Reviewer's report

Title: Generalizability of guidelines and physicians’ adherence. Case study on the JNC VI guidelines on hypertension

Authors: 
Dr Claudio Pedone (claudio_pedone@rm.unicatt.it) 
Kate L Lapane (kate_lapane@brown.edu)

Version: Date: 13 May 2003

Reviewer: Richard Thomson

Level of interest: A paper whose findings are important to those with closely related research interests

Advice on publication: Accept after discretionary revisions

Thank you for asking me to consider this paper again; the authors have responded to many of the comments made and have provided a robust and structured response to the previous suggestions.

This is a complex paper and analysis, giving the authors something of a challenge in terms of communicating their methods, results and conclusions. These could be clarified further and the conclusions may still benefit from some revision.

The authors state that they sought “to test the hypothesis that physicians adherence is lower in groups of people to whom guidelines are not generalisable”. I think that this statement remains ambiguous; it might be easier to structure their paper more clearly and communicate their results more clearly were they to clarify this point.

The authors have undertaken several analyses which they have then tried to integrate in their conclusions. The analyses are as follows:

1. They have determined the number of patients in their population that would be advised to take anti-hypertensive therapy on the basis of the inclusion criteria of the guidelines (table 1).

2. They have then determined which of these were and were not treated (on the basis of self-reported hypertensive therapy) giving an overall proportion of 69%. They have then compared those who were treated and those who were not on the basis of demographic and clinical characteristics in order to explore what features might be influencing decision making on whom to treat.

3. In addition, they have looked at the "generalisability of the guidelines". This they have done by taking their population with hypertension (both treated and untreated, but the latter excluding treated and controlled) and assessing the proportion of this population that would have been included within the trials that underpin the JNC VI guidelines on the basis of each individual trial's inclusion and exclusion criteria (column 3 of table 3). They have also determined the proportion of patients that would have been included in at least one or two trials (respectively 57.5% and 52.5%). Finally, in figure 1 they have graphically presented the proportion of hypertensive patients treated in selected JNC VI guideline's groups, giving total proportions and proportions to which the trials were generalisable.
4. Finally they have looked at the use of anti-hypertensive drugs in those treated.

My reading of the conclusions from their data is as follows:

1. The type of population (hypertensive patients as defined by JNC VI guidelines inclusion categories) represent a small proportion of the patients included within individual trials based on their inclusion/exclusion criteria.

2. Nonetheless, over 50% would have been included in more than one trial.

3. This demonstrates some interesting issues around the extension of guidelines conclusions beyond the trials from which they are derived, i.e. there may be some extrapolation, but to an extent guidelines need to do this, since decisions need to be made on patients who have high blood pressure but might not have been represented in the trials.

4. In terms of those with diagnosed hypertension (i.e. have been told by a doctor) those who were self-reportedly taking anti-hypertensive medication differed from those who were not in several key characteristics. In the unadjusted analysis (OR) patients treated were older, more likely to be women more likely to have MI, stroke and heart failure (these are significant differences). When adjusted for demographic and clinical characteristics, those who were treated were still significantly more likely to be older and female and there was a suggestion that black patients were more likely to be treated than other ethnic groups, although the other variables became non-significant. Importantly, the issue of eligibility in two or more trials was not a significant feature in either analysis, though the point estimate of the odds ratio did change direction.

To my mind, whilst the authors have addressed some of the limitations of their study, they have not addressed all of them and continue to over-interpret or misinterpret some of their data. Their overall conclusion is (in their abstract) "JNC VI guidelines may not be generalisable to their target population". This is ambiguous (see above re their hypothesis). They have shown that 69% of those with a doctor diagnosis who fitted JNC VI guidelines categories were treated according to the guidelines (albeit 30% were therefore not treated). Nonetheless the authors' conclusions relate more to the issue of whether their target population with hypertension (as defined by JNC VI categories) reflect the characteristics of patients included within the trials.

There is still a fundamental problem with this in that the exclusion criteria of the trials were not determined on the basis of capacity to benefit (or not) from anti-hypertensive therapy, but by other criteria determined by the trial design. For example, the exclusion of people who have MI, stroke and heart failure is excluding people who may have greater capacity to benefit from treatment. Thus the implication that patients diagnosed as hypertensive in the community on the basis of the JNC VI guidance do not reflect inclusion criteria, does not appear to invalidate their treatment or consideration for treatment.

Similarly, the statement in the abstract that "we found a weak association between generalisability and physicians' adherence to guidelines" is still not a correct conclusion. In table 4 eligibility for two or more trials is not significantly different between treated and untreated patients in either unadjusted or adjusted analyses. In Figure 1 there is no statistical analysis presented to support such a conclusion.

Furthermore, the conclusion in the abstract that "baseline risk was the major determinant of the decision to treat" is I still think not fully justifiable by the results.

It is true that the authors have softened their conclusions in the body of the paper itself, although the conclusion about a weak association remains (as above). Furthermore, the conclusion that the individual risk profile influences the role of physicians' decision to treat more than blood pressure levels may be in part justified by the finding that older people, women and possibly black patients are
In conclusion, I think the attempt to bring together the issue of generalisability based on inclusion and exclusion criteria to the trials, and adherence to the guidelines based on clinical characteristics and guidelines categorisation is tenuous given the cross-sectional nature of the study, the fact that patients are already treated and will have their blood pressure to an extent controlled, the fact that controlled hypertensives are excluded, and the fact that exclusion criteria for the trials often reflect inclusion criteria for the guidelines (e.g. risk factors such as diabetes, cardiovascular disease and renal failure).

Other points
The results sections on pages 12 and 13 still report data without reference to whether the differences are significant or not (see my summary above). This does need to be addressed, since equal weight is given to significant and non-significant findings in these paragraphs. Furthermore, too much weight is given to the change in the odds ratio for inclusion within two or more trials when it is not significant in either adjusted or unadjusted analysis. Furthermore, the conclusions from figure 1 are based on no significance testing at all as far as I can see.

In the discussion, I think the statement on page 16 that "the risk profile is much more important in influencing treatment than the actual blood pressure levels" is in part justifiable (see above), but doesn't actually reflect the issue of generalisability of the guidelines since one would expect this given the nature of the guidelines categories. Furthermore the supportive statement that begins "in fact, people with stage 2/3 hypertension ..." derives from figure 1 and has no statistical basis to it. Is there a significant difference or not? The following sentence beginning "the high prevalence of treatment in people at higher risk ..." suggests that the characteristics of individual patient are a major determinant of the decision to treat" if based on table 4 is in error since it mentions diabetes mellitus as a factor and, if based on figure 1, does not appear to derive from any analysis of statistical differences between the categories.

On page 17 the authors state "our data show no association between the generalisability of the trials and the decision to prescribe an anti-hypertensive medication". This appears to contradict their other statements, but is perhaps more appropriate based on the absence of significant associations. Furthermore, the statement in the same paragraph that "people to whom the clinical trials are not generalisable are more likely to be treated" is again an over-interpretation of data - see my comment above that exclusion criteria in the trials are often inclusion criteria for drug treatment in the JNC VI guidelines. The authors correctly identify the fact that the clinical trials considered tended to exclude high risk people but again I think the emphasis of this and other conclusions does not fully reflect that analysis.

Minor points
The legend to figure 1 should make it clear that trial generalisability in this setting refers to inclusion in more than two trials (but see above for limitations of this analysis anyway). The legend for table 4 should make it clear that these are diagnosed patients who self-reported taking anti-hypertensive medication and not "who were told to take anti-hypertensive medication".

In table 3 I think the footnote should refer to table 2 and not table 1.
Conclusions
The authors have responded to several comments in my previous review and have done so effectively. Nonetheless, I still have significant concerns about this paper. In part this is because it is a complex analysis and interpretation; the authors have a challenge in presenting this paper in a way that is readily accessible to the reader. Nonetheless, I am particular concerned that the conclusions, because of the methodological issues addressed above, tend to either go beyond the data (in terms of placing similar weight on significant and non-significant findings) or may need some re-interpretation given the nature of their analyses.

At this stage I still don't feel that this paper is publishable, although I think there are elements of it that are undoubtedly of considerable interest and value. It may be that a more focused analysis and presentation of the results would be more helpful, concentrating on the one hand on the nature of the populations being treated by JNC VI criteria compared to trial conclusions, and on the other hand on factors that influence application of the guidelines in practice (e.g. table 4 perhaps without the issue of eligibility in two or more trials being included here.)

Competing interests:

None declared.