Assessment of a non-physician screening program for hypertension and cardiovascular risk in community pharmacies

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Results. According to the proposed cut-offs, prevalence of hypertension was respectively of 31%, 45% and 59.5%, and it increased among younger subjects (31-65 y.) when the lowest cut-offs were applied. High BP was found in a large percentage of subjects self-declared on-/not on-treatment (uncontrolled hypertensives) or normotensives (presumptive hypertensives) and among those not aware of their own BP values (presumptive hypertensives). Prevalence of CV risk factors was higher in hypertensives than in normotensives.
Conclusions. Our findings demonstrated that a community pharmacy-based screening is feasible and attracts the interests of many subjects, improving awareness on their BP status. The screening was also showed to be useful in order to detect potentially uncontrolled and/or suspected new hypertensives, especially among young adults, to refer to general practitioners for confirmatory diagnosis or further evaluation.

ASSESSMENT OF A NON-PHYSICIAN SCREENING PROGRAM FOR HYPERTENSION AND CARDIOVASCULAR RISK IN COMMUNITY PHARMACIES

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All the authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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Abbreviations list

CKD = Chronic Kidney Disease; CV = Cardiovascular; BP = Blood Pressure; HR = Heart Rate; SD = Standard Deviation

1. Introduction

Arterial Hypertension is one of the most important risk factors for cardiovascular (CV) and chronic kidney disease and affects more than 20% of the world's population (almost one billion people) [1]. Its effect on damaging vessels and target organs is well known [2], nevertheless it has been estimated to be responsible for more than 7 million deaths for year and 90 million disability-adjusted life-years [3]. Considering the magnitude of these data, prevention plays a strategic role. At present, however, hypertension is screened routinely mainly by primary care physicians and, in recent years, some events, such as the World Hypertension Day or the World Heart Day promoted by international scientific societies, have been created in order to "Promote and ensure capacity and accountability of the health system to conduct surveillance and monitoring, and respond appropriately to blood pressure levels" [4]. During these events, specialists and health personnel in the field of hypertension measure blood pressure (BP) and provide information on hypertension and other CV risk factors to all individuals willing to participate. Along this line, a systematic review demonstrated that community-based non-physician screening or self-screening programs may lead to new hypertension diagnosis or new antihypertensive therapy in 44% of subjects that have been referred to primary care immediately after the screening program. However, this systematic review included studies, which are poorly comparable for high methodology heterogeneity [5]; therefore further and more standardized studies are needed to clarify the role of these alternative screening programs. In this view, community pharmacies, for their widespread diffusion in the territory and accessibility, may represent a valid partner to the healthcare system for hypertension management, as already recognized by the World Health Organization [6].

The aims of this survey were (i) to assess the feasibility of a non-physicians pharmacy-based screening program on hypertension in the North-West of Italy and (ii) to describe the BP status and the CV risks of subjects who volunteered to participate to the campaign, by using a validated questionnaire.

2. Methods

The project was promoted in northwest of Italy (Piedmont, Liguria and Aosta Valley) in 2017 by the Department of Science and Technology of Drugs and Medical Sciences of the University of Torino and Federfarma Piemonte (Turin, Italy). The project, addressed to pharmacists willing to take part of it on a voluntary basis, was designed into two parts: the first one consisted in a 6-hours training course addressed to the involved pharmacists on the correct BP measurement technique, hypertension

epidemiology and CV risk factors management [7]; the second part took place in the pharmacies, where the trained pharmacists administered an anonymous questionnaire to their costumers aged 18 years or older who accepted to participate in the study and gave a support to the measurement of participants BP and heart rate (HR) values.

94 community pharmacies of Piedmont, Liguria and Aosta Valley took part to the project. From May to July 2017, 2731 customers participated to the study on a voluntary basis. All subjects participating to the survey were informed on the characteristics and the purpose of the study. No personal data were collected and there was no way to trace back the answers to a specific responder. Individuals were asked to answer to an anonymous questionnaire on personal CV risk, validated by the arterial Hypertension Italian Society during the World Hypertension Day □8□ and already used in previous published studies [9-10], and then the trained pharmacists gave a support to the measurement of their BP values, following the European Society of Hypertension (ESH) standards □2□ (3 consecutive BP readings after 5 min rest). The geographical location of the pharmacies, generally very far from each other, made unlikely that the same subject would be screened twice; furthermore, before starting submitting the questionnaire, pharmacists asked costumers if they had already taken part in the project and, if so, the subjects were excluded.

The mean of the 3 measurements was used as BP and HR reference values. Each pharmacy was provided of the same validated device, Omron HEM 1040-E (Omron Corporation, Kyoto, Japan), an upper arm BP oscillometric monitor for measuring BP and HR, with an adjustable cuff angle correcting the body posture, which tends to be stooped □11□. Demographic and CV risk factors data, as well as information on people knowledge about hypertension and its risk, were collected through the questionnaire. All data about CV risk factors (diabetes, chronic kidney disease, hypertension and dyslipidaemia) and other related comorbidities (cardiac ischemic and cerebrovascular events) were self-reported. Anamnesis and reported CV risk factors data were collected as categorical variables. Pharmacists reported the questionnaire replies and the BP and HR values on an online platform, accessible through personal credentials. No information about individual's drug treatment was collected during the screening: in fact, neither the questionnaire nor this project had the attempt to provide such data.

Currently, there are no clear indications about how the BP values measured in pharmacy are related to office or out-of-office BP and how these measurements should be used in the management of patients

with hypertension. Therefore, we adopted 3 different cut-off in order to assess BP status and identify patients suspected to be hypertensive or uncontrolled hypertensive at pharmacy-based BP measurements: BP ≥ 140/90 mmHg corresponding to office BP threshold [2], BP ≥ 135/85 mmHg corresponding to daytime hypertension cut-off of Ambulatory Blood Pressure Monitoring [2], that a recent meta-analysis identified as higher sensitivity threshold for community pharmacy BP readings[12]; finally, BP ≥ 130/80 mmHg, the threshold proposed by the 2017 ACC/AHA guidelines [13]. We analysed the characteristics of the general population and those of the hypertensive subgroups selected according to the 3 different cut-offs.

2.1 Statistical analysis

Statistical analysis were carried out using STATA®14 (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP). Continuous variables are expressed as mean± standard deviation (SD), and comparisons were performed with a Student *t*-test. Categorical data are expressed as absolute number and/or percentage, comparisons were performed with the McNemar test and correlations were assessed by using the Pearson's chi-square test. Statistical significance of 0.05 was fixed for all hypothesis tests.

3. Results

The population consisted of 2731 individuals, predominantly women (58%), aged 58 ± 15.9 years (range from 18 to 95 years). Dividing the sample into age categories: 6% of subjects were 18-30 years; 59% were 30-65 years; 35% were older than 65 years (Table 1).

Among CV risk factors, 757 subjects (28%) were current smokers, 971 (36%) had a body mass index (BMI) > 25 kg/m^2, 920 (34%) referred a positive history of dyslipidaemia and 344 (13%) of diabetes. Positive family history for CV events was reported by 28% of subjects. Regarding the complications of hypertension, 4% of subjects reported a previous chronic kidney disease (CKD), 8% reported a previous cardiac ischemic events and 4% a previous stroke/transient ischemic attack.

Mean systolic and diastolic BP values were 130/79 ± 18/10 mmHg and mean HR was 73 ± 10 bpm.

According to the proposed BP targets (140/90, 135/85 and 130/80 mmHg), high BP values were found respectively in 31%, 45% and 59.5% of the individuals (Fig. 1).

In our sample 1126 (41%) subjects declared to be pharmacologically treated hypertensives, 159 (6%) untreated hypertensives, 1130 (41%) normotensives and 316 (12%) affirmed to be not aware of their own BP values (Fig. 2). According to 140/90 mmHg cut-off high BP values were found respectively in 10%, 46% and 66% of normotensives, treated hypertensives and untreated hypertensives, while according to the 130/80 mmHg threshold this percentage raised respectively to 39%, 76% and 85.5%. In patients not aware of their own BP values, high BP was found in 35% and 63% when using respectively 140/90 and 130/80 mmHg cut off (Fig. 3).

Considering hypertensives all individuals reporting a diagnosis of hypertension at the moment of the screening (both controlled and uncontrolled at the pharmacy measurement) and presumptive hypertensives all subjects with high BP values among those who self-declared normotensives or not aware of their own BP status, the percentage of subjects with high BP values increased. Indeed, the prevalence of hypertension in our population raised from 47% to 55% and 70.5% when using respectively 140/90, 135/85 and 130/80 mmHg cut off (Fig. 4).

Dividing the population into 3 age subgroups (18-30 years, 31-65 years, over65 years) the major amount of subjects with high BP values was in the over 65 group (51%, for a total of 428 subjects) when the 140/90 mmHg target was applied, while, using the lower targets of 135/85 and 130/80 mmHg, the percentage of high BP was higher in the 31-65 age range (53%; n=651 and 55%; n=894 respectively).

The number of overweight subjects was significantly higher among patients with raised BP values when compared to normotensives, whatever threshold was applied (49% vs. 29.5%, 44% vs. 28%, 42.5% vs. 25%, $p<0.001$ respectively for 140/90, 135/85 and 130/80 mmHg).

Prevalence of dyslipidaemia was significantly higher in patients with increased BP values than in normotensives (45%, vs. 28.5%, 42% vs. 27%, and 39.5% vs. 25% according to the 3 different BP targets, $p<0.001$). Prevalence of both diabetes and CKD was also higher in those with high BP measurements. In particular, more than 17% of patients with raised BP values were diabetic (according the different BP cut-offs: 21% vs. 9%, 19% vs. 7.5% and 17% vs. 6%, $p<0.001$) and, among the same group of subjects, the number of individuals with CKD was almost twice whatever the BP target was used (6% vs. 3%, 5% vs. 3%, 5% vs. 2% $p<0.001$). Also the percentage of subjects with previous cardiac ischemic event, among those who reported high BP values at the pharmacy based measurements, was almost twice than normotensives, and this data did not differ with the different BP

targets (13% vs. 6.5%, 11% vs. 6%, 10% vs. 5%$p<0.001$). The same results were observed for previous cerebrovascular events, with the exception that it became not significant when using the target of 135/85 mmHg ($p=0.005$ for 140/90 mmHg target; $p=0.057$ for135/85 mmHg target; $p=0.014$ for130/80 mmHg target). Furthermore no statistically differences were found when hypertensives and normotensives were compared about history of hypertension (30% vs. 27%, $p=0.185$; 29% vs. 27% $p=0.471$; 29% vs. 26.5% $p=0.183$).

Finally, 1023 subjects (37.5%) indicated the pharmacy as the most common place where they usually measure BP and normotensives seemed to be more accustomed than hypertensives to measure BP in pharmacy (40% vs. 31%, 42% vs. 32%, 45% vs. 33% according to the 3 different BP targets, $p<0.001$), especially among individuals with higher educational levels (27% of subjects measuring BP in pharmacies had a university degree or more).

4. Discussion

To our knowledge this is the first extensive hypertension screening program conducted in community pharmacies in Italy by collecting data from a large sample in the Northern Italy, including rural as well as urban areas and using a unique protocol.

First, we demonstrated that a pharmacy-based non-physicians screening is feasible and very attractive, as more than two thousands seven hundreds subjects were voluntarily enrolled in a short period of time (3 months). More than a half of the participating subjects (59%) were young adults (age range 30-65 years), thus allowing focusing on a subset of population that, for many reasons (no free time available, working duties mismatching with physician's timetables), is likely to less attend general practitioner's consultations, remaining less screened for CV risk factors, such as hypertension, which is often asymptomatic. In fact, unlike general practitioners, community pharmacies may represent, especially for working adults, an easier accessible site, where being correctly educated on BP measurement, having their BP measured and, thus, improving their awareness on BP status.

Second, in our project, we tried to overcome some limitations of BP measurement in pharmacies: the preliminary training courses on hypertension as a risk factor, its management and the BP measurement methods allowed to train the pharmacists and reduce possible bias in the second part of the study; the use of a single validated device and standardised protocols for measuring BP allowed to reduce heterogeneity and bias during the BP measurement [14]. However, the lack of recommended BP target

for this out-of-office measurement technique makes unclear how to use community pharmacies' BP values for hypertension diagnosis and management. A recent meta-analysis [12] suggested the adoption of the daytime ambulatory blood pressure monitoring thresholds of 135/85 mmHg for detecting patients with raised BP in pharmacies; however this finding needs to be supported by more adequately powered and methodologically consistent studies (particularly regarding BP measurement technique and devices).

Third, despite these limitations and the undeniable need of a confirmatory diagnosis of hypertension with either office or other out-of-office techniques (i.e. ambulatory BP monitoring), in our study we decided to assess the prevalence of hypertension by using three different cut-offs: 130/80 and 140/90 mmHg, proposed by the new American and European guidelines [2-13] and 135/85 mmHg suggested by the recent meta-analysis [12].

Our results showed a high rate of hypertension presumptive diagnosis, to be confirmed by further office and/or out-of-office measurements, with a percentage ranging from 10 to 39% among those self-declared normotensives and from 35 to 62% among those not aware of their own BP status, according to different BP thresholds. In this way, the pharmacy-guided screening campaign allowed focusing on a suspect of hypertension in individuals that otherwise would have been considered strictly normotensives and not possibly adequately followed and treated. Even the BP control was unsatisfactory: uncontrolled BP levels were found in 66% and 76% of treated hypertensive patients according to 140/90 and 130/80 mmHg cut off respectively. These data, according with those reported in previous studies [15 -16], showed that BP control is still inadequate, possibly as result of many factors such as inadequate therapy, incorrect BP monitoring, clinicians' inertia, poor drug adherence and low awareness of cardiovascular risk among individuals [17]. Notably patients with raised BP values, whatever BP target applied, reported other major CV risk factors in comparison to normotensive subjects.

Moreover, we found that, using the lower cut-off, the percentage of individuals with raised BP was higher among those aged 31-65 years. Subjects belonging to this relatively younger age group are generally healthy and have few reasons to refer to their general practitioners, being often unaware of their own BP status, although, their BP is often around of the "normal-high" BP range, with the consequent need of a closer control. Therefore, for these subjects, community pharmacies, more frequently attended than clinical practitioners, could represent a place where easily measuring BP and

eventually detecting hypertension, which should be then confirmed after referring to the general practitioner. At the same time, in this age group, CV risk is mostly determined by modifiable risk factors, on which potential benefits deriving from lifestyle intervention and early pharmacological treatment may be greater than in older people, as demonstrated in many studies [8-18]. By contrast, the same rate of undiagnosed or unknown presumptive hypertension among subjects of the same age affected by other comorbidities may not be found, probably because they are already under medical follow-up, even if most of them remain not at target, as demonstrated in other reports [19].

Our results showed that non-physicians screening program based in community pharmacies are feasible and largely attractive for the population, especially among young adults. Furthermore, an important proportion of subjects attending community pharmacies shows BP values higher than currently established cut-offs. Despite their utility, community pharmacies cannot substitute clinician consultations and physician office and/or out-of-office BP measurements and pharmacy-based evaluation should be included in a well-defined integrated program of diagnosis and follow up. In this perspective, community pharmacies, with a "next door" availability, could play a crucial role as "sentinels" of hypertension, firstly educating the costumers on how to properly measure BP and modify CV risk factors, and secondly detecting presumptive hypertensive subjects, especially among young adults, to be referred to general practitioners for a confirmatory diagnosis. Finally, the "community pharmacy model" can therefore be of potential interest in the health policies for the management of chronic diseases.

4.1 Study limitations

A sampling bias could be occurred because of the recruitment method (voluntary participation of each subjects to the study). Furthermore some of the data may not be accurate enough as a result of self-reported information. No data about home BP values or ambulatory BP monitoring readings were available: therefore a comparison between these values and those collected in the pharmacies cannot be performed. The design of the study did not include a medical follow-up to establish the degree of agreement between hypertension presumptive diagnosis according to community pharmacies BP measurements and office/out-of-office ones, and whether the awareness of own BP status could improve its management. In future studies, we will involve general practitioners in order to offer a path

in which pharmacists could act as “sentinels”, identifying people at risk and directing them to the general practitioner that will evaluate the more appropriate therapeutic intervention, if needed.

4.2. Conclusion

This is the first pilot project conducted with a rigorous methodology on cardiovascular area in the attempt to involve community pharmacies in an extensive and standardized screening program for hypertension . Other previous projects involving community pharmacies on chronic diseases, not only in the same Italian regions, have reported interesting results [20-22]. Our survey clearly demonstrated the feasibility of a pharmacy-based non-physicians screening on hypertension, which resulted also very attractive, especially among young adults.

Currently, evidences of effectiveness of community-based BP screenings by non-physicians are very poor and they cannot be recommended [23]. Further and more extensive surveys studies, with the involvement of general practitioners, are needed in order to confirm the potential aid that community pharmacies could provide to physicians on hypertension detection and management and on CV risk reduction.

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Tables

Patients with raised BP values	N = 2731	≥140/90 mmHg[2] **n=841**	≥135/85 mmHg[2] **n=1234**	≥130/80 mmHg[11] **n=1626**
Males (%)	1161 (42.5%)	448 (53.3%)	613 (49.6%)	794 (48.8%)
Age:				
○ **18-30 years (%)**	152 (5.6%)	5 (0.6%)	18 (1.5%)	33 (2.0%)
○ **31-65 years (%)**	1613 (59.1%)	408 (48.5%)	651 (52.7%)	894 (55.0%)
○ **> 65 years (%)**	966 (35.4%)	428 (50.9%)	566 (45.8%)	699 (43.0%)
Body Mass Index > 25 kg/m^2 (%)	971 (35.6%)	414 (49.2%)	548 (44.4%)	691 (42.5%)
Current smokers (%)	757 (27.7%)	256 (30.4%)	369 (29.9%)	479 (29.5%)
Dyslipidaemia (%)	920 (34%)	381 (45.3%)	521 (42.2%)	643 (39.5%)
Diabetes mellitus (%)	344 (12.6%)	179 (21.3%)	231 (18.7%)	281 (17.3%)
Chronic Kidney Disease (%)	98 (3.6%)	49 (5.8%)	59 (4.8%)	78 (4.8%)
Cardiovascular events (%)	229 (8.4%)	107 (12.7%)	136 (11.0%)	170 (10.5%)
Cerebrovascular events (%)	101 (3.7%)	44 (5.2%)	55 (4.5%)	72 (4.4%)
Family history of hypertension (%)	762 (27.9%)	249 (29.6%)	353 (28.6%)	469 (28.8%)

Table 1. Characteristics of general population and of the subgroups of patients with raised BP values according to different cut-offs.

Values are expressed as absolute number and percentage. Raised BP was defined by systolic and/or diastolic BP equal or higher than the cut-off.

Figures Legends

Figure 1. Percentage of subjects with high BP values according to different cut-offs*.

BP values were measured in pharmacy.

* Cut-offs: ≥140/90 mmHg office BP threshold for diagnosing of hypertension according to ESH/ESC 2013 guidelines[2], ≥135/85 mmHg daytime ABPM threshold for diagnosing of hypertension according to ESH/ESC 2013 guidelines[2], ≥130/80 mmHg new office BP threshold for diagnosing of hypertension according to ACC/AHA 2017 guidelines[10].

Values are expressed as percentages.

Figure 2. Awareness of hypertension at screening.

Values are expressed as percentages.

Figure 3. Prevalence of uncontrolled hypertension (between treated and untreated patients) and of presumptive hypertension (between self-declared normotensives and those not aware of their own BP status) after the screening.

Values are expressed as percentages.

Figure 4.Prevalence of hypertension before and after the screening.

°Percentage of subjects with a diagnosis of hypertension (both on treatment and not on treatment) before the screening.

*Percentage of subjects with a diagnosis of hypertension after the screening, according to the two different cut-offs proposed [2,10], including both subjects with a previous diagnosis of hypertension (both controlled and uncontrolled) and subjects with high BP values among those self-declared normotensives or not aware of their own BP status (presumptive hypertensives).

Cut-offs: ≥140/90 mmHg office BP threshold for diagnosing of hypertension according to ESH/ESC 2013 guidelines [2], ≥130/80 mmHg new office BP threshold for diagnosing of hypertension according to ACC/AHA 2017 guidelines [10].

Values are expressed as percentages.

Table(s)

Tables

Patients with raised BP values	N = 2731	≥140/90 mmHg[2] **n=841**	≥135/85 mmHg[2] **n=1234**	≥130/80 mmHg[11] **n=1626**
Males (%)	1161 (42.5%)	448 (53.3%)	613 (49.6%)	794 (48.8%)
Age:				
○ **18-30 years (%)**	152 (5.6%)	5 (0.6%)	18 (1.5%)	33 (2.0%)
○ **31-65 years (%)**	1613 (59.1%)	408 (48.5%)	651 (52.7%)	894 (55.0%)
○ **> 65 years (%)**	966 (35.4%)	428 (50.9%)	566 (45.8%)	699 (43.0%)
Body Mass Index > 25 kg/m^2 (%)	971 (35.6%)	414 (49.2%)	548 (44.4%)	691 (42.5%)
Current smokers (%)	757 (27.7%)	256 (30.4%)	369 (29.9%)	479 (29.5%)
Dyslipidaemia (%)	920 (34%)	381 (45.3%)	521 (42.2%)	643 (39.5%)
Diabetes mellitus (%)	344 (12.6%)	179 (21.3%)	231 (18.7%)	281 (17.3%)
Chronic Kidney Disease (%)	98 (3.6%)	49 (5.8%)	59 (4.8%)	78 (4.8%)
Cardiovascular events (%)	229 (8.4%)	107 (12.7%)	136 (11.0%)	170 (10.5%)
Cerebrovascular events (%)	101 (3.7%)	44 (5.2%)	55 (4.5%)	72 (4.4%)
Family history of hypertension (%)	762 (27.9%)	249 (29.6%)	353 (28.6%)	469 (28.8%)

Table 1. Characteristics of general population and hypertensive subgroups according to different cut-offs.

Values are expressed as absolute number and percentage. Hypertension was defined by systolic and/or diastolic BP equal or higher than the cut-off.

Figure 1

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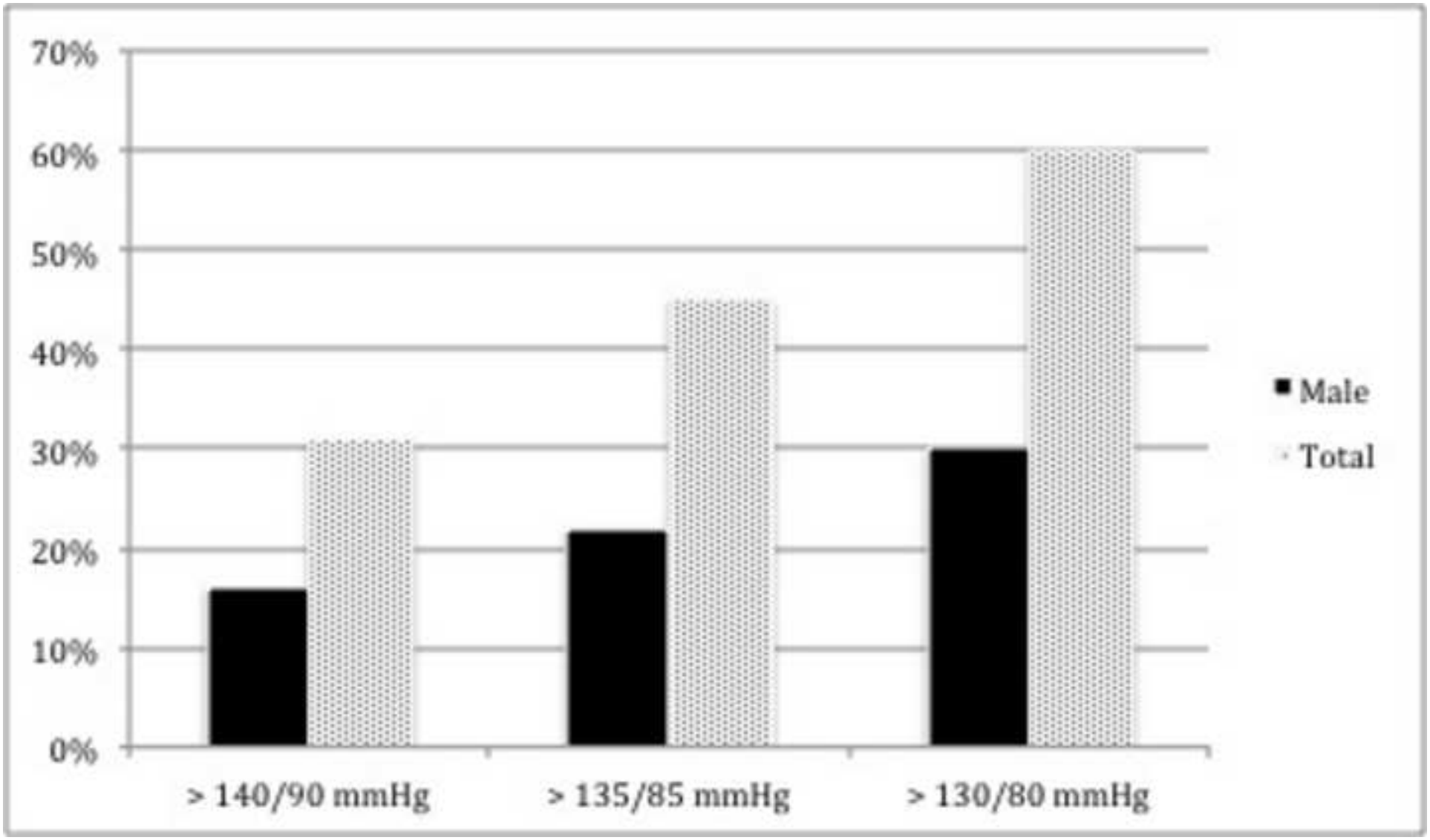

Figure 2

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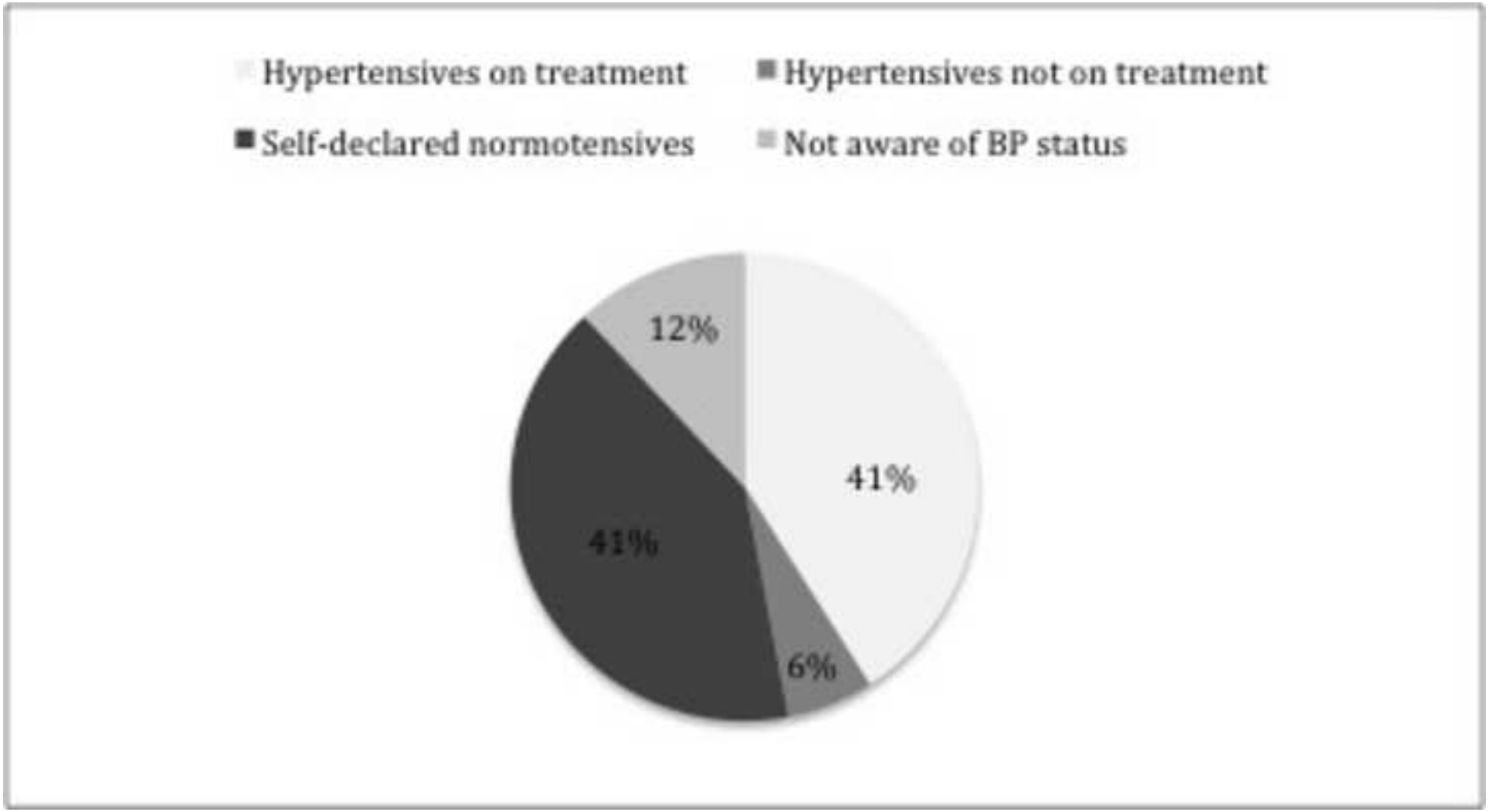

Figure 3

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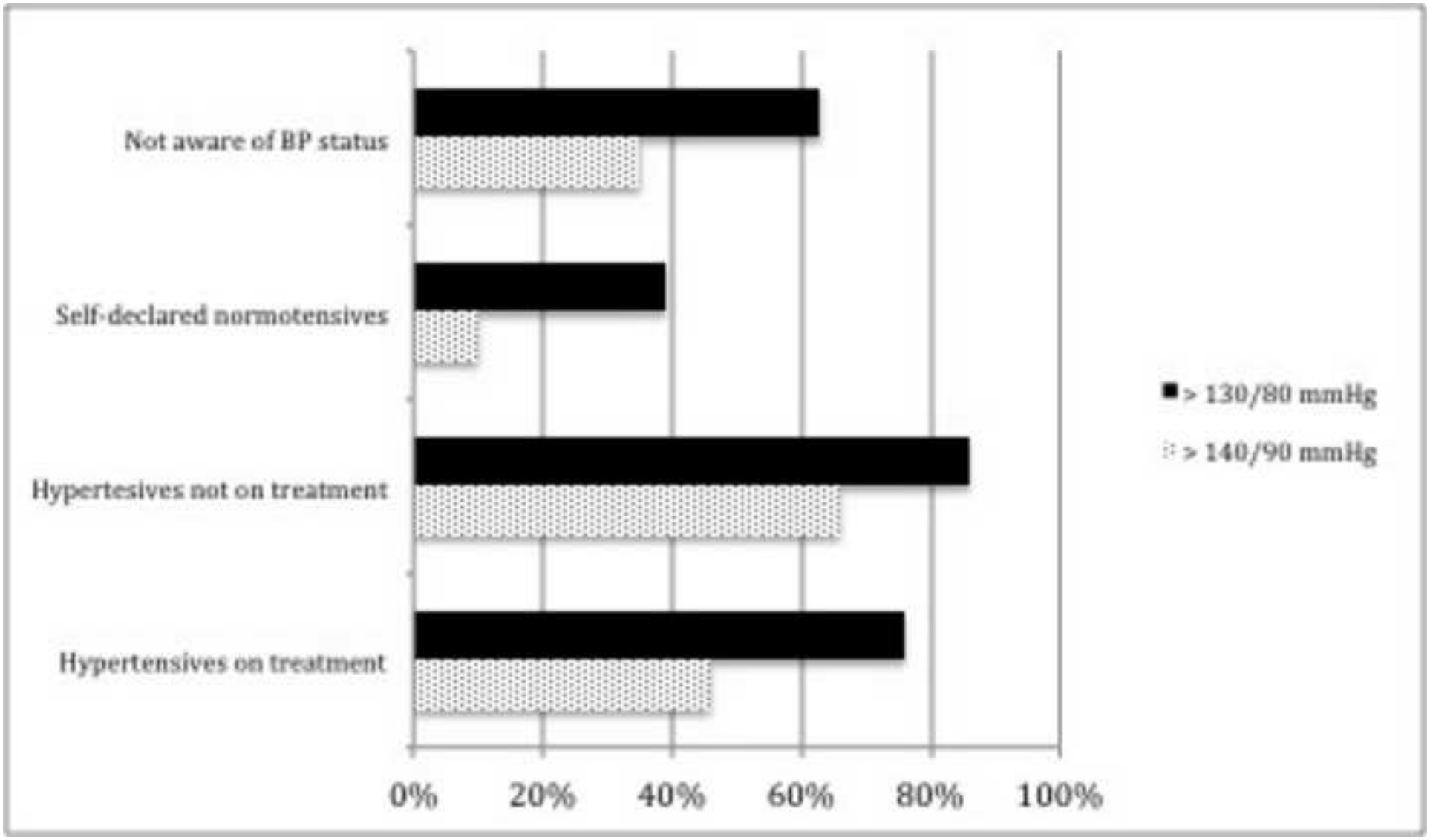

Figure 4 -Revision
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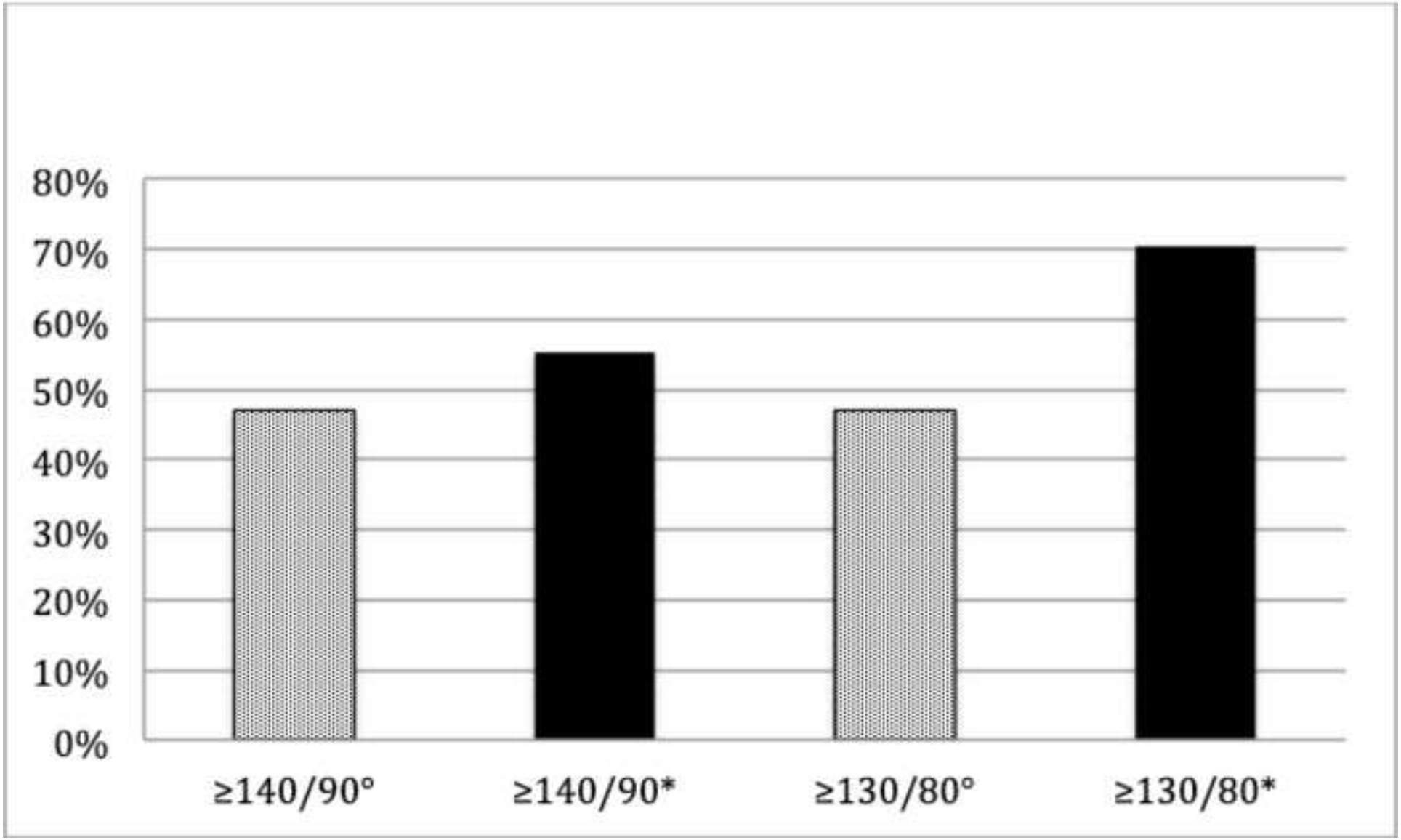

Supplemetary file 1. Questionnaire

READINGS

	SBP	DBP	HR	TIME
1st reading				
2nd reading				
3rd reading				

GENERAL DETAILS

Age: **Sex**: M /F **Weight** (kg): **Height**(cm):

Education: Primary □ Middle school □ High School diploma □ Degree □

QUESTIONNAIRE

Smoker: Yes / No **Chronic Kidney Disease**: Yes /No **Diabetic**: Yes/ No

Have you ever suffered cardiac ischemic attacks in the past? (acute myocardial infarction, acute coronary syndrome, angioplasty, by-pass etc.) Yes / No

Do you have high cholesterol levels? Yes / No

Have you ever suffered cerebrovascular events in the past? (stroke, TIA, etc.): Yes / No

Has either of your parents ever suffered or does one currently suffer from cardiac ischemic conditions? (acute myocardial infarction, by-pass etc.) Yes □ No □

Do you suffer from hypertension? Yes; currently on medication for high blood pressure□
Yes; not on medication for high blood pressure□ No □ Do not know □

Have you ever been treated at an ER or hospitalised for hypertension? Yes / No

In your opinion, what percentage of the population in Western countries suffers from hypertension? < 10%□ 10-30%□ 30-50%□ 50-70%□ >70%□ Do not know □

Are you aware of the health risks associated with hypertension? (more than one possible answer)
Cardiac ischemia/ acute coronary syndrome/acute myocardial infarction□ Cerebral ischemia/cerebral infarction □ Renal damage □
Liver diseases□ Blindness □ Diabetes Mellitus□

Do you know how to reduce the risk of hypertension and cardiac diseases? (more than one possible answer):
Adopt a high-protein, low-calorie diet□
Drink a glass of red wine a day □ Do not drink coffee □
Go for a check-up as soon as the symptoms appear, but not before □
Reduce alcohol consumption □ do at least 30 minutes of exercise every day □
Stop smoking □ Adopt a low-fat, low-salt diet, high in fibre and vitamins □
Intensive sports are the only way to reduce the risk of heart disease □
Have regular check-ups even if there are no symptoms □

How often do you measure blood pressure?
daily□ weekly □ monthly □ annually □

Where do you measure blood pressure? (more than one possible answer)

At general practitioner □ At home □ At a pharmacy □

*Highlights (for review)

Highlights

- A non-physician screening program based in community pharmacies is easily feasible
- A pharmacy-based screening program is attractive for subjects, especially for young adults.
- Non-physician screening programs could underline how hypertension is undiagnosed
- Non-physician screening programs could underline how BP control is unsatisfactory
- Screening programs allow to detect new presumptive hypertensives among apparently healthy individuals