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Measuring, Analyzing, and Managing Drug Adherence in Resistant Hypertension

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The management of hypertension is based on 2 major approaches: a modification of lifestyle and the lifelong prescription of antihypertensive drugs.[1,2] All hypertension guidelines recognize that "…the most effective therapy prescribed by the most careful clinician will control hypertension only if the patient is motivated to take the prescribed medication and to establish and maintain a health-promoting lifestyle." This statement clearly emphasizes the importance of supporting drug adherence (ie, adherence to the prescribed dosing regimens for prescribed medications) for patients to gain the maximal benefits of their therapy. Unfortunately, drug adherence in cardiovascular prevention remains low in the population. Thus, in a recent meta-analysis of data on 376 162 patients from 20 studies assessing drug adherence using prescription refill frequency for 7 preventive drug classes (aspirin, statins, and 5 antihypertensive drug classes) prescribed for primary and secondary prevention of cardiovascular diseases, mean adherence over all studies was only 57% after a median of 2 years. Furthermore, mean drug adherence was substantively and statistically significantly lower in primary than in secondary prevention.[3]

The role of drug adherence is particularly relevant in clinical situations in which drug therapies do not provide the expected results. This is typically so in resistant hypertension, commonly defined as the failure to reach blood pressure goals in patients adhering to adequate or maximal doses of an appropriate 3-drug regimen that includes a diuretic. Obviously, this definition of resistant hypertension implies that patients fully adhere to their therapy. This might actually be one of the reasons why the true prevalence of patients with resistant hypertension in the population remains largely ambiguous.[4,5] In clinical trials, 10% to 30% of patients are estimated to present with resistant hypertension.[6] In the National Health and Nutrition Examination Survey conducted between 2003 and 2008, 8.9% of all US adults with hypertension and 12.8% of the treated hypertensive population met the criteria of resistant hypertension.[7] A large Spanish survey has recently examined the clinical characteristics of patients with resistant hypertension and found it to be present in 12% of the treated population, although approximately one third of these patients had a white-coat hypertension during ambulatory blood pressure (BP) monitoring.[8] These 2 studies included in their evaluation patients with controlled resistant hypertension (ie, patients controlled on ≥4 medications). The cardiovascular risk profile of resistant hypertensive patients was higher than in nonresistant patients.

Interestingly, in none of these surveys was drug nonadherence considered as a potential cause of apparent resistant hypertension. In fact, in the discussion of his paper, the author of the National Health and Nutrition Examination Survey analysis admits that "the medication use questionnaire used in National Health and Nutrition Examination Survey does not distinguish whether medications were used consistently, only that they were used at all during the month before the examination. Some participants who were not fully adherent to their antihypertensive medication, discontinued a medication, or switched from one medication to another within the past month could be falsely classified as resistant."[7] This same ambiguity has confounded attempts to estimate adherence in other clinical situations that call for long-term use of prescribed medications.[9] Thus, the prevalence of nonadherence in resistant hypertension was very likely much higher than that actually published and was recently confirmed in a clinical study in which toxicological urine assessments were performed without patients' awareness of the test to evaluate drug intake in apparent resistant hypertension. In this study, the majority of resistant patients were either poorly adherent or totally nonadherent to their drug therapies.[10]

The absence of consideration of drug adherence before establishing a diagnosis of resistance to treatment is a serious limitation that may have important clinical and financial implications, especially now that new, surgery-based therapeutic strategies, such as renal denervation or baroreceptor stimulation, are being developed and proposed to treat resistant hypertension.[11,12] When dealing with such patients, physicians can evoke numerous reasons for not taking the proposed therapy, but the 2 most commonly encountered reasons are (1) nonadherence, often clinically unrecognized, to rationally prescribed drugs of proven efficacy and reliable bioavailability, and (2) pharmacological nonresponse to rationally prescribed, correctly administered drugs of proven efficacy and reliable bioavailability. The following sections review lines of evidence that support this conclusion.

Nonadherence: A Topic Burdened by Poor Methods and Many Misconceptions

One of the main reasons why drug adherence remains generally ignored, outside of clinical trials and prospective surveys, is the lack of reliable, easy to use, and economical methods to assess drug adherence in clinical practice. Since the 1980s, much effort has gone into devising methods for reliably quantifying ambulatory patients' adherence to prescribed medications, especially those intended for long-term use against various major chronic diseases (eg, hypertension, diabetes mellitus, osteoporosis, glaucoma, lipid disorders, asthma, posttransplant organ rejection, HIV-AIDS, chronic myelogenous leukemia, and others). This work and the methods that support it have recently been reviewed.[13] The best of the available methods provide for the reliable capture, storage, analysis, and communication of dosing history data in ways that make it difficult or impossible for patients or trial staff to censor or otherwise manipulate the data. Methods that meet these criteria today include the following: (1) retrospective analysis of prescription refill records, (2) analysis of chemical markers of drug exposure, and (3) automatic electronic time-stamping and compilation of events more or less strongly linked to the act of medication (eg, package opening, dosage form dissolution). Other methods, such as questionnaires, interviews, and periodic counts of patients' returned, untaken doses, are subject to many uncertainties and easy manipulation by patients.[13]

One of the most important results of adherence research in the past 3 decades has been the repeated finding, in a wide variety of clinical circumstances and prognoses, that substantive nonadherence to prescribed drug dosing regimens is much more commonly occurring than what many prescribers and clinical researchers had considered a priori or recognized clinically. This discrepancy has several sources: one of them is that prescribing physicians have been shown to have good ability to recognize good adherence but poor ability to recognize poor adherence unless patients admit that they are not taking their drug. So the net result is that prescribers' judgments about their patients' adherence have been aptly described as no better than a coin toss.[14] On their side, clinical trialists continue to report counts of returned, untaken doses (pill counts) from subjects enrolled in trials, despite strong evidence for their unreliability and consistent overestimation of trial patients' adherence to protocol-specified dosing regimens. In the late 1980s, careful work by Pullar et al[15] with a well-validated, low-dose chemical marker method showed that counting returned, untaken tablets or other dosage forms grossly overestimates adherence. Overestimation occurs because many patients discard or hoard untaken doses rather than returning them to the trial staff, thus biasing upward the estimate of the patient's adherence because the method is based on the assumption that all unreturned doses have been taken by the patient. That assumption is contradicted by 2 observations: first, what patients return when they have been given substantially more doses than needed for full adherence during the intervals between successive clinic visits and, second, the consistently higher estimates of adherence by returned tablet counts than by electronic monitoring methods.[16]

Analysis of Chemical Markers of Drug Exposure

Chemical methods certify that drug has been ingested but they are labor intensive and tend to be costly. These methods also have some critical shortcomings: although they unequivocally document the ingestion of doses, they cannot provide information on when doses were taken or omitted. This limitation is important because of the basic pharmacological principle that the size of patients' responses to prescribed drugs is determined not only by the size of doses taken but also by the time intervals between successive doses.[16] Much of the work on adherence research has neglected this fact and has, instead, used imprecise, often misleading surrogate measures of patients' exposure to prescribed drugs (eg, the percentage of prescribed doses taken, the proportion of patients who had, during an arbitrary time interval, taken more or less than an arbitrary percentage of prescribed doses). The proper specification of drug exposure should be robust enough to serve as input to appropriately formulated pharmacokinetic models for the ADME characteristics of the drug in question—absorption, distribution, metabolism, excretion, the 4 key parameters of pharmacokinetics—resulting in an accurate projection of the continuous time course of drug concentration in plasma,[17–19] which is verifiable by intermittent, direct chemical measurements of the concentrations in plasma of the drugs in question.

Drug measurements are also affected by the white-coat adherence phenomenon whereby patients tend to improve their adherence before and after clinical visits.[20] White-coat adherence was identified in the first years of electronic monitoring of ambulatory patients' drug intake.[20,21] In 1990, Cramer et al[21] showed that the analogous white-coat dosing behavior occurred in seizure-prone patients prescribed antiepileptic drugs: those with frequent erratic dosing histories tended to revert to punctual oral dosing in the several days before a clinic visit. It is a phenomenon that has been repeatedly observed in other therapeutic fields, including in hypertensive patients (Figure 1). Its practical effect is to mask usually poor adherence by creating a false clinical impression that good adherence is maintained over long periods of time. This misimpression is reinforced by the fact that many drugs have pharmacokinetics that can bring the concentration of drug (or active metabolite) from zero up into the usual therapeutic range by the prior ingestion of only 1 or 2 doses of drug. Thus, patients who take 1 or 2 doses in a day or 2 before a scheduled clinical or laboratory visit can readily create false impressions of good adherence, provided that the pharmacokinetics and pharmacodynamics of the drug in question allow fast responses to fast changing dosing histories.

Concentrations in plasma of antihypertensive drugs actually failed to find broad clinical use in the heyday of therapeutic drug monitoring, which occurred in the latter 1970s. Part of the problem has been the limitations of single-point assays for the concentration of drugs in plasma, many of which have large peak-to-trough swings within the intervals between properly timed, sequential doses. These big fluctuations preclude simple, intuitive recognition of concentration–effect relationships. The resulting lack of evident clinical explanatory power of single-point values of most antihypertensive drugs and the fact that not all antihypertensive drugs were detectable in urine or plasma closed that chapter in hypertension research.

Drug adherence (%)
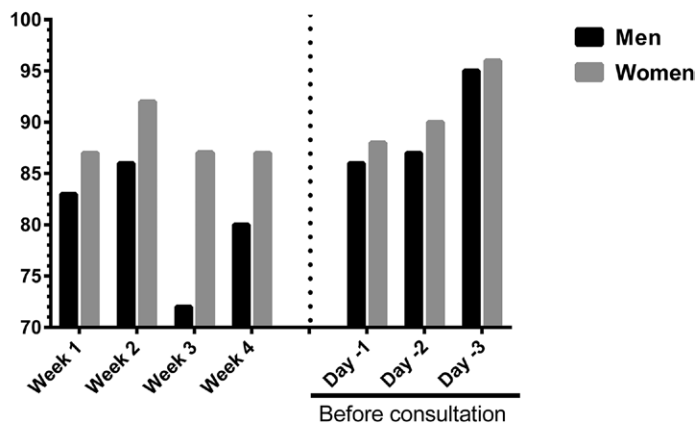
Figure 1. An example of white-coat adherence in hypertensive patients receiving once-daily diuretic therapy. Note the progressive decline in drug adherence over weeks and the sudden improvement in drug adherence during the 3 days preceding the medical visit.

As mentioned previously, a recent study proposed single-point measurements of drug concentration in urine samples in patients with resistant hypertension.[10] The authors found that a large proportion of samples had very low or zero concentrations of drug in this population. The problem posed by this approach is that, for ethical reasons, such measurements need to be done with informed consent of patients and thus tend to stimulate white-coat adherence. In overview, the use of spot checks of urinary drug or drug metabolite concentration requires one to reconcile the needs for (1) more than a single sample; (2) disclosure of the testing to patients; and (3) avoiding the upward bias created by white-coat adherence. It is doubtful that these needs can be simultaneously met well enough to result in a reliable test.

The crucial variable in the measurement of patient adherence is the patient's drug dosing history, from which it is possible to project, noninvasively, the continuous time course of drug concentration in plasma. The accuracy of these projections is subject to verification by occasional direct measurements.[17–19] But for the occasional direct sampling of blood for validation purposes, these projections are noninvasive. Temporary bursts of white-coat adherence or other transient biases may occur, but are set in the context of the patient's longer-run dosing history. Thus, the patient's exposure to the drug in question is not dominated by temporary aberrations in the long-running time series of doses taken and the complete time course, over days or weeks of drug dosing, of the drug's concentration in plasma. The capability of making these data-rich projections noninvasively puts the clinical correlates of patient adherence and pharmacokinetics into a long-term perspective and is a practical therapeutic consequence of the combined use of electronic medication event monitoring and modern pharmacometric methods of model-based analysis. Thus, ideally, drug measurements should be combined with a precise dosing history data enabling to interpret drug concentrations in relation to the dosing interval.

Electronic Monitoring Methods of Assessing Adherence

Because of their automaticity and precision of timing when patients take or omit doses, electronic monitoring methods have opened a new era in understanding the sequences of drug exposure and clinical events during prescribed pharmacotherapy for leading chronic diseases, including hypertension.[22] Electronic monitoring methods have followed several approaches, starting with eye drop dispensing in the treatment of sight-threatening glaucoma and ocular hypertension[23,24] and then into orally administered tablets or capsules. Two approaches to electronic monitoring of orally administered drugs have been developed: medication event monitoring system (MEMS; AARDEX Group, Ltd, Sion, Switzerland), which time stamps and stores times/dates of each opening of the drug package[13,16] and the recent innovation by Proteus Digital Health Inc (Redwood City, CA), which incorporates into each dose of drug a specially designed microchip that, on ingestion and solubilization, emits a brief, low-strength, radio signal that is detected, amplified, and transmitted onward by an adhesive patch worn by the patient.[25] The signal then passes, via a Bluetooth link, to a nearby wireless phone that communicates the dosing time data to a computer, which can be situated wherever there is a phone link. Error rates with both types of electronic monitoring have been reported to be $\approx 3\%$.[13,25]

Of the foregoing methods, MEMS monitoring has had the most extensive use, having been marketed as a scientific product for use in drug trials since 1988, with >570 completed clinical research studies based on uses of MEMS monitoring and published in peer-reviewed journals. The references to these publications are accessible at www.iadherence.org. MEMS monitoring is based on an indirect measurement—packaging opening time—but this method has been extensively validated in the past 3 decades.[17–19] Several studies have been conducted in the field of hypertension using the MEMS monitoring system, including in resistant hypertension.[22,26–28]

What Lessons Have We Learned About Patient Adherence, its Detection, and its Analysis?

The greatest catalysts for adherence research have been the succession of stark discrepancies between advances in pharmacological power and shortcomings in the clinical realization of therapeutic benefit from powerful drugs as observed today in resistant hypertension. During the last half-century, islands of special awareness of the importance of patient adherence have formed, as new and unprecedented, dose- and time-dependent actions, and therapeutic power was seen to be thwarted by patient nonadherence (eg, antibiotic and chemotherapeutic treatment of tuberculosis[29]; oral steroidal contraception[30]; antiretroviral treatment of HIV/AIDS[31];

immunosuppressant-based management of recipients of transplanted organs[32] and of course treatment of hypertension).[33,34]

The most recent studies on drug adherence have taught us several important clinical lessons. The most fundamental point is that adherence is not a therapeutic parameter that can be described by a single number, as usually reported in the literature. Adherence is essentially a dynamic process, with sometimes slow-to-change effects on drug actions of variable exposure to prescribed drugs. A major step toward defining the best metrics for properly quantified drug dosing histories is the recent publication of the ABC Taxonomy for Describing and Defining Patient Adherence to Medications.[13] In this context, it became evident that setting arbitrary cutoffs, such as 80%, are of little clinical interest for many reasons. One of them is that an adherence of 80% can be achieved in many different ways, each with a very different clinical impact (eg, 1 missed dose every 5 days or 1 missed week of doses every 5 weeks). Furthermore, no one really knows what level of adherence is sufficient to obtain the full benefit of a drug because drugs were rarely investigated in this respect. Thus, depending on the pharmacological characteristics of the prescribed drug, 80% of prescribed doses taken may be sufficient or not for full therapeutic benefit. Thus, in resistant hypertension, we reported an increase in BP when drug adherence was <90% of prescribed doses being taken.[26] Short-term drug omissions may have less impact on clinical parameters and cardiovascular end points, with drug having a long duration of action.[35] This observation was the base of the concept of forgiving drugs.[36] At this point, it is also important to point out that the time of discontinuation of dosing, as measured by prescription refill intervals, is highly uncertain, because it takes 2 sequentially missed refills to support the conclusion that the patient has stopped taking the medicine. Because refill intervals are typically 2 to 3 months, this means 4 to 6 months of uncertainty as to when the patient quit taking the medicine.

The electronic monitoring of drug adherence provides a unique description of the temporal patterns of drug intake and behavior in the population, including in the hypertensive population. This point is illustrated in a recent analysis of 4783 patients who participated in 1 of 21 different phase IV studies involving 43 different once-daily antihypertensive drugs, mostly of relatively recent origin, including recipients of angiotensin II receptor blockers (n=2088), calcium channel blockers (n=937), angiotensin-converting enzyme inhibitors (n=665), β-adrenergic receptor inhibitors (n=195), and diuretics (n=155).[37] The study encompassed 478 630 days of dosing history data. These data were gathered from a series of organized phase IV clinical studies, not from routine care.

Three types of deviation from prescribed dosing instructions are shown in Figure 2, which extended the results of the above-mentioned analysis in hypertension to 36 907 patients prescribed oral medications for one of a variety of medical conditions in 95 studies[16]: (1) noninitiation; (2) short persistence; or (3) nonexecution of the dosing regimen.

Noninitiation is indicated by an abrupt decline of ≈4% in the dark blue line; it is small in this set of clinical circumstances, but there are other clinical situations in which noninitiation can be much larger. In the context of this review, the main point is that noninitiation is a situation-specific part of the overall adherence story. Noninitiation needs to be measured and included in the overall analysis of adherence within every study involving ambulatory patients who have the responsibility for medication-taking.

Short persistence is indicated by the gradual but inexorable downward movement of the dark blue line, falling more rapidly during the first 90 days than later, reaching the 50% point at 330 days after the start of treatment. These patients ceased their engagement with the dosing regimen on their own initiative—an act that is inherently willful, not arising from forgetfulness.

Lapses in implementation (or execution) of the once-daily dosing regimen gave rise to the irregular red dashed line, which reflects the fact that, on any given day, ≈8% to 10% of patients omitted that particular day's scheduled once-daily dose, although the patients could be seen to have remained still engaged with the dosing regimen, in that they returned to dosing after ≥1 days of omitted doses. Lapses in implementation (or execution) are typically a consequence of forgetfulness or negligence: most of such errors involve a single day's dose, but some are part of a multiday sequence of omitted doses, thus giving rise to exceptionally long intervals between sequential doses, so-called drug holidays, which are an important aspect of patient nonadherence. The frequency of occurrence of lapses in dosing has been analyzed recently.[37] From this analysis, it seems that longer lapses occur less frequently than shorter lapses.

Figure 3 shows the similarity of 4 studies of patients' persistence with antihypertensive drugs in routine practice.[38–41] There is remarkable similarity between the results of these 4 pharmaco-epidemiological studies of in-practice persistence with antihypertensive drugs, but there is also remarkable similarity of these pharmaco-epidemiological results to the aggregated results of the 21 clinical trials from Figure 2. There is no evidence here for a substantive difference between in-practice and in-trial adherence.

Drug Adherence and BP Control

As shown above, approximately half of the patients who start treatment for hypertension abandon treatment during the first year of treatment. Other studies show that nonpersistence continues to reduce the number of patients still engaged with antihypertensive drug dosing regimens out to ≥5 years after the onset of treatment, by which time only 10% to 15% of the originally treated patients are still engaged with the regimen. These strikingly high rates of abandonment of drug treatment help explain why a substantial majority of patients with resistant hypertension turn out, after careful evaluation, to be nonadherers, with pharmacological nonresponders being only a minority of patients. Some propose to use the term pseudoresistance for the nonadherers, but, given that nonadherers constitute the vast majority of patients deemed resistant, they deserve a straightforwardly descriptive term instead of a euphemism. Thus, the identification of resistant hypertension is a unique opportunity to reconsider drug adherence and to investigate this issue adequately.

Of note, a relationship between the percentage of drug adherence and the level of BP control has been difficult to demonstrate in hypertension.[42] Several reasons can explain why it has been so difficult to establish such a relationship.
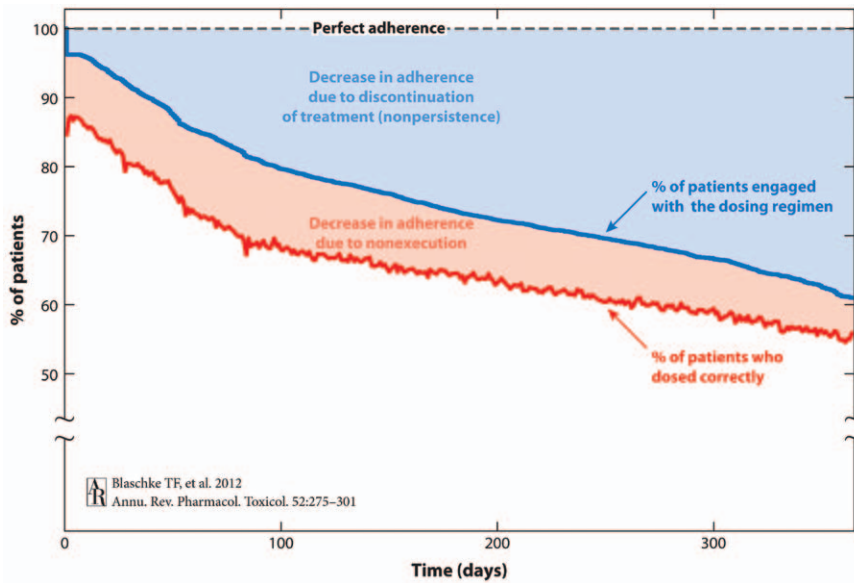
Figure 2. Kaplan–Meier plots of the time course of adherence parameters of 36 907 patients prescribed oral medications for one of a variety of medical conditions in 95 studies during the first year of electronic compilation of the patients' dosing histories. The horizontal dashed line at the top illustrates how perfect adherence of all patients would be depicted. The dark blue line shows the percentage of patients still engaged with their dosing regimen as time passed after the start of treatment. The abrupt drop in the dark blue line at zero time reflects noninitiation of treatment by ≈4% of the patients. The subsequent decline of the dark blue line arises from patients' permanent discontinuation of their dosing, as they ended their persistence with the prescribed once-daily dosing regimen. The irregular red line shows the percentage of patients who were (1) still engaged with the dosing regimen and (2) who dosed correctly on each day of the observation. The slight wobble in the red line arises from day-to-day variation in the proportion of patients who dosed correctly on each day. The pink area between the dark blue line and the irregular red line indicates the shortfall in drug intake that arose from intermittently omitted doses. The light blue area between the horizontal dashed line and the dark blue line indicates the shortfall in drug intake arising from the combined influences of (1) noninitiation of dosing by ≈4% of the treated patients and (2) early, complete discontinuation of dosing, also known as short persistence, by ≈35% of the patients. Data from the iAdherence database (www.iadherence.org). Adapted with permission from Blaschke et al.[16]

First, as soon as the attention is focused on drug adherence, the latter increases substantially in all groups, including controls. Hence the difference between the intervention and the control is reduced, leading to the absence of statistically significant differences in BP, as differences between treated and control patients narrow and the variances in the 2 sets of data increase. It is also possible that patients who accept to participate in adherence studies have a higher drug adherence than those who refuse to be enrolled (selection bias). And finally, any measure of adherence per se increases the patient's adherence. In fact, the latter observation has been used clinically to determine the true efficacy of a prescribed drug regimen.[26,43] We observed that the monitoring of drug adherence during a period of 2 months, without changing the prescribed treatment, enables to assess how much BP decreases when the therapy is taken adequately. This approach provides an opportunity to interfere with the real problem, that is, with drug adherence if the patient does not take his/her medications or with the drug prescription if adherence is good but BP remains uncontrolled.[26] In our study, about a third of patients with resistant hypertension normalize their BP on monitoring adherence, whereas another third of patients improve their BP control and the last third remain uncontrolled. However, among patients of the last category some were truly nonadherent but some were adherent, but either did not receive adequate treatment or had a secondary form of hypertension. In a recent assessment of resistant hypertension, increasing treatment intensity resulted in an improved 1-year BP control in a large proportion of patients, suggesting that insufficient treatment is also an important issue to consider.[44]
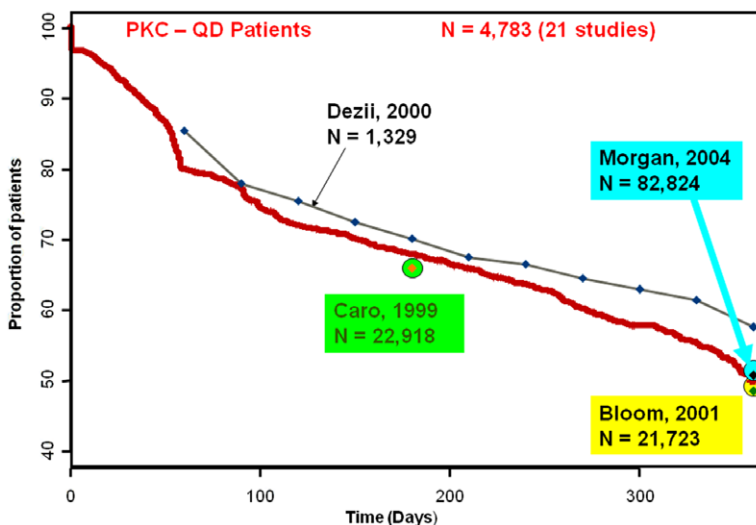
Figure 3. The red line in this figure is the same as the dark blue line in Figure 2, showing the time course of early discontinuation of (short persistence with) the prescribed once-daily dosing regimen for each of the 43 once-daily antihypertensive drugs tested in the 21 phase IV studies summarized in Figure 2 and based on data generated by continuous electronic monitoring. The individual points in, respectively, yellow,[33] blue,[34] green,[35] and black[36] show persistence reported by 4 different trials in which adherence to once-daily antihypertensive drugs was studied by means of prescription refill records. The ubiquity of short persistence is indicated by both methods. PKC indicates pharmacokinetics.

Drug Adherence and the Occurrence of Cardiovascular Events

Intuitively, patients with a better adherence to their antihypertensive therapy should have a better BP control and hence a lower incidence of cardiovascular complications. As discussed above, the relationship between drug adherence and BP control is not straightforward. Nonetheless, the results of retrospective cohorts using refill adherence data have demonstrated that a high level of refill adherence is associated with a significantly lower risk of stroke and death.[45–47] Similarly, in another survey, patients with a low adherence were more likely to have coronary disease (odd ratio, 1.07; 95% confidence interval, 1.00–1.13), cerebrovascular disease (odd ratio, 1.13; 95% confidence interval, 1.03–1.25), and chronic heart failure (odd ratio, 1.42; 95% confidence interval, 1.27–1.58) within a 3-year follow-up period.[46] A close relationship between cardiovascular events and drug adherence in hypertension has also been found using administrative databases providing information on renewal of prescription in huge numbers of patients in a real-life setting.[48] These observations are noteworthy and indeed suggest that good drug adherence is associated with a better clinical prognosis. In a more recent study conducted in Spain, the efficacy of a multifactorial intervention to improve adherence to antihypertensive medication was evaluated in 877 hypertensive patients followed for a mean of 39 months. The intervention was indeed effective in improving both drug adherence and BP control, but it did not change the incidence of cardiovascular events.[49]

Whether ameliorating drug adherence will reduce cardiovascular events remains, therefore, uncertain. In any case, it is always difficult to conclude that the better prognosis is due uniquely to the better adherence to antihypertensive drugs. Indeed, Simpson et al[50] reported in a recent meta-analysis that a good adherence is associated with a positive health outcome. However, a good adherence to placebo was also associated with a lower mortality, implying the phenomenon of healthy adherer whereby patients adhering to drugs have an overall healthier behavior leading to a better cardiovascular prognosis. A similar observation has recently been made in a study in patients with heart failure.[51] Most studies that purport to show a beneficial effect of adherence to placebos are secondary prevention trials, in which clinically important, nontrial medications are in use. The strong linkage of adherence to concomitantly prescribed drugs (eg, trial placebo and nontrial medications) is likely to play a major role in the occurrence of better clinical results in good adherers compared with poor adherers.[52] Of note, in some cases, a low adherence may be protective if active treatment causes a greater risk as observed with antiarrhythmic drugs.[50]

How Can We Improve Drug Adherence?

Returning to Figure 2, the large differences in the areas created by short persistence, on the one hand, and forgotten or neglected doses, on the other hand, show that short persistence, which is not a direct consequence of forgetfulness, creates by far the biggest shortfall in adherence—many times bigger than the shortfall in implementation (execution), which is mainly driven by forgetfulness. In contrast to these data, a superabundance of reminder products are currently being promoted for solving the adherence problem, strikingly discordant with what the data show.

What are the clues to improve the execution pattern and most importantly the long-term persistence to antihypertensive therapy? The day-to-day execution can be improved in several ways, including with the use of reminders (phone calls, SMS, and so on) or pill organizers. The patient can be involved in the measurement of home BP, and family members can be asked to support these efforts. These simple interventions can be successful, but in the long run their impact on drug adherence seems to remain modest.[53] In some countries, a multidisciplinary approach that includes pharmacists and nurses has been shown to be effective in improving adherence, but the approach may or may not be economical.[54,55]

Because the complexity of the treatment is a hurdle that tends to lower drug adherence, one frequently proposed strategy is to simplify the treatment scheme using single-pill combination enabling once-daily dosing.[56,57] The combination should preferably contain long-acting substances to maximize forgiveness against brief periods of dose omissions. Studies have demonstrated that the use of single-pill combinations has some advantages. But it also has drawbacks. Indeed, if the patient omits several consecutive doses of a single-pill combination, he/she actually misses 2 or 3 drugs simultaneously, increasing the risk of hypertension rebound effects (eg, with non-intrinsic sympathic activitiy β-adrenergic blocking agents). In fact, although a twice-daily regimen creates twice as many opportunities for missing a dose as does a once-daily regimen, the twice-daily regimen appears to be better at maintaining continuity of drug exposure than does the once-daily regimen, although a somewhat higher percentage of prescribed doses are omitted. The underlying pharmacokinetics are such that it takes ≈3 consecutive dose omissions from a twice-daily dosing regimen to have the same impact on drug action as a single dose omission from a once-daily dosing regimen.[58] That is the basis of the paradox of the so-called twice-daily advantage: better maintenance of drug action despite a somewhat higher percentage of prescribed doses omitted. Thus, the once-daily treatment should not be a dogma, particularly in difficult-to-treat hypertensive patients.

Improving long-term persistence to therapy is a much more difficult task because there are many hurdles to overcome in a lifelong treatment, including drug efficacy, drug side effects, and occurrence of complications, concomitant diseases, fears, and beliefs. A major issue is the provision of correct information for the patient on the risks and benefits of the therapy and on the goals to be achieved. It is also important to identify risk factors for a low adherence. In a recent American survey, patients with apparent resistant hypertension were more likely to be black, men, to have less than a high school education and a low annual income, and to have elevated depressive symptoms.[59] Interestingly, this profile of risk is very similar to that of patients with a low adherence. Drug adherence should be addressed during every follow-up visit, with specific questions that emphasize the importance of long-term persistence. Studies have actually shown that nonpersistence is significantly higher in newly treated hypertensive patients, who thus deserve special attention.[60] In this context, persistence

can be enhanced with more frequent visits. Of note, although simple combinations have been shown to improve execution, the impact on persistence is only modest, with a 10% to 20% improvement over 1 year.[61]

One solution to improve the long-term control of hypertension would be the development of new therapeutic strategies that avoid drugs. The immunization against the renin-angiotensin system was developed with this intention,[62] but it has thus far remained unsuccessful. Renal denervation and baroreflex stimulation could also be considered as new ways to avoid drug use.[11,12] So far, however, these interventions have been investigated in resistant hypertension only, and, in this context, neither renal denervation nor baroreflex stimulation has proven to be a way to avoid the use of antihypertensive drugs. Indeed, although marked and significant decreases in BP have been obtained with these approaches, most patients have to stay on drug after the intervention. In some studies, a reduction in doses was reported, but in others the doses were either unchanged or increased.[11,63] Thus, in resistant hypertension, renal denervation or baroreflex stimulation cannot, at present, be considered as an opportunity to avoid problems with drug nonadherence. However, the situation might be different if these techniques were to be applied in earlier stages of hypertension, but remains to be seen. This hypothesis will certainly be tested in the near future.

Disclosures

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