PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Intervention for control of hypertension in Catalonia, Spain (INCOTECA Project): results of the multicentric non-randomised quasi-experimental controlled intervention study
AUTHORS	Roser Vallès-Fernández, Teresa Rodriguez-Blanco, Lucas Mengual-Martínez, Magdalena Rosell-Murphy, Gemma Prieto-De Lamo, Fina Martínez-Frutos, Sonia Mimoso-Moreno, Eva Bellerino-Serrano, Alícia Álvarez-Lázaro, Alícia Franzi-Sisó, Juan Carlos Martínez-Vindel, Mª Socorro Alonso-Ortega, Imma Olmedo-Muñoz, and Josep Mª Bonet-Simó,

VERSION 1 - REVIEW

REVIEWER	Benjamin T Allaire, Research Economist RTI International, United Kingdom
REVIEW RETURNED	23/12/2011

GENERAL COMMENTS	COMMENTS FOR THE AUTHOR GENERAL COMMMENTS This study evaluates a quality initiative plan for improving blood pressure. The authors provided training sessions at 5 clinics. The control group consisted of 12 clinics. Electronic health records were examined for pre/post differences in BP control, SBP, and DBP. The authors find modest improvements for SBP (2.1 mmHg) and DBP 0.9 mmHg). This is a clever and well done study. It has a strong design and would be a welcome addition to the literature. The authors note that their effect sizes are not nearly as large as others, but I believe this is a strength, not a weakness of the study. Large effect sizes on a population this large would lack credibility. My concerns are minor, but may warrant a few additional sensitivity checks. 1) The two populations differ on age and initial SBP. Is there an explanation for that? The SBP difference is not very large, but when we're talking about a population of this size and final outcomes this small (a change of only 2 BP points), then there may be some concern associated with that. 2) Given these differences in the two populations, why not propensity score match them? That's not to say PSM is a panacea, but I'd like to know the authors reasoning behind this choice. 3) No reasoning was given as to how were the comorbidities chosen. Please explain why you chose these. Presumably, it was because of their relation to hypertension, but why these and not, say, COPD?

	4) You say, "The use of two or more antihypertensive drugs was associated with a significant decreased BP control and higher SBP, but lower DBP." This is a puzzling result and ought to be addressed somewhere. 5) The paper is well-structured, but there are a few minor English mistakes. The paper could benefit from some light editing.

REVIEWER	Tom Fahey, Professor of General Practice RCSI Medical School, Dublin
REVIEW RETURNED	13/12/2011

THE STUDY	Thank you for asking me to review this study. Overall, I found it well written and well conducted. My comments relate to making the outcomes more clinically relevant and transparent. My main concern relates to two issues: Clinical measurement of blood pressure control- the authors describe the respective thresholds that constitute controlled blood pressure but report the impact of the intervention that makes it difficult to assess the clinical importance of the intervention. In order to address this the authors should provide descriptive statistics of the number (%) of individuals who reach BP target goal, at baseline and at the different follow up time points. As it stands, the clinical importance appears modest (their Table 2- with SBP reduced by -1.9mmHg, and DBP reduced by -0.7mmHg). Process measurement of medication intensification- in tandem in reporting proportion with "controlled" blood pressure, the authors should report how much intensification of blood pressure drugs occured and was likely to account for improvements in reaching BP targets. Further clarification is also necessary to see whether those who were not taking BP medications at baseline (10.7% and 10.1% in the standard and intervention groups respectively) were initiated on BP medications.
RESULTS & CONCLUSIONS	See initial section in terms of reporting of BP control threshold reached and intensification of BP medications. Reporting in this way will enable readers to judge the value/clinical importance of the complex intervention.

VERSION 1 – AUTHOR RESPONSE

RE: bmjopen-2011-000507
Dear editor:
The group of authors is pleased to have the opportunity to respond to the reviewers' comments. We have also revised the manuscript accordingly and resubmitted online with the changes highlighted in yellow.
We are very grateful for the comments made about our manuscript, which were both encouraging and helpful in further improving the presentation of our study.
Sincerely,
Roser Vallès
Senior Pharmacist
Catalan Institute of Health (ICS)

Reviewer: Tom Fahey

Professor of General Practice,
RCSI Medical School,
Dublin

I declare no conflicts of interest

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Authors' response: The results requested by the reviewer were described in Table 2 of the previous manuscript and can be found in the current manuscript in the second and fifth column of Table 2 for the standard care and intervention groups, respectively.

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Authors' response: Following the recommendations of the reviewer we present the table with the distribution of number of antihypertensive drugs (BP drugs) for the entire population and specifically for those not taking medication at baseline (see the table)

Standard care group (n=21704)
Baseline[n(%)] 4 months [n(%)] 9 months [n(%)] 1 year [n(%)]
nºBP drug
0 2319 (10.7) 1946 (9.0) 1867 (8.6) 1785 (8.2)
1 10501 (48.4) 10467 (48.2) 10280 (47.4) 10169 (46.9)
2 6212 (28.6) 6501 (30.0) 6639 (30.6) 6698 (30.9)
>=3 2672 (12.3) 2790 (12.9) 2918 (13.4) 3052 (14.1)

Intervention group (n=9877)

Baseline[n(%)] 4 months [n(%)] 9 months [n(%)] 1 year [n(%)]
nºBP drug
0 996 (10.1) 932 (9.4) 911 (9.2) 851 (8.6)
1 4708 (47.7) 4581 (46.4) 4492 (45.5) 4414 (44.7)
2 2856 (28.9) 2951 (29.9) 2963 (30.0) 3018 (30.6) >=3 1317 (13.3) 1413 (14.3) 1511 (15.3) 1594 (16.1)

Paqtients without BP drugs at baseline:

Standard care group (n=2319)
4 months [n(%)] 9 months [n(%)] 1 year [n(%)]
nºBP drug
0 1531 (66.0) 1348 (58.1) 1254 (54.1)
1 627 (27.0) 756 (32.6) 820 (35.4)
2 138 (6.0) 187 (8.1) 216 (9.3)
>=3 23 (1.0) 28 (1.2) 29 (1.3)

Intervention group (n=996)

4 months [n(%)] 9 months [n(%)] 1 year [n(%)]
nºBP drug
0 792 (79.5) 726 (72.9) 661 (66.4)
1 171 (17.2) 224 (22.5) 274 (27.5)
2 27 (2.7) 39 (3.9) 52 (5.2)
>=3 6 (0.6) 7 (0.7) 9 (0.9)

Time-varying covariables were taken into account in the repeated measures analysis (Table 3). At each stage each individual is assessed using the variables corresponding to that stage, which may be different from the previous stage. As was stated in the statistical analysis section, “Level 1 covariables vary by measurement occasion”. We modified the manuscript and added to the results section the following sentence: “In phases 2, 3 and 4, the percentage of patients who were not taking antihypertensive drugs (BP drugs) at baseline and remained free of BP drugs was 79.5%, 72.9% and 66.4% in the intervention group and 66.0%, 58.1% and 54.1% in the standard care group, respectively”.

Reviewer: Benjamin T Allaire
Research Economist
RTI International

This study evaluates a quality initiative plan for improving blood pressure. The authors provided training sessions at 5 clinics. The control group consisted of 12 clinics. Electronic health records were examined for pre/post differences in BP control, SBP, and DBP. The authors find modest improvements for SBP (2.1 mmHg) and DBP 0.9 mmHg).

This is a clever and well done study. It has a strong design and would be a welcome addition to the literature. The authors note that their effect sizes are not nearly as large as others, but I believe this is a strength, not a weakness of the study. Large effect sizes on a population this large would lack credibility My concerns are minor, but may warrant a few additional sensitivity checks.

1) The two populations differ on age and initial SBP. Is there an explanation for that?

Authors’ response: In the case of the covariable age, the difference between the two groups is 1.5 years, with a broad age range (standard care group, 18.8 -103.2 years; intervention group, 22.8 -100 years), while the difference in the covariable SBP is 0.6 mmHg. Although due to the large sample size these differences are statistically significant, they cannot be considered clinically relevant. If we compare the groups on a measure of distribution that is not sensitive to sample size, standardized differences or effect size, the effect size is 0.13 for the age variable and 0.04 for the SBP variable. Standardized differences of greater than 0.1 are typically considered meaningful (Cohen J. Statistical Power Analysis for the Behavioral Sciences. 2nd ed. Associates, New Jersey: LE Associates: 1988) but only the covariable age exceeds this value, and only by .01 (0.11). To minimize this imbalance, regression models have been adjusted for these covariables.

The SBP difference is not very large, but when we're talking about a population of this size and final outcomes this small (a change of only 2 BP points), then there may be some concern associated with that.

Authors’ response: It’s true that the SBP difference is not very large but it should be noted that baseline levels of SBP and DBP are low (138.7 mmHg and 79.5 mmHg, respectively, in the intervention group), making it more difficult to lower these levels. If these values had been higher at baseline and at each follow-up appointment, the SBP and DBP might have decreased more (see Table 2).
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2) Given these differences in the two populations, why not propensity score match them? That's not to say PSM is a panacea, but I'd like to know the authors reasoning behind this choice.

Authors’ response: A strength of our study is that it was targeted to the whole hypertensive population, so it reinforced the external validity of the findings. Propensity score matching reduces the sample size and diminishes the power of the study to detect intervention effects. Moreover, that approach replaces the collection of many confounding covariables with one function of these covariables, called the propensity score, which is then used as if it were the only confounding covariable (Rubin DB. Estimating causal effects from large data sets using propensity scores. Ann Intern Med. 1997; 127(8 Pt 2):757-763). In our case we have a limited number of covariables, of which only age and baseline SBP showed small differences and these were not found to be clinically relevant. These small differences between the two groups cannot accumulate into a substantial overall difference. In addition, the main advantage of regression techniques is that they use data from all participants. The validity of the results from regression models assumes that if the intervention effect differs across subgroups defined by baseline characteristics, separate effect estimates should be calculated through inclusion of interaction terms. In the regression analysis, all the possible interactions between covariables and treatment groups have been evaluated. In the repeated measures analysis, all the measurements for each participant (baseline and follow-ups) have been taken into account, which has allowed a more reliable estimate of treatment effect and modelling of the within– and between– persons variation in the outcome, while taking into account the correlation between measurements obtained from the same individual.
In the statistical analysis section of the current manuscript, we have added: "Interactions between covariables and the covariable “group” were assessed".

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3) No reasoning was given as to how were the comorbidities chosen. Please explain why you chose these. Presumably, it was because of their relation to hypertension, but why these and not, say, COPD?

Authors' response: The diseases that are considered in the cardiovascular risk calculation tables in the ICS clinical practice guideline used in this study, and also in other international guidelines, are heart failure, kidney failure and diabetes mellitus. In the presence of these conditions the values of SBP and DBP indicating good control of hypertension are stricter than those for the rest of the hypertensive population; for this reason alone, we studied the presence of these diseases to assess comorbidity.
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4) You say, "The use of two or more antihypertensive drugs was associated with a significant decreased BP control and higher SBP, but lower DBP." This is a puzzling result and ought to be addressed somewhere.

Authors' response: The coefficients of a regression model give the average increase or decrease in the whole sample population. As shown in Table 3, these coefficients represent the average population values at one-year follow-up (in our case, 4 repeated measures for each patient) and compares individuals taking 2 or more antihypertensive drugs with the reference group of patients taking 1 BP drug, controlling for the other variables in the model. Although at one-year follow-up the SBP value increased, the rate of change throughout the follow-up for systolic and diastolic blood pressure in patients using 2 or more antihypertensive drugs has decreased (and therefore BP control increased) compared to patients using 1 drug (SBP adjusted Beta for 2 drugs -0.92; DBP adjusted Beta: -0.52; adjusted beta BP: 0.26 and the same direction for 3 drugs or more). Moreover, patients with poorly controlled hypertension usually need more than one antihypertensive drug with no guarantee of clinically achieving good control. Clinical evidence shows that it's easier to decrease DBP than SBP values. This could be the explanation for lower DBP but not SBP at one-year follow-up in our study, and therefore the end result is poorly controlled hypertension: both SBP and DBP must be within the range established to be considered a good control.

We added this paragraph to the results section of the revised manuscript:
"At one year of follow-up, another associated factor which increased the probability of BP control was the presence of a cardiovascular event, also significantly associated with a reduction in SBP and DBP. Furthermore, the presence of comorbidity was associated with lower DBP but with a worse BP control and higher SBP. The use of two or more antihypertensive drugs was associated with a significantly decreased BP control and higher SBP, but lower DBP compared to patients using one antihypertensive drug."
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5) The paper is well-structured, but there are a few minor English mistakes. The paper could benefit from some light editing.

Authors' response: We regret that the original manuscript had even minor English mistakes. An experienced medical and scientific editor who is a native English speaker has reviewed the revised manuscript.

VERSION 2 – REVIEW

REVIEWER	Benjamin T Allaire, Research Economist RTI International, United Kingdom
REVIEW RETURNED	05/03/2012

GENERAL COMMENTS	The authors have adequately addressed my concerns. My only comment would be that the authors reference, in the body of the text, how they arrived at the comorbidities they chose. It is a worthwhile fact for readers to know. estimates of the coefficient and relative 95%CI? The results would be much more easy to read.

