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REVIEW ARTICLE

'Under pressure': The role of therapeutic drug monitoring in the treatment of hypertension

Jorie Versmissen[1,2] | Job van Steenkiste[1,3,4] | Birgit C. P. Koch[1] | Laura E. J. Peeters[1,5]

[1]Department of Hospital Pharmacy, Erasmus MC, University Medical Centre Rotterdam, Rotterdam, the Netherlands

[2]Department of Internal Medicine, Erasmus MC, University Medical Centre Rotterdam, Rotterdam, the Netherlands

[3]Maasstad hospital, Department of Internal Medicine, Rotterdam, the Netherlands

[4]Department of Management Sciences, Open University Netherlands, Heerlen, the Netherlands

[5]Department of Hospital Pharmacy, Maasstad hospital, Rotterdam, the Netherlands

Correspondence
Laura E. J. Peeters, Department of Hospital Pharmacy, Erasmus University Medical Centre, Postbus 2040, 3000 CA Rotterdam, the Netherlands.
Email: lejpeeters@gmail.com

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Abstract

Antihypertensive drugs do not qualify as optimal candidates for therapeutic drug monitoring (TDM), given their obvious physiological effect, the absence of a clear relationship between drug concentrations and pharmacodynamic outcomes and their wide therapeutic range. However, since non-adherence is a major challenge in hypertension management, using drug concentrations can be of value to identify non-adherence as a first step towards better blood pressure control. In this article we discuss the key challenges associated with measuring and interpreting antihypertensive drug concentrations that are important when TDM is used to improve non-adherence. Additionally, we elaborate on the role of TDM in optimizing antihypertensive drug treatment besides addressing non-adherence by highlighting its value in specific patient groups with altered pharmacokinetic parameters such as female *vs.* male or elderly patients.

KEYWORDS
adherence, antihypertensive drugs, hypertension, therapeutic drug monitoring

1 | INTRODUCTION

Over time, the cornerstone principles for the meaningful use of therapeutic drug monitoring (TDM) for medicines have been explicitly defined and include three specific recommendations.[1] First, TDM is useful for drugs where the efficacy cannot be measured by a physiological effect. Second, drugs that could benefit from TDM have a clear relationship between the dose, drug concentration in body material and pharmacodynamic outcomes. Lastly, drugs where TDM is applied usually have a narrow therapeutic range and a large inter-individual variation in drug concentrations.[2] None of these recommendations can be applied to antihypertensive drugs (AHDs). The efficacy of AHDs can easily be measured by monitoring blood pressure, there is no clearly determined relationship between dose and drug concentrations in blood and AHDs do not have a narrow therapeutic window.

Although these specific recommendations for TDM do not apply to AHDs, TDM can be a very effective tool to improve antihypertensive drug therapy.[3,4] Despite the availability of several categories of AHDs, each containing multiple drugs, a significant proportion of patients with hypertension remains poorly controlled.

Furthermore, some patients with poorly controlled blood pressure are diagnosed with so-called resistant hypertension. Resistant hypertension is defined as inadequate blood pressure control (office blood pressure >140/90 mmHg) despite the prescription of three AHDs including a diuretic or four or more AHDs in a maximal tolerable dose.[5] For a major part, this resistance to AHDs can be explained by non-adherence rather than real 'resistance' to therapy.[6,7] However, in clinical practice, non-adherence is frequently overlooked, and healthcare providers commonly overestimate patient adherence rates. Consequently, this results in increased prescriptions of AHDs and higher

dosages. Conversely, the greater the number of AHDs prescribed to a patient, the higher the likelihood of full or partial non-adherence.[8] This highlights the need for an alternative approach, with TDM emerging as a promising solution for achieving improved outcomes in such cases. Measuring drug concentrations is a reliable method to identify non-adherence, and identification is an important first step to improve adherence and consequently blood pressure regulation.[9] Other purposes for TDM of AHDs in clinical practice are limited up to the present.

Considering the high prevalence of hypertension,[10] a limited number of dosing regimens ('one size fits all') is most convenient, without the need for regular blood sampling for assessing efficacy and/or safety using TDM. This approach has led to the introduction of most AHDs without extensive knowledge of normal drug levels and their variability.[4] In this article, we describe the pitfalls, challenges and applicability of TDM for AHDs with a focus on its role in improving adherence. Additionally, we briefly discuss other purposes for TDM in hypertension such as its use in optimizing antihypertensive drug treatment in specific subgroups.

2 | TDM TO ASSESS NON-ADHERENCE IN HYPERTENSIVE PATIENTS

Hypertension is a major risk factor for ischaemic heart disease, kidney damage and stroke.[5] Treatment of hypertension is therefore often initiated directly after diagnosis, depending on the initial blood pressure levels and the presence of other cardiovascular risk factors like age, presence of diabetes, smoking, sex and cholesterol levels that all in itself contribute to a 10-year risk of developing cardiovascular disease.[11]

Guidelines recommend five different drug classes as the basis of antihypertensive treatment strategies: angiotensin converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), beta-blockers (BBs), calcium channel blockers (CCBs) and diuretics.[5,12] When patients are diagnosed with resistant hypertension, a comprehensive work-up is warranted including an assessment of adherence and additional diagnostics to investigate potential underlying causes.

Moreover, the identification of non-adherence in patients with (pseudo-)resistant hypertension might prevent the consideration of more expensive and/or experimental treatments.[7,13] For this specific purpose, recent hypertension guidelines acknowledged the use of TDM as a valid and objective method to assess non-adherence to AHDs.[5]

3 | MATRICES USED FOR TDM OF ANTIHYPERTENSIVES

The assessment of AHDs through TDM offers valuable insights into treatment efficacy and patient adherence. Multiple laboratories can measure AHDs, using various matrices, primarily urine and blood plasma, for this purpose. The choice of matrix depends on the drugs being measured, with each matrix having its advantages and disadvantages. For diuretics, there is a small advantage of urine considering the longer time window of detection. For other AHDs, blood plasma measurements are more specific, especially in the case of low bioavailability or limited renal excretion of the drug.[14] Other matrices, like hair and saliva, have been described but clinical application is still limited.[15]

To increase the applicability of TDM, alternative sampling methods are currently being investigated. Multiple studies report the development of a dried blood spot (DBS) test or volumetric absorptive microsampling (VAMS) using whole blood obtained by a fingerprick (Table 1).[16–24] The main advantage of this method is its ease of use: the blood spot can be obtained anywhere anytime by either a healthcare provider or even the patient themselves.[25] The primary challenge that can arise from using DBS is accurately measuring numerous drugs from a single blood spot, especially at their lowest concentrations. Measuring at low concentrations is hampered due to the small volumes of material that are used with DBS.[26] Also, quantification is

TABLE 1 Overview of available studies that developed and validated an analytical method to assess non-adherence to more than one different antihypertensive drug using a dried blood spot method.

Article	Sampling method	Number of AHDs included in analysis [metabolites]	Analytical validation according to guidelines (FDA, EMA) YES/NO	Clinical validation according to guidelines[40] YES/NO
Bernieh et al., 2017[53]	DBS	8	FDA, EMA	NO
Kim et al., 2019[20]	DBS	9	FDA	NO
Peeters et al., 2020[16]	DBS	8 [4]	EMA	YES
Peeters et al., 2022[17]	DBS	12 [4]	EMA	NO
Rao et al., 2011[24]	DBS	3	NO	NO
Tanna et al., 2014[19]	DBS	3 [1]	FDA	NO
Tanna et al., 2015[18]	DBS	5	FDA	NO
Uribe et al., 2019[23]	DBS	2	NO	NO
Jacobs et al., 2021[21]	VAMS	10	EMA	YES
Jacobs et al., 2023[22]	VAMS	7	EMA	YES

Abbreviations: AHDs = antihypertensive drugs, DBS = dried blood spot, EMA = European Medicines Agency, FDA = Food and Drug Administration, VAMS = volumetric absorptive microsampling.

sometimes more difficult due to two main factors. Firstly, incorrect sampling procedures can introduce significant errors. Secondly, the extensive work-up process increases the likelihood of additional errors. Another limitation of the DBS method is that material is destroyed during the analysis, which makes re-analysis of a single blood spot impossible.[17]

When looking at the different matrices, plasma is the most convenient to measure as many AHDs as possible, hair is the most convenient method to assess non-adherence over time and saliva and blood sampling with a fingerprick are the most convenient sampling methods.[27] For adherence purposes focusing solely on detecting the presence or absence of a drug in the body, various matrices can be used interchangeably as long as they are capable of measuring drug concentrations at least 24 h after intake.[16]

4 | INTERPRETATION OF ANTIHYPERTENSIVE DRUG CONCENTRATIONS IN BLOOD

To interpret antihypertensive drug concentrations in blood for adherence purposes, it is vital to know something about the following subjects: (1) the different forms of non-adherence, (2) other methods to measure adherence that can be used in combination with TDM, and (3) the limitations of measuring drug concentrations for the identification of non-adherence and the pharmacokinetics of AHDs. All these subjects are discussed in the following subsections.

4.1 | Different forms of non-adherence

Non-adherence can exist in several forms and often varies during the treatment. Some patients occasionally miss a dose, while others omit several doses in a row, known as a drug holiday, or patients discontinue therapy entirely, known as non-persistence of therapy.[28] When using TDM to identify non-adherence, these different forms of adherence cannot be distinguished from each other. Therefore, the measured drug concentrations only represent a snapshot of the adherence at that particular time. A partial solution for this is increasing the frequency of measurements. Repeated measurements could provide more insight into a more subtle form of non-adherence and can partly cover the white-coat adherence problem. Also, the intra-patient variability of antihypertensive drug concentrations could be determined with repeated measurements, which could serve as an indicator of not taking medication as prescribed (usually once daily at the same time point).[29] It should be mentioned that this calculated intra-patient variability as a measure for non-adherence was already suggested for immunosuppressant therapy after transplantation, but although a high variability increased the risk of rejection, no clear relationship was found between the variability and adherence.[29,30] When samples are taken for TDM, it is essential to conduct simultaneous blood pressure measurements for the optimal interpretation of adherence.[31] With parallel measurements, blood pressure values represent the drug concentration at the exact moment of sampling and can therefore reveal white-coat adherence in patients and will refute the diagnosis of true resistant hypertension. This information will help healthcare providers to initiate a conversation to improve therapy.

4.2 | Optimizing adherence assessment with multiple methods

Even though multiple measurements can give an indication of non-adherence over time, white-coat adherence remains an issue. Therefore, the optimal approach to assess adherence to AHDs most likely involves a combination of different methods. For instance, a highly objective method like TDM combined with methods that determine adherence over time, like a medication event monitoring system (MEMS), adherence questionnaires or pharmacy refill data.[32] The decision regarding the choice of the additional method depends on the accuracy with which it can determine non-adherence, as well as the associated costs.[33] Although MEMS is one of the most accurate methods to determine adherence over time, the expensive nature of this device and other similar devices make them a less favourable choice for widespread implementation in clinical practice.[34]

A less expensive but still relatively objective method to measure adherence over time are pharmacy refill data. However, it remains necessary to carefully interpret the refill data and clear definitions on the definition of non-adherence are yet to be established.[35]

Lastly, the use of home blood pressure telemonitoring (HBPT) could be used as a second method besides TDM.[36] Currently, evidence is being gathered on the direct effects of HBPT on adherence of AHDs as measured by TDM.[37] However, modern day HBPT platforms not only allow for blood pressure monitoring, they offer various digital possibilities (like automated reminders, digital medication schedules) to improve adherence. Furthermore, patients included in a HBPT care pathway are usually managed by specialized nurses who are trained to provide targeted information to improve adherence in patients with off-target blood pressures.

4.3 | Limitations of measuring drug concentrations

If TDM is used to objectively determine non-adherence to AHDs, correct validation of the analytical method like a method using ultra-high-performance liquid chromatography–tandem mass spectrometry (UHPLC–MS/MS) as well as a clinical validation is crucial to minimize false positive and false negative results (Figure 1).[38,39] There are no specific guidelines for the set-up of a bioanalytical method for non-adherence and therefore the general guidelines for the validation of a bioanalytical method need to be used.[38,39] For the analytical validation, specific parameters are determined including selectivity, carry-over, lower limit of quantification (LLOQ), accuracy, precision, matrix effects and stability.

For the clinical validation, the concentrations measured with the new matrix are compared to the established matrix, typically plasma,

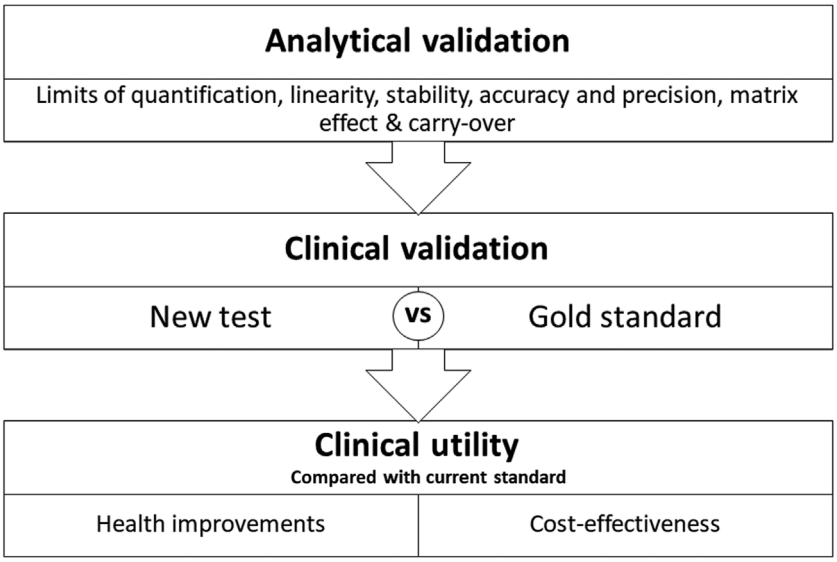

FIGURE 1 Steps that need to be completed and evaluated before implementation of a new assay in clinical practice can be carried out: analytical validation, clinical validation and clinical utility assessment.

and are sampled concurrently.[27] This comparison helps determine if the lower limit of detection (LLOD) in both methods yields consistent results. Prior clinical validation studies indicated that certain AHDs measured in plasma remained detectable for longer durations compared to concentrations measured from DBS.[4,16] However, this extended period spanned more than 1 day, thereby minimizing the risk of false accusations of non-adherence since at least one dose would have been missed during that timeframe. The guidelines for the clinical validation of DBS are established by the International Association for TDM and Clinical Toxicology (IATDMCT), but they make no distinction between the purpose of the measurement, as stated before.[40]

The validation methods outlined in these guidelines prove challenging when employing DBS as a sampling method, particularly in achieving accurate quantitative values across a broad concentration range for a large number of AHDs within a single UPLC-MS/MS run. On the other hand, for determination of longitudinal adherence, as mentioned before, it can be useful to measure exact drug concentration. Therefore, the purpose of the method should be considered when developing a TDM method for AHDs to identify non-adherence. An overview is given in Table 1 of studies measuring AHD concentrations in DBS. This overview shows that only a limited number of studies performed an analytical validation according to the guidelines for bioanalytical methods and even fewer performed a clinical validation. Because of this lack in correct validation, the risk of false negative and positive results is increased and thereby the clinical applicability is potentially limited.

On top of these difficulties, there are a few specific demands for a method to accurately assess adherence to AHDs. First, during the analytical validation process, it is important to strive for the detection of drug concentrations at the most minimal levels feasible, to prevent incorrect assumptions of non-adherence. This is to preserve an optimal patient–healthcare provider relationship.[17] Second, the method needs to include as many of the available AHDs on the market as possible to ensure availability for as many patients as possible. As stated before, current hypertension guidelines do not express a clear preference for one particular drug from one of the five preferred drug classes when no comorbidities are present.[5] Because of this, antihypertensive drug therapy can exist of a variation of the more than 50 different AHDs available, making the analytical validation extremely challenging.[17,41]

4.4 | Knowledge of pharmacokinetics of AHDs required for assessing adherence

After correct validation of a new matrix for TDM of AHDs, drug concentrations have to be interpreted correctly. It is important to consult the patient for this, not only to establish the correct time of intake but also to potentially identify specific individual reactions to AHDs.[9]

Also, it is still unknown what concentration in blood is leading to the desired effect for individual patients.[42] The development of population pharmacokinetic/pharmacodynamic (PK/PD) models could shed a light on this. However, for these models it is necessary to accurately measure quantitative drug concentrations, which needs validation studies according to the aforementioned guidelines. As only a limited number of studies correctly validated their AHD assessment method (Table 1), quantitative drug concentrations currently lack the ability to offer detailed adherence assessment. As a result, only when drug concentrations fall below the LLOD can non-adherence be established.[4]

Drawing conclusions of adherence based on drug concentrations exceeding the LLOD may lead to an overestimation of adherence. Nevertheless, at present, this approach represents the most viable method for evaluating adherence through antihypertensive drug concentrations. This was also confirmed by a meta-analysis by Groenland et al. that evaluated a screening method for AHDs in blood that was based on pooled trough concentrations.[41] The use of pooled trough concentrations provided for an easier alternative to analyse high

numbers of drugs in one method, but could possibly lead to more false accusations of non-adherence and, more importantly, is not in accordance with the current validation guidelines.[39]

5 | CLINICAL UTILITY

As described, there are currently many methods available that were developed to assess non-adherence to AHDs. However, to the best of our knowledge, almost none of these methods are implemented in clinical practice. This could be a result of a lack of research into the clinical utility of these methods.. Clinical utility includes information on the health improvement and cost-effectiveness of the new method compared to the gold standard/standard of care (Figure 1).[43] Health improvements are described in the next paragraph. One of the aspects that is important for the cost-effectiveness is the cost implications associated with performing TDM. Current hypertension guidelines state that TDM is perceived as a costly method, which could lead to some reluctance to apply this method in clinical practice.[5] However, it is already known that non-adherence to medication leads to a serious cost burden on healthcare systems which will exceed the costs for TDM per patient multiple times.[44]

Given the challenges in validating TDM methods across a wide range of AHDs and the nuanced interpretation required, it is advisable to conduct these measurements in hospitals with expertise in this area.[22] Concentrating these measurements in specialized hospitals offers several advantages, including cost reduction through bundling multiple samples, shorter turnaround times for results when more measurements need to be performed per week, and increased expertise in interpreting antihypertensive drug concentrations.[22] Before a TDM method is developed, it is advisable to take inventory of existing antihypertensive drug TDM methods in the region, nationally or internationally, and check if hypertension specialists or GPs use this method in their practice to find out if all the necessary validation work is of added value.

Another problem that limits the clinical utility of TDM for AHDs is the misconceptions around the use of plasma and DBS. Drawing blood through a venipuncture is often seen as invasive, but especially for patients in secondary and tertiary hospitals, this is a very convenient sampling method while lab values like kidney function are already measured.

6 | TDM TO IMPROVE ADHERENCE?

One of the misconceptions when TDM is used for adherence purposes is that it will automatically lead to improved adherence.[45] TDM is solely a method of identification and will establish whether certain drugs are ingested. Although feedback on low drug levels can lead to short-term improved awareness and thus adherence, TDM alone will not improve long-term adherence.[45] This means that additional steps need to be taken in the process that will lead to improved adherence. We previously published a three-step method, including an identifying method like TDM, to increase adherence to AHDs.[9] Additionally, the randomized Telemonitoring and E-Coaching in Hypertension (TECH) trial, which is currently being conducted,[37] will further determine the role of HBPT as an addition to TDM in optimizing adherence.

Our study 'Resistant Hypertension: MEasure to ReaCh Targets' (RHYME-RCT) was the first study to combine TDM to identify non-adherence with a comprehensive feedback conversation to improve adherence to AHDs and subsequently blood pressure in patients with (pseudo-)resistant hypertension after 1 year of follow-up. RHYME-RCT had a randomized controlled study design and the intervention consisted of discussing the results of antihypertensive drug concentrations during a personalized feedback conversation with the patient at baseline and at 3 months follow-up. This study showed that adherence significantly improved in patients randomized to the intervention arm after 1 year of follow-up. Also, a decrease in blood pressure, and thereby a reduced prevalence of resistant hypertension, was observed, but this decrease in blood pressure was not different between the standard-of-care arm and intervention arm and could not be related to the improvements in adherence.[31]

The results of RHYME-RCT do not stand on their own. Several randomized controlled trials have been conducted to improve blood pressure by improving adherence, but without TDM as the non-adherence identification method.[46,47] These trials focused mainly on hypertensive patients rather than patients with (true) resistant hypertension. These trials found an improvement in adherence in the intervention arm, but no difference in blood pressure between the control and intervention arm, which is in accordance with the RHYME-RCT trial. This shows that proving the efficacy of a communication-based intervention, whether or not combined with an adherence assessment method, to improve adherence is difficult.

Because most methods, like TDM, will only measure non-adherence, but will not improve it, it is difficult to compare them with each other in terms of efficacy. However, when measuring drug concentrations in blood, the patient's influence on adherence measurement results can be reduced to a minimum, particularly when the measurement is conducted without prior notice.

7 | USING TDM FOR OPTIMIZATION OF ANTIHYPERTENSIVE DRUG THERAPY

Over the past few years, TDM of AHDs is also used to investigate if optimization of therapy is possible for certain populations. While sex differences in the dosage and side effects of AHDs are recognized, a limited number of studies have conducted TDM to investigate the underlying reasons for these variations.[4,48,49] A study by Peeters et al. found that females had significantly higher plasma concentrations of canrenone as compared to males when taking the same dose.[4] They also found that certain other patient characteristics could influence the variability in drug concentrations in blood like body mass index or age.[4]

A study that was conducted to address sex differences for metoprolol revealed that females exhibited higher peak concentrations of

metoprolol and had a higher average AUC compared to males.[50] While this study is often cited and considered valid, it is important to note that the trials' external validity is limited as young healthy volunteers were used instead of patients. However, it shows that TDM for AHDs might be useful. In addition, a cohort study by Santema et al. showed that in clinical practice females already received lower dosages of beta-blockers as compared to males.[51] This could imply that the elevated concentrations found in the blood of females led to a higher efficacy, but also more side effects, and therefore resulted in lower dosages in clinical practice. However, this remains a theoretical proposition based on various studies, with no specific research conducted to comprehensively explore sex differences in dose, drug concentrations and efficacy.

Another population where TDM is used to optimize AHD treatment is the elderly. Results of studies that investigate antihypertensive drug treatment in the ageing population indicate that elderly patients would possibly benefit from lower AHD dosages than currently available on the market.[52] The most important limitation of all these studies is that no data on the blood pressures are available. Therefore, it is difficult to draw conclusions based on the measured drug concentrations. A study by Hassan et al. is one of the first that tackled this knowledge gap with a still ongoing study on PK/PD differences of losartan and perindopril between elderly (>70 years) and young patients (<50 years).[42] These data could be used to develop a population pharmacokinetic model (popPK model) to predict the correct starting dose in elderly with hypertension.

These recent developments indicate that the journey of AHD TDM is just beginning, offering the potential to individualize treatment. This may provide valuable insights into the optimal AHD and AHD dose for specific patient groups, potentially encouraging more individuals to initiate and adhere to AHD therapy.

8 | CONCLUSION

Classically, TDM is used for drugs with a narrow therapeutic range to optimize dosing strategies. However, in patients with hypertension, measuring drug levels to identify non-adherence can also be considered as a treatment optimization since it is the first step towards improving blood pressure regulation. Furthermore, TDM of AHDs in combination with popPK modelling could lead to the optimization of AHD therapy in specific patient categories such as the elderly.

AUTHOR CONTRIBUTIONS

Jorie Versmissen and Laura E. J. Peeters drafted and reviewed the manuscript. Job van Steenkiste and Birgit C. P. Koch reviewed the manuscript and added specific information on telemonitoring and technical aspects of drug level measurements, repectively. Job van Steenkiste performed the literature search on available studies on DBS and VAMS and produced Table 1.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

ORCID

Jorie Versmissen https://orcid.org/0000-0003-0674-7765
Birgit C. P. Koch https://orcid.org/0000-0002-1202-3643
Laura E. J. Peeters https://orcid.org/0000-0002-6148-9714

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