Chapter 7

Adherence by Patients with Hypertension to Treatment with a Single-tablet Combination of Bisoprolol and Amlodipine

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Sub-optimal adherence to antihypertensive therapy is common and is associated with both diminished control of blood pressure (BP) and increased risk of death and adverse cardiovascular outcomes. Complex regimens significantly contribute to sub-optimal adherence to therapy. Single-tablet combinations of antihypertensive agents, including a bisoprolol/amlodipine combination tablet, have been shown to support good adherence to antihypertensive therapy.

The problem of low adherence to antihypertensive treatment

Measuring adherence to treatment

There is no consensus on methodology for measuring adherence to a therapeutic regimen. In practice, most studies have used one of two

Table 1 Overview of common methods for measuring adherence to pharmacological treatment.

Method	Description
Proportion of Days Covered (PDC)	Proportion of days within a fixed observation period where the patient has medication to follow the regimen (expressed as a percentage).
Medical Possession Ratio (MPR)	Days of medication supply from the first to the last prescription fill in the study period divided by the number of days in the study period.
Tablet counting	Proportion of tablets prescribed that were taken, based on a count of tablets not taken, over the defined study period.

Compiled from information presented in references [1–3].

closely related measures, the Proportion of Days Covered (PDC) or the Medical Possession Ratio (MPR). Arbitrary cut-offs, e.g. PDC <0.8, may be used to define low adherence using these measures. Alternatively, tablet counting involves calculation of the number of tablets taken by examination of the tablets *not* taken, often at a clinic visit. Table 1 provides definitions for these measures [1–3].

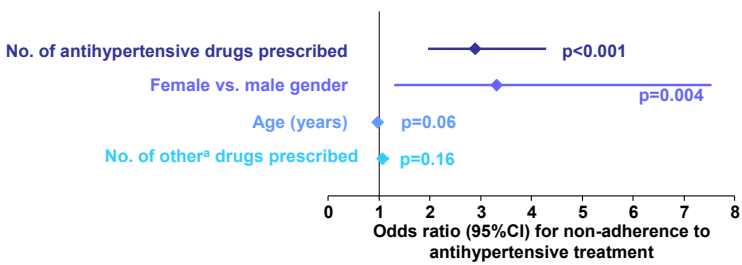
Scale of the problem of non-adherence

Prevalence

Successful pharmacological control of BP in a patient with hypertension requires two conditions to be met: the prescription of appropriate BP-lowering medications, and the patient taking those medicines as directed [3]. The prevalence of non-adherence to antihypertensive medication is difficult to quantify and is likely to vary between regions and cultures [4], nevertheless, non-adherence to antihypertensive medication is common. An expert review in this field considers that reported levels of adherence to antihypertensive medication are commonly <50%, which is intriguingly similar to the proportion of patients with hypertension and well controlled BP in most countries (see also Chapter 3 of this book) [3]. Forty-eight percent of people among a population of 2,532,582 hypertensive patients from 19 developing countries in Asia were described as non-adherent to antihypertensive medication in one systematic review [5].

Measurement of drugs and their metabolites in urine and serum has been used in a number of studies to quantify the level of non-adherence among patients with hypertension in an objective manner. One such study demonstrated substantial proportions of non-adherent patients in the United Kingdom (UK) (41.6%) and Czechia (31.5%) [6]. Another study using this technique found that 25% of patients with hypertension in the UK were partially or totally non-adherent to their antihypertensive medication, with non-adherence higher in patients with inadequate BP control [7]. Interestingly, this study also compared BP levels according to the number of antihypertensive medications prescribed, compared with the number of drugs detected in the patients' plasma; average BP increased by 3/3 mmHg for every drug that was prescribed but not taken. A further study found that up to about one-quarter of patients considered to have drug-resistant hypertension may, in fact, be partially or completely non-adherent to their antihypertensive medication [8]. The pattern of non-adherence among such patients is complex: a study in the UK of patients with a diagnosis of treatment-resistant hypertension found a non-adherence rate of 40% overall, but within that population 26% were non-adherent to one or more, but not all, antihypertensive medications, while 14% did not take any of their antihypertensive medications [9]. Women were 3-fold more likely to be non-adherent than men in this study (Figure 1) [9].

Figure 1 Influence of number of antihypertensive drugs in the regimen on non-adherence to antihypertensive therapy.



CI: confidence interval; No.: number.
[a]Medications for conditions other than hypertension.
Drawn from data presented in reference [9].

Estimates of non-adherence may also vary with the methodology used to measure it. For example, a study of older adults in the United States of America found that 24% demonstrated low adherence to antihypertensive therapy defined as PDC <0.8, but a much higher proportion (39%) were low-adherent when a validated instrument for measuring adherence was used (the Krousel-Wood Medication Adherence Scale) [10]. A systematic review of studies in patients with hypertension (available at the time of writing as a preprint) found that indirect measures of non-adherence (e.g. based on prescription refills) yielded a prevalence estimate of non-adherence of 25%, while direct methods (e.g. measurement of drugs in plasma) gave a figure for non-adherence of 44% [11]. These findings raise the possibility that standard measures for measuring adherence, such as the PDC, may underestimate the problem of low adherence to antihypertensive therapy.

Implications for long-term outcomes

Non-adherence to antihypertensive medication has serious clinical consequences and Table 2 summarises the findings of several studies in this area [12–19]. Lower versus higher adherence was associated with a range of adverse clinical outcomes including death from any cause, death from ischaemic heart disease, incident cardiovascular disease or hospitalisation for cardiovascular diseases or stroke, and cognitive impairment. Importantly, these associations were seen in some studies in patients with newly-diagnosed hypertension, and in younger patients with hypertension.

Among these studies, a large meta-analysis of 16 cohort studies that included a total of 2,769,700 patients with hypertension found that the risk of adverse cardiovascular outcomes decreased as adherence to antihypertensive medications increased; every 20% increase in adherence was associated with a 13% reduction in the risk of cardiovascular events [12]. Another large study (Table 2) demonstrated a strong relationship between the level of adherence and the risk of adverse cardiovascular outcomes in patients with newly-diagnosed hypertension [18]. Figure 2 summarises important findings from this study; a significantly lower risk of adverse cardiovascular outcomes was seen with better adherence to

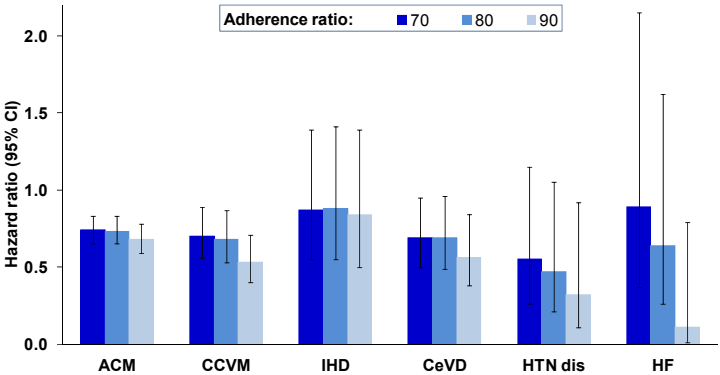
Table 2 Overview of studies that associated sub-optimal adherence to antihypertensive medications with clinical outcomes.

Ref	Design	N	Key findings
[12]	Meta-analysis	2.8 million	RR for CV events was 0.66 for the highest vs. lowest adherence categories; each 20% increase in adherence was associated with a 13% reduction in the risk of a CV event.
[13]	Retrospective cohort	124,899	Cost-related non-adherence to treatment among people with hypertension was associated with higher all-cause mortality (HR 1.22 [1.2 to 1.3]) and hypertension-related mortality (HR 1.08 [0.9 to 1.3])
[14]	Retrospective cohort	40,408	Non-adherence associated with increased risk of all-cause death (HR 1.48 [1.30 to 1.68]), hosp. for CVD (HR 1.25 [1.12 to 1.39]) and hosp. for stroke (HR 1.51 [1.29 to 1.77]); no significant association with hosp. for IHD.
[15]	Retrospective cohort	123,390	HR for incident CVD was 1.57 (1.45 to 1.71) for non-adherent vs. adherent in young adults (<44 y); risk of CVD events increased with quartiles of non-adherence.
[16]	Retrospective cohort	33,728	Non-adherent had increased risk of death from IHD (HR 1.64 [1.16 to 2.31]), cerebral haemorrhage (HR 2.19 [1.28 to 3.77]), and cerebral infarction (HR 1.92 [1.25 to 2.96]) in patients with newly-diagnosed hypertension; risks of hosp. for these events were similar.
[17]	Prospective cohort	242,594	25% (20% to 29%) reduction in risk of CV events for high vs. low adherence.
[18]	Retrospective cohort	20,836	Lower risk for higher vs. lower adherence in 1st year of death from any cause (0.74 [0.65 to 0.83]) or stroke (HR 0.70 [0.56 to 0.89]) in newly-diagnosed hypertension ; also significant benefits for incidence of HF, hypertensive disease and IHD.
[19]	Retrospective, cross-sectional	9,036	Higher risk of cognitive impairment for lower adherence (HR 1.32 [1.14 to 1.54]) in older (>65 y) hypertensive patients.

CI: confidence interval; CV: cardiovascular;
CVD: cardiovascular disease; HF: heart failure; hosp.: hospitalisation; HR: hazard ratio;
IHD: ischaemic heart disease; Ref: reference; RR: relative risk; y: year.
Comparisons are for higher vs. lower measures of adherence, see source publications for further details. Numbers in parentheses are 95% CI.

antihypertensive therapy for all-cause and cardiovascular mortality, and for incident cerebrovascular disease, hypertensive disease (complications of hypertension) and heart failure (however, no significant association was seen for ischaemic heart disease) [18].

Figure 2 Associations between adherence to antihypertensive therapy and 10-year clinical outcomes in patients with newly-diagnosed hypertension.



CI: confidence interval.
Clinical outcomes were ACM: all-cause mortality; CCVM: cardio-cerebrovascular mortality (includes the outcomes shown to the right of this category); CeVD, cerebro-vascular disease; IHD: ischaemic heart disease; HTN dis: hypertensive disease; HF: heart failure. Adherence ratio was based on the number of filled prescriptions during the first year after diagnosis of hypertension (higher values of compliance ratio mean better adherence).
Drawn from data presented in reference [18].

Causes of poor adherence to antihypertensive medication

Many factors contribute to the problem of low adherence to antihypertensive therapy [4]. Forgetting to take medication, followed by stress/anxiety/depression, lack of knowledge and side-effects were the most common reasons given by patients for poor adherence to antihypertensive therapy in one systematic review [20]. Diuretic treatment was a risk factor for non-adherence in one study conducted in two countries in Europe [7]. The use of traditional remedies and poverty have also been associated strongly with low adherence in developing countries [6, 21].

Patients' personal beliefs about hypertension and its consequences impact adherence to treatment, and these vary widely between individuals and regions [22]. For example, even where a patient professes to believe strongly in the efficacy of an antihypertensive medicine, they may use it only intermittently due to incorrect beliefs about hypertension being an intermittent disorder (or only important at times of stress), or through

misplaced fears of addiction or dependence on antihypertensive therapy [23, 24]. Higher levels of self-efficacy in managing hypertension have been associated with higher rates of medication adherence [12]. Health education holds the key to improving health literacy and understanding of the nature of hypertension; however, a systematic review found that patient education was successful in increasing health literacy and adherence to treatment for people with diabetes, but not for people with hypertension [25]. Pharmacist-led interventions [26, 27] within communities, and programmes administered by community health workers [28], have been shown to be a valuable resource for improving rates of health knowledge, adherence and BP control locally. A substantial body of clinical evidence now supports "mhealth" or "telehealth" approaches based on the use of communications technology (especially mobile phone technology) to provide education and reminders for patients to maintain good self-care of hypertension [29, 30].

A background of complex drug regimens and polypharmacy adds to the difficulty of following a therapeutic regimen well, especially for older patients with multiple comorbidities that require pharmacological intervention. There is no doubt that complex regimens contribute significantly to the problem of non-adherence in hypertension and other medical conditions [3–11], with higher levels of non-adherence among patients with hard-to-treat hypertension likely to require complex antihypertensive regimens [8, 9]. For example, one study summarised above found that each additional antihypertensive agent present within a therapeutic regimen increased non-adherence to therapy by 85% for patients in the UK and by 77% in Czechia [7]. More data from the UK showed that each additional antihypertensive medication prescribed for the management of treatment-resistant hypertension increased the risk of non-adherence by 2.9-fold, and was second only to female gender as a predictor of non-adherence (Figure 1) [9]. A study from Egypt presented a remarkable finding that 99% of people with hypertension adhered well to a once-daily treatment, compared with only 0.8% of people receiving a twice-daily treatment [31].

The following section summarises clinical evidence of the benefits of single-tablet antihypertensive combinations in simplifying the regimen,

improving adherence to treatment, and improving the quality of BP control in patients with hypertension.

Single-tablet antihypertensive combination therapy as a strategy for improving adherence in hypertension

Experience with bisoprolol/amlodipine combination tablets

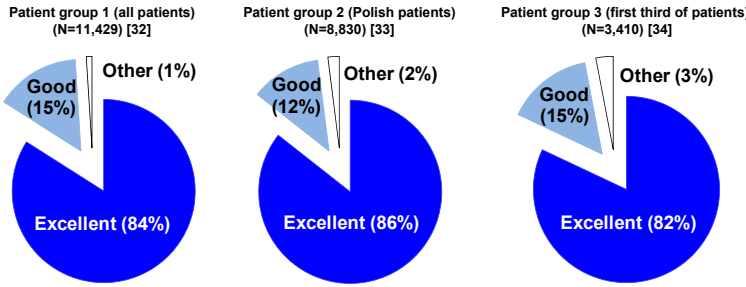
Adherence to therapy was the primary study outcome for a 6-month observational, non-interventional study on the effects of bisoprolol/amlodipine combination tablets in patients with hypertension. Tablet counting was used to measure adherence to therapy in each study [32–34]. For the study, patients with hypertension were switched from a previous, co-administered free combination of bisoprolol and amlodipine to the combination tablet at least 4 weeks before the start of the study.

Adherence was rated as "Excellent" (90% of prescribed tablets taken) or "Good" (76–90% of prescribed tablets taken) in 97–99% of patients during the study (Figure 3). There was no difference in rates of adherence to the combination tablet according to gender [33]. A further analysis from this study explored the effects of important comorbidities on adherence [35]. Adherence was "Excellent" or "Good" in 99% of patients whether or not they had diabetes, cardiovascular disease, both, or neither in addition to their hypertension.

Other clinical evidence

A recent (2021) systematic review and meta-analysis of clinical studies evaluated the impact of single-tablet combination therapy on adherence to antihypertensive therapy [1]. Adherence to therapy was higher for single-tablet versus free combinations in 18/23 studies. Systolic BP improved statistically significantly after the switch from a free combination to a single-tablet antihypertensive combination in 6/9 studies that

Figure 3 Adherence to bisoprolol/amlodipine combination tablets in a 6-month observational study.



This was a non-interventional cohort study in patients with hypertension switched from a co-administered combination of bisoprolol and amlodipine to the combination tablet ≥4 weeks previously.
Categories for adherence were "Excellent" = 90%; "Good" = 76–90%; "Moderate" = 51–75%; "Bad" = ≤50%. "Moderate" and "Bad" categories are pooled here for clarity.
Drawn from data presented in references [32–34].

measured this, with the remaining three studies demonstrating numerical reductions in BP that were not subjected to statistical analysis. Three of six studies that used ambulatory BP recording demonstrated comparable results. Similarly, 7/8 studies demonstrated a significant or numerical decrease in diastolic BP following a switch from a free to a single-tablet antihypertensive combination. Pooled data showed that the antihypertensive benefit of the single-tablet versus the free combination became larger as the duration of the studies increased. Patients were more likely to achieve BP targets on single-tablet versus free antihypertensive combinations in 5/9 studies in this analysis, consistent with the other findings summarised above.

The analysis described above confirmed and extended the results of earlier systematic reviews/meta-analyses. Medication adherence was 14.9% higher for single-tablet versus free combinations of antihypertensive agents, and patients were 1.8-fold more likely to persist with therapy with the single-tablet combination in one meta-analysis [36]. A meta-analysis of 12 studies found a similar (13%) improvement in adherence with single-tablet versus free combinations [37].

The analyses summarised above focussed on the use of single-tablet combinations to improve adherence to therapy, which in turn has the

potential to improve BP control. Any intervention that improves adherence is likely to have this benefit. For example, a systematic review demonstrated a modest, but significant improvement in mean BP following interventions designed to improve adherence to therapy of –2.7 (95% confidence interval [CI] −4.17 to −1.26) and −1.25 (95% CI −1.72 to −0.79) mmHg, although there was considerable variation between studies [38]. Lower adherence to an antihypertensive regimen was also associated with lower health-related quality of life among older people with hypertension [5]. Two meta-analyses described above found only non-significant trends towards improved BP control associated with the better adherence, however [37, 39].

Conclusions

Sub-optimal adherence to antihypertensive therapy is common, and is associated with both diminished control of BP and increased risk of death and adverse cardiovascular outcomes associated with high BP. There are many contributors to poor adherence to therapy. Complex regimens are an important factor, and the use of single-tablet combinations, including a tablet containing bisoprolol and amlodipine, has been shown to support good adherence to therapy. Indeed, adherence to the bisoprolol/amlodipine combination tablet was 97–99% during a 6-month observational study [32–34].

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