Blood Pressure Monitoring in Clinical Trials in Obese Subjects

PEER REVIEWED

The World Health Organization (WHO) classification system for obesity is based on body mass index (BMI). A BMI of 25.0 to 29.9 kg/m² is considered overweight, and ≥30 is considered obese. According to a 2016 WHO report, the worldwide prevalence of obesity nearly tripled between 1975 and 2016. 39% of the world's adult population aged 18 years and over (1.9 billion adults) are overweight and 13% are obese (650 million)[1]. With the current trend, it has been estimated that the global prevalence of obesity will reach 18% in men and exceed 25% in women by 2025[2]. Based on this very high prevalence in the general population and the tight association between obesity, hypertension and cardiovascular risk, it seems inherently important to understand whether new drugs cause an increase of systolic or diastolic blood pressure and more specifically, how such an effect translates into cardiovascular risk in obese subjects.

This brief review gives a short summary of the association between obesity, cardiovascular risk and hypertension and outlines the emerging FDA guideline on the need for blood pressure monitoring in the development of new drugs[3].

Obesity and CV Risk

Obesity is associated with an increased cardiovascular risk and obese subjects often suffer from other conditions, which also increases this risk, such as type 2 diabetes, hypertension, elevated plasma lipids, left ventricular hypertrophy, atherosclerosis and obstructive sleep apnea[4]. The physiologic and metabolic changes associated with obesity, which contribute to increased cardiovascular risk, include insulin resistance, dyslipidemia (lower HDL, increased triglycerides, smaller LDL particles, increased apolipoprotein B level), systolic and diastolic hypertension, obstructive sleep apnea, increased systemic inflammation, and endothelial dysfunction. These changes manifest in varied conditions including coronary artery disease, stroke, left ventricular hypertrophy, heart failure, and atrial fibrillation. Consequently, obesity is categorised as an independent risk factor for cardiovascular disease according to 2013 Joint AHA / ACC / TOD guidelines for the management of overweight and obese adults[5].

There is strong, consistent evidence in multiple epidemiological studies for the association between obesity and cardiovascular disease in general, individual cardiovascular disease outcomes, cardiovascular mortality and all-cause mortality[4]. As an example, 16,288 men and 7325 women were followed for up to seven years in the Münster Heart Study[6]. There was a graded and continuous positive relationship between BMI and coronary heart disease (CHD) with risk factors including age, total serum cholesterol, low-density lipoprotein (LDL) cholesterol, and systolic and diastolic blood pressure. The increase of CHD death associated with BMI was completely accounted for and mediated by these risk factors. In a meta-analysis of 21 cohort studies involving more than 300,000 patients that assessed the association of obesity and risk of CHD, a 29% increase of events related to CHD was observed for each five-unit increase in BMI[7].

Obesity as a risk factor for CHD is confounded by the frequent comorbidities of hypertension, dyslipidemia, and diabetes. However, even the metabolically healthy obese subjects, the risk for cardiovascular disease increases with every unit increase in BMI[8].

Prevalence of Hypertension in Obese Subjects

The association between obesity and hypertension is well recognised. In a Canadian cross-sectional, population-based survey published in 2010 of 2510 adults, aged 20 to 79 years, it was observed that the prevalence of hypertension increased with BMI and age. In the population older than 60 years of age, the prevalence of hypertension was of 51% for overweight subjects, 59% in obese subjects and 68% in severely obese subjects, as compared to 36% in lean individuals[9]. Using Framingham data, it has been shown that every 5% increase of weight was associated with a 20 to 30% increase of the incidence of hypertension[10].

Emerging evidence suggest that obesity in itself causes hypertension through several different mechanisms, i.e., is a causative factor[11]. Main components involve i) overactivation of the sympathetic nervous system, ii) stimulation of the renin-angiotensin-aldosterone system (RAAS), iii) insulin resistance, iv) alterations in adipose-derived cytokines, and v) structural and functional renal changes. *Sympathetic nervous system overactivation* in obese subjects is thought to be the result of abnormal adipokine secretion from adipose tissue, indirectly through stimulation of the RAAS, insulin resistance and baroreceptor dysfunction[12]. Also, obstructive sleep apnea is frequent in obese subjects, which leads to intermittent hypoxia and upregulation of sympathetic nervous system activity through carotid body chemoreceptors. There are several ways that *activation of the RAAS* may occur in obese subjects, which involves a bidirectional influence between the sympathetic nervous system and the RAAS leading to elevated renin levels. Levels of angiotensinogen, angiotensin-converting enzyme (ACE), and aldosterone are also elevated, which in turn induce systemic vasoconstriction and simulate the production of aldosterone from the adrenal cortex. This leads to increased renal tubular sodium reabsorption and water retention with expansion of intravascular volume and resulting hypertension. *Insulin resistance* and hyperinsulemia leads to sympathetic activation and renal sodium retention and blunted response to the normal vasodilatory effect of insulin through endothelial dysfunction, with increased vasoconstrictor tone[13].

Emerging FDA Guidelines on Blood Pressure Monitoring in Clinical Trials

Background

In May 2018, FDA issued draft guidance on the importance of blood pressure evaluation in drug development[3]. To clarify the background and the underlying thinking, FDA and the Duke-Margolis Center for Health Policy arranged a public meeting in Washington DC in February 2019 with attendance from FDA, pharmaceutical sponsors and academia. At this meeting, sponsors were informed that FDA will institute an interdisciplinary review team (IRT) for blood pressure (BP) evaluation in clinical trials; this group will comprise of cross-divisional FDA staff and provide advice to reviewing divisions

on study protocols in which blood pressure evaluation is included to ensure consistent advice across therapeutic areas. This is much the same approach that FDA has taken in regard to QT assessment, for which an IRT was established shortly after the endorsement of the ICH E14 guidance on this topic in 2005. At the meeting, there were several presentations from FDA staff from the cardiorenal division, who also are involved in the IRT for QT studies; these presentations have been summarised in a recent publication by Garnett *et al.*[14].

FDA Guidance on BP Evaluation in the Clinical Development of New Drugs

The FDA guidance distinguishes between drugs intended for short term, i.e., less than 12 weeks' treatment, and chronic usage[3]. For drugs intended for short-term use, large blood pressure-increasing effects may be of concern, and careful assessment using cuff BP measurements during routine study visits is recommended with the objective to exclude, e.g., a mean increase of systolic blood pressure (SBP) of more than 4 mmHg. It is pointed out that when in-clinic cuff blood pressure measurement is deemed appropriate, accuracy can be improved by collecting triplicate measurements of sitting blood pressure in all subjects at baseline (predose), at several visits, at the end of the inter-dosing interval (trough measurement; predose), and at peak concentrations of the drug.

For drugs intended for chronic use, ambulatory blood pressure monitoring (ABPM) over 24 hours is clearly the preferred method. The BP evaluation should be performed in the targeted patient population when the drug pharmacodynamically has reached steady state. In general, the results should be based on the integrated mean 24-hour blood pressure (i.e., area under the curve, a time-weighted average of the blood pressure throughout the day). If no effect is observed by ABPM in a patient study that is appropriately powered to exclude a small effect, subsequent studies (e.g., later Phase II, Phase III) can utilise monitoring by routine cuff blood pressure measurements. On the other hand, if the drug increases blood pressure in the overall patient population, the sponsor should obtain additional information about the BP effects in subsets of the population with potentially larger effects, e.g., patients with pre-existing hypertension, diabetes, renal impairment, African-American and the elderly.

ABPM has several advantages as compared to BP measurements performed at study visits in the clinic or at home:

- ABPM allows for the assessment of blood pressure effects over a 24-hour period, thereby also capturing potential effect on the diurnal variation of BP as well as potentially variable effects of the drug on BP over the full dosing interval. It is thought that in most cases, drug-induced effects on BP can be seen as a shift over the full 24 hours, even though there are also examples where the effect is directly related to Cmax of the drug;
- ABPM devices can be programmed to collect measurements at specified time points;
- ABPM devices can be programmed to enable focus on prespecified time-windows for drugs with transient effect, i.e., with more intense collection;
- Importantly, ABPM, similar to BP assessment with other automated devices, is free of potential investigator bias.

As a preparation for the February 2019 meeting, members of the FDA's cardiorenal division at the agency compiled a research database with data from 22 ABPM studies with more than 20 subjects per treatment arm[14]. Most of these studies (n=16) were old studies in patients with hypertension, conducted more than 25 years ago (between 1986 and 1995), but there are also more current studies (n=6) in the database, including the Precision-ABPM study[15] and the SYNERGY study[16]. Eleven of the studies included a placebo group with a total of 456 subjects. Each study had an ABPM session at baseline and at least one and up to three post- baseline visits with a median number of measurements of four per hour during daytime and three during the night and a median study duration of six weeks (range: two to 12 weeks). This research database was used as a data source from which a large number of studies with different assumptions were simulated. This approach allows for the evaluation of different design features of ABPM studies[14,17], with the objective to understand how these can be conducted in an efficient way and yet with the power to exclude small BP effects[18].

Primary endpoint: ABPM provides a large number of blood pressure measurements throughout the day, and by using an average across all time points a more precise assessment is obtained. Based on practical considerations, the device is often programmed to perform more measurements during daytime as compared to night and then a 'weighted' average should be used, taking into account the frequency of hourly values. However, for drugs that produce a transient effect on BP that is directly proportional to plasma concentrations, the peak BP effect would be expected to occur close to the peak plasma level of the drug. In such cases, the schedule of measurements using the ABPM device can be tailored to capture effects through more intense frequency over predefined time-windows, and the primary endpoint may focus on a more limited period of time[14].

Placebo: In the original May 2018 FDA guidance, it is stated that in general, it is desirable to include a placebo group as the control group[3]. At the Duke-FDA meeting, FDA however presented data, which suggest that there is not much of a difference between the baseline assessment and on-treatment with placebo for study durations up to 12 weeks (Figure 1). The concern is also that through inclusion of placebo, variability of data increases and much larger sample sizes would be needed to exclude a small effect. Using simulated studies, it was shown that with no underlying BP effect of the drug, the sample size needed to exclude a 4 mmHg effect on the 24-hour SBP increased almost four-fold, from 30 subjects without placebo to 114 subjects in a placebo-controlled study. The recommendation at the meeting and in a subsequent publication[14] was therefore that placebo in most cases is not needed for studies intended to exclude a small BP effect. Examples in which a placebo-controlled evaluation is warranted include studies in which procedures as such can have an effect, e.g., counselling on diet and exercise to achieve weight loss, studies of very long duration (e.g., more than six months) and when subjects with very high blood pressure are enrolled into studies to control regression-to-the-mean phenomenon. It should, however, be acknowledged that more

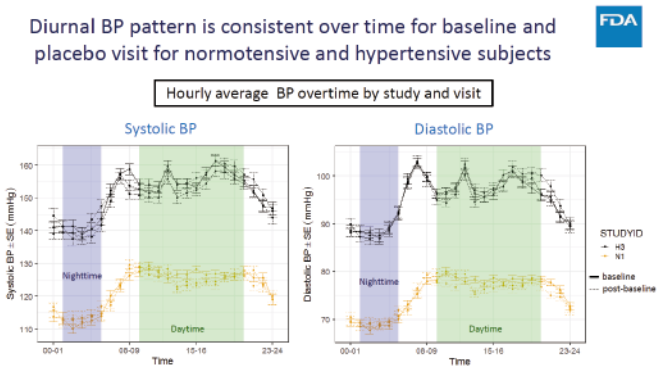

Figure 1, panel A: In both subjects with hypertension (black lines; H3) and in healthy volunteers (yellow lines; N1), there are only small changes from the baseline ABPM session (solid lines) to on-treatment visits, with unaffected diurnal pattern. Source:[17]

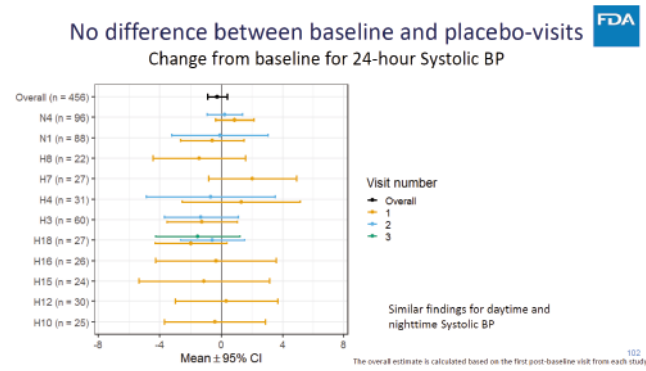

Figure 1, panel B: Change-from-baseline of mean 24-hour systolic blood pressure in subjects on placebo across 11 studies in the FDA's research database. Changes were overall small and in most cases below 2 bpm. Source:[17]

experience is needed to understand to what extent the inclusion of a placebo group may improve the ability to exclude a BP effect by accounting for trial conditions or period effects.

Number of BP measurements per hour and validity criteria: Using the simulation approach, data were also presented demonstrating that the accuracy and precision of ABPM studies using the 24-hour endpoint were not materially influenced by the number of measurements per hour, or by reducing criteria for a valid ABPM session from the standard 70% of expected measurements in clinical practice to 50%[18]. It was, therefore, advocated that no more than two measurements per hour are needed and that criteria to define a valid ABPM session can be set to 50% of expected measurements. It should be noted that even with two measurements per hour, day and night, the target of having 50% good measurements may be challenging if interpreted as a requirement of having at least one good measurement per hour, especially at night-time.

Cardiovascular Risk and the Threshold of Concern in Regard to Pressor Effect

The FDA draft guidance does not define one single threshold of concern, i.e., which effect level should be excluded to claim that a drug is devoid of any safety concern in regard to BP effects. At the FDA-Duke meeting, SBP effect levels between 1 and 4 mmHg were discussed and it was pointed out that there are many factors that may influence this threshold, such as patient population and the extent and duration of the BP effect. A study that was thoroughly discussed and used as an example on how to perform ABPM studies was the Precision-ABPM study[15]. The Precision study compared the cardiovascular safety profile of three non-steroidal anti-inflammatory drugs – celecoxib, naproxen and ibuprofen – in more than 24,000 patients with osteoarthritis or rheumatoid arthritis with increased cardiovascular risk, by looking at the rates of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke during more than two years' follow-up[19]. The ABPM sub-study enrolled 444 patients, who were randomly assigned to each of the three drugs and underwent an ABPM session at baseline and after four months' treatment. Celecoxib did not have an effect on the mean 24-hour BP, in contrast to ibuprofen that exhibited a small, 3.7 mmHg effect on SBP (Figure 2, Panel A). Obviously, the ABPM sub-study was not powered to evaluate the effects on cardiovascular end points, but these were numerically fewer in patients treated with celecoxib (n=7) as compared to patients on ibuprofen (n=9). In the larger study, celecoxib was non-inferior to ibuprofen and to naproxen in terms of cardiovascular events after 30 months' treatment (Figure 2, Panel B).

In the recent publication by FDA staff who presented at the meeting, the threshold of regulatory concern was further discussed and some interesting examples from approved drugs were given[14].

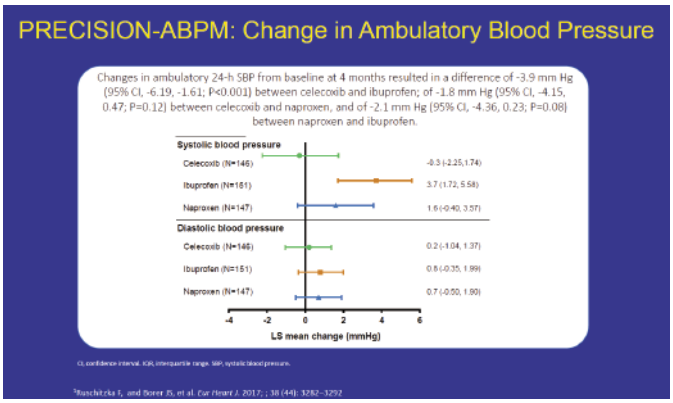

Figure 2, panel A: Change-from-baseline systolic blood pressure measured by ABPM in the PRECISION-ABPM study. Four months treatment with celecoxib did not have an effect on mean SBP over 24 hours, whereas ibuprofen caused a statistically significant increase of 3.7 bpm. Source:[21]

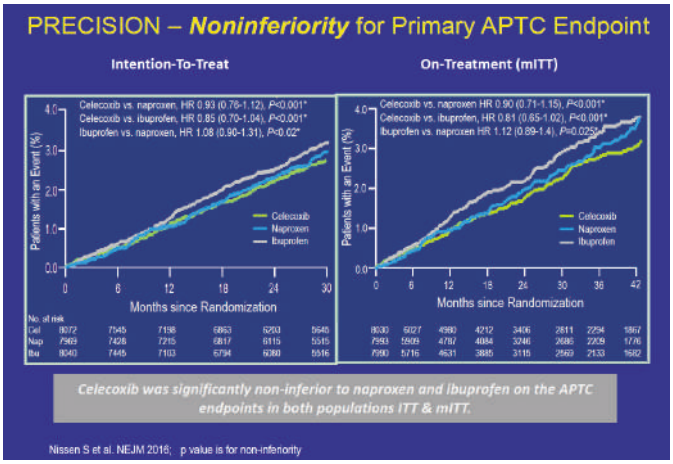

Figure 2, Panel B: In the main PRECISION study (19), celecoxib was non-inferior to ibuprofen and naproxen in terms of the primary composite outcome in the time-to-event analysis, i.e., the first occurrence of an adverse event that met APTC criteria (death from cardiovascular causes, including haemorrhagic death; non-fatal myocardial infarction; or non-fatal stroke), with a p value of <0.001 for both comparisons. Source:[21] *APTC: Antiplatelet triallists collaboration.*

Bremelanotide is indicated for treatment of generalised hypoactive sexual desire disorder in premenopausal women. In an ABPM study, it was shown that the drug was associated with a transient, small effect on SBP of 3 mmHg within eight hours of dosing and thereafter returning to baseline. This effect level in a population with low cardiovascular risk should be of little concern. On the other hand, drugs with a more pronounced, albeit transient effect, can be of concern in a vulnerable population. Esketamine nasal spray, approved in conjunction with oral antidepressants for treatment-resistant depression, caused a mean increase of SBP of 7 to 9 mmHg, which lasted for four hours. However, in 8% and 17% of patients the increase of SBP and/or diastolic blood pressure (DBP) was larger than 40 and 25 mmHg at least once within the first 1.5 hours post-dose. Therefore, the label advises prescribers under Warning and Precautions that '*patients with cardiovascular and cerebrovascular conditions and risk factors may be at an increased risk of associated adverse effects*'. Small, but chronic effect may also be of concern when indicated in patients at a relatively high cardiovascular risk. APBM studies in men have shown that some testosterone replacement products, e.g., testosterone undecanoate and testosterone enanthate, caused a 5 mmHg and 4 mmHg mean effect on SBP, respectively, throughout the day. Since these products may be taken by older men with age-related low testosterone levels and with a high cardiovascular risk, there is a black box warning in regard to the risk of major adverse cardiovascular events, including non-fatal myocardial infarction, non-fatal stroke and cardiovascular death.

Practical Considerations for ABPM in Obese Subjects

Many patients struggle to tolerate ABPM monitoring. Wearing the device for 24 hours, even when placed on the non-dominant arm, is inconvenient, usually causes sleep disturbance and can be uncomfortable. As with any population, accurate blood pressure monitoring requires proper upper arm measurement and cuff size assignment. Incorrect sizing can lead to inaccurate BP results, poor cuff positioning, slipping, inflation failure or unnecessary discomfort. While the patient is instructed not to remove the cuff anytime during the monitoring period, patients often do to rest their arm, especially when struggling to sleep or during their morning routine.

Obese patients in particular struggle with compliance. Big cuffs on big arms mean longer inflation and deflation times. While cuffs may be adjusted slightly to better fit the upper arm shape, it can be difficult to properly fit conically shaped arms. Hyper-inflation and inflation repeats are more frequent as the ABPM device tries to detect the systolic signal on larger and conically shaped arms, resulting in more discomfort. Another common complaint is excessive sweating on the cuffed arm, especially during summer months. All these factors explain why compliance challenges are more frequent in an obese population.

There are ways to help mitigate these issues and good compliance starts with good patient coaching. Site staff need to take the time to sit with the patient, explain the experience and set expectations in a realistic way. Allow the patient time to practise wearing the cuff and practise repositioning and self-applying the cuff. Disposable cuff barriers can help alleviate excessive sweating and position shifting. Applying surgical tape on cuff edges can be used to reduce skin chafing on obese or skin-sensitive arms. Utilise cuffs that have a D-ring to enable self-application. When the patient returns to the clinic at the end of the monitoring period, blood pressure results should be reviewed immediately to assess whether there are a sufficient number of measurements to constitute a valid session, e.g., more than 50% of expected measurements.

Discussion

The FDA guidance *Assessment of Pressor Effects of Drugs* has been debated within the agency for several years and it is not yet clear whether it will be universally applied across all therapeutic areas. The fact that an IRT for BP studies now has been established is however, in our view, a clear indication that the guidance is progressing and will be finalised within a foreseeable future. Meanwhile, it seems likely that there will be specific requests from the FDA forthcoming, and to-date we have seen such requests for development programmes of drugs intended for long-term treatment of non-alcoholic steatohepatitis (NASH) and type 2 diabetes mellitus; indications that are highly relevant for the obese population. Additionally, individual sponsors have proactively chosen to perform such an evaluation in selected development programmes.

For drugs intended for more than 12 weeks' use, ABPM sessions should be performed in the targeted patient population. In each patient, one valid ABPM session will be needed at baseline and one on-treatment at anticipated pharmacodynamic steady state, e.g., after four, eight or 12 weeks' treatment. Given the numbers needed to exclude a small effect on BP (see below) and the population, it is advisable to place the BP evaluation in a Phase II study. An ABPM session is relatively cumbersome for the patient and sponsors should strive to utilise a strategy to minimise the number of patients with missing data; this can be achieved through education and training of sites and of patients, but also by performing the sessions in a way that will allow repeat of failed sessions. The baseline session can therefore be performed during the screening period, well in advance of the days immediately before the first dose, with the option to repeat just before the first day of dosing; the same applies for the on-treatment session, which in a Phase II study can be placed at, e.g., four or eight weeks, with the option to repeat at 12 weeks. In support of this approach, the site should have the capability to immediately view the quality of the ABPM session to determine whether a session contains an acceptable number of acceptable measurements. It remains to be seen how strictly the criterion on having at least one measurement per hour, especially at night-time, will be implemented by the FDA.

The power of an ABPM study is driven by the underlying effect of the drug, the observed variability and which effect level needs to be detected or excluded. In FDA's research database, the observed variability, measured as the standard deviation of the change-from-baseline SBP (ΔSBP) was between 8.5 mmHg for mean 24 hour SBP and 11.6 mmHg for the night-time mean SBP. This is also consistent with our internal experience and a published sample size calculation for an ABPM study[20]. With this as a basis, the sample size of ABPM studies can be estimated across different effect levels on BP. For a drug with no BP effect at all (assumed underlying effect of 0 mmHg), a sample size of 122 subjects per group in a parallel designed study will provide 90% power to exclude a 3 mmHg drug effect, i.e., the upper bound of the 1-sided 95% confidence interval (CI) of the placebo-corrected ΔΔSBP will fall below 3 mmHg. Table 1 provides sample size calculation for SD of ΔSBP between 8 and 12 mmHg to achieve a power of 80% and 90%, respectively.

	Standard deviation of ΔBP (mmHg)		
Power to exclude 3 mmHg drug effect on SBP (or DBP)	***8***	***10***	***12***
80%	89	138	199
90%	122	191	275
Power to exclude 5 mmHg drug effect on SBP (or DBP)			
80%	32	50	72
90%	45	69	99

*Table 1. Sample size per group required to exclude an effect of 3 or 5 mmHg change for SBP or DBP**

**: The upper bound of the 2-sided 90% confidence interval of ΔBP falls below 3 mmHg; based on the assumption of no underlying BP effect of the drug. ΔBP: Change-from-baseline of 24-hour mean blood pressure; SBP: Systolic blood pressure; DBP: Diastolic blood pressure;*

We encourage sponsors to think proactively in terms of BP evaluation, particularly in therapeutic areas in which the target patient population, or subgroups thereof, may be seen as vulnerable. Drugs intended for long-term use in young, relatively healthy patients may face less scrutiny than drugs intended for older patients with multiple risk factors for cardiovascular disease and stroke. In such cases, it is advisable to rule out that a new drug has a pressor effect, and to perform this evaluation strategically, which in most cases will mean during Phase II, and well before entering into pivotal, confirmatory trials.

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