Taylor & Francis
Taylor & Francis Group

Expert Review of Pharmacoeconomics & Outcomes Research

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/ierp20

Physician and patient adherence in hypertension trials: a point of view on an important issue to resolve

Michel Burnier

To cite this article: Michel Burnier (2024) Physician and patient adherence in hypertension trials: a point of view on an important issue to resolve, Expert Review of Pharmacoeconomics & Outcomes Research, 24:6, 749-758, DOI: 10.1080/14737167.2024.2363401

To link to this article: https://doi.org/10.1080/14737167.2024.2363401

Published online: 05 Jun 2024.

EXPERT REVIEW OF PHARMACOECONOMICS & OUTCOMES RESEARCH
2024, VOL. 24, NO. 6, 749–758
https://doi.org/10.1080/14737167.2024.2363401

Taylor & Francis
Taylor & Francis Group

REVIEW

Physician and patient adherence in hypertension trials: a point of view on an important issue to resolve

Michel Burnier

Faculty of Biology and Medicine, University of Lausanne, Lausanne, Switzerland

ABSTRACT

Introduction: Randomized controlled trials (RCTs) are important sources of evidence that strongly influence guidelines for patient management, including for elevated blood pressure in adults.

Areas covered: Critical questions regarding the interpretation of hypertension trial results have recently increased, especially for concerns over methodology. In particular, investigator adherence to the protocol and patient adherence to investigational drugs are often far from optimal. These issues may be ignored or underreported because physicians' behavior during trials is often not monitored and patients' medication adherence is neither measured adequately nor reported or analyzed in the final report or in the publication. This situation may lead to misinterpretations of study results and misevaluations of the safety and efficacy profile of new drugs. In this short review, the problem of measuring, reporting, and analyzing drug adherence in RCTs is discussed and illustrated with several examples in the field of hypertension.

Expert opinion: The main conclusion is that drug adherence should always be measured in clinical trials, possibly with more than one method. In addition, prespecified analyses of adherence data should be included in the statistical plan of all trials to improve their overall quality.

ARTICLE HISTORY
Received 13 February 2024
Accepted 30 May 2024

KEYWORDS
Clinical trials; persistence; implementation; drug adherence; methods

1. Introduction

In international guidelines on the management of hypertension in adults, such as the recent 2023 guidelines of the European Society of Hypertension [1] or the 2020 Practice Guidelines of the International Society of Hypertension [2], authors consider that results obtained from randomized controlled trials (RCTs) with cardiovascular outcomes (or any meta-analysis of these trials) provide the highest level of evidence enabling high-level clinical recommendations. Sometimes, large observational studies are also considered especially when their results align with those of RCTs [3]. The main assumption is that RCTs produce solid conclusions because they follow a strict protocol with enough patients carefully selected based on inclusion and exclusion criteria and their statistical power is adequate. Patients enrolled in these trials are usually motivated [4] and are supposed to follow all the instructions they have received for participating in a clinical trial, including those regarding drug intake, the report of side effects, the completion of questionnaires and the need to follow carefully the schedule of visits. Moreover, non-adherent patients are often excluded during the run-in phase [5] and enrolled patients are monitored very closely with a high frequency of visits during the trial follow-up. Therefore, medication adherence is thought to be much higher in clinical trials than in the real life where it averages ~50% in most chronic diseases [6–10]. In a review of 192 RCTs assessing pharmacological treatments in 6 major chronic diseases, including hypertension, drug adherence was assessed only in 35% of trials [11]. When reported, the median intake of prescribed medication was 93%, and the median proportion of 'nonadherent' patients was 6.2% but with a large variability [11].

For their part, participating physicians must follow strictly the protocol in all its aspects including the monitoring of drug intake or up- and down-titration of medications whenever recommended by the protocol. However, it seems that this ideal pattern is not always respected in RCTs. Regarding the adherence to the protocol, several factors that might reduce confidence in a RCT are known such as failure to conceal allocation, failure to blind, failure to adapt treatments as requested, or use of unvalidated outcome measures [3]. However, critical assessments of investigator adherence are rare. In a post-hoc analysis of four very large clinical trials in hypertension (LIFE, ASCOT, VALUE and ACCOMPLISH), Kjeldsen et al. [12] have analyzed the reasons why large fractions of patients in these trials remained uncontrolled for their high blood pressure (BP) at the end of the study. It appears from this analysis that many investigators did not uptitrate the study drugs to higher dosing levels or did not use drug combinations according to the study protocols. This lack of adherence to the protocol, that one could also call medical inertia, was a major cause of not reaching BP targets in these trials. This observation illustrates the importance of poor adherence and protocol violations within large clinical trials, which should not be underestimated as they may jeopardize the quality of the trials by enhancing patients' withdrawal and reducing the ability to complete the study with a sufficient statistical power and hence to draw valid scientific conclusions. For these reasons,

CONTACT Michel Burnier michel.burnier@netplus.ch Faculty of Biology and Medicine, University of Lausanne, Derrey le Motty 8, Lausanne 1806 Switzerland

Article highlights

- Data on drug adherence are important for an adequate interpretation of clinical trial results when investigating new drugs or therapeutic strategies.
- Today, adherence data in large clinical trials are either missing or poorly reliable or underused as they are rarely considered in statistical analyses.
- The lack of integration of adherence data in study analyses may lead to important clinical consequences such as a wrong interpretation of efficacy and safety data.
- The expert suggests that important improvements should be made for a better integration of drug adherence in trials starting with a generally accepted definition of what is a good adherence and improvements in the way drug adherence is measured.
- Investigators should consider the use of new methods taking advantage of the most recent developments in digital technologies.
- In any case, drug adherence should always be measured (possibly with more than one method) and analyzed like any other clinical parameter in trials.
- To this purpose, analyses of adherence data should always be included in the statistical plan of new trials to improve their overall quality.
- Lastly, increasing the awareness of the problems associated with a poor adherence to medication is an important target in clinical studies as well as in clinical practice.

strict adherence to the protocol deserves to be considered as a major parameter in clinical trials, which contributes to their success.

2. Prevalence and reporting of poor adherence in clinical trials

Measuring patient adherence in clinical trials submitted for registration is of upmost importance as a poor adherence in trial may lead to inaccurate estimates of the efficacy, safety, and benefit – risk balance of a new medicine or treatment strategy. Early analyses of RCTs have reported that only 43% to 78% of participants receiving treatment during a clinical trial for chronic conditions could be classified as being adherent [13]. More recently, Mantila et al. [14] performed a cross-sectional analysis of European Medicines Agency marketing authorization dossiers for new medicines submitted between 2010 and 2020. Their analysis covered 5 medical topics e.g. diabetes, respiratory conditions, cardiovascular diseases, infectious diseases, and oncology. Overall, 253 clinical trials were reviewed and among them, only one did not measure adherence. Assessment of adherence was done using quantitative methods in 87% of studies while 13% of trials monitored adherence but did not further quantify it. In this analysis, pill count (52.7%) was the most frequently used method of adherence monitoring either as a single method or in combination with another method, mainly with diaries. Electronic assessment of adherence represented only about 2–3% of assessment methods. According to this analysis, the reported mean adherence rates were very high in all medical conditions usually > 95% [14]. However, the definition of adherence was not homogeneous between trials and there was a wide heterogeneity in the way adherence figures were reported. Interestingly, the range of adherence levels (from minimum to maximum) was often high (from 0 to 100%) with frequent measurements > 100% suggesting a potential problem with the drug management or with the method used to assess adherence. Indeed, when the medication possession ratio (MPR) is used to measure drug adherence, results could be greater than 100% because the method accounts for stockpiling. When adherence is measured using the percentage of days covered (PDC), then adherence ranges between 1–100%. When strictly limited to the pill count, adherence may also be greater than 100% because patients receive a higher number of pills than needed to cover the days between two terms to prevent a gap in treatment if the term is delayed. These data actually confirm older observations, which concluded that the variability of drug pill count can be large and that reports of overall pill counts are generally suboptimal with a tendency to overestimate the true adherence rate [15]. In another post-hoc analysis of 95 clinical studies, Blaschke et al. reported that ~ 50% of 16'907 study participants exhibited substantial deviations from the dosing regimen outlined in the study protocol [16]. In hypertension, analysis of 21 phase IV clinical studies showed that about half of the patients who were prescribed an antihypertensive drug had stopped taking it within one year [7]. Dodd et al. [17] reviewed the extent to which non-adherence to treatment protocol was reported and addressed in 100 publications of RCTs randomly selected from the British Medical Journal, the New England Journal of Medicine, the Journal of the American Medical Association and The Lancet during 2008. Specifically, they reviewed the extent and nature of reported non-adherence to treatment protocol, and whether statistical methods were used to examine the effect of non-adherence on both benefit and risk analyses. Interestingly, non-adherence to treatment protocol was reported in 98 of the 100 trials, but the reporting was often considered as vague or incomplete. Reporting of treatment initiation and completeness was inadequate in 2/3 of trials with short-term interventions and 89% of trials with long-term interventions. Of note, adherence to randomized interventions was also poor (~42%) in the reporting and analysis of these published RCTs.

The above-mentioned observations on adherence monitoring and reporting in RCTs explain why, in the absence of a standardized reporting procedure of adherence issues, it is difficult to estimate precisely the prevalence of non-adherence in RCTs.

3. Methods used to assess adherence in clinical trials

There is no gold standard method for the measurement of drug adherence in clinical trials as well as in real-life clinical practice. Thus, several methods have been used, each of them having its own advantages and limitations as reviewed recently by Vrijens et al. [18] and summarized in Table 1.

3.1. Pill count

As mentioned above, pill count is the most frequent method used to monitor drug adherence in clinical trials. The principle is simple, cheap and easy to apply. It consists in counting manually the number of pills or tablets remaining in

Table 1. Methods used to assess drug adherence in randomized control studies (RCTs) and observational studies (OS).

	Pill count	Self-report	Drug levels in blood or urine	Electronic monitoring packages	Smart pills	Direct observed treatment	Administrative and pharmacy claims	New technologies (biosensors, implantable devices)
Frequency of use in RCTs or OS	++++	+++	++	++	±	+	++ in OS Not in RCTs	+ in OS Not in RCTs
Advantages	Simple, cheap	Simple, cheap	• Ascertain drug intake • May support adherence	• Provide a dosing history • May support adherence	• Ascertain intake • Provide dosing history	Ascertain drug intake	• Cheap • Possible dosing history	Continuous monitoring
Limits	• Counting errors • Desirability bias • No defined threshold • Possible manipulation	• Desirability and acquiescence bias • Recall bias • High variability	• Ability to measure drugs and metabolites • Impact of PK • Punctual • white coat adherence • Cost	• No proof of drug intake • Availability • Reconditioning of drugs in OS • Cost	• Very high cost • Tolerance of external patch • Acceptance by patients	• Cumbersome method • Need staff • Costly • Use mainly with small number of participants	• Not available in all countries • Ethical aspects (confidentiality) • Multiple sources (pharmacies) • Not objective	• Acceptance by patients • Technical and ethical acceptability need to be validated • Cost?
Overall reliability	• Low • Overestimate adherence	• Low • Overestimate adherence	• High • Overestimate adherence	• High • Recommended by FDA	• High	• High	• Medium • Underestimate adherence • Need validation	• Unknown, possibly high

a medication container at study visits. The assumption is that the number of pills dispensed minus the number of pills remaining reflects the number of doses that have been effectively taken by the patient. By comparing the expected number of pills to be taken with the actual count, researchers can estimate the average level of adherence to the prescribed medication regimen.

This method has some obvious limitations including errors in counting pills, patients not consuming the pills removed and instances where patients drop pills prior to their visit to please the investigators and to avoid being excluded from the trial (desirability bias). Thus, this procedure, like many others, is exposed to a high risk of manipulation inducing an overestimation of adherence. Other important issues regarding the use of the pill count in RCTs are: i) the incapacity to define scientifically what is an acceptable threshold. This latter is often set at > 80% without a real pharmacological justification [19] and ii) data from pill count are often unavailable to study statisticians and are not utilized for analyses according to the level of adherence or for a risk-based quality management. Actually, several of these limitations are not specific of the pill count method are shared by other methods discussed below. Thus, although pill count is frequently used in RCTs to document a presumed adequate adherence, it remains a poorly reliable method that should not be used alone.

3.2. Patient self-reported adherence

In fact, pill count is often associated with patient self-reported data collected using either questionnaires or diaries. Self-reported adherence is used in about 27% of RCTs [18]. Patient self-reported adherence and pill count share some common limitations. One of them is the *desirability bias* and the generation of a favorable adherence profile answering positively to all questions. Other possible bias may be the *acquiescence bias* whereby individuals agree regardless of how they feel and the *extreme positive bias* when subjects remember positive or pleasant aspects more accurately than negative ones. When using questionnaires, a great variability has been observed associated with the profile and attitude of the person administering and completing the questionnaire. In addition, the quality of answers may be affected by the time component, a recall period longer than 4 days backwards about medication adherence being particularly imprecise [20], even though longer recall windows of up to 30 days have been found to be valid for example in HIV studies [21].

Diaries can be in paper or electronic forms and are designed to capture several information needed from participants during a clinical trial such as the time of medicine intake or the tolerability of the investigational compound. Diaries are usually easy to develop and to use but subjects may forget to complete them. Transferring data from paper diaries to electronic database may be cumbersome. Today, electronic versions of diaries using tablets or the patient's phone are preferred because they can also record the day and the time when data were entered thus preventing last minute completion of diaries. This approach appears to be more reliable than paperwork although it has a limited use for monitoring drug intake. Indeed, as the action of recording the event is often disconnected from the actual medication intake, data generally lead to exaggerated levels of adherence.

Therefore, self-reported adherence is also considered as a method with a low reliability due to a high variability and a significant tendency to overestimate the true level of adherence.

3.3. Measurements of medicine levels in blood or urine

The measurement of drug levels in blood and urine should be the most reliable method to assess drug adherence in RCTs as it confirms that the drug under investigation has been ingested and circulates in the body [22]. In the field of hypertension, drug measurements in urine have become increasingly popular to identify the potential causes of apparent resistant hypertension, a clinical situation in which patients remain hypertensive despite the prescription of at least 3 antihypertensive drugs [22–24]. A recent study has shown that when combined with personalized feedback in resistant hypertension, drug concentration measurements can improve drug adherence significantly [25]. Yet, this method has also some intrinsic limitations. The first is that not all compounds and their metabolites are measurable in blood or urine. The second is the lower limit of detection of the method as non-adherence can be confirmed only when no drug is found in the urine or plasma [26]. The third is that the presence of the drug in the blood or urine at trough depends on the pharmacokinetics of the drug. Thus, some drugs may disappear rapidly from the body in rapid metabolizers. At last, the most important limitation is that the reliability of this adherence measure is limited to a few days preceding the sampling and these measurements may be influenced by the *white-coat adherence*, according to which drug adherence increases a few days before and after medical terms [27].

Rather than measuring drug levels, it is also possible to monitor drug adherence by measuring the biological target of the drug such as glucosuria in the case of SGLT2 inhibitors, heart rate with the administration of beta-blockers or a marker of angiotensin-converting enzyme (ACE) activity (urinary N-acetyl-seryl-aspartyl-lysyl-proline/creatinine ratio) when ACE inhibitors are prescribed [28]. These approaches may be easier and cheaper. However, they are not recognized as reliable methods to measure adherence.

3.4. Electronic monitoring of drug intake

The use of electronic monitoring packaging systems to measure drug adherence in clinical studies started more than 20 years ago with the development of the Medication Event Monitoring System (MEMS®) [29]. The first device consisted of a chip integrated in the cap of a pillbox. The chip automatically recorded the date and the time of each box opening. The main advantage of the system is that one can obtain a real-time dosing history. Of course, opening the box does not necessarily mean that a pill is taken and ingested. Therefore, pill count is often associated to the electronic monitoring. However, important information can also be obtained from the non-openings. In that case, it is certain that no pill was taken. In validation studies, electronically recorded dosing

histories align with bioanalytical measures in 97% of cases [30]. When compared directly with the results of the MEMS device, median adherence is grossly overestimated by 17% using self-report and by 8% using pill count [29]. Thereafter, the electronic monitoring system has been improved with the addition of a LCD (liquid crystal display) on the cap indicating how often the box has been opened during the last 24 h and later the system has been adapted to blisters, inhalers, cream tubes, eye drop containers and injectables.

In addition to providing a dosing history, the use of electronic monitoring systems, such as the MEMS device, offers the possibility to give a feedback to patients regarding their adherence over weeks or months and to discuss with them the difficulties and barriers they have encountered with the management of their drugs [31]. This empowerment of patients has a very positive impact on long-term adherence to medications. Electronic monitoring packaging systems have been used increasingly in RCTs with some success. In a systematic review of 32 studies among which 22 tested the ability of electronic medication packaging to improve drug adherence as an integrated intervention, the difference in mean adherence between the placebo and the interventional group ranged between 1% and 34% [32]. As illustrated in Figure 1, the improvement depended on the level of adherence in the placebo group. In RCTs, one advantage of this methodology is that data can be utilized statistically to evaluate the impact of adherence on prespecified outcomes [33].

The concept of electronic monitoring of adherence has further evolved with the development of 'smart pills' with the integration of the chip directly in the pill [34]. The sensor emits a signal when it encounters the acidic environment of the stomach, and the signal is detected by a wearable external patch and linked to a mobile device app. With this approach, longitudinal adherence data are collected in the form of daily progress charts for sensed dosing events and the pill ingestion is ascertain. Patients can also obtain medication adherence feedback consulting their phone or tablet. This approach has been tested in patients with hypertension and type 2 diabetes [34,35]. Interestingly, although patient know they were monitored, adherence is not 100% in most patients because there are several ways to escape the monitoring. So far, the very high cost of this technique has limited its use in clinical trials as well as in clinical practice.

3.5. Direct observation

This approach involves participants being observed taking their investigational drug during the trial. With this method drug intake is ascertain but it is a costly and time-consuming process for both the participant and the study staff. The method has been used essentially in the development of tuberculosis therapies [36]. This method could be used in RCTs involving a small number of subjects, for example in phase 1 or 2 studies. It may also be used in trials where the drug needs to be given by medical staff, e.g. by injection or infusion. For example, this has been the case with the subcutaneous injection of the small RNA interference therapeutic agent zilebesiran to block angiotensinogen generation and hence to lower blood pressure in hypertensive patients [37].

3.6. Administrative and pharmacy dispensing claims

In the last decade, new trial designs have been proposed that could progressively replace RCTs [38]. These new experimental designs, named for example umbrella study, basket study, platform study or master observational trials (MOT), should enable to obtain high-quality evidence in a cheaper and more effective way than RCTs and to include several new aspects of research such as genomics or new biomarkers [38]. These new types of observational studies might use

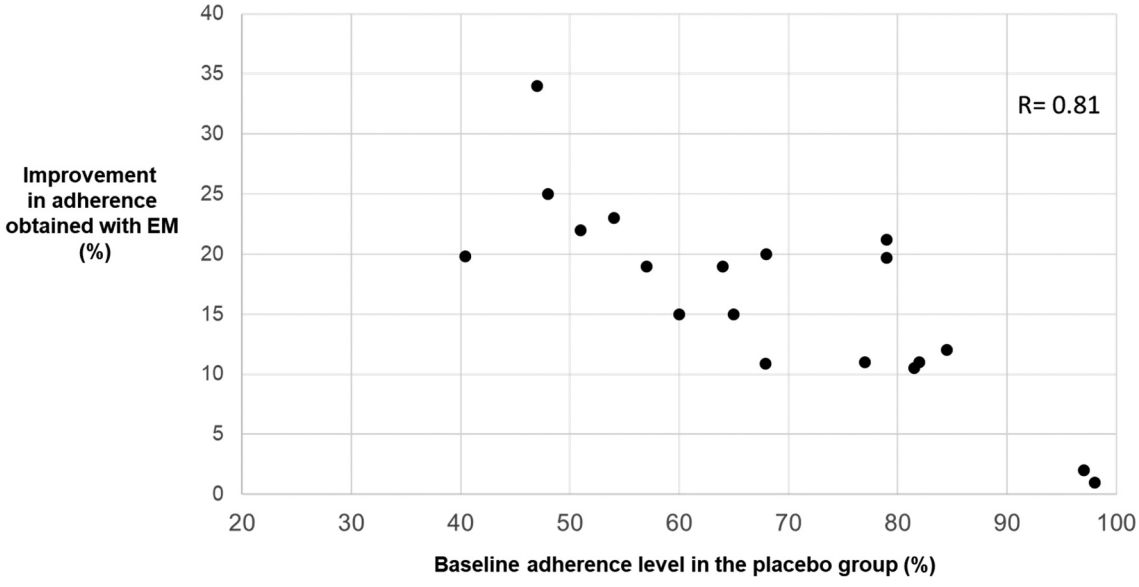

Figure 1. Relation between adherence levels in the placebo group and the improvement in adherence induced by electronic monitoring packaging systems in the interventional group. This figure has been created de novo based on data collected in a recent review by Checchi et al. [32].

EM: electronic monitoring.

different sources of data to assess adherence [38,39]. Indeed, in many countries, nationwide administrative and prescription claims have become more accessible, and this could enable to identify non-adherent patients in studies. This approach was investigated by Glassberg et al. [40] in 1425 patients. Patients with more than a 30-day gap in refill history were identified using prescription claims and were interviewed by pharmacists to assess the reasons for nonadherence. The positive predictive value of claims records in identifying nonadherent patients was 0.72 suggesting that prescription claims may underestimate adherence. Authors identified two reasons for patients to be misclassified e.g. discontinuation of medication on prescribers' directions and having an alternate channel for receiving the medication.

Thus, administrative as well as prescription claims might become a new tool to assess drug adherence in large clinical trials after some improvements and additional validation studies.

3.7. New technologies

In recent years, great efforts have been made to develop new technological approaches taking advantages of the multiple new developments in biosensor technologies resulting in wearable or implantable sensors enabling a continuous monitoring of drug levels in acute as well as in chronic clinical conditions [41]. These approaches may provide the opportunity to obtain an automated, non-invasive

monitoring with a continuous follow-up of drug levels or biochemical parameters and the possibility to adapt the drug dosing online using artificial intelligence combined with implanted drug delivering devices and biomarker monitoring as it is already possible in patients with diabetes [42,43]. Long-acting drug delivery systems, including injectable depots, refillable devices and in situ-forming hydrogels, are being developed to improve medication adherence, reducing the need for frequent drug administration [44]. Yet, these developments will need to be validated not only for their reliability but also for their technical and ethical acceptability. Their usefulness in RCTs will have to be demonstrated particularly in placebo-controlled studies.

4. Impact of non-adherence on device and drug efficacy studies

A poor adherence to studied medications or devices can have a major impact on the validity and interpretation of study results. As illustrated in Table 2, the consequences of patients' non-adherence and its negligence in the analysis of trial data are multiple from the inability to assess the efficacy and safety of an investigational drug or to conclude on a new treatment strategy to an inappropriate interpretation of study results.

In the field of hypertension, two recent examples of the negative impact of significant variations in drug adherence on study results were published. The first concerned the demonstration of the antihypertensive efficacy of renal denervation in patients with resistant hypertension. In this prospective, single-blind, randomized, sham-controlled trial, Bhatt et al. [45] could not demonstrate a significant reduction of BP in patients with resistant hypertension 6 months after renal-artery denervation as compared with the sham procedure. The main reason was that a marked reduction in BP (−11.7 mmHg systolic BP) was observed in the sham-controlled group. This marked decrease in BP was probably due to significant variations in drug adherence between baseline and the follow-up period. Indeed, all patients were receiving at least 3 antihypertensive drugs, which should have been maintained stable throughout the study period and this was probably not the case in the control group. In fact, several authors reported significant variations in drug adherence in patients treated with a renal denervation, which could reach up to 31% in some studies [46–50]. One group of investigators concluded their renal denervation study affirming '*Changes over time in adherence are common and affect treatment estimates considerably. Objective measurement of medication adherence during follow-up is strongly recommended in randomized trials*' [47].

Table 2. Some possible unwanted consequences of non-adherence in clinical trials.

	Unwanted consequences
Scientific: Efficacy	Inability to reach valid study conclusions
	Production of outcomes on study endpoints unrelated to treatment assignment
	Falsely negative or inconclusive results
	Inaccurate determination of the optimal dosing in drug development studies leading to overestimation of dose requirements
Scientific: Safety	Inappropriate assessment of drug safety
Statistics	Adverse impact on sample size and statistical power
	Increase patient withdrawal and the need for new patients' recruitment
Economic	Increased costs
	Delay in drug registration

Another example of an excessive 'placebo effect' due to variations in drug adherence was reported in the study of the new endothelin receptor antagonist aprocitentan in patients with resistant hypertension [51]. In the first phase of the study, a significant initial decrease in systolic BP was observed in the placebo group (−11.5 mmHg), which considerably blunted the difference between the aprocitentan and the placebo groups. In this context, one hypothesis was that patients withdrew their baseline treatment during the run-in phase to meet the inclusion criteria. Once enrolled, however, patients restarted their therapy leading to a significant reduction of BP in the placebo group. This observation nicely illustrates the need to monitor drug adherence adequately during the entire study period starting during the run-in phase to avoid such disturbing artifacts.

Analyzing efficacy data according to drug adherence may also change the interpretation of study results. One example comes from the study of Azizi et al. [52] who compared a treatment strategy based on sequential nephron blockade (SNB) to a strategy based on sequential blockade of the renin-angiotensin system (RAS) in patients with resistant hypertension. In their first publication [52], they demonstrated that SNB was slightly superior to sequential RAS blockade with a greater number of patients having a well-controlled BP at the end of

Table 3. Suggested ways to mitigate the impact of non-adherence in randomized controlled trial.

- Identify adherence issues in the trial preparation and run-in phases
- Identify approaches to directly improve adherence to the trial protocol and/or the investigational drug.
- Identify and select patients who are likely to adhere to treatment, but only prior to randomization, not afterward. Use subject registries if available.
- Prespecify who will be included in the final analysis based on information available on subjects prior to randomization.
- Consider performing pharmacokinetic sampling on background treatments and consider a biomarker or medication adherence technology during the run-in phase.
- Provide standard adherence monitoring and support to all participants in both active and placebo arms.
- Monitor individual subject adherence with a medication adherence technology, not pill counts alone; when appropriate, provide subjects and investigators with prompt feedback when nonadherence is detected.
- Discontinue promptly subjects who are deceptive, duplicate, or egregiously nonadherent. This may be desirable to minimize the negative impact of these subjects' data.
- Include a prespecified analysis of adherence data in the statistical plan.
- Consider stratification of subpopulations based on adherence and behavior.
- Utilize known adherence data when designing a new protocol and taking go/no-go decisions in later studies.

the observation period. However, in a pre-specified analysis taking into account the level of drug adherence during the study, the ability of SNB to lower BP was significantly greater than that of sequential RAS blockade and in addition, a significant regression of target organ damages (left ventricular hypertrophy and pulse wave velocity) could be demonstrated with the SNB but not with sequential RAS blockade [53].

Yet, whether data should be analyzed according to the level of adherence in all RCTs remains controversial. Indeed, on one hand, investigators advocate that study results should be analyzed independently of drug adherence during the trial as this may better reflect the real-life situation. Moreover, depending on the drug profile, non-adherence may limit side-effects including life-threatening events [54]. On the other hand, one can argue that when investigating the efficacy and safety of a new drug, results obtained in non-adherent patients are not relevant and only those data obtained from fully adherence patients should be taken into account. Scientists want to know the efficacy and safety of drugs when they are taken correctly. The advantage of including reliable data on drug adherence in statistical plan offers the possibility to do both, i.e. to have an estimation of efficacy in the entire group of enrolled patients as well as in fully adherent patients. Today, these aspects are bypassed using statistical methods such as intention to treat or per-protocol analyses.

5. Conclusions

There is now increasing evidence demonstrating that the level of adherence has an important impact on the quality of RCTs. The multiple negative consequences of either a poor respect of the study protocol by investigators or a low patient adherence to investigational drugs are now well recognized. Without data on adherence, investigators are unable to define the appropriate dosage, often leading to overestimated dosing requirements, and cannot evaluate reliably the efficacy and the safety of drugs [18] or devices [50]. Consequently, drug doses put on the market are frequently set too high, resulting in an elevated risk of side effects and treatment discontinuation [55]. Therefore, several groups of experts such as those of the International Society for CNS Clinical Trial Methodology (ISCTM) Working Group on Non-adherence [56] or those of the European Society for Patient Adherence, COMpliance, and Persistence (ESPACOMP) Medication Adherence Reporting Guideline (EMERGE) [33,57] have proposed recommendations on how to mitigate the effects of non-adherence and how to prevent, report and include in the statistical plan, data on adherence in RCTs. Some of the main recommendations are listed in Table 3.

To adequately interpret the results of RCTs, it is crucial to consider the variations in adherence during the study. This aspect is now strongly recommended by registration authorities. In the future, adherence should be monitored adequately in all RCTs preferably using more than one method. Drug adherence data should be reported and analyzed in the same way other biological and clinical parameters are. Prespecified analyses of the efficacy and safety in relation to the levels of adherence should be provide in all RCTs.

6. Expert opinion

Non-adherence to the study protocol by investigators and to medication intake by patients are key issues, which deserve more attention when planning and conducting a large hypertension RCT. Unfortunately, these important issues, particularly drug adherence, have been largely underestimated or even ignored during the last decades even though most studies have included some form of drug adherence monitoring and follow-up of protocol violations by investigators. Yet, to impact relevant real-world outcomes deducted from the results of RCTs, improvements are still necessary. This concerns the way adherence is defined, measured, and analyzed in trials.

A first step is the necessity to improve the definition of adherence in RCTs as well as the methodology used to assess it reliably throughout the study. As mentioned previously, most studies monitor drug adherence but the definition of adherence and the thresholds for considering drug adherence as acceptable and sufficient differ markedly between studies.

Techniques used to measure adherence, pill count being the most used technique, are known to have a poor reliability because they are exposed to several potential bias. Today, new strategies are already available, such as the integration of a microchips in each pill, that can circumvent several of the known limitations of classical approaches including the most advanced ones (measurements of drug levels, electronic monitoring). An intense research activity is ongoing on how to improve adherence measurements using digital technologies [41,44]. At last, research is also

focusing on the development of new types of clinical studies based on large populations [38]. One good example is the ability to gather important clinical information on new drugs/treatments based on administrative and pharmacy claims gathering data and information from very large patient populations. These ongoing developments will enable to enhance the awareness of adherence as a key parameter to assess the safety and efficacy of drugs. They will have to be considered with more attention in the future and implemented in new trials to obtain strong scientific conclusions in all study aspects e.g. efficacy, safety and analyses of the clinical and socio-economic benefits.

In this respect, it is also mandatory that drug adherence data are reported as any other biological parameter and analyzed correctly in all statistical analyses. One strong recommendation is that adherence and their analyses belong to the prespecified statistical plan. This approach is easy to implement and will definitively provide a lot of new clinical information for researchers and clinicians. The major advantage of integrating such improvements in the management of RCTs is the prevention of misinterpretations of clinical results and safety issues, which may have a substantial impact on patients' health. Analyses performed according to the level of drug adherence might actually limit the late discovery of adverse events.

Today, we are still lacking a 'gold standard' for the measurement of drug adherence in trials as well as in clinical practice. Nonetheless, substantial novel improvements and alternatives are under investigation, which will probably change our approach to drug development. Per se, the increasing awareness of the problems associated with a poor adherence to medications in trials and in real life can already be considered as a major step forward.

Funding

This paper was not funded.

Declaration of interest

The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Mancia G, Kreutz R, Brunstrom M, et al. 2023 ESH guidelines for the management of arterial hypertension the task force for the management of arterial hypertension of the European society of hypertension: endorsed by the international society of hypertension (ISH) and the European Renal Association (ERA). J Hypertens. 2023;41(12):1874–2071. doi: 10.1097/HJH.0000000000003480
2. Unger T, Borghi C, Charchar F, et al. International society of hypertension global hypertension practice guidelines. Hypertension. 2020;75(6):1334–1357. doi: 10.1161/HYPERTENSIONAHA.120.15026
3. Caparrotta TM, Dear JW, Colhoun HM, et al. Pharmacoepidemiology: using randomised control trials and observational studies in clinical decision-making. Br J Clin Pharmacol. 2019;85(9):1907–1924. doi: 10.1111/bcp.14024
4. Anastasi JC, Norton M, McMahon DJ, et al. Recruitment and retention of clinical trial participants: understanding motivations of patients with chronic pain and other populations. Front Pain Res. 2024;44. doi: 10.3389/fpain.2023.1330937
5. Rothwell PM. Factors that can affect the external validity of randomised controlled trials. PLOS Clin Trial. 2006;1(1):e9. doi: 10.1371/journal.pctr.0010009
6. Lee EKP, Poon P, Yip BHK, et al. Global burden, regional differences, trends, and health consequences of medication nonadherence for hypertension during 2010 to 2020: a meta-analysis involving 27 million patients. J Am Heart Assoc. 2022;11(17):e026582. doi: 10.1161/JAHA.122.026582
7. Vrijens B, Vincze G, Kristanto P, et al. Adherence to prescribed antihypertensive drug treatments: longitudinal study of electronically compiled dosing histories. BMJ. 2008;336(7653):1114–1117. doi: 10.1136/bmj.39553.670231.25
8. Cea-Calvo L, Marin-Jimenez I, de Toro J, et al. Different associations of intentional and non-intentional non-adherence behaviors with patient experience with healthcare and patient beliefs in medications: a survey of patients with chronic conditions. Patient Prefer Adherence. 2020;14:2439–2450. doi: 10.2147/PPA.S281985
9. Sabaté E. Adherence to long-term therapies: evidence for action. World Health Organization; 2003. p. 196.
10. Foley L, Larkin J, Lombard-Vance R, et al. Prevalence and predictors of medication non-adherence among people living with multimorbidity: a systematic review and meta-analysis. BMJ Open. 2021;11(9):e044987. doi: 10.1136/bmjopen-2020-044987
11. Gossec L, Tubach F, Dougados M, et al. Reporting of adherence to medication in recent randomized controlled trials of 6 chronic diseases: a systematic literature review. Am J Med Sci. 2007;334(4):248–254. doi: 10.1097/MAJ.0b013e318068dde8.
    • **An interesting paper provided numbers regarding the reporting of adherence in trials.**
12. Kjeldsen SE, Julius S, Dahlof B, et al. Physician (investigator) inertia in apparent treatment-resistant hypertension – insights from large randomized clinical trials. Lennart Hansson memorial lecture. Blood Press. 2015;24(1):1–6. doi: 10.3109/08037051.2014.946787
13. Osterberg L, Blaschke T. Adherence to medication. N Engl J Med. 2005;353(5):487–497. doi: 10.1056/NEJMra050100
14. Mantila KM, Pasmooij AMG, Hallgreen CE, et al. Medication adherence measurement methods in registration trials supporting the approval of new medicines: a cross-sectional analysis of centralized procedures in the European Union 2010–2020. Clin Pharmacol Ther. 2022;112(5):1051–1060. doi: 10.1002/cpt.2709
15. Rudd P, Byyny RL, Zachary V, et al. Pill count measures of compliance in a drug trial: variability and suitability. Am J Hypertens. 1988;1(3 Pt 1):309–312. doi: 10.1093/ajh/1.3.309
16. Blaschke TF, Osterberg L, Vrijens B, et al. Adherence to medications: insights arising from studies on the unreliable link between prescribed and actual drug dosing histories. Annu Rev Pharmacol Toxicol. 2012;52(1):275–301. doi: 10.1146/annurev-pharmtox-011711-113247
17. Dodd S, White IR, Williamson P. Nonadherence to treatment protocol in published randomised controlled trials: a review. Trials. 2012;13(1):84. doi: 10.1186/1745-6215-13-84
18. Vrijens B, Pironet A, Tousset E. The importance of assessing drug exposure and medication adherence in evaluating investigational medications: ensuring validity and reliability of clinical trial results. Pharmaceut Med. 2024;38(1):9–18. doi: 10.1007/s40290-023-00503-w
    • **This is an important paper defining the problem of adherence in trials.**

19. Baumgartner PC, Haynes RB, Hersberger KE, et al. A systematic review of medication adherence thresholds dependent of clinical outcomes. Front Pharmacol. 2018;9:1290. doi: 10.3389/fphar.2018.01290
20. Reynolds NR, Sun J, Nagaraja HN, et al. Optimizing measurement of self-reported adherence with the ACTG adherence questionnaire: a cross-protocol analysis. J Acquir Immune Defic Syndr. 2007;46(4):402–409. doi: 10.1097/qai.0b013e318158a44f
21. Wilson IB, Lee Y, Michaud J, et al. Validation of a new three-item self-report measure for medication adherence. AIDS Behav. 2016;20(11):2700–2708. doi: 10.1007/s10461-016-1406-x
22. Lane D, Lawson A, Burns A, et al. Nonadherence in hypertension: how to develop and implement chemical adherence testing. Hypertension. 2022;79(1):12–23. doi: 10.1161/HYPERTENSIONAHA.121.17596
23. Tomaszewski M, White C, Patel P, et al. High rates of non-adherence to antihypertensive treatment revealed by high-performance liquid chromatography-tandem mass spectrometry (HP LC-MS/MS) urine analysis. Heart. 2014;100(11):855–861. doi: 10.1136/heartjnl-2013-305063
24. Berra E, Azizi M, Capron A, et al. Evaluation of adherence should become an integral part of assessment of patients with apparently treatment-resistant hypertension. Hypertension. 2016;68(2):297–306. doi: 10.1161/HYPERTENSIONAHA.116.07464
25. Peeters LEJ, Kappers MHW, Hesselink DA, et al. Antihypertensive drug concentration measurement combined with personalized feedback in resistant hypertension: a randomized controlled trial. J Hypertens. 2024;42(1):169–178. doi: 10.1097/HJH.0000000000003585
26. Peeters LEJ, Feyz L, Boersma E, et al. Clinical applicability of monitoring antihypertensive drug levels in blood. Hypertension. 2020;76(1):80–86. doi: 10.1161/HYPERTENSIONAHA.120.15038
27. Burnier M, Egan BM. Adherence in hypertension. Circ Res. 2019;124(7):1124–1140. doi: 10.1161/CIRCRESAHA.118.313220
28. Azizi M, Ezan E, Nicolet L, et al. High plasma level of N -acetyl-seryl-aspartyl-lysyl-proline. Hypertension. 1997;30(5):1015–1019. doi: 10.1161/01.hyp.30.5.1015
29. El Alili M, Vrijens B, Demonceau J, et al. A scoping review of studies comparing the medication event monitoring system (MEMS) with alternative methods for measuring medication adherence. Br J Clin Pharmacol. 2016;82(1):268–279. doi: 10.1111/bcp.12942
30. Vrijens B, Urquhart J. Methods for measuring, enhancing, and accounting for medication adherence in clinical trials. Clin Pharmacol Ther. 2014;95(6):617–626. doi: 10.1038/clpt.2014.59
31. Burnier M, Schneider MP, Chiolero A, et al. Electronic compliance monitoring in resistant hypertension: the basis for rational therapeutic decisions. J Hypertens. 2001;19(2):335–341. doi: 10.1097/00004872-200102000-00022
32. Checchi KD, Huybrechts KF, Avorn J, et al. Electronic medication packaging devices and medication adherence: a systematic review. JAMA. 2014;312(12):1237–1247. doi: 10.1001/jama.2014.10059
    - **This is an interesting paper describing new technologies in packaging.**
33. Eliasson L, Clifford S, Mulick A, et al. How the EMERGE guideline on medication adherence can improve the quality of clinical trials. Br J Clin Pharmacol. 2020;86(4):687–697. doi: 10.1111/bcp.14240
    - **This is a very important paper providing potential solutions on how to improve clinical trials.**
34. Frias J, Virdi N, Raja P, et al. Effectiveness of digital medicines to improve clinical outcomes in patients with uncontrolled hypertension and type 2 diabetes: prospective, open-label, cluster-randomized pilot clinical trial. J Med Internet Res. 2017;19(7):e246. doi: 10.2196/jmir.7833
35. Thompson D, Mackay T, Matthews M, et al. Direct adherence measurement using an ingestible sensor compared with self-reporting in high-risk cardiovascular disease patients who knew they were being measured: a prospective intervention. JMIR mHealth uHealth. 2017;5(6):e76. doi: 10.2196/mhealth.6998
36. Karumbi J, Garner P. Directly observed therapy for treating tuberculosis. Cochrane Database Syst Rev. 2015;2015(5):CD003343. doi: 10.1002/14651858.CD003343.pub4
37. Desai AS, Webb DJ, Taubel J, et al. Zilebesiran, an RNA interference therapeutic agent for hypertension. N Engl J Med. 2023;389(3):228–238. doi: 10.1056/NEJMoa2208391
38. Subbiah V. The next generation of evidence-based medicine. Nat Med. 2023;29(1):49–58. doi: 10.1038/s41591-022-02160-z
    - **Very interesting paper on the future of clinical trials.**
39. Strom JB, Tamez H, Zhao Y, et al. Validating the use of registries and claims data to support randomized trials: rationale and design of the extending trial-based evaluations of medical therapies using novel sources of data (EXTEND) study. Am Heart J. 2019;212:64–71. doi: 10.1016/j.ahj.2019.02.007
    - **This is an interesting paper that describes new approaches using registry claims.**
40. Glassberg MB, Trygstad T, Wei D, et al. Accuracy of prescription claims data in identifying truly nonadherent patients. J Manag Care Spec Pharm. 2019;25(12):1349–1356. doi: 10.18553/jmcp.2019.25.12.1349
41. Bian S, Zhu B, Rong G, et al. Towards wearable and implantable continuous drug monitoring: a review. J Pharm Anal. 2021;11(1):1–14. doi: 10.1016/j.jpha.2020.08.001
42. Renard E. Implantable glucose sensors for diabetes monitoring. Minim Invasive Ther Allied Technol. 2004;13(2):78–86. doi: 10.1080/13645700410026993
43. Domingo-Lopez DA, Lattanzi G, L HJS, et al. Medical devices, smart drug delivery, wearables and technology for the treatment of diabetes mellitus. Adv Drug Deliv Rev. 2022;185:114280. doi: 10.1016/j.addr.2022.114280
44. Baryakova TH, Pogostin BH, Langer R, et al. Overcoming barriers to patient adherence: the case for developing innovative drug delivery systems. Nat Rev Drug Discov. 2023;22(5):387–409. doi: 10.1038/s41573-023-00670-0
45. Bhatt DL, Kandzari DE, O'Neill WW, et al. A controlled trial of renal denervation for resistant hypertension. N Engl J Med. 2014;370(15):1393–1401. doi: 10.1056/NEJMoa1402670
46. Azizi M, Pereira H, Hamdidouche I, et al. Adherence to antihypertensive treatment and the blood pressure–lowering effects of renal denervation in the renal denervation for hypertension (DENERHTN) trial. Circulation. 2016;134(12):847–857. doi: 10.1161/circulationaha.116.022922
47. de Jager RL, de Beus E, Beeftink MM, et al. Impact of medication adherence on the effect of renal denervation: The SYMPATHY trial. Hypertension. 2017;69(4):678–684. doi: 10.1161/hypertensionaha.116.08818
48. Schmieder RE, Ott C, Schmid A, et al. Adherence to antihypertensive medication in treatment-resistant hypertension undergoing renal denervation. J Am Heart Assoc. 2016;5(2). doi: 10.1161/jaha.115.002343
49. Hosohata K. Impact of medication adherence on renal denervation trials in resistant hypertensive patients. Hypertens Res. 2023;46(10):2419–2420. doi: 10.1038/s41440-023-01381-0
50. Kario K, Kai H, Nanto S, et al. Anti-hypertensive medication adherence in the REQUIRE trial: post-hoc exploratory evaluation. Hypertens Res. 2023;46(8):2044–2047. doi: 10.1038/s41440-023-01333-8
51. Schlaich MP, Bellet M, Weber MA, et al. Dual endothelin antagonist aprocitentan for resistant hypertension (PRECISION): a multicentre, blinded, randomised, parallel-group, phase 3 trial. Lancet. 2022;400(10367):1927–1937. doi: 10.1016/S0140-6736(22)02034-7
52. Azizi M, Perdrix L, Bobrie G, et al. Greater efficacy of aldosterone blockade and diuretic reinforcement vs. dual renin–angiotensin blockade for left ventricular mass regression in patients with resistant hypertension. J Hypertens. 2014;32(10):2038–2044. doi: 10.1097/HJH.0000000000000280

53. Beaussier H, Boutouyrie P, Bobrie G, et al. True antihypertensive efficacy of sequential nephron blockade in patients with resistant hypertension and confirmed medication adherence. J Hypertens. 2015;33(12):2526–2533. doi: 10.1097/HJH.0000000000000737
54. Simpson SH, Eurich DT, Majumdar SR, et al. A meta-analysis of the association between adherence to drug therapy and mortality. BMJ. 2006;333(7557):15. doi: 10.1136/bmj.38875.675486.55
55. Ogata A, Kaneko M, Narukawa M, et al. Lower-dose prescriptions in the post-marketing situation and the influencing factors thereon. PLOS ONE. 2019;14(6):e0218534. doi: 10.1371/journal.pone.0218534
56. Shiovitz TM, Bain EE, McCann DJ, et al. Mitigating the effects of nonadherence in clinical trials. J Clin Pharmacol. 2016;56(9):1151–1164. doi: 10.1002/jcph.689
•• **This is an important paper providing potential solutions.**
57. De Geest S, Zullig LL, Dunbar-Jacob J, et al. ESPACOMP medication adherence reporting guideline (EMERGE). Ann Intern Med. 2018;169(1):30–35. doi: 10.7326/m18-0543