The impact of therapeutic inertia on long-term blood pressure control: a Monte Carlo simulation study

Alexandry Augustin[1], Louise Coutts[1], Lorenzo Zanisi[1], Anthony S Wierzbicki[2], Francesco Shankar[1], Phil J Chowienczyk[2,3], Christopher N Floyd[2,3]

[1] School of Physics and Astronomy, University of Southampton
[2] Guy's & St Thomas' NHS Foundation Trust, London
[3] King's College London British Heart Foundation Centre, School of Cardiovascular Medicine and Sciences, King's College London

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Correspondence to:
Dr Christopher N Floyd
Clinical Research Facility,
4th Floor, St Thomas' Hospital,
London,
SE1 7EH
Email: christopher.floyd@kcl.ac.uk

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Abstract

Antihypertensive drug treatment is based on stepped titration in response to elevated blood pressure (BP) measurements. However, measurements do not necessarily represent an individual's true BP (due to random error and biological variability) and medications are not always increased when measurements are above target (therapeutic inertia).

We developed a Monte Carlo model with a 10-year horizon to investigate how measurement error impacted systolic BP (SBP) control in the presence of therapeutic inertia. When SBP measurements were in the range 140-159 mmHg, the probability of escalating treatment was determined by a Bernoulli probability mass function parameterised by weighting functions exploring distinct inertia profiles.

Simulating inertia with the weighting function that approximated to clinical practice resulted in ~50% of individuals failing to achieve their SBP target within the 10-year time horizon. An inverse relationship was observed between measurement error and SBP control. This suggests that the value of accurate SBP measurement is only realised if it changes the underlying probability of inertia - i.e. patients/clinicians believe a measurement to be accurate and so are more likely to act upon it. Removal of inertia during treatment initiation (i.e. stepped titration until SBP measurement was below target) improved true SBP control for all simulations.

Our simulations show that the impact of therapeutic inertia during treatment initiation persists during long-term follow-up. Strategies to remove therapeutic inertia during treatment initiation (i.e. dual antihypertensive therapy) are likely to improve long-term BP control irrespective of BP measurement technique.

Keywords: Hypertension, Blood Pressure, Monte Carlo Method, Modelling, Uncertainty, Antihypertensive Agents

Introduction

The importance of achieving blood pressure (BP) control is well-established, as individuals with uncontrolled hypertension remain at an increased risk of fatal and non-fatal cardiovascular disease (CVD) events [1]. Despite recognition of the importance of BP-lowering, global rates of achieving BP control are as low as 15-20% when the target is set to <140/90 mmHg [2, 3]. The reasons for poor BP control are multi-factorial and include healthcare models, the logistics of delivery and, especially in low and medium income countries, structural issues and socio-economic challenges leading to poor access to healthcare. In more developed healthcare settings, a failure to achieve higher rates of BP control commonly arise due to individual decisions not to increase antihypertensive medication, despite evidence suggesting that an individual's BP is uncontrolled [4-6].

'Clinical inertia' was first described in 2001 as a "*failure of health care providers to initiate or intensify therapy when indicated"* in relation to chronic and often asymptomatic conditions such as hypertension, dyslipidaemia and diabetes mellitus [7]. The concept has since been explored across the medical spectrum, with the term 'therapeutic inertia' now more widely used in the field of hypertension [8]. Whilst there are many situations where such a decision is clinically appropriate to not increase an individual's antihypertensive medication despite their measured BP being above target, often arising from an informed discussion between patient and clinician, it is recognised that factors such as physician education, disjointed healthcare delivery and reimbursement models all contribute [9]. However, for those individuals in whom antihypertensive medication is eventually increased, delays of more than 1.4 months in implementing treatment escalation are associated with adverse CVD outcomes [10].

Retrospective cohort studies have attempted to model therapeutic inertia to both understand its components and to predict which patients are at greater risk. Factors such as older age, number of co-morbidities, number of antihypertensive medications, visit frequency and closeness to target BP are all inversely correlated with medication escalation [5, 6, 11]. However, attempts to combine these factors into a prediction model have had little success, as how these factors influence visit-to-visit decision making for an individual are unknown. One predictive model used data from 2,595 patients over 13,792 visits and could only explain 25% of variability in therapeutic inertia, with visit characteristics (measured BP and current antihypertensive regimen) contributing 19% [5].

It is recognised that BP is a variable biomarker and that accurate measurement is essential for the diagnosis and management of hypertension [12-14]. However, even the most accurate non-invasive measurement techniques are unlikely to provide an accurate estimation of an individual's true BP due to the presence of random measurement error and physiological variability. As therapeutic decisions with regard to initiation and/or escalation of treatment are mainly based on a measured BP, measured BP is the main determinant of inertia [5, 11, 15]. We have previously used Monte Carlo simulations to show that measurement error has a substantial impact on the proportion of individuals who achieve short-term BP control in the absence of therapeutic inertia [16]. This approach was inspired by methods used in the astrophysical domain to study the impact of model interpretation against given data sets, when accounting for diverse observational uncertainties [17]. Here we evaluate how therapeutic inertia impacts both short- and long-term BP control in the presence of measurement error and consider strategies to improve BP control.

Methods

The data that support the findings of this study are available from the corresponding author upon reasonable request. The structure of the Monte Carlo model used is shown in **Figure 1**. To simulate long-term hypertension management, the simulations were run for multiple cycles each of which represented one year. These were divided into a short treatment initiation phase (cycle 1) and a prolonged follow-up phase (cycles 2-10). Within each cycle individuals could undergo any number of treatment steps, each of which represented the addition of an antihypertensive medication.

Individuals entered cycle 1 with a pre-treatment true SBP ($tSBP_n$; a hypothetical measurement made without error or physiological variability) and received a single antihypertensive medication. An individual's post-medication true SBP ($tSBP_{n+1}$) was calculated by sampling from a Gaussian probability density function defined by the expected mean tSBP reduction ($drug_{eff}$) and its standard deviation (SD; σ_{drug}) [18]. A truncated distribution was selected so that the addition of antihypertensive medication could not increase tSBP.

Further treatment decisions were based on an individual's measured SBP (mSBP). This value was sampled from a Gaussian probability density function defined by tSBP and the SD of the measurement error (σ_{meas}). Where measured SBP (mSBP) was below target (<140 mmHg), no further medication was added, and the individual progressed to the next cycle. Where mSBP was above target (≥140 mmHg) additional medication was considered based on the probability density functions described below. Individuals remained in a cycle, progressing through treatment steps, until either mSBP<140 mmHg or a decision was made not to increase medication. In the follow-up phase, cycles 2-10 all started with the generation of a

mSBP value based on the tSBP value carried over from the end of the previous cycle. Further details of the model are presented in the **Online Supplement**.

For the base case, all individuals entered the simulation with a pre-treatment tSBP 160 mmHg; a value chosen as it would likely lead to treatment initiation irrespective of cardiovascular risk [19-21]. The SD of the measurement distribution (σ_{meas}) was set to 10 mmHg as this approximates to variability in clinical measurements [11, 22]. Simulations were run for ten cycles in a population of 1000 individuals over 15 repetitions. It is an assumption of the model that all individuals have the potential to achieve tSBP control and do not have an underlying secondary cause or true resistant hypertension [23].

Modelling therapeutic inertia

Individuals with 140≤mSBP<160mmHg were determined to be 'at risk' of therapeutic inertia [5, 11]. Treatment decisions within this mSBP range were modelled with a Bernoulli probability mass function which essentially distilled treatment decisions to a coin toss, where the probability of heads or tails (treatment or no treatment) was conditioned on mSBP. Probability to receive the treatment escalation was

$$\text{Treatment} \sim \text{Bernoulli}\,(p|\text{mSBP}).$$

The probability of no treatment escalation for an individual was $1-p$. We introduced a weighting function $f: \mathbb{R}^+ \to [0,1]$ that mapped mSBP to a probability of receiving a treatment such that

$$p = \begin{cases} 0 & \forall \text{mSBP} < 140, \\ f(\text{mSBP}) & \forall \text{mSBP} \in [140,160], \\ 1 & \forall \text{mSBP} > 160. \end{cases}$$

As there is uncertainty in how to characterise therapeutic inertia, we compared five different functional forms for the weighting function *f* which were selected based on clinical experience and to examine the sensitivity of the analysis to the form of the function. These are shown graphically in **Figure S2**.

1. The *"hard"* case $f(\text{mSBP}) = 1$ where all individuals were treated (i.e. no inertia).
2. The *"constant"* case $f(\text{mSBP}) = 0.5$ where there was a 50% chance of treatment.
3. The "*linear*" case $f(\text{mSBP}) = \frac{\text{mSBP}}{160-140} - 7$ where the probability of treatment monotonically increased linearly with mSBP.

4. The "*quadratic*" case $f(\mathrm{mSBP}) = \left(\frac{\mathrm{mSBP}-140}{160-140}\right)^2$ where the probability of treatment monotonically increased with the square of mSBP.

5. The *"quartic"* case $f(\mathrm{mSBP}) = \left(\frac{\mathrm{mSBP}-140}{160-140}\right)^4$ where the probability of treatment monotonically increased with the fourth degree of mSBP.

Sensitivity analyses and strategies to reduce therapeutic inertia

Sensitivity analyses were run to determine how SBP control was affected by different pre-treatment tSBP values (150, 160 and 170 mmHg) and the presence of a white coat effect through shifted or skewed Gaussian distributions. Subsequently, three strategies were employed to investigate their impact on therapeutic inertia. Firstly, the impact of measurement error was investigated (σ_{meas} 5, 10 and 15 mmHg). These values do not correspond to specific measurement techniques, but rather potential within-individual distributions when a particular measurement technique is used. However, lower values of measurement error are more likely to correspond to home or ambulatory BP measurement. Secondly, during the follow-up phase a second mSBP measurement was made when the first was ≥140 mmHg, with the decision whether to escalate medication based on this second value. This approach represented increased reluctance to escalate antihypertensive medications when control had previously been achieved. Finally, the simulations were run with therapeutic inertia functions only applied to the follow-up phase (cycles 2-10). This analysis represented patients and clinicians being more likely to escalate therapy if BP control had not previously been achieved.

Statistical outputs

The Monte Carlo simulations were used to estimate the proportion of individuals who appeared to achieve SBP target (mSBP<140 mmHg) according to UK guidelines [21], the proportion who actually achieved SBP target (tSBP<140 mmHg), the proportion who were overtreated (tSBP<120 mmHg), mean tSBP and the number of antihypertensive medications. Mean data are presented in the text, with a 95% confidence level (mean±1.96*SD).

Results

Therapeutic inertia reduced the proportion of individuals who achieved both measured and true SBP targets during stepped initiation of antihypertensive medications (**Figure 2**). In the absence of therapeutic inertia (the hard case), all individuals achieved mSBP<140 mmHg, but only 53.5% achieved tSBP<140 mmHg. The curves plateau as individuals exit the simulation. The quartic function had the greatest effect on tSBP control, with only 5.5% achieving tSBP<140 mmHg during initial medication titration.

Beyond the treatment initiation phase (cycle 1), the simulation demonstrated that therapeutic inertia had a substantial effect on the proportion of individuals who achieved long-term SBP control (**Figure 3**). In the absence of therapeutic inertia (the hard case), all individuals achieved tSBP<140 mmHg by cycle 10, with a mean tSBP 124 mmHg on 4.4 antihypertensive medications. For the quartic case, only 55.0% achieved tSBP<140 mmHg, with mean tSBP 135 mmHg on 2.5 medications. Only the hard case resulted in a non-negligible percentage of the population being overtreated (19.6% tSBP<120 mmHg), with all other functions <5% by cycle 10. Sensitivity analyses showed consistent results irrespective of pre-treatment tSBP (**Figure S4**). Simulation of a white coat effect increased both the proportion who achieved tSBP<140 mmHg, and the proportion who were overtreated (tSBP<120 mmHg) (**Figure S6).**

Impact of measurement error

In the absence of therapeutic inertia, the degree of measurement error applied did not substantially affect the proportion of individuals who achieved tSBP<140 mmHg by cycle 10 (the hard case; **Figure 4**). However, tSBP target for the inertia-free population was reached more slowly as measurement error increased. Additionally, lower measurement error resulted in fewer medications (cycle 10, 3.7 versus 5.0) and less overtreatment (cycle 10 tSBP<120 mmHg, 0.3% versus 48.2%; **Online Supplement**).

When therapeutic inertia was simulated (all other cases), measurement error was inversely associated with the proportion who achieved tSBP target (**Figure 2**). For the quartic function, 15.9% achieved tSBP<140 mmHg with low measurement error, compared to 80.2% with high error. This difference was without a clinically meaningful increase in overtreatment (0.0% versus 1.8% tSBP<120 mmHg) despite additional antihypertensive medications (1.9 versus 3.1 medications).

In all analyses, therapeutic inertia did not only impact the proportion of individuals who achieved tSBP target, but also the degree to which the target was missed (**Figure 4**). The quartic function consistently resulted in higher mean tSBP across all cycles irrespective of measurement error.

Strategies to reduce therapeutic inertia

Adding the requirement for repeat elevated measurements before treatment escalation in the follow-up phase (cycles 2-10) resulted in a reduced proportion achieving tSBP target for all simulations (**Table 1 and Figure 5**). Conversely, removal of therapeutic inertia from treatment initiation (cycle 1) increased the proportion who achieved long-term tSBP control

by cycle 10 and reduced the impact of measurement error. When both strategies were implemented simultaneously (removal of inertia during treatment initiation and adding repeat measurments during follow-up), long-term tSBP control was worse than removal of inertia as a single intervention. For all strategies the mean tSBP in individuals who were above target was less than 145 mmHg for the quartic case by cycle 10 (**Table 1**).

Discussion

In this study we model the long-term impact of therapeutic inertia on SBP control, and investigate strategies to mitigate it. The Monte Carlo simulations expand on our previous findings that measurement error impacts short-term SBP control [16]. Here we extended the time horizon beyond treatment initiation and into a prolonged follow-up phase, which approximates to 10 years assuming annual review [21]. In the absence of therapeutic inertia, the titration algorithm resulted in almost all individuals achieving tSBP control, irrespective of measurement error. SBP measurement made with lower error resulted in SBP target being achieved faster for the inertia-free population (the hard case) and as a consequence would be expected to improve CVD outcomes [18, 24].

The addition of therapeutic inertia to our model had a substantial impact on the proportion of individuals who achieved both short- and long-term tSBP control, and altered the impact of measurement error on these outcomes. Our simulations suggest that for individuals with a pre-treatment tSBP of 160 mmHg, almost half will not achieve their tSBP target despite 10-year follow-up.

We simulated therapeutic inertia using a Bernoulli probability function which provided a number of advantages beyond the recognition that mSBP is the strongest determinant of therapeutic inertia [5, 11]. Firstly, it enabled decisions to be made for each individual at each visit rather than determining allocation at a population level. Secondly, it intrinsically simulated the 'unknown' factors which contribute to therapeutic inertia as the probability of each decision was independent of past and future decisions. Finally, as the relationship between mSBP and treatment decisions are poorly characterised (studies generally consider SBP in coarse bands of ≥10 mmHg) it enabled five different weighting functions to be

investigated. The functions applied tested a number of hypothetical decision-making strategies including immediate intervention when above threshold (the hard case), an intervention allowing for a fixed 20 mmHg variability in SBP (the constant case), and three higher-order models based on a linear or more complex interpretation (the quadratic and quartic cases) of SBP-led decision making. Whilst it is unlikely that any individual function can accurately describe the complexities of therapeutic inertia, all of the functions may apply some of the time. Critically, all functions investigated broadly reached the same conclusions.

The implications of therapeutic inertia

The value in the approach we have used here is that it enables the exploratory investigation of treatment strategies without either the expense or time-delay inherent to randomised controlled trials (RCTs). To better understand the implication of therapeutic inertia on SBP control we explored three different strategies.

Firstly, we investigated how measurement error affected SBP control across the different weighting functions. It is universally accepted that accurate measurement of blood pressure is essential for the diagnosis and management of hypertension [12-14]. It was therefore surprising to find that measurements made with high error resulted in improved SBP control compared to those made with low error. Approaches to minimise measurement error will therefore not necessarily improve BP control unless they simultaneously alter the therapeutic inertia probability function. Practically, this would involve clinicians and patients having increased confidence in readings - i.e. that mSBP≥140 mmHg truly represented uncontrolled hypertension. In other therapeutic areas this has been achieved by altering the

diagnostic markers used (e.g. glycosylated haemoglobin versus plasma glucose). In hypertension, this could be achieved though repeated blood pressure measurements in an individual to provide an understanding of their personal mSBP distribution. Where the mSBP distribution is narrow, both clinician and patient may be more confident that mSBP values which are only marginally above target represent uncontrolled tSBP and the consequent probability of therapeutic inertia decreased. This approach compares to current practice where clinicians are more likely to consider the population variance of a technique, rather than its application for a given individual.

Secondly, we implemented more stringent criteria for adding additional medications during the follow-up phase. In the base case, an increase in antihypertensive medications was considered when a single SBP measurement was ≥140 mmHg. This approach however suggested that both clinicians and patients would consider acting on a single elevated measurement when control appeared to have been achieved previously. To reflect clinical uncertainty in measurements we now required two elevated measurements before treatment escalation was considered [20]. This reduced the proportions who achieved their BP target, but also reduced the proportion overtreated.

Thirdly, we investigated the impact of removing therapeutic inertia from the treatment initiation phase (cycle 1) and applying only to the follow-up phase (cycles 2-10). This strategy had a profound impact, improving 10-year tSBP control across all simulations without a substantial impact on the proportion overtreated.

Finally, we considered how both removing therapeutic inertia during treatment initiation and requiring consecutively elevated measurement during follow-up would impact on simulation outcomes. This approach achieved less BP control that removing therapeutic

inertia alone, but resulted in fewer individuals being overtreated. It may therefore be a suitable strategy for those more at risk of hypotension.

Limitations of the model

There are inherent limitations when trying to apply the results from simulations to real-world scenarios. The predictive ability of a model is dependent on its architecture and input data, yet each additional model input risks introducing systematic error (random error is intrinsic to Monte Carlo simulations) which can be propagated and amplified through repeated cycles. It is for this reason that we selected mSBP as the sole determinant of therapeutic inertia. However, similar to previous models which view therapeutic inertia as a continuous positive percentage [5], this approach did not consider the impact of hypotension and antihypertensive de-escalation.

The major assumption within the model was that the distribution of mSBP for each individual was Gaussian with the mean defined by tSBP. Depending on measurement method (e.g. office versus home) this might not be the case due to a white-coat or masked effect. Sensitivity analyses using alternative mSBP distributions maintained the benefit from removing inertia during the treatment initiation phase.

There are a number of limitations in relation to the simulated population. Firstly, all individuals have the capacity to achieve tSBP<140 mmHg if given sufficient antihypertensive medications. The simulations therefore do not consider the small proportion of individuals (<5%) who have uncontrolled hypertension despite confirmed medication adherence [23]. Secondly, the BP-lowering effects of antihypertensive medications are based on aggregated RCT data and so cannot necessarily be directly applied to a real-world population [25]. We

did not explicitly model incomplete medication adherence due to the high number of assumptions which would be required; adherence is often class specific and variable, with pharmacokinetic/pharmacodynamic relationships critical to the interaction between adherence and mSBP values [26-28]. However, as single tablet combination therapies have been shown to increase medication adherence [29], the clinical implications of this work are unlikely to be substantially affected.

Despite these limitations, the quartic weighting function appears to reflect clinical practice within the UK, as the cycle 10 data for this case most closely corresponds to clinical outcomes [30].

Perspectives

Our simulations have demonstrated how the random error intrinsic to SBP measurement impacts long-term SBP control in the presence of therapeutic inertia. Whilst the choice of weighting function did determine the proportion who achieved their SBP target (i.e. worse long-term control where probability of no treatment was higher) there was agreement in which strategy was most effective at mitigating its impact. Removal of therapeutic inertia from the treatment initiation phase (i.e. stepped titration until SBP measurement below target) improved both short- and long-term SBP control across all simulations. Furthermore, such an approach removed much of the variability associated with measurement error. This could be achieved without substantially changing current practice, since initiating dual antihypertensive therapy effectively removes the potential for therapeutic inertia when compared to stepped titration of monotherapy [29, 31].

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Disclosures

None

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Novelty and Significance

What is New?

- We have assessed the impact of therapeutic inertia on long-term blood pressure (BP) control, and investigated how the inherent variability of BP measurement affects treatment decisions.
- This study used Monte Carlo modelling to simulate repeated clinical encounters in which BP measurements were made with random error, and subsequent treatment decisions were based on probabilistic functions conditioned to the measurement value.
- Strategies to mitigate the effects of therapeutic inertia and measurement error were explored.

What is Relevant?

- The presence of therapeutic inertia during the initial titration of antihypertensive therapy impacts the proportion of individuals who achieve their long-term BP target.

Summary

This newly developed Monte Carlo model suggests that strategies to remove therapeutic inertia from medication initiation (such as dual antihypertensive therapy) are likely to improve long-term BP control irrespective of BP measurement technique.

Figure Legends

Figure 1: Model structure.

Within each cycle individuals underwent successive treatment steps until mSBP<140 mmHg or a decision was made not to increased medication.

[mSBP: measured systolic blood pressure; tSBP: true systolic blood pressure; σ_{meas}: standard deviation of measurement error; $drug_{eff}$: mean drug response; σ_{drug}: standard deviation of drug response]

Figure 2: **Impact of therapeutic inertia on short-term systolic blood pressure (SBP) control.**

Each individual exited the simulation once mSBP<140 mmHg, or a decision was made not to increase medications. 'Treatment Step' represents the number of medications for individuals who remain in the simulation. All other input parameters as per base case. Data plotted for cycle 1 only (treatment initiation phase) and shown as mean with a 95% confidence level.

[mSBP: measured SBP; tSBP: true SBP]

Figure 3: Impact of therapeutic inertia on long-term blood pressure control.

All input parameters as per base case. Data plotted as mean with a 95% confidence level.

[tSBP: true systolic blood pressure]

Figure 4: Interaction between measurement error and therapeutic inertia on long-term blood pressure control.

Columns represent different values for measurement error (σ_{meas}). Bottom row splits population based on whether tSBP is above or below target at each cycle. All other input parameters as per base case. Data plotted as mean with a 95% confidence level. [tSBP: true systolic blood pressure]

Figure 5: Strategies to reduce the impact of therapeutic inertia.

Columns represent different values for measurement error (σ_{meas}). Top row: Escalation decisions based on repeat systolic blood pressure measurement during follow-up phase (cycles 2-10). Middle row: Removal of therapeutic inertia during medication initiation phase (cycle 1). Bottom row: simultaneous implementation of both strategies described. All other input parameters as per base case. Data plotted as mean with a 95% confidence level. The full set of simulation outputs are presented in the **Online Supplement**. [tSBP: true systolic blood pressure]

Tables

Table 1: Reducing the impact of therapeutic inertia.

Output parameter	Measurement error (σ_{meas}) 5 mmHg	10 mmHg	15 mmHg
Base case scenario:			
tSBP<140 mmHg (%)	15.9	55.4	80.2
tSBP<120 mmHg (%)	<0.1	<0.1	1.4
Mean tSBP | tSBP≥140 (mmHg)	143	142	142
Therapeutic inertia reduction strategies:			
(i) Repeat measurements during follow-up (cycles 2-10)			
tSBP<140 mmHg (%)	13.7	39.8	59.2
tSBP<120 mmHg (%)	<0.1	<0.1	<0.1
Mean tSBP | tSBP≥140 (mmHg)	144	143	143
(ii) No therapeutic inertia during treatment initiation (cycle 1)			
tSBP<140 mmHg (%)	70.4	78.9	89.0
tSBP<120 mmHg (%)	<0.1	0.5	3.7
Mean tSBP | tSBP≥140 (mmHg)	142	142	142
(iii) No therapeutic inertia during treatment initiation (cycle 1) *and* repeat measurements during follow-up (cycles 2-10)			
tSBP<140 mmHg (%)	69.1	70.7	76.5
tSBP<120 mmHg (%)	<0.1	0.5	1.4
Mean tSBP | tSBP≥140 mmHg	142	142	142

Simulation parameters as per base case with the quartic case function applied. Data shown as population mean at cycle 10. [tSBP: true systolic blood pressure]