

The potential for overdiagnosis and underdiagnosis because of blood pressure variability: a comparison of the 2017 ACC/AHA, 2018 ESC/ESH and 2019 NICE hypertension guidelines

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Objective: To estimate the extent that BP measurement variability may drive over- and underdiagnosis of 'hypertension' when measurements are made according to current guidelines.

Methods: Using data from the National Health and Nutrition Examination Survey and empirical estimates of within-person variability, we simulated annual SBP measurement sets for 1 000 000 patients over 5 years. For each measurement set, we used an average of multiple readings, as recommended by guidelines.

Results: The mean true SBP for the simulated population was 118.8 mmHg with a standard deviation of 17.5 mmHg. The proportion overdiagnosed with 'hypertension' after five sets of office or nonoffice measurements using the 2017 American College of Cardiology guideline was 3–5% for people with a true SBP less than 120 mmHg, and 65–72% for people with a true SBP 120–130 mmHg. These proportions were less than 1% and 14–33% using the 2018 European Society of Hypertension and 2019 National Institute for Health and Care Excellence guidelines (true SBP <120 and 120–130 mmHg, respectively). The proportion underdiagnosed with 'hypertension' was less than 3% for people with true SBP at least 140 mmHg after one set of office or nonoffice measurements using the 2017 American College of Cardiology guideline, and less than 18% using the other two guidelines.

Conclusion: More people are at risk of overdiagnosis under the 2017 American College of Cardiology guideline than the other two guidelines, even if nonoffice measurements are used. Making clinical decisions about cardiovascular prediction based primarily on absolute risk, minimizes the impact of blood pressure variability on overdiagnosis.

Keywords: blood pressure, evidence-based medicine, hypertension, medical overuse, reproducibility

Abbreviations: ABPM, ambulatory blood pressure monitoring; ACC, American College of Cardiology; AHA, American Heart Association; BP, blood pressure; CMR, cardiac magnetic resonance; ESC, European Society of

Cardiology; ESH, European Society of Hypertension; HbA1C, haemoglobin A1c; HBPM, home blood pressure measurement; LVNC, left ventricular noncompaction; NHANES, National Health and Nutrition Examination Survey; NICE, National Institute For Health And Care Excellence; OBPM, office blood pressure measurement

INTRODUCTION

Overdiagnosis causes well people to be labelled as abnormal or diseased with possible adverse psychosocial and financial consequences, and usually results in overtreatment with possible physical harms [1–3]. It may occur because of overdetection because of increased sensitivity of a new test, and/or overdefinition because of expanded definition of disease (including lowered thresholds) [1,4,5]. A recent example of overdefinition is the expanded definition of 'Hypertension' by the 2017 ACC/AHA high BP Guideline to include 46% of the adult population, by lowering the diagnostic threshold from 140/90 to 130/80 mmHg [6]. Most of the newly classified are unlikely to benefit from their diagnosis in terms of cardiovascular disease prevention, but may be harmed as a result of disease labelling, adverse drug effects or having to now

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TABLE 1. American College of Cardiology/American Heart Association 2017 Guideline recommendations for number of measurements for diagnosis of hypertension

Type of blood pressure measurement	Recommendation
Office measurement	Occasion: two readings (1 min apart) BP level: use average of all readings obtained on at least two occasions
Ambulatory BP measurement	Occasion: readings over 12–24 h (15–60 min apart) BP level: use average of all readings obtained on at least occasion
Home BP measurement	Occasion: two readings (1 min apart) twice daily. BP level: use average of all readings made on at least two occasions

BP, blood pressure.

declare a pre-existing “disease” to organisations, such as insurance companies [7].

The 2017 ACC/AHA guideline recommends averaging at least two office measurements before making a diagnosis of ‘hypertension’ on an individual patient, and ideally confirming this diagnosis by then averaging multiple out-of-office measurements (Table 1). The guideline’s emphasis on accurate measurement technique, both in office and at home, has been commended [8,9] and some have suggested that this may prevent overdiagnosis of ‘hypertension’ in individual patients [9]. However, lowering the diagnostic threshold to a level close to the population average means that measurement variability, even if reduced by averaging multiple measurements, may have a large clinical impact. This can happen as the large proportion of adults who have a SBP just below the new diagnostic threshold [10] may have an average that still tips them over the threshold and results in a ‘hypertension’ label.

Measurement variability in BP is well recognized, and exists whether measurements are made in the doctor’s office, via ambulatory devices, or in the home [11]. Both SBP and DBP vary because of physiological fluctuations throughout the day, from day to day, and week to week. Additionally, there are differences in the results that are ultimately recorded, because of differences in type of sphygmomanometer, its calibration and precision, and inter-observer differences in how the person recording the measurement interprets the reading. Systematic bias may be dealt with by calibrating sphygmomanometers [12] or standardizing the time of day that measurement is done. But even after taking steps to standardize measurement, considerable variability may remain, with approximately 10 mmHg standard deviation [13,14], or 8.6% coefficient of variation [15], for repeat measurements made at clinic (office) visits over a few weeks.

In contrast to the 2017 ACC/AHA guideline, the 2018 European Society of Cardiology/European Society of Hypertension (ESC/ESH) guideline [16] and the 2019 National Institute For Health And Care Excellence (NICE) guideline [17] did not lower the threshold for the diagnosis of ‘hypertension’, which remains at 140/90 mmHg. These guidelines also emphasize accurate measurement including out-of-office BP.

In this article, we explore the effects of BP variability on the cumulative probability of overdiagnosis and underdiagnosis of hypertension made according to the 2017 ACC/AHA guideline’s diagnostic criteria (threshold 130/80 mmHg) compared with the 2018 ESC/ESH and 2019 NICE guidelines’ criteria (threshold 140/90 mmHg). In so doing we aim to address the question confronting a physician in practice: what are the chances that this patient in front of me is going to be over/under- diagnosed on the basis of the BP measurements I (or they) have taken? Furthermore, we use this example to illustrate the problem of test variability causing overdiagnosis and underdiagnosis and how changes in test thresholds can increase the problem.

METHODS

We used the summary statistics from the National Health and Nutrition Examination Survey (NHANES) of the US adult population aged at least 20 years (noninstitutionalized) who are not taking antihypertensive medication [18] to simulate a distribution of blood pressure measurements for 1 000 000 individuals. Each simulated SBP was taken as the true SBP for an individual (i.e. their true underlying average BP). We then applied estimates of within-person variability (coefficients of variation) to our population of true SBPs in order to generate observed SBPs for five independent sets of measurements, representing an annual assessment of blood pressure over 5 years. Each set of measurements represented: the average of two separate office measurements (taken in duplicate and repeated 6 weeks apart; equivalent to office blood pressure measurement); 1 day of ambulatory measurements (daytime average from 24-h ambulatory monitoring); or 1 week of home measurements (home self-monitoring of blood pressure from 7 days of self-monitoring with replicate measurements taken twice daily and the first day’s data discarded, equivalent to home blood pressure measurement). We used estimates of the co-efficient of variation from the largest primary study, derived from a randomized clinical trial of 163 subjects [15]. (Further details of the primary study for the estimates of within person variability [15] are provided in the S1 Appendix, <http://links.lww.com/QAD/B792>.)

We then calculated the cumulative probability that at least one set of BP measurements would be above a threshold (130 mmHg for office/nonoffice measurements as per the 2017 ACC/AHA guideline, or 140 mmHg for office and 135 mmHg for nonoffice measurements [6] as per the 2018 ESC/ESH and 2019 NICE guidelines), and that no set of BP measurements would be above the threshold. We grouped the simulated population by the true SBP (<120, 120–129, 130–139, ≥140 mmHg) to obtain the expected proportion who had at least one or no sets of measurements above the threshold. In this way, we were able to estimate the probability of overdiagnosing hypertension in people who truly have low SBP (where just one set of measurements needs to be randomly high enough to be over the diagnostic threshold), or alternatively the probability of underdiagnosing hypertension in people who truly have elevated SBP (where all sets of measurements are randomly low enough to be under the diagnostic threshold).

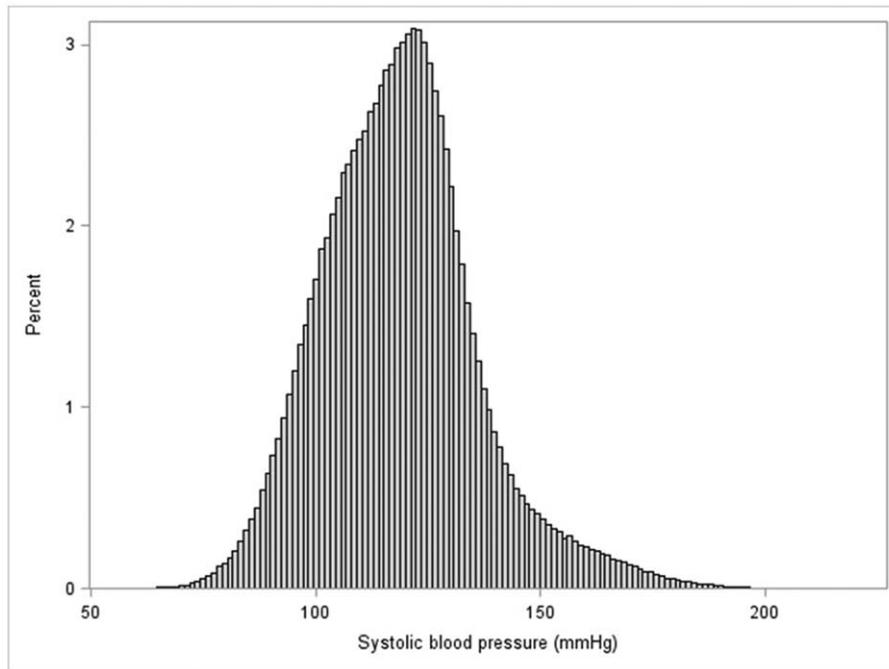


FIGURE 1 Simulated SBPs for US adult population not taking blood pressure-lowering drugs. Simulation made on the basis of summary statistics of SBP for the US adult population not taking antihypertensive medication reported in [18].

The simulations and other calculations were done using SAS 9.4, SAS Institute Inc., Cary, North Carolina, USA.

RESULTS

The simulated SBPs for 1 000 000 US adults aged 20 years and older who are not taking BP-lowering drugs, are presented in Fig. 1. The distribution was slightly skewed with a long upper tail. The SBPs ranged from 65 to 235 mmHg, with mean SBP of 118.8 mmHg (median 118.3 mmHg), and a standard deviation of 17.5 mmHg. Allowing for the 24.1% of the US adult population who take BP-lowering drugs, the proportion of the population

with a SBP <120 mmHg was 42.3%, 120–129 mmHg was 12.1%, 130–139 mmHg was 13.7% and at least 140 mmHg was 7.7%, in line with the empirical estimates underpinning the simulation [18].

Probability of ‘hypertension’ overdiagnosis

Using the definition of hypertension from the 2017 ACC/AHA guideline, the proportion of people with a true SBP less than 120 mmHg who were overdiagnosed with ‘hypertension’ after five sets of office measurements was 5.2% (Table 2). The proportion was smaller with ambulatory monitoring or home BP measurement, but was still over

TABLE 2. Percentage of people with observed SBP greater than 130 mmHg (office, ABPM or HBPM) who would be diagnosed with ‘hypertension’ according to 2017 American College of Cardiology/American Heart Association guideline

True SBP (mmHg)	Percentage of population ^a	Method of measurement	One set	Two sets	Three sets	Four sets	Five sets
<120	42.3%	OBPM ^b	1.1%	2.2%	3.3%	4.2%	5.2%
		ABPM ^c	0.8%	1.5%	2.2%	2.9%	3.5%
		HBPM ^d	0.6%	1.2%	1.7%	2.2%	2.8%
120–129	12.1%	OBPM	25.8%	43.4%	55.9%	65.0%	71.7%
		ABPM	23.9%	40.5%	52.4%	61.2%	67.8%
		HBPM	22.9%	38.9%	50.4%	58.9%	65.4%
130–139	13.7%	OBPM	68.4%	88.8%	95.7%	98.2%	99.3%
		ABPM	70.0%	89.6%	96.0%	98.4%	99.3%
		HBPM	70.9%	90.0%	96.2%	98.5%	99.4%
≥140	7.7%	OBPM	97.0%	99.8%	100.0%	100.0%	100.0%
		ABPM	97.8%	99.9%	100.0%	100.0%	100.0%
		HBPM	98.2%	99.9%	100.0%	100.0%	100.0%

Data from [6]. HBPM, home BP, one set of measurements is the average of two duplicate self-measurements taken twice daily over 6 days.

^aOn the basis of coefficients of variation reported in Warren et al. [15].

^bPercentages do not add to 100% as excludes 24.1% of adult population who are taking BP lowering medication.

^cOBPM, office BP, one set of measurements is the average of 2 duplicate clinic measurements, repeated after 6 weeks.

^dABPM, ambulatory BP, one set of measurements is the average of ambulatory BP measurements taken over 12 h (daytime).

TABLE 3. Percentage of people with observed SBP greater than 140 mmHg (OBPM) or greater than 135 mmHg (ABPM or HBPM), who would be diagnosed with 'hypertension' according to 2018 ESC/ESH or 2019 NICE guidelines^a

True systolic BP (mmHg)	Percentage of population ^b	Method of Measurement	One set	Two sets	Three sets	Four sets	Five sets
<120	42.3%	OBPM ^c	0.0%	0.1%	0.1%	0.1%	0.1%
		ABPM ^d	0.1%	0.2%	0.3%	0.4%	0.5%
		HBPM ^e	0.1%	0.1%	0.2%	0.3%	0.3%
120–129	12.1%	OBPM	3.1%	6.1%	8.9%	11.5%	14.0%
		ABPM	8.5%	15.9%	22.4%	28.0%	33.0%
		HBPM	7.6%	14.2%	20.0%	25.1%	29.7%
130–39	13.7%	OBPM	24.9%	42.4%	54.9%	64.2%	71.1%
		ABPM	45.5%	68.2%	80.5%	87.6%	91.9%
		HBPM	45.3%	67.8%	79.9%	87.0%	91.4%
≥140	7.7%	OBPM	82.6%	94.3%	97.8%	99.1%	99.6%
		ABPM	93.2%	98.9%	99.8%	100.0%	100.0%
		HBPM	93.8%	99.1%	99.8%	100.0%	100.0%

Data from 2018 ESC/ESH [15] and NICE [17] guidelines.

^aOn the basis of coefficients of variation reported in Warren *et al.* [15].

^bPercentages do not add to 100% as excludes 24.1% of adult population who are taking BP-lowering medication.

^cOBPM, office BP, one set of measurements is the average of two duplicate clinic measurements, repeated after 6 weeks.

^dABPM, ambulatory BP, one set of measurements is the average of ambulatory BP measurements taken over 12 h (daytime).

^eHBPM, home BP, one set of measurements is the average of two duplicate self-measurements taken twice daily over 6 days.

2% after five sets of measurement. Using the 2018 ESC/ESH or 2019 NICE guidelines, the proportion of people with a true SBP less than 120 mmHg who were overdiagnosed was less than 1% after five sets of BP measurement for all types of measurement (Table 3).

For those with a true SBP 120–129 mmHg, using the 2017 ACC/AHA guidelines the proportion of people who were overdiagnosed with 'hypertension' was 71.7, 67.8 and 65.4% after five sets of office, ambulatory and home BP measurements, respectively (Table 2). Using the 2018 ESC/ECC or 2019 NICE guidelines, the proportion of people overdiagnosed was 14, 33 and 29.7% after five sets of office, ambulatory and home BP measurements, respectively (Table 3).

Probability of 'hypertension' underdiagnosis

Using the 2017 ACC/AHA guideline, the proportion of people with a true SBP at least 140 mmHg who were underdiagnosed with 'hypertension' was 3% or less for one set of BP measurements for all types of measurement (Table 2). Using the 2018 ESC/ECC or 2019 NICE guidelines, the proportion who were underdiagnosed was 17.4% for one set of office measurements, but less than 7% if there was at least one further set of office measurements, or if one set of nonoffice measurements was made (Table 3).

DISCUSSION

The probability that a patient is overdiagnosed with 'hypertension' on the basis of the BP measurements taken, increases with repeated annual blood pressure checks. We estimate that 65–72% of people with a true SBP of 120–129 mmHg will be overdiagnosed after five repeat sets of measurements made using the ACC/AHA guideline recommendations. The proportion of people who are overdiagnosed using the 2018 ESC/ESH or 2019 NICE guidelines is lower, although the risk of underdiagnosis is higher: 17% of people with a true SBP at least 140 mmHg are

underdiagnosed after one set of office measurements. However, this proportion can be minimized if the set of office BP measurements is repeated even once, or if just one set of nonoffice measurements are made. Unless a fall in blood pressure can be attributed to another disease (e.g. cardiac failure), then a 'hypertension' diagnosis is usually for life. Once a person is diagnosed with 'hypertension', they do not later become undiagnosed as a result of lower BP measurements, but rather they are said to have 'controlled hypertension' [15]. Thus, where BP measurements are repeated (e.g. at routine check-ups), the cumulative probability of overdiagnosis tends to increase and of underdiagnosis decrease. As well as psychosocial harms caused by the disease label, overdiagnosis of 'hypertension' may cause physical harm where there is also overtreatment, with the potential for adverse effects from unnecessary BP-lowering drugs.

These findings add to our previous analysis of empirical data on incremental benefits and harms of the lower threshold for 'hypertension' proposed by the ACC/AHA guideline for individuals [7]. In that analysis, we found that for the 80% of those newly diagnosed by the ACC/AHA threshold who have a 10-year CVD risk less than 10%, there is no incremental benefit in CVD risk reduction, but potential incremental harms from disease labelling, drug treatment, and costs. The current study builds on those findings to show that the newly diagnosed may also include individuals with a true SBP lower than 130 mmHg. We may expect that an even higher proportion of such individuals would have a 10-year risk less than 10%, and be at risk of harm.

The problem illustrated is an example of a broader phenomenon known as 'capitalization of chance' whereby erroneous conclusions are made by applying decision rules to chance differences. A common example is the use of *P*-value thresholds to determine significance of results, the validity of which has been called into question [19]. Just as one solution to 'p-hacking' may be to stop applying thresholds to *P* values, one way to prevent

overdiagnosis of ‘hypertension’ from measurement variability may be to stop applying a diagnostic threshold to the single risk factor of blood pressure. Instead of focusing on just the individual’s BP, and whether they have ‘hypertension’, the measurement can be combined with other risk factors to calculate the absolute risk of a cardiovascular event within 5–10 years. The absolute risk approach minimizes the consequences of BP measurement variability as it matters less whether you are just over or just under a certain blood pressure value [20]. By moving away from using the ‘hypertension’ label, we may prevent the overdiagnosis of a ‘disease’ in people who are otherwise at low risk of a cardiovascular event yet still effectively intervene in people at high risk [21]. The increasing use of a ‘risk-based’ approach for making decisions on cardiovascular preventative treatment, and recommendations on this in all the new guidelines, are encouraging signs that clinical practice is moving in this direction. Newer risk equations that include people at younger and older ages (QRISK3: 25–84 years [22], PREDICT: 30–74 years [23]) support wider application of the risk-based approach in clinical practice.

Not only is the absolute risk approach less likely to result in overdiagnosis (and underdiagnosis) from measurement variability in BP, importantly it allows the patient and doctor to better assess the size of potential benefits and harms of starting treatment for more informed shared decision-making [24,25]. The decision to start preventative treatment is sensitive to an individual’s values and preferences, with some people willing to accept a small increased risk of a cardiovascular event in order to avoid taking medications, whereas others are not [26]. For example, a web-based decision support tool may be used to present the individualized risk estimates with and without taking medication, so that the patient and clinician may reach a decision while taking into account the patient’s values and preferences [27]. However, to also prevent the overtreatment of low-risk people that may result from measurement variability in the risk scores, we need minimum treatment thresholds, set at a risk level where treatment has net benefit for the population.

If we consider cardiac tests more generally, the problem of measurement variability contributes to overdiagnosis whether the test results are continuous (like BP or HbA1c) or categorical [like cardiac MRI for the cardiomyopathy, left ventricular noncompaction (LVNC) [28,29]]. Once you have diabetes or a cardiomyopathy, you have that diagnosis for life. Repeated testing is, therefore, more likely to result in overdiagnosis than underdiagnosis. Thresholds are particularly problematic where they are expanded to include many people at low risk of developing adverse outcomes from the condition.

There are several potential solutions to prevent over (and under) diagnosis arising from measurement variability in diagnostic tests. Guideline groups considering expansion of disease definitions, need to have a greater understanding of how test variability contributes to overdiagnosis and underdiagnosis, and to consider these issues in their guidance to clinicians regarding repeat testing and testing intervals. Where diseases are defined on single risk factors (e.g. HbA1c for diagnosis of type II diabetes mellitus),

laboratory staff could issue reports, perhaps through the use of visual scales [30] that highlight the uncertainty around such values and promote the averaging of multiple measurements. The report could also prompt the physician to explicitly consider the benefits and harms of treatment. Physicians and patients can also try to minimize overdiagnosis by averaging multiple measurements, particularly where a result is close to a threshold (e.g. repeat HbA1c measurements [31] or a second/third radiologist opinion on a cardiac MRI), and extending the interval before the tests are repeated. This increases the chance of detecting a true change on the test rather than random noise [32–35]. A primary care-led, people-centred approach to reforming disease definitions [36], aims to explore ways to delay diagnoses or make them more temporary while results are uncertain, and to allow de-diagnosis where new results indicate the person probably does not have disease (rather than saying they have ‘well controlled’ hypertension or diabetes, for example).

For our estimates of measurement variability we used the best and largest dataset available internationally, which was from the controlled setting of a clinical trial. Although this study population was small, and likely less diverse than that of the US population, the estimates are consistent with other albeit smaller studies of within-person variability of BP for office and for out-of-office measurement variability [11,14,37–40]. We also averaged more measurements than would usually be done in routine clinical practice. In addition, our calculations of the proportion overdiagnosed are based on measurements of SBP only. As either a systolic or diastolic measurement over the diagnostic threshold is enough for a diagnosis of ‘hypertension’, this will further increase the risk of overdiagnosis, and decrease the risk of underdiagnosis. Therefore, the proportion overdiagnosed may well be higher than what we have calculated.

Our simulation did not investigate the possibility of discordant results between different types of measurement, such as high office BP and normal ambulatory BP or home BP in people with a true SBP <140 mmHg (‘white-coat hypertension’) or normal office BP and high ambulatory BP or home BP in people with true SBP at least 140 mmHg or abnormal BP response (including ‘masked hypertension’, ‘nocturnal hypertension’ and an exaggerated blood pressure response to exercise), nor the possibility that BP variation itself provides important prognostic information [41]. However, we note that when using a risk-based approach rather than focusing on blood pressure alone, the addition of out-of-office measurements (including night time BP and measures of variability) [42,43] or indeed repeated office measurements [44,45] appear to have minimal impact on clinical decision-making. Finally, we did not explore psychosocial consequences of over diagnosis and underdiagnosis, clinical consequences of overtreatment and undertreatment and health resource use/cost consequences. Future research on the downstream consequences of measurement variability will be valuable.

In conclusion, measurement variability in diagnostic tests, including blood pressure measurement, is an important and underrecognized source of overdiagnosis that might be prevented.

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Conflicts of interest

There are no conflicts of interest.

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