are being used to describe appropriate care based on scientific evidence.[3] Another proposed use of guidelines is for profiling and resource utilization reviews.[4]

Despite evidence of effectiveness and widespread implementation efforts, adherence to guidelines is variable and generally poor.[5–7] The factors involved in a physician's adherence to guidelines have been extensively studied. Lack of familiarity and inertia to previous practice, characteristics of the health care professional and of the practice setting, physician perception of guidelines' usefulness, incentives, regulation and patient-related factors are common barriers to guideline adherence.[8–10] The quality of

Table 1: Recommendation of the JNC VI according to blood pressure and presence of additional risk factors.[17]

Blood pressure*	Recommendation
High normal	
Group risk** A	Lifestyle modification
Group risk B	Lifestyle modification
Group risk C	*Drug therapy*
Stage 1	
Group risk A	Lifestyle modification (up to 12 months)
Group risk B	Lifestyle modification (up to 6 months)
Group risk C	*Drug therapy*
Stage 2/3	
Group risk A	*Drug therapy*
Group risk B	*Drug therapy*
Group risk C	*Drug therapy*

* High normal: 130–139/85–89 mmHg. Stage 1: 140–159/90–99 mmHg. Stage 2/3: ≥ 160/100. ** Group risk A: no risk factors (smoke, dyslipidemia, male gender, age ≥ 60 years, family history) or target organ disease (cardiovascular diseases, renal failure) or diabetes mellitus; Group risk B: at least one risk factor with no target organ disease or diabetes mellitus; Group risk C: target organ disease or diabetes mellitus.

the guidelines and the clarity and specificity of their recommendations seems also to play an important role.[11]

Problems related to the generalizability of clinical practice guidelines, especially for pharmacological interventions, have received much less attention in the medical literature. This could be an issue because intervention guidelines should base their recommendations on scientific evidence from randomized clinical trials.[12] While randomized controlled clinical trials are considered the gold standard for evaluating the efficacy of pharmacological interventions, [13] their generalizability is often questionable, mostly because of stringent inclusion and exclusion criteria imposed.[14,15] This is particularly true for special populations, such as elderly people, who are systematically excluded from clinical trials.[16]

We hypothesized that the limited generalizability of the evidence on which guidelines are based may reduce physicians' adherence to them. We performed a case study on guidelines to lower blood pressure to test the hypothesis that physicians' adherence is lower in groups of people to whom guidelines are not generalizable.

Methods

Clinical practice guidelines recommendations

For this study, we used the JNC VI guidelines issued by the National Heart, Blood and Lung Institute, and endorsed by the American Medical Association along with other 44 US organizations.[17] The contributing team members reviewed the relevant articles in English language published since 1992 to gather scientific evidence. The data were synthesized into recommendations by consensus of the executive committee.

The JNC VI categorizes blood pressure levels as optimal (<120/80 mmHg), normal (<130/85 mmHg), and high normal (130–139/85–90 mmHg). Hypertension is classified as stage 1 (140–159/90–99 mmHg), stage 2 (160–179/100–109 mmHg) or stage 3 (≥ 180/≥ 110 mmHg). The recommendations for treatment are based on both hypertension stage and risk for category, and are reported in table 1.

Conceptual definition of the study population

The population of this study is composed of people who should be receiving drug treatment according to the guidelines of the JNC VI (see Table 1). For the analysis of the characteristics of people with or without a prescription of an anti-hypertensive drug, we also required that a physician diagnosed the hypertension.

Operational definition of the study population

Information on the US hypertensive population was obtained from the National Health and Nutrition Examination Survey III (NHANES III). This study was designed to provide national estimates of health and nutritional estimates of health status of the community-dwelling population of the United States. Eighty-nine survey locations were randomly divided into two sets, that were allocated to different study period. To obtain reliable estimates of health statistics in ethnic minorities as well as on extreme age groups (children and elderly), these groups were oversampled. NHANES includes data on 33,994 persons aged 2 months or older. For the present study, we considered only the adult population (age ≥ 17 years). All participants had blood pressure measurements obtained during the household interview and during the examination visit using a mercury sphygmomanometer according to the standardized protocol recommended by

Table 2: Trials on diuretics and/or β-blockers on which the recommendation of the JNC VI are based.

	Eligibility criteria			Exclusion criteria*			
	Age (years)	Gender	Blood pressure** (mmHg)	Myocardial infarction	Stroke	Heart failure	Renal impairment
VA-NHBLI [36]	35 – 55	Males	DBP: 85–105	Excluded	Excluded	Excluded	Excluded
HDPF [37]	30 – 69	Both	DBP ≥ 90	Included	Included	Included	Included
Oslo [45]	40 – 50	Male	SBP: 145–180 DBP<110	Excluded	Excluded	Excluded	Excluded
Australia [43]	30 – 70	Both	DBP: 95–110 SBP<200	Excluded	Excluded	Included	Included
MRC [40]	35 – 64	Both	DBP: 90–109	Included	Included	Included	Included
VA I [34]	< 70	Male	DBP: 115–129	Included	Included	Included	Included
VA II [35]	< 70	Male	DBP: 90–114	Included	Included	Included	Included
PHS [44]	< 55	Both	DBP: 90–114	Excluded	Excluded	Excluded	Excluded
HSCSG [33]	< 75	Both	SBP: 140–220 DBP: 90–115	Included	Included	Included	Excluded
Barraclough [32]	56 – 69	Both	DBP: 100–120	Included	Included	Included	Included
Carter [38]	< 80	Both	BP≥ 160/110	Included	Must have one in the previous 3 months	Excluded	Excluded
EWPHE [39]	≥ 60	Both	DBP: 90–119 SBP: 160–239	Included	Included	Excluded	Excluded
Coope [42]	60 – 79	Both	DBP≥ 105 SBP≥ 170	Excluded	Excluded	Excluded	Excluded
MRC – O [29]	65 – 75	Both	DBP<115 SBP: 160–209	Included	Included	Excluded	Excluded
SHEP [41]	≥ 60	Both	DBP<90 SBP: 160–219	Excluded	Excluded	Excluded	Excluded
STOP [30]	70 – 84	Both	DBP: 90–120 SBP: 180–130	Included	Included	Included	Included

* We considered only these exclusion criteria because they are the most important factors influencing the base line risk in hypertensive people ** SPB: Systolic Blood Pressure; DBP: Diastolic Blood Pressure

the American Heart Association, [18] which is similar to the one recommended by the JNC VI.[19] We used the mean of three measurements to determine extent of hypertension. Because of the variable time between the household interview and the examination visit, we only considered the blood pressure measurements taken during the household interview.

We could not establish from the NHANES data the length of time lifestyle modification (diet, exercise) had been tried. Therefore, we decided to focus only on people for whom the JNC VI suggest drug therapy as a first option (people with cardiovascular diseases or target-organ damage or diabetes mellitus, or people with stage 2 or stage 3 hypertension). To identify such people, we used the blood pressure measurements (average of three measurements), self-reported history of cardiovascular disease or diabetes, and the measurement of serum creatinine (>2 mg/dl) indicating impaired renal function. Our definition does not take into account those with a diagnosis of hypertension but with normal blood pressure levels. We decided to exclude these people from our population because we were unable to evaluate if the prescription was in line with the JNC VI indications in the absence of an uncontrolled blood pressure measurement.

Conceptual definition of generalizability

Generalizability is defined as the extent to which the findings obtained on a specific sample can be applied to the target population.[20] This definition does not imply that all the characteristics of the sample should be similar to those of the target population, although it is intuitive that lack of representativeness in the study sample affects generalizability. Since the objective of the study was to analyze the effects of generalizability on adherence to guidelines, we decided to focus on the demographic and clinical characteristics that are most likely to influence the decision to treat, that in our specific case are those related to the risk/benefit ratio of using anti-hypertensive drugs. We compared the population that was included in the trials on which the JNC VI recommendations are based with the US hypertensive population. We only considered controlled clinical trials because recommendations were mostly based on the evidence from these studies and from meta-analyses of these studies. To evaluate the generalizability, we used the following criteria for eligibility in the trials: age, gender, and blood pressure levels at the moment of the admission in the study. The exclusion criteria considered were history of myocardial infarction (MI), heart failure (HF), stroke, and renal impairment because these target organ diseases increase the risk of poor outcomes in hypertensive people and are frequently used as inclusion/exclusion criteria in clinical trials. In some instances, it was not clear from the methods section of the trials if the presence of one of these diagnoses resulted in the exclusion from the study. In these cases, we used a conservative approach and the variable was not considered as exclusion criteria (Table 2).

Operational definition of generalizability

According to the JNC VI, diuretics and beta-blockers should be used as first line pharmacologic therapy to treat

hypertension.[17] We identified the clinical trials on which this recommendation was made. First, we calculated the proportion of hypertensive people in the NHANES population that would have been eligible for the trial on the basis of their age, gender and blood pressure measurements. Second, we calculated the proportion of people that would have been excluded because of a history of MI, stroke, HF or renal failure. Third, we calculated the resulting proportion of people to which the trial is generalizable. Finally, we calculated the proportion of people to which the results of at least two trials were generalizable. We decided to use two trials because we felt that the results of only one trial were not sufficient to evaluate the effects of a treatment. This is also in line with Food and Drugs Administration's regulation requiring the evidence from at least two randomized clinical trials to establish a drug's efficacy.

Conceptual definition of adherence to guidelines

We considered the prescription of any anti-hypertensive medication as an indicator of physician's adherence to guidelines. Although the JNC VI indicates diuretics and β-blockers as first line therapy, we decided to include all the prescriptions in our definition because different drugs are allowed or even suggested in particular situations.

Operational definition of adherence to guidelines

To exclude people that had unrecognized hypertension, we calculated an adherence rate only in those people who were told by their doctor that they were hypertensive. We used the self-reported prescription of an anti-hypertensive medication to measure the physicians' adherence to guidelines. This approach was chosen instead of using the actual use of antihypertensive medications to avoid the confounding effect due to participants' lack of compliance to medical directives.

Analytic plan

We calculated the proportion of people to which each trial was generalizable, as well as the proportion of people that would have been included in at least two trials. We estimated the rate of adherence to guidelines, and compared the socio-demographic (age, gender, ethnicity) and clinical (diagnosis of MI, angina, HF, stroke, diabetes, renal impairment, chronic obstructive pulmonary disease) characteristics of people according to whether they were in the group for which the guidelines were followed or not. We also estimated the association of generalizability with adherence to guidelines using an odds ratio (OR). A multiple logistic regression model provided an estimate of the association between generalizability and adherence corrected for demographic and clinical variables.

We evaluated the rate of adherence to guidelines in each of the different risk categories identified by the JNC VI (Table 1) as requiring anti-hypertensive drugs. The risk factors taken into account to assign people to each risk category were gender (male), age ≥ 60 years, current smoking, parent with cardiovascular disease before the age of 50, self-reported diagnosis of hypercholesterolemia, and diabetes mellitus or target organ disease.

Among people that had a prescription of an anti-hypertensive medication and that were actually taking a drug, we analyzed the prevalence of use of diuretics, β-blockers, ACE-inhibitors, calcium antagonists, and α-blockers. We evaluated the use of these drugs both in combination and used as mono-therapy.

The data reported are weighted proportions using the applicable weights.[21] The calculation of the standard errors was performed taking into account the non-random sampling strategy of NHANES III. All analyses were performed using SAS™ Version 8 (SAS Inc., Cary NC) and SUDAAN™ Version 7.5.6 (RTI, Research Triangle Park, NC).

Results

The JNC VI recommends the use of diuretics or β-blockers as first line therapy in hypertension on the basis of the results of two meta-analyses.[22,23] We found some differences in the studies included in these meta-analyses: Psaty et al. did not include some of the studies that were used by MacMahon et al., because of the use of multiple interventions, [24] the use of drugs different than diuretic of β-blockers, [25,26] or because the study directly compared diuretics to β-blockers.[27] Furthermore, Psaty et al. included 3 studies that had not been published at the time when MacMahon et al. published their results.[28–30] For these reasons, we used the trials included in the meta-analysis by Psaty et al. We were unable to retrieve information from a small study (n = 91) performed in Japan [31] that was used by Psaty et al. The final number of studies considered was 16.[29,30,32–45]

Table 2 shows the inclusion and exclusion criteria in the trials considered. While most trials had advanced age as exclusion criteria, seven enrolled people aged > 70 years. The majority of these trials included people with diastolic hypertension, typically with diastolic blood pressure around 90 – 120 mmHg. Myocardial infarction was an exclusion criterion in 6 trials, stroke in 6 trials, HF in 8 trials, and renal failure in 9 trials.

The Adult Survey section of the NHANES III had information on 20,050 participants. About 23% of this population had a diagnosis of hypertension, and of these 11% had hypertension requiring treatment according to the recommendations of the JNC VI. The proportion of people with a diagnosis of hypertension but not included in

Table 3: Generalizability of the individual trials to the hypertensive population.

	% of the pop. eligible* for trial	% of the eligible pop. that would be excluded**	% of the pop. to which the trial is generalizable
VA-NHBLI [36]	9.7	14.1	8.3
HDPF [37]	28.8	0	28.8
Oslo [45]	3.3	10.6	2.9
Australia [43]	18.1	5.7	17.1
MRC [40]	21.0	0	21.0
VA I [34]	0.4	0	0.4
VA II [35]	18.9	0	18.9
PHS [44]	18.5	9	16.9
HSCSG [33]	1.2	1.1	1.2
Barraclough [32]	11.0	0	11.0
Carter [38]	2.6	25	1.8
EWPHE [39]	37.4	22.3	32.8
Coope [42]	14.2	22.1	11.1
MRC – O [29]	14.8	9.7	13.2
SHEP [41]	22.0	26.5	16.2
STOP [30]	2.1	3.2	2.1

* Eligibility criteria shown in table 2. People with hypertension and controlled blood pressure was excluded from the analysis. ** Exclusion criteria shown in table 2.

our population because they had normal blood pressure was 17%. In this subgroup of people, 62% reported a prescription of an anti-hypertensive medication. In our study population, 4.1% had stage 2/3 hypertension with no other risk factors; 39.2% had stage 2/3 hypertension with at least one risk factor, 17.3% had high normal blood pressure and target organ damage or diabetes, 26.1% had stage 1 hypertension with target organ damage or diabetes, and 13.3% had stage 2/3 hypertension with target organ diseases or diabetes. The mean age was 63 years (range 17 – 90), 50% were women and 82% were white.

Table 3 shows the proportion of the people with hypertension requiring drug treatment according to the JNC VI. The first column reports the percent of the total hypertensive population that would be eligible for each trial according to their age, gender and blood pressure levels. The second column reports the proportion of people that would have been excluded from the trials because of MI, stroke, HF, and renal impairment. Finally, we report the proportion of the hypertensive population that would potentially be enrolled in each trial. We observe a marked variability in the generalizability of the trials, ranging from 0.4% (VA I) to 33% (EWPHE). Only four trials were generalizable to more than 20% of the hypertensive population. Such poor generalizability appeared to be a function of the eligibility rather than of the exclusion criteria. Most people were not eligible because high levels of diastolic blood pressure that were required to be enrolled in the trials, as well as of age limits for inclusion in the trials. Overall, the proportion of people in our sample that would potentially have been enrolled in at least 1 trial was 57.5%, and 52.5% would potentially be enrolled in at least 2 trials.

About 60% of hypertensive people requiring drug treatment according to the JNC VI had been told by a doctor that they had hypertension. Of these, 69% reported having a current prescription for anti-hypertensive drugs. Table 4 compares the characteristics of people reporting a prescription for anti-hypertensive drugs vs. those not reporting a prescription for an antihypertensive medication. People in the first group were more likely to be elderly (42.3% treated vs. 16.4% not treated). Fifty-six percent of diagnosed hypertensives who were treated were women compared to 43.2% who were not treated. The distribution of race/ethnicity varied slightly according to treatment with a lower prevalence of whites among the treated group (81.5% vs. 85.5% not treated). Stroke, HF and renal failure were associated with more than a doubling of the probability of having a prescription for anti-hypertensive drugs. The prevalence of MI was 23% among those with prescription, and 15.5% among those without a prescription. Diabetes (28.8% vs. 25.9%) and chronic obstructive pulmonary disease (16.2% vs. 13.4%) were not associated with treatment. We observed a lower prevalence of people that would have been enrolled in at least two trials in the group receiving drug treatment. People similar to the population enrolled in clinical trials were 30% less likely to receive any hypertensive treatment, although the confidence intervals were wide (OR: 0.7, 95% CI: 0.4 – 1.3).

Table 4: Comparison of the characteristics of people with diagnosed hypertension who were told to take antihypertensive medications vs. people not told.

	Treatment prescribed %	Treatment not prescribed %	Odds Ratio (95% C. I.)	Adjusted Odds Ratio (95% C. I.)
Age ≥ 70 years	42.3	16.4	3.8 (2.6 – 5.4)	4.1 (2.9 – 6.0)
Women	55.8	43.2	1.7 (1.1 – 2.5)	1.5 (1.0 – 2.5)
Race / Ethnicity				
White	81.5	85.5	1.0	1.0
Black	16.3	12.0	1.4 (0.9 – 2.2)	1.7 (1.1 – 2.6)
Other	2.1	2.2	1.0 (0.2 – 4.3)	0.9 (0.2 – 4.1)
Myocardial infarction	23.0	15.5	1.6 (1.0 – 2.8)	1.5 (0.9 – 2.7)
Stroke	13.1	6.0	2.3 (1.3 – 4.20)	1.9 (0.9 – 4.1)
Heart failure	16.3	8.3	2.2 (1.1 – 4.2)	2.1 (0.8 – 5.5)
Renal impairment	4.8	1.7	3.0 (0.7 – 13.6)	2.5 (0.4 – 14.6)
Diabetes	28.9	25.9	1.2 (0.7 – 1.9)	1.4 (0.8 – 2.5)
Chronic pulmonary disease	13.4	16.2	0.8 (0.4 – 1.6)	0.7 (0.3 – 1.1)
Physical impairment	13.3	11.6	1.2 (0.7 – 2.1)	0.6 (0.3 – 1.1)
Eligible in 2 or more trials	53.3	62.4	0.7 (0.4 – 1.3)	1.2 (0.6 – 2.8)

After adjustment for demographic and clinical characteristics, the direction of the association between generalizability and treatment was reversed, with people similar to those included in clinical trial being 20% as likely to receive an antihypertensive medication than those without such characteristics (OR: 1.2; 95% CI: 0.6 – 2.8). The estimated association for the other variables was unchanged, except for physical impairment, which after the adjustment was associated with a decreased probability of being prescribed an antihypertensive drug.

Figure 1 shows the rate of adherence to guidelines among the group to which the trials were generalizable compared to those to whom the trials were not generalizable. Adherence to guidelines was in general higher in the groups with target organ diseases or diabetes mellitus. In the group with high normal blood pressure and target organ disease, we found nobody that would have been included in at least two trials. In the other groups, generalizability had little effect on the adherence rate. People in the group to which the trials can be generalizable had a lower prevalence of treatment, although the differences were small. An exception was the group with stage 2/3 hypertension and at least 1 risk factor, in which people that would have been enrolled in at least two trials were more likely to be treated (81% vs. 75%).

Of hypertensive people who had both a diagnosis and a prescription made by their physician, 76% were actually taking any medication at the time of the interview. Table 5 shows the type of treatment reported. When we considered only drugs used in mono-therapy, we found that calcium channel blockers were the drugs most frequently used (15%), followed by diuretics and ACE-inhibitors (11%). β-blockers were taken as mono-therapy by 9% of persons. Considering any prescription, diuretics were the drugs most commonly used (41.5%), followed by calcium channel blockers (38.8%) and ACE-inhibitors (31.6%), and β-blockers (26.1%).

Discussion

The JNC VI bases its recommendations on the drug treatment of hypertensive people on a convincing scientific basis. The pooled results of the trials on diuretics and/or β-blockers considered as the basis for the guidelines show a clear reduction in stroke, [22,46] congestive HF and total cardiovascular mortality.[22,23,46] Nonetheless, differences between the populations studied and the populations actually receiving the medications pose the problem of the generalizability of the results. Using only few eligibility/exclusion criteria, we found that the generalizability of the individual trials was poor. Forty percent of the population would not have been enrolled in at least one trial, and half of the population was not eligible for at least two trials.

The JNC VI extends its recommendation to people with blood pressure levels generally lower than the population included in the trials. In one of the groups for which treatment is recommended by the JNC VI (i.e. people with high normal blood pressure and target-organ disease or diabetes), we found nobody that would be included in at least two trials. This is problematic. Since characteristics of the population translate into different baseline risks, the absolute benefits observed in trials may be different than those observed in the general population.[47] While it is arguable that clinical trials, excluding people with substantial comorbidity, underestimate the real benefit of the

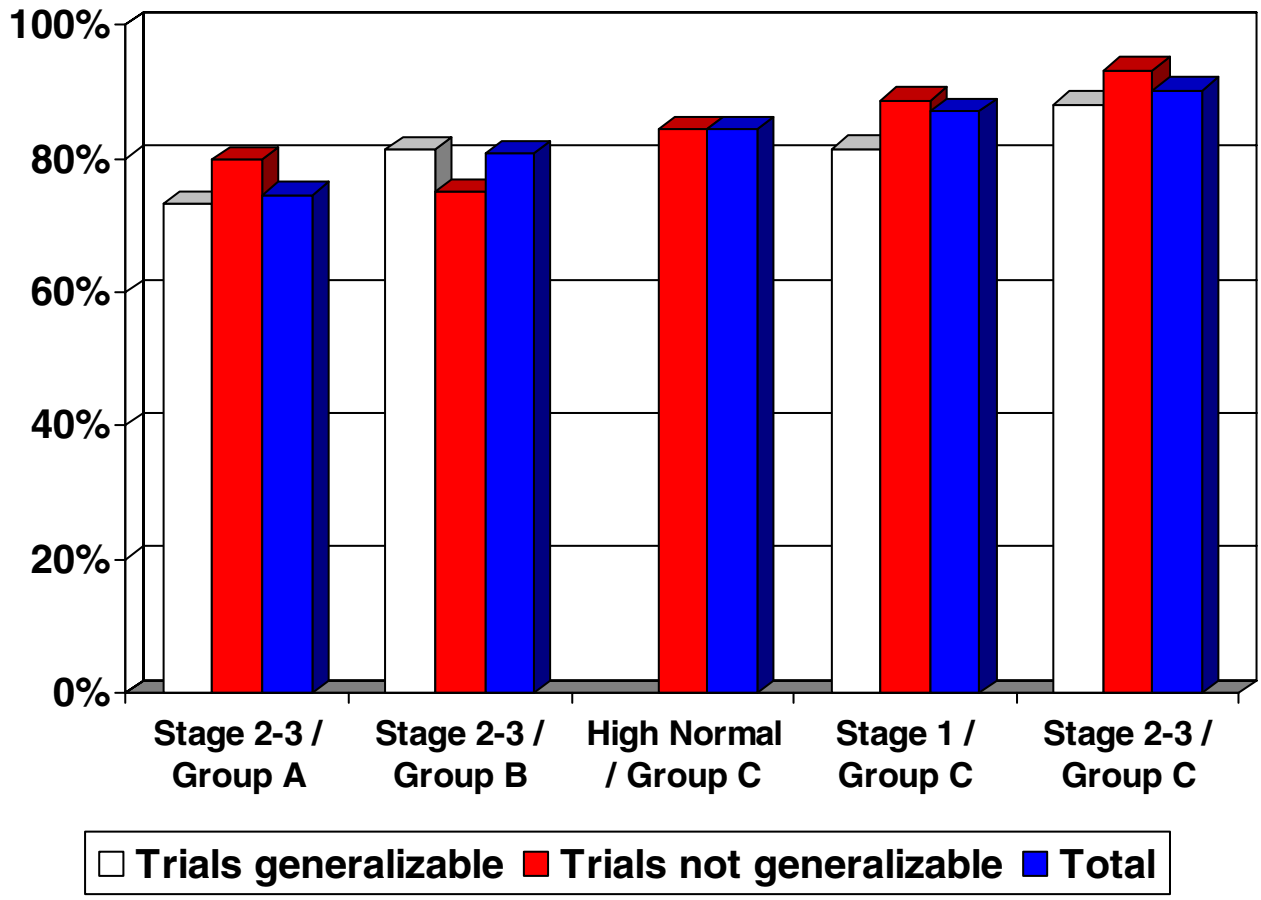

Figure 1
Proportion of people receiving drug treatment according to trials' generalizability. Stratified by blood pressure and risk category as defined in table 1.

Table 5: Use of anti-hypertensive drugs among people who had a medication prescribed by their doctors and that were taking the drug at the time of the interview.

Monotherapy	
Diuretics	11.2
β-blockers	9.1
ACE-inhibitors	10.9
Calcium antagonists	14.9
Alpha adrenergic / alpha blockers	3.7
Treatment taken alone or in combination	
Diuretics	41.5
β-blockers	26.1
ACE-inhibitors	31.6
Calcium antagonists	38.8
Alpha adrenergic / alpha blockers	10.2

treatment, [48] any generalization to a population with a baseline risk level different the one studied in an individual trial needs to be evaluated. Furthermore, since the risk of adverse drug reactions increases with the underlying clinical severity, [49] it is seldom easy to estimate the real risk/benefit ratio when data are not available in a specific population.

Our data show that a substantial proportion of people (30%) with a diagnosis of hypertension and that should receive treatment according to the JNC VI guidelines have not been prescribed any antihypertensive drug. Our results are in line with another report from NHANES III showing that about 50% of all people with a diagnosis of hypertension (regardless of the actual blood pressure) were not receiving treatment.[50]

The decision not to treat might be a due to poor familiarity with the JNC guidelines, [51] to a risk/benefit evaluation tailored to the individual patient, or to patient preference.[52] Our data show that the risk profile is much more important in influencing treatment than the actual blood pressure levels. In fact, people with stage 2/3 hypertension but without risk factors or target-organ disease were treated less frequently than people with lower blood pressure with additional risk factors or target-organ diseases. The higher prevalence of treatment in people at higher risk (advanced age, cardiovascular diseases, and diabetes mellitus) suggests that the characteristics of the individual patient are a major determinant of the decision to treat. Although this finding might be an artefact due to the fact that people receiving treatment for hypertension are likely to have normal blood pressure levels and therefore not captured by our study, other data from different settings support this interpretation. A community-based study in a older population showed that hypertensive people with additional risk factors were more likely to receive antihypertensive medications, [53] while a prospective study in a family medicine setting found that treatment for hypertension was independent from the actual blood pressure readings.[54] Concomitant cardiovascular diseases were associated with increased use of antihypertensive in a nursing home population.[55] The explanation that physician's own clinical judgment might override guidelines' recommendation is also in accordance with data on compliance with guidelines on diabetes care.[56]

We found that, among people with a prescription and taking an antihypertensive drug at the time of the interview, the type of medication was not following the indication of the JNC VI. This failure of the JNC guidelines in influencing the type of therapy described has already been described in a study examining the effect of the fifth report of the JNC.[57] However, it must be noted that this is a cross-sectional study and we have no information on which drugs have previously been tried.

Our data show no association between the generalizability of the trials and the decision to prescribe an antihypertensive medication. This study is underpowered to rule out an association, but the comparison of the point estimates of the OR of being treated in the crude analysis and the adjusted model confirms the role of the clinical characteristics in physicians' adherence. In the crude analysis, where this baseline risk is not taken into account, people to whom the clinical trials are *not* generalizable are more likely to be treated. In the multivariable analysis taking into account the baseline risk, the direction of the association is reversed. The reason for this finding probably lies in the fact that clinical trials considered tend to exclude high risk people (see table 2), who are the most likely benefit from treatment and therefore to be treated in clinical practice.

Translating trial findings into clinical decision making is never an easy task, and generalizability is one of the factors that should be taken into account when trying to implement "evidence based" interventions. Other related factors are also likely to play a role. Patient's preference is one of these, and has more far-reaching implications than just treatment choice. The prescription of a drug that the patient deems effective may have a beneficial effect in and of itself, something that has been defined "therapeutic effect of patient preference".[58] While controlled clinical trials can avoid this problem by blinding the patients to the treatment they are receiving, in the clinical practice setting this is impossible. Furthermore, patients with strong preference are likely to refuse randomization, and this clearly affects generalizability. One possible solution is to use information coming from settings more similar to the clinical practice when making recommendations. For example, beside observational studies, valuable information can come from "pragmatic trials", that are performed in the real clinical practice, and aim to inform choices between treatments rather than to measure the benefit of a treatment under ideal circumstances.[59]

Limitations

The results of this study should be evaluated taking into account the limitations of our approach. First, people receiving an antihypertensive medication are more likely to have normal blood pressure, therefore were not in our sample. Although the proportion of people whose high blood pressure was controlled by anti-hypertensive drugs was relatively low (10%), this bias potentially leads to an underestimation of the adherence to guidelines. However, the treatment rate in this population (70%) is similar to that reported in another study in a different setting, in

which the prevalence of treatment among people with known hypertension was 80%.[60]

The diagnosis of hypertension and the decision on drug treatment were made before the blood pressure levels used in this study were measured. Therefore, the blood pressure at the time of the last physician's visit was not necessarily as high as at the moment of the study interview. The result would be an underestimation of the adherence rate. Although this bias cannot be discounted, the rate of treatment that we observed is similar to that observed in other studies.[61,62] Furthermore, blood pressure was measured at a single point in time, and there is the possibility that a regression to the mean effect have reduced the number of patients appropriate for the JNC VI guidelines. Another source of bias might come from people who were prescribed lifestyle modification, and whose blood pressure had increased to level requiring drug treatment at the time of the interview. Again, we would have underestimated the adherence rate.

We control only for only a few eligibility/exclusion criteria. It is probable that the proportion of people that would have been enrolled in the clinical trials we considered is actually much lower than we report. For example, in the SHEP trial only 2.7% of people screened were eligible to the first baseline visit. Of these, less than half was actually randomized. If people to whom the trials are generalizable were actually more likely to receive treatment, this misclassification would result in a spurious negative association between generalizability and treatment. On the contrary, if people excluded from the trial are more likely to receive drug treatment, we might underestimate the negative association between generalizability and adherence to guideline. Data from the literature show that the second scenario is more likely, with people with risk factors that lead to exclusion from the clinical trial being more likely to be treated.

Finally, the precision of our estimates was quite low, and the inferences that can be made on the basis of our data are limited by this lack of statistical power.

Conclusion

Guidelines on drug treatment of hypertension are based on evidence obtained in general on samples that are different from the target population with regard to important clinical characteristics. These differences may translate in a different baseline risk profile, and consequently with a different risk/benefit ratio of antihypertensive therapy.

Our data suggest a weak association between generalizability and adherence rate, although our findings are not statistically significant. We found that the individual risk profile influence role on physicians' decision to treat more than blood pressure levels. Differences in the risk profile between people enrolled in the studies on which clinical practice guidelines and the target population might affect the adherence rate.

Competing interests

None declared.

Author's contributions

CP conceived the study. Both authors participated equally in the study design, data analyses, writing and revision.

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