THE QUESTION

Nonadherence to treatment regimens is all too often the bane of disease management, and this is also a challenge in hypertension. The reasons behind nonadherence are numerous and complex, perhaps not so surprisingly dependent on the patients, the disease, and the treatment, but also even on the physicians prescribing the therapies. Understanding how to combat this issue from patient and physician education to simplification of therapeutic regimens through combination-pill treatments are discussed.

Challenge of medication nonadherence in daily practice

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Hypertension remains a very significant risk factor for the development of premature cardiovascular disease, stroke, and heart failure. Over the decades, despite the emergence of multiple classes of medications effective in controlling blood pressure, hypertension control remains dismal.

Similar to observations worldwide, hypertension prevalence in the Philippines has continued to grow over the past 2 decades. The National Registry for the Prevalence of Hypertension in the Philippines[1] in 1993 showed hypertension prevalence in the Philippines to be 11%. PRESYON 1 (The Philippine Heart Association-Council on Hypertension Report on Survey of Hypertension in the Philippines) in 1997-1998 and PRESYON 2-TOD (PRESYON 2–Target Organ Damage) in 2007, showed the Philippine hypertension prevalence to have increased significantly to 22% and 21% respectively.[2,3] Subsequently, PRESYON 3 in 2012-2013 showed hypertension prevalence in adults aged 18 and over to have increased dramatically to 28%, with the current hypertension control rate being 23% (Figure 1[1-6]).[4]

Dyslipidemia is likewise a pressing problem in the Philippines. Based on the 2008 data from the National Nutrition and Health Survey,[6,7] the true prevalence of dyslipidemia is 72.9% (79% for males and 62.3% for females), which increased from the 2003 prevalence of 62.5% with mean values for total cholesterol (186.6 mg/dL), low-density-lipoprotein cholesterol (LDL-C; 118.3 mg/dL), high-density-lipoprotein cholesterol (HDL-C; 40.1 mg/dL), and triglycerides (141.3 mg/dL) respectively. The high prevalence was mainly due to the high prevalence of low HDL-C at 64.1% compared with the prevalence of high triglycerides, high LDL-C, and high cholesterol at 14.6%, 11.8%, and 10.2% respectively.

Good blood pressure (BP) control is highly reliant on identifying the appropriate medication for each patient and good adherence to the prescribed regimen. Adherence to medication is defined as the extent to which patients follow the recommendations for prescribed treatments; medication nonadherence has been identified as a possible contributor to the persistent poor BP control worldwide. Nonadherence to medication is a complex and multidimensional health care problem that may be related to the patient, treatment, and/or health care provider.[8] For example, patients commonly stop taking medications once they are asymptomatic and have obtained good BP control because of the mistaken notion that their hypertension has been cured and because of a fear that medications could lead to organ damage, particularly for the kidneys. The cost of medications has also been identified as a significant factor for treatment nonadherence, especially in societies where treatment costs are largely out-of-pocket, like in the Philippines.

Occasionally, even physicians can contribute to poor BP control because of reluctance to aggressively treat hypertension for fear of possible adverse events and hypotension.[9] They may even delay modifying treatment because they perceive that it may take months before the maximal effect of treatment is reached.[10]

Generally, adherence rates to medications are higher among patients with acute conditions than in patients with chronic diseases.[11] Consistent adherence among patients with chronic conditions drops most dramatically after the first 6 months of therapy.[12] This is particularly true for hypertension, as medications may be expensive and most patients would require

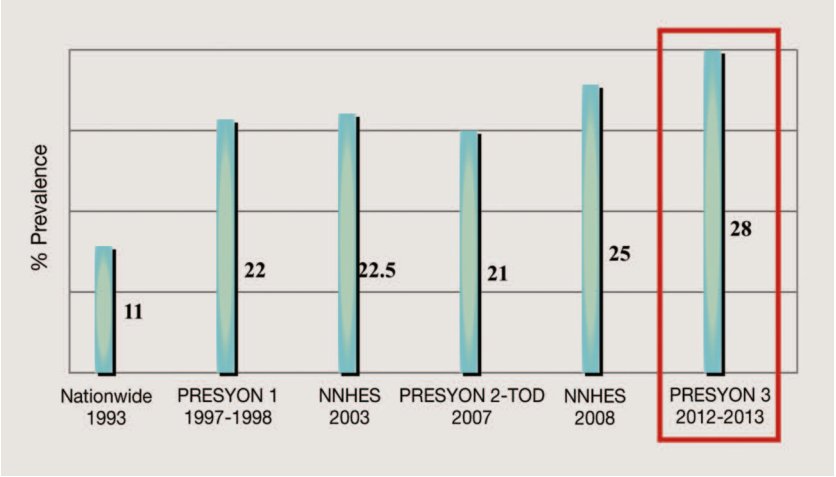

Figure 1. *Prevalence of hypertension in adults as shown nationwide, in PRESYON 1, NNHES 2003, PRESYON 2-TOD, NNHES 2008, and PRESYON 3.*

In PRESYON 3, the prevalence of hypertension in adults aged 18 years and over in the Philippines was 28% (50% female, 50% male; n=933/3334).

Abbreviations: *NNHES, National Nutrition and Health Survey; PRESYON, The Philippine Heart Association-Council on Hypertension Report on Survey of Hypertension in the Philippines; TOD, Target Organ Damage.*
Based on references 1-6.

multiple drugs—as seen in multiple landmark trials—in order to adequately control BP.[13-22]

There remains an urgent need to improve medication adherence in order to achieve good hypertension control. This would entail ongoing education of patients on the necessity to continue medication for adequate BP control. Also, physicians need to be kept up-to-date on current guidelines for therapies to improve BP control. More importantly, simplification of treatment regimens is an important tool to improve patient adherence. In this aspect, single-pill combinations appear to be very effective, as they allow for multiple medications to be given as a single pill, and patients may find this the best approach to improve their adherence to medications that should be maintained for a lifetime in order to decrease morbidity and mortality related to hypertension.

In summary, despite advances in current modes of treatment for hypertension, the Philippine prevalence just like the worldwide prevalence continues to rise through the years. One of the most significant factors for this failure to control hypertension is medication nonadherence. As such, strategies to improve medication adherence are necessary, including strategies that simplify medication schedules such as once-a-day hypertension medications and fixed-dose drug combinations for those requiring multiple drugs. A hypertension clinic hotline may also be effective for addressing patients' questions and issues about their illness and treatment strategies.

However, a cornerstone to the success of hypertension treatment would be patient education. Patients need to be aware and educated about their condition, their risk factors, and goals of treatment. Patients must be made aware of clear instructions for lifestyle modification, including salt restriction, diet modification, importance of exercise, what type of exercise they need to engage in, and sometimes even resting schedules. Patients must not be passive receivers of medications only but should be an active component of the treatment itself. Physicians together with their patients must identify the current problem, the lifestyle modifications that need to be adopted, and the medications to be started, including the rationale for these medications. The goals for treatment and measures for success need to be identified together with positive motivation strategies to keep patients adherent to the treatment regimen. ■

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The World Health Organization emphasizes that cardiovascular diseases account globally for one-third of annual deaths, a phenomenon strongly driven by commonly prevalent metabolic risk factors including raised blood pressure (BP) and elevated cholesterol.[1] Although hypertension and high blood lipids are modifiable with pharmacological and nonpharmacological treatment, their overall long-term control remains insufficient.[2-4] It is estimated that globally, only one-third of those hypertensive patients receiving pharmacological treatment are characterized by BP of less than 140 mm Hg over 90 mm Hg.[5] Notably, in light of recently modified targets for BP and low-density-lipoprotein cholesterol (LDL-c) serum concentrations, achieving the lower goals may be even more challenging.[6-8] In high-cardiovascular-risk European countries—eg, Poland—where prevalence of hypertension is about 11 million, and high cholesterol is diagnosed in 60% to 70% of the adult population, effective treatment and control could translate into a sizable benefit.[4,9,10] In fact, sufficient BP control in Poland increased twofold over the last decade; however, it remains as low as 26%. Unfortunately, hypercholesterolemia awareness and control rates are even worse than that. Up to 60% of Poles with high cholesterol are unaware of it, and only 6% are treated and achieve the treatment target.[9] Although long-term cardiovascular disease risk factors control things such as high BP and high blood lipids are a rather multifactorial problem, there is compelling evidence indicating that poor adherence to therapy is one of the most important causative factors responsible for this matter.[11]

This is of substantial clinical importance, as several studies have documented that adequate adherence to antihypertensive and statins administration may independently translate to lower rates of organ damage and of all-cause mortality.[11,12] The size-effect of so-called good adherence (expressed in medicines possession) to a drug regimen have been associated with lower relative risk (RR) for all-cause mortality estimated at 0.71 (95% confidence interval [CI], 0.64-0.78) and 0.55 (0.46-0.67) for BP-lowering agents and statins, respectively, as recently confirmed in a large meta-analysis (approximately 2 million nonoverlapping patients).[12] These data strongly suggest that the interventions aimed at the improvement in adherence to BP-lowering and lipid-lowering therapies should become priorities in everyday clinical practice.

Unfortunately, practitioners are incapable of identifying patients who are nonadherent. As shown in one study that compared two modalities to assess patients' adherence, ie, subjective (ascertained by health care provider) vs objective (tablet monitoring), physicians are able to identify nonadherent patients in approximately 50% of them only, which is no more effective than a coin flip.[13]

Since nonadherence develops soon after the initiation of antihypertensive and blood-lipids–lowering therapy (after 6 months of therapy, only one in three patients may be considered adherent to both medications),[14] it is justified to analyze all possible causes of patients' reluctance to continue to receive their drugs and to seek effective measures to sizably aid the problem. Nonadherence may be explained by several factors (some causes partially overlap) including: unsuccessful treatment, especially at treatment initiation (eg, administration of short-acting drugs, suboptimal doses, incorrect combination), too many medications, frequent changes in drug regimens, necessity to foot the entire cost, development of or the fear of development of drug side effects, absence of symptoms (common in primary cardiovascular disease [CVD] prevention), insufficient education about the goals of treatment, mistrust and contradicting information, fear of developing drug dependency, or leaving of the decision to modify drug regimens to patients themselves, just to name a few. Evidently, education and comprehensive information presented to patients, as well as encouraging patients to get involved in the therapeutic process, eg, self-monitoring BP at home, may further increase adherence to treatment.[6] Nevertheless, in real life, it will not ensure complete success reflected in acceptable drug regimen adherence.

Bearing this in mind, and the fact that approximately 80% of all hypertensive patients may be sufficiently controlled within only two decision-making steps, recent European Society of Cardiology (ESC)/European Society of Hypertension (ESH) guidelines changed the paradigm on how we should initiate and continue the treatment of hypertensive patients with available BP-lowering agents.[6]

As the number of prescribed antihypertensive drugs inversely translates into pharmacotherapy adherence,[15] the fundamental change in hypertension treatment in 2018 was to simplify pharmacotherapy, with high priority given to use of single-pill combinations (SPCs).[6] The SPCs therefore should be a mainstay of hypertension treatment as they ensure faster BP control (different pathological mechanisms addressed), less variability in response (almost everyone responds), better tolerance (side effects of one drug are counterbalanced by the complementary one), and fewer pills (promotes treatment adherence/persistence).

One of the controversies related to recent pharmacotherapy guidelines is whether or not to initiate treatment with SPCs. Actually, the two arguments favor such a strategy; thus, it should be promoted for most. First, as the goal of treatment for the majority of patients under 65 years old is to achieve a systolic BP under 130 mm Hg, only stage 1 hypertensive patients would require an 11 to 30 mm Hg decrease in systolic BP (not to mention stage 2 hypertensives), which is rarely possible with one drug only. Second, the delay in reaching the anticipated goals, ie, time needed to adjust and individualize treatment, is another factor negatively influencing treatment adherence and is thus unwanted. Except for the minority of patients (elderly, frail, young with low CVD risk, or slight elevation of BP at the time of hypertension diagnosis), BP lowering should be based on drug-combination therapy at the earliest convenience.[6] On top of that, it is worth considering the polypill therapy as an option to manage both hypertension and high blood lipids (these two CVD risk factors usually coexist). One practical aspect of such a strategy is the fact that the BP readings may be considered an immediate proxy to monitor adherence to dual therapy (and the other way round).

Taken together, there is compelling evidence that supports strategies aimed to improve adherence to long-term BP-lowering and lipid-lowering therapies, which is a powerful means to better control these CVD risk factors and CVD morbidity and mortality. Simplification of a drug regimen with priority given to a decrease in the number of administered pills is the cornerstone of this strategy. ■

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Medication nonadherence is one of the most common and crucial causes of low treatment effectiveness and cardiovascular complications.

Hypertension and hyperlipidemia are the two main cardiovascular risk factors. They commonly coexist, with a comorbidity rate of 15% to 30% in the adult population.[1] In Russia, the rate of coexistent hypertension and hyperlipidemia is even higher, varying from 42%-52% to 70%-78% depending on age and sex.[2] Adequate and timely control of these risk factors is the key issue in cardiovascular prevention. However, low treatment adherence significantly hampers potential benefits.[1]

Treatment adherence depends on several factors that can be grouped into the following four categories: patient-related factors, disease-related factors, physician-related factors, and treatment-related factors.

Patient-related factors *include the patient's personality and psychological traits. Typically, people find it difficult to maintain long-term motivation to follow medical recommendations, and the adherence is inversely proportional to the number of medications prescribed.*

Disease-related factors, *or disease manifestations, imply higher adherence in more symptomatic cases. Patients tend to follow medical advice more precisely when the complaints are more severe and evident. Both hypertension and dyslipidemia are commonly asymptomatic. In case of hypertension, patients can easily measure the key parameter (blood pressure, [BP]) at home, and this provides a stimulus for adherence. However, dyslipidemia is a different story. The patient cannot measure lipids in everyday life, and this contributes to the decline in adherence.*

Physician-related factors; *of these, medical inertia heads the list.[1] A recent analysis showed a significant underuse of the fixed-dose-combination products in diabetes, hypertension, and dyslipidemia.[3] Physicians continue to prescribe single-agent pairs rather than simplify the regimen. This reluctance or hesitancy to upgrade the therapy to a combination pill is maintained by the lack of routine assessment of treatment adherence and witnessed drug intake, which are complicated, expensive, and limited to single cases.*

Treatment-related factors *include a variety of characteristics, with the key one being the number of medications. Decreasing the number of pills helps raise adherence. The European Society of Cardiology (ESC)/European Society of Hypertension (ESH) 2018 guidelines on the management, diagnosis, and prevention of hypertension support this. They state that most hypertensive patients require combinations of drugs acting via different mechanisms owing to the multifactorial nature of hypertension.[1] Thus, monotherapy appears to be inadequate in most cases. The ACCOMPLISH study (Avoiding Cardiovascular events through Combination therapy in Patients LIving with Systolic Hypertension) demonstrated that initial combination therapy enables more rapid achievement of the target BP.[4] The guidelines encourage the use of single-pill combinations as initial therapy in the majority of hypertensive patients.[1] Moreover, fixed combinations are associated with greater cardiovascular risk reduction than observed for free combinations (38.5% vs 35.4%, respectively), as well as with better BP control and more evident cholesterol decrease (the ALL-IN-ONE study; also called the Once-daily Fixed Combination of Three Antihypertensive Drugs [ONE&ONLY] trial).[5]*

The HOPE-3 study (Heart Outcomes Prevention Evaluation-3) demonstrated that combining a dual antihypertensive and a statin agent significantly lowers the risk of cardiovascular events compared with dual placebo (at 5.6-year follow-up, 29% relative risk and 1.4% absolute risk reduction was seen) in primary prevention. Importantly, the doses of single components can be reduced owing to their synergistic effect.[6] According to the data from a large-scale Australian database, initial therapy with the fixed-dose combinations including statins and antihypertensives led to higher adherence in those who previously took statins.[7]

There are still open questions to be addressed within all four categories of the mentioned factors. One (treatment-related) aspect of a single-dose polypill is the tablet technology. There are a number of novel approaches (coamorphous formulations, oral disintegrating pills, etc) that increase stability, bioavailability, and effectiveness of the medication.[8,9] A patient-related challenge is the timing of the polypill intake. Personal circadian rhythms should be considered, as well as their interaction with the substance pharmacokinetics and pharmacodynamics, and environmental factors.[10-12] Therefore, the strategy of combining fixed-dose formulations is highly attractive and promising. The integration of a statin and an antihypertensive agent into one pill will help control both hypertension and dyslipidemia and increase treatment adherence. ■

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