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- Peter Sever

Introduction: Is adherence to medication the elephant in the room?



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Most medications act best when patients take them; and this appears to be the case also for antihypertensive drugs. Unfortunately, there is evidence that patients stop taking treatment that is intended to be taken lifelong. This is unfortunate and will reduce the potential preventive effects of their medication. Thus, adherence to antihypertensive medication is inversely related to cardiovascular outcomes^[1]. Similar findings have been demonstrated in other chronic disease conditions with high cardiovascular risk, such as diabetes^[2] and coronary heart disease^[3]. Adherence to medication is generally greater in secondary prevention of cardiovascular disease (approximately two thirds adherent) than in primary prevention (approximately one half adherent)^[4]. Of note, adherence to

cardiovascular preventive medication is generally not related to drug class, suggesting that other factors than side effects are important^[4].

There are several ways to assess adherence in clinical practice. They all have their advantages and disadvantages, and no way is perfect. Tablet counts, often used in clinical studies, and questionnaires, such as the commonly used Morisky adherence questionnaire, are often used but of limited value. Other methods, which appear to provide better information, include the combined use of electronic health records, data registries, and data on dispensed drug prescriptions; electronic pill containers recording opening and closing of the container; observed therapy units; and monitoring of drug concentrations in blood or urine. However, there are important ethical considerations to the assessment of adherence to treatment that should be considered.

Lack of adherence to medication is the elephant in the room. In order to improve blood pressure control we need to pay more attention to patient adherence to antihypertensive medication. The essays presented below will hopefully contribute to this.

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- Thomas Kahan

Registries – the golden standard for assessment of adherence to antihypertensive treatment?



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There is no perfect way to measure patient adherence. Methods that rely on patients' self-reporting are biased and those based on measurements taken during a consultation are subject to "white-coat adherence", i.e. improved adherence before a scheduled visit to the clinic or laboratory. One opportunity is to use registries increasingly available in healthcare since they may provide large samples of patients with hypertension, followed over long time with minimal risk for bias.

We live in the era of digitalization in healthcare. During the last decades, progress in computer technology allowed rapid access to data that in the past were very time consuming to collect and compile. During the 70s the first databases based on administrative claims data were established in North America and Europe. Today, an increasing number of healthcare organizations in North America, Europe and Asia have established large registers on diagnoses and dispensed prescription drugs—in many cases with the possibility of linkage to clinical data⁽¹⁻⁴⁾. The potential for analyzing drug utilization has further developed with the introduction of electronic health records containing not only prescription drug data but also clinical parameters, such as diagnosis, vital signs, laboratory data and more or less structured clinical notes.

Adherence research has been confusing due to the lack of universally accepted standards regarding terminology and methods. A few years ago, Vrijens et al, proposed an analytical framework where adherence consists of three different components⁽⁵⁾; *initiation* of the treatment (if the patient takes the first dose), *implementation* of the dosing regimen (the extent to which a patient's actual dosing corresponds to the prescribed dosing regimen) and *discontinuation* of therapy (if patient stops taking the prescribed medication). *Persistence* may be defined as the length of time between initiation and discontinuation of

therapy. Registers may be useful to measure all these components of adherence. Electronic medical records recording prescriptions issued by physicians can be linked to dispensing databases to assess the proportion not filling their first prescription, i.e., failure in the initiation of therapy. Longitudinal analyses of pharmacy dispensing data can be used to monitor implementation over time and to identify if the patient discontinues. Dispensing databases is a rather rough measure of implementation since it only allows for analyses of appropriate volumes dispensed according to the prescribed regimen and not to what extent patients actually take medications as prescribed. However, given the large unbiased samples of data closer to patient behavior than the medical records, dispensing data is considered as the golden standard in analyses of medication persistence⁽⁵⁾.

Today, a majority of all studies on adherence in hypertension uses data from registers⁽⁶⁾. Originally, there were limited opportunities linking dispensing data to clinical information. During the last decades, these opportunities have grown in many countries. We have used Swedish registry data and linked electronic medical records from 48 primary healthcare centers with national registers on sociodemography and dispensed prescription drugs to create a database for hypertension research, the Swedish Primary Care Cardiovascular Database (SPCCD)⁽⁷⁾. In a study on persistence to antihypertensive therapy we showed that only two percent of patients did not visit the pharmacy to claim their first prescription. However, many patients discontinued treatment early, with one sixth of all patients discontinuing directly after they purchased their first prescription, and one third had discontinued their medication after two years⁽⁸⁾.

There is a large range in persistence rates found in different studies (see Figure). This variation is not

surprising given the large discrepancies between studies in populations studied, ranging from elderly male American veterans with cardiovascular comorbidity to young patients in Italy being diagnosed with hypertension in primary care for the first time in life. It is also important to acknowledge the large differences in methods with, e.g., some studies having a diagnosis of hypertension as inclusion criteria while others include all patients initiated on antihypertensive drugs regardless of the underlying diagnosis. Furthermore, some studies assess therapy persistence (the proportion remaining on any antihypertensive therapy) while others assess class persistence (the proportion remaining on a specific drug class). Finally, there are inconsistencies in how exposure is measured and the gap applied on dispensing patterns to define discontinuation. It is important to critically assess the methods applied since they may introduce bias in analytical studies assessing differences in adherence between different pharmacological groups.

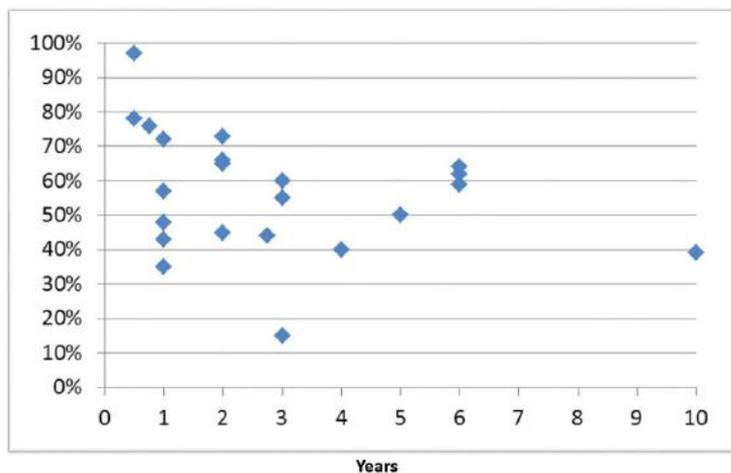


Figure legend: Therapy persistence rates in 20 studies on antihypertensive drugs. Studies from Europe, Australia and North America published 2002-2016

Many patient, provider or health system characteristics may influence adherence and persistence. A majority of studies include age, sex and comorbidity in the analyses. Others have analyzed adherence and persistence in relation to patient characteristics such as income, living area, ethnicity, social insurance, health status, education and marital status or provider characteristics such as organization of the clinic or physician education specialty and qualifications. In our studies we found the major determinants of discontinuation of antihypertensive drug treatment to be male sex, young age, mild-to-moderate systolic blood pressure elevation, and birth outside of Sweden^(8,9). Furthermore, we found no major differences in persistence between different drug classes⁽⁹⁾. Our conclusions on key determinants are in agreement with many other studies, but there are also studies showing the opposite. Studies assessing difference between antihypertensive drug classes have also shown conflicting

results. Unfortunately, we believe that this could partly be explained by methodological flaws and the fact that factors known to be associated with poor persistence are not taken into account.

Registers will continue to be important tools for research on adherence and persistence in hypertension. Future studies would benefit from applying a common terminology, improving the clarity in the methods section to enable critical assessment, conducting appropriate adjustment for potential confounders and including sensitivity analyses to assess the robustness of the study design. Finally, it is important to acknowledge the limited information available in registers about life style and attitudes to treatment among patients and physicians. The opportunities to acquire such information will increase substantially the coming years as a result of the increasing use of electronic patient surveys, smartphones monitoring patients' activity and real-time alerting medical devices.

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- Björn Wettermark & Miriam Qvarnström

Clinical aspects of screening for non-adherence to antihypertensive medications



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Non-adherence is defined as “the extent to which a person’s behaviour - taking medication, following a diet, and/or executing lifestyle changes - corresponds with agreed recommendations from a health care provider”. {1789 World Health Organisation 2003¹}

The term “compliance” was commonly used in the past to define non-adherence, but its use is not favoured now due to its negative connotation of the patient–doctor relationship.² Non-adherence is very common; around 5% of patients never initiate their treatment and 50% have a low persistence. The latter is defined as the period (measured in days/months) between the initiation and the subsequent non-adherence.

There are various measures that can be used to assess non-adherence in clinical practice. Physicians’ perception is considered to be no better than tossing a coin, and patient-reported questionnaires such as the commonly-used Morisky Adherence Questionnaire (MAQ), although inexpensive, generally tend to over-report adherence by up to by one fifth due to patients’ desire to appear to be “doing the right thing”.

Prescription refill rates are inexpensive and have the added benefit of providing information on persistence. Their accuracy depends on patients attending a single health system with seamless electronic records.³ Furthermore, the records may not reflect a patient’s current disease status or medication-taking behaviour. Medication event monitoring systems (MEMS) record dispensation of medicines. They are accurate, provide detailed data on dosing times and patterns of non-adherence but are expensive and can suffer from malfunction. A majority of these devices are also currently limited to recording a single medication per container.

All these above methods suffer from a key limitation in that they are surrogate measures which do not equate to ingestion of medication. Hence, direct objective measures such as directly observed therapy (DOT) clinics have been used. In DOT clinics, patients ingest their antihypertensive medications sequentially at intervals under continuous observation by a nurse. This is an expensive process and can be potentially dangerous due to symptomatic hypotension developed by non-adherent patients further

to taking several powerful blood pressure lowering medications.⁴

Digital pills are a recent new innovation. These pills, developed by the company Proteus, are licensed for use in Europe and USA. The pills contain ingestible sensors that are activated by gastric juices in the stomach and a signal is emitted which is detected by a patch worn by the patient. The information can then be transmitted wirelessly. These are expensive and are currently in very limited use, and patient acceptance of this method is unclear.

We and others have developed a biochemical method using high performance liquid chromatography–tandem mass spectrometry (HPLC-MS/MS) to assess non-adherence to antihypertensive medications in urine or blood.⁵⁻⁸ Non-detection of medication in urine implies that it has not been ingested for at least four half-lives prior to the sample collection and for the majority of anti-hypertensive medications this is greater than 24 hrs. The impact on persistence is unclear and the method may be susceptible to tooth-brush adherence - i.e. patient taking the medications just prior to the clinic visit (akin to the behaviour of brushing teeth prior to a dental visit).

We set the method in 2011, starting with a test for a single medication, and sequentially expanded to the current full screen of more than 40 antihypertensive medications.⁵ We receive samples from around 20 centres across the UK and have analysed more than 2000 samples to date. The method is reliable, robust and objective, being derived from forensic medicine. Our method requires 5-10mL of a random urine sample which can be transported by routine post and kept frozen until analysis. Samples are analysed in batches of 20.

There is a pre-analytical sample preparation step that requires around two hours of time for a mid-level laboratory technician. This is followed by analysis on HPLC-MS/MS. The run time is 30-40 minutes per sample (to detect all analytes). Subsequent to this, the results are interpreted by a senior technician and then authorised by a Laboratory Medicine Physician (Chemical Pathologist). The method requires relatively expensive instrumentation (~£200,000-£250,000) and significant technical expertise.

In our clinic, we request a urine sample from the patient on the day of their visit after verbal consent. The results are then discussed with the patient at their subsequent visit. We find that the objective result allows an open and non-confrontational discussion. It brings to the fore the patient's concerns about medication side effects and/or their beliefs that medications are not required given the asymptomatic nature of hypertension. We also address

issues like polypharmacy, and address forgetfulness by recommending dosette boxes.

The test is repeated at subsequent visits and in our experience this improves the adherence status of the majority of patients in only two to three visits. Our experience for the last 5 years has been that there is widespread acceptance of the test by patients. The HPLC-MS/MS-based test is particularly useful to confirm non-adherence in patients with suboptimal blood pressure response to medications. We have demonstrated the utility of this test early in the diagnostic pathway to resistant hypertension to prevent unnecessary and expensive investigations.⁹

In summary, non-adherence needs to be routinely assessed in patients especially those with suspected pseudo-resistance. Objective methods are to be preferred and we suggest that biochemical testing if available, be used as the method of choice.

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Monitoring antihypertensive treatment by drug analyses – critical issues and ethical concerns



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Poor adherence to prescribed drug therapy is a common and potentially modifiable reason for inadequate treatment effects, not least in chronic and (usually) asymptomatic conditions like hypertension [1,2]. The introduction of invasive treatment by renal denervation for patients with resistant hypertension has prompted the need for exclusion of modifiable causes behind the persistently elevated blood pressures before subjecting the patient to the risks associated with renal denervation. Before considering renal denervation in a presumably resistant hypertensive patient the possibility to control the patients' blood pressure with a regimen consisting of at least three drugs from different classes at optimal dosages should be ruled out whether the clinical setting is a trial or routine care. Adherence is an important issue in this context [1-4].

Long-term adherence to a complex treatment regimen is notoriously difficult to document. Interviews, pharmacy claims and electronic pill boxes are tools that yield some information but none of them actually prove that the drugs are taken as prescribed by the patient. Screening of the prescribed drugs or their metabolites in serum/plasma or urine has therefore evolved as an "objective" method for verifying adherence [3,4]. Finding drug/metabolite levels compatible with intake of appropriate dosages of the drug despite persistently elevated blood pressures would then support the contention that there is resistance to treatment. Absence of any of the analytes sought in the sample would argue

for poor adherence as a causative factor behind the "resistant" hypertension. However, it is important to know the robustness of a negative result (drug levels missing or too low) and what the positive predictive value of a positive result (all drugs found) is. Furthermore, there are ethical issues that need consideration and which may also influence the meaningfulness of the testing.

An important issue is the "time window" that the drug/metabolite analysis covers. This is for most antihypertensive drugs rather short – probably one or a couple of days depending on the drug/metabolite in question, its excretion pattern in the patient (which can vary) and the sensitivity of the assay. In drugs of abuse testing urine samples are preferred (although the samples can be adulterated to hide drug intake) since measurable levels persist longer in urine than in blood. What are the detection times in blood or urine (with confidence limits) for the drugs tested, taking both the dosing and the interindividual variability in pharmacokinetics into consideration? Is urine or blood the best matrix for the analysis? The time windows will be rather short and the analysis will provide information of a "snap shot" nature rather than proving that the patient is adherent in the therapeutic sense. The "tooth brush" effect, i.e. taking the prescribed treatment before a visit to the doctor, is a well-known phenomenon which cannot be excluded with assays that measure recent drug intake only. Long term information could be obtained by repeated measurements, but the tooth brush effect will probably be encouraged upon repeated monitoring. The best method for bioanalytical documentation of long term adherence would be to measure drug/metabolite levels in hair, which would cover a time frame of months, but I do not know if that is feasible.

How should the patient be informed about the drug testing? Informed consent is mandatory whenever this is possible in a research project [5]. Should this not be the case also in routine health care? Using a sample for

reasons other than those disclosed to the patient is unethical and confrontation of patients with negative test results will no doubt endanger the patient's trust of the doctor responsible for clandestine testing and, in the worst case, perhaps even of health care in general. A falsely negative result would be disastrous. If informed consent is obtained, when should this be? After sampling but before the analysis? Or before the sampling? In the former case the patient may feel that it is difficult to withdraw consent when the sample has already been taken. Regardless of the timing of the information, the possibility to obtain samples from unprepared patients will disappear after the first sampling. Most patients with "resistant" hypertension due to poor adherence will probably anticipate renewed testing and take their drugs before future visits, thereby avoiding negative test results even if they do not follow the therapeutic regimen between visits. The value of monitoring adherence by drug/metabolite analyses is thus limited for both analytical (detection periods) and ethical (informed consent) reasons. What are then the alternatives?

The key to good adherence and long-term persistence in a patient with hypertension lies in convincing the patient that taking the treatment as prescribed is in his/her best interest. The patient could become his/her own doctor and monitor the therapy with home blood pressure measurements. Electronic devices such as the MEMS monitor can be helpful for pedagogical purposes and pill

boxes that remind the patient or a Dosette with dispensed medicines can help the patient remember to take the drugs. Repressive measures such as witnessed drug intake and monitoring drug intake by bioanalytical techniques should be handled with great care. Most importantly, the integrity of the patient should be respected by informing him/her adequately about the purpose of sampling and at the same time the doctor should recognize the limited value of "snap shot" testing, especially if it is performed repeatedly.

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