Czarnecka · Drager · Gaciong · Gilyarevsky · Gottwald-Hostalek · Khurana · Li · Mahfoud · Stolarz-Skrzypek · Sun

# 10 Years of Experience with a Fixed-Dose Combination of Bisoprolol and Amlodipine

Springer Healthcare Education

Danuta Czarnecka · Luciano F Drager · Zbigniew Gaciong · Sergey Gilyarevsky · Ulrike Gottwald-Hostalek · Rohit Khurana · Yi-Heng Li · Felix Mahfoud · Katarzyna Stolarz-Skrzypek · Ningling Sun

# 10 Years of Experience with a Fixed-Dose Combination of Bisoprolol and Amlodipine

Springer Healthcare Education

Content and Editorial Services provided by Springer Healthcare Limited, 2022.



This content was prepared by Springer Healthcare with input and financial support from Merck Healthcare KGaA, Darmstadt, Germany.

A medical writer (Dr Mike Gwilt, GT Communications, mikegwilt@gtcomm.myzen.co.uk) provided editorial assistance, funded by Merck Healthcare KGaA, Darmstadt, Germany.

# Contents

# Foreword

# 10 Years of Experience with a Combination of Bisoprolol and Amlodipine

A solid evidence base, stretching back for decades, has established beyond doubt that uncontrolled hypertension brings a crushing burden of myocardial infarctions, strokes and other cardiovascular complications that threaten both the quality and duration of patients' lives. Conversely, the timely and rigorous application of antihypertensive therapy reduces the risk of these complications, and supports patients in achieving longer, fuller and more productive lives.

We also know that only a fortunate few patients achieve optimal blood pressure with a single antihypertensive agent. Indeed, most people with hypertension require two or more antihypertensive agents to control their blood pressure, as recommended by the guidelines. The increased efficacy of the combination therapy approach is offset by the accompanying increase in the complexity of the regimen, especially as many of these patients will already be taking multiple other medications for multiple other comorbid conditions.

Once-daily, single-tablet combination therapy provides a means of resolving this conundrum, delivering combination treatment in a manner that is no more complex than monotherapy. In this book, we describe the properties of a new, single-tablet combination of bisoprolol (a highly cardioselective β-blocker) and amlodipine (a long-acting, dihydropyridine calcium channel blocker). These agents have been in clinical use individually for decades, and their efficacy and safety profiles are well understood. Given together, their proven efficacy and complementary mechanisms of action suggest an important role in the management of hypertension.

Our book contains nine chapters, each authored by an expert in the field. We describe the epidemiological links between hypertension and adverse outcomes, followed by a detailed description of the pharmacokinetic, pharmacodynamic and clinical properties of bisoprolol and amlodipine in combination. As co-editors of the book, we thank our chapter authors for their important contributions. Above all, we hope you find our book of interest, and useful in your clinical practice.

**Dr Zbigniew Gaciong**
Department of Internal Medicine,
Hypertension and Vascular Diseases,
Medical University of Warsaw, Warsaw, Poland

**Dr Ulrike Gottwald-Hostalek**
Merck Healthcare KGaA, Darmstadt, Germany

# Chapter 1

# Prevalence and Long-term Consequences of Hypertension

**Sergey Gilyarevsky**
Russian Medical Academy of Continuous Professional Education,
Department of Clinical Pharmacology and Therapy

**Global surveys of blood pressure (BP) have shown that at least one person in four world-wide has hypertension. Moreover, the number of people with hypertension has increased markedly in recent decades. High blood pressure increases the risk of adverse cardiovascular events (coronary heart disease, heart failure and stroke) and premature death, among other adverse outcomes. Controlling high BP with antihypertensive therapies is proven to improve clinical outcomes in people with hypertension.**

## Definitions of hypertension

The BP cut-off values used to diagnose arterial hypertension differ to some extent between guidelines and regions. Moreover, classifications of the severity of hypertension also differ. Table 1 summarises these classifications from three influential guidelines proposed by the European Society of Cardiology (ESC) [1], the American Heart Association (AHA)

and the American College of Cardiology (ACC) [2], and the National Institute for Health and Care Excellence (NICE) in the United Kingdom (UK) [3]. The two guidelines originating from Europe set the cut-off for systolic/diastolic BP (SBP/DBP) at 140/90 mmHg, although the ESC guideline considers three categories of non-hypertensive BP as "optimal", "normal" and "high normal" BP. Further grades of increasing severity of hypertension are diagnosed using cut-off values of 160/100 mmHg and 180/110 (or 120) mmHg. The US guideline considers that an individual with BP even slightly above 140/90 mmHg already has Stage 2 hypertension, having defined normal BP as <130/80 mmHg. No further categories of severity of hypertension are provided by the US guideline. Using higher or lower cut-off values to diagnose hypertension will lead to lower and higher (respectively) estimates of the prevalence of hypertension, and this should be remembered when interpreting the results of epidemiological studies in this field.

**Table 1 Examples of current definitions of hypertension from major guidelines.**

| | ESC (2018) [1] | AHA/ACC (2017) [2] | NICE (2022) [3] |
|---|---|---|---|
| **Normal BP** | <120/<80 mmHg (= "**Optimal**" BP)<br>120–129/80–84 mmHg (= "**Normal**" BP)<br>130–139/85–89 mmHg (= "**High normal**" BP) | <120/<80 mmHg<br>120–129/<80 mmHg ("**elevated**" BP) | <140/90 mmHg |
| **Cut-off for diagnosis of hypertension** | ≥140/90 mmHg (**Grade 1 hypertension**) | ≥130/80 mmHg (**Stage 1 hypertension**) | 140/90 mmHg (**Stage 1 hypertension**) |
| **Additional grades of severity of hypertension** | ≥160–179/100–109 mmHg (**Grade 2 hypertension**)<br>≥180/110 mmHg (**Grade 3 hypertension**) | ≥140/≥90 mmHg (**Stage 2 hypertension**) | ≥160/100 but <180/120 mmHg (**Stage 2 hypertension**)<br>SBP ≥180 mmHg or DBP ≥120 mmHg (**Stage 3** or "**severe**" **hypertension**) |

ACC: American College of Cardiology; AHA: American Heart Association; BP: blood pressure; ESC: European Society of Cardiology; SBP/DBP: systolic/diastolic blood pressure.

# Prevalence of hypertension

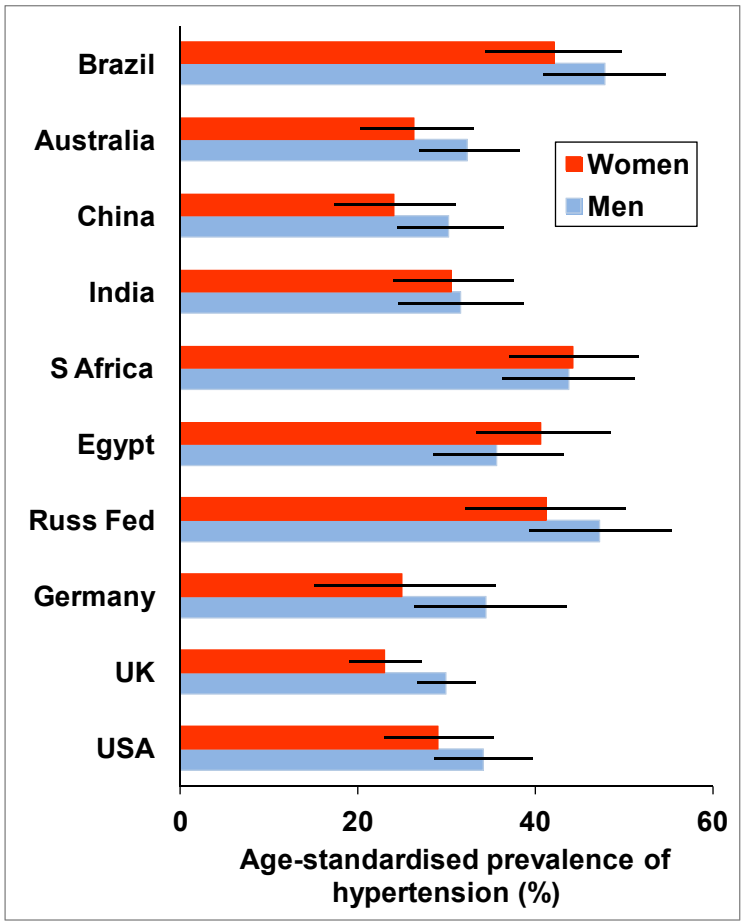
## *Global prevalence of hypertension*

Figure 1 shows the age-standardised prevalence of hypertension in adults for the year 2019 in selected countries around the world, from a global survey conducted by the Non-Communicable Diseases (NCD) Risk Factor Collaboration under the auspices of the World Health Organization (WHO) [4]. For this study, hypertension was defined as SBP ≥140 mmHg, DBP ≥90 mmHg, or receipt of antihypertensive medication. There is no doubt that the prevalence of hypertension is high worldwide: the proportions of people with hypertension in the countries highlighted in Figure 1 range from about 1 in 4 individuals to about 2 in 5. This survey also found that the number of people with hypertension worldwide approximately doubled between 1990 and 2019, from 648 million people to 1.3 billion. This doubling increased in the absence of a marked change in the age-standardised prevalence of hypertension, in the setting of a global population that is increasing in number and increasing in average age. Another global survey estimated the prevalence of hypertension to be 31.1% in 2010, with a higher prevalence in low or middle income countries (31.5%) compared with high-income countries (28.5%) [5].

## *The problem of unawareness of hypertension*

Unawareness of hypertension is also common and Figure 2 illustrates the magnitude of the problem in the same selection of countries from the global hypertension survey [4]. Among these countries, the proportion of patients unaware of/with undiagnosed hypertension was lowest in the United States of America (USA) and the Russian Federation (especially for women), where about 80% of people with hypertension were aware of having the condition. The proportion with diagnosed hypertension was lower in other countries, including some relatively high-income countries like the UK and Australia, where about 60% of the total population with hypertension were aware of having it. Rates of awareness of hypertension had increased from the 1990s to the

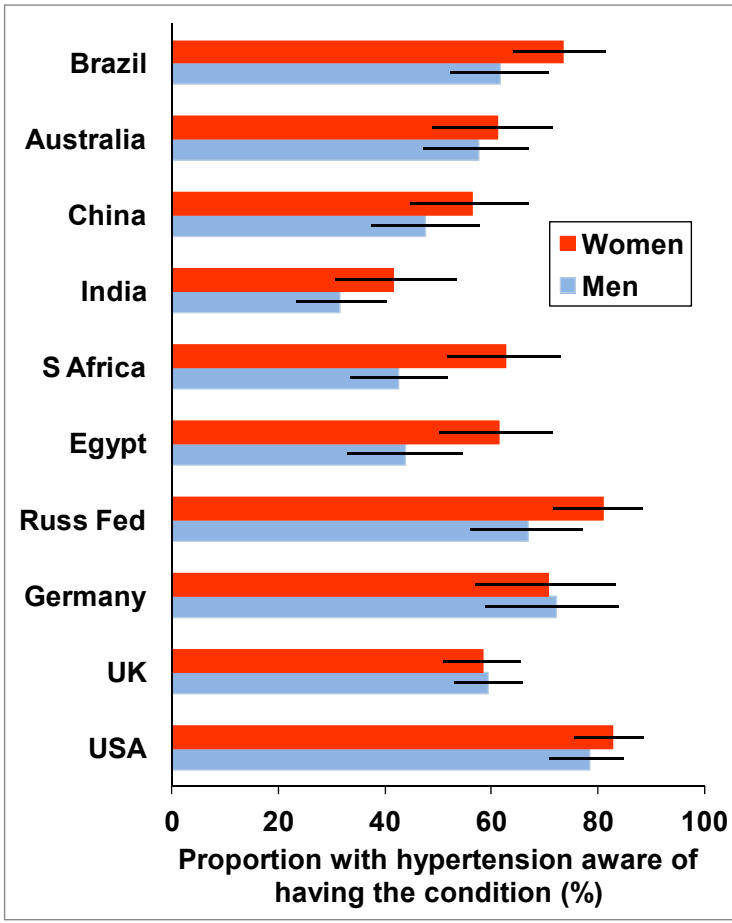
**Figure 1 Age-standardised prevalence of hypertension in men and women aged 30–79 years in selected countries [4].**




Bars are 95% credible intervals. Drawn from data presented by the Non-Communicable Diseases (NCD) Risk Factor Collaboration [4]. Russ Fed: Russian Federation; S Africa: South Africa; UK: United Kingdom; USA: United States of America.

early 2000s, but progress has plateaued more recently, with continuing marked variation in the rates of awareness of hypertension between countries [6].

**Figure 2 High prevalence of unawareness of hypertension in selected countries from a global survey of hypertension in adults [4].**




Bars are 95% credible intervals. Drawn from data presented by the Non-Communicable Diseases (NCD) Risk Factor Collaboration [4]. Russ Fed: Russian Federation; S Africa: South Africa; UK: United Kingdom; USA: United States of America.

## *High prevalence of hypertension conditions associated with insulin resistance*

Some populations have an especially high prevalence of hypertension. For example, high BP is one of the five criteria for diagnosing metabolic syndrome, so it is perhaps unsurprising that the prevalence of hypertension approaches 80% among this population [7]. Type 2 diabetes, which accounts for about nine people in ten with diabetes, is also associated patho-physiologically with insulin resistance, metabolic syndrome and associated cardiovascular risk factors. Accordingly, hypertension is common among people with diabetes, as shown by data from the USA, where 69% of people with diabetes have hypertension [8]. Similarly, a study in Jordan found that 75% of people with diabetes also have hypertension, with a 1-year incidence of hypertension of 26% among people with diabetes who were normotensive at baseline [9]. Other cross-sectional studies found that 60% of 378 people with type 2 diabetes at a tertiary hospital in Ethiopia also had hypertension [10], and that 60% of 3,092 people with diabetes in India had uncontrolled hypertension [11]. A systematic review of observational studies demonstrated that the prevalence of hypertension in diabetes is as high as 80–90% in some countries [12]. The presence of obesity, also associated closely with insulin resistance, metabolic syndrome and type 2 diabetes, almost doubles the likelihood of having hypertension compared with people of normal weight [13].

## *Epidemiological transitions in the developing world*

Historically, infectious diseases have been a leading cause of morbidity and mortality in the developing world. Advances in recent decades in the management of infectious and deficiency diseases (particularly HIV in sub-Saharan Africa) and general improvements in healthcare provision are driving an epidemiological shift from infectious diseases to non-communicable diseases (NCDs) as the predominant burden of illness in these countries [14–16]. The underlying reasons for the epidemiological shift are complex, and include a greater likelihood of living to an age when NCDs may develop, access to high-energy diets, increased use of alcohol and tobacco, and increased sedentariness secondary to shifts of the

population from a rural to an urban setting [14–17]. As an example, deaths from NCDs have risen by 31% during the last 25 years in India, with hypertension the main driving force for the development of cardiovascular diseases [18]. The developing world already bears a disproportionate burden of hypertension, and the continued emergence of hypertension, diabetes, cardiovascular disease and other NCDs will provide an increasing challenge to healthcare systems there.

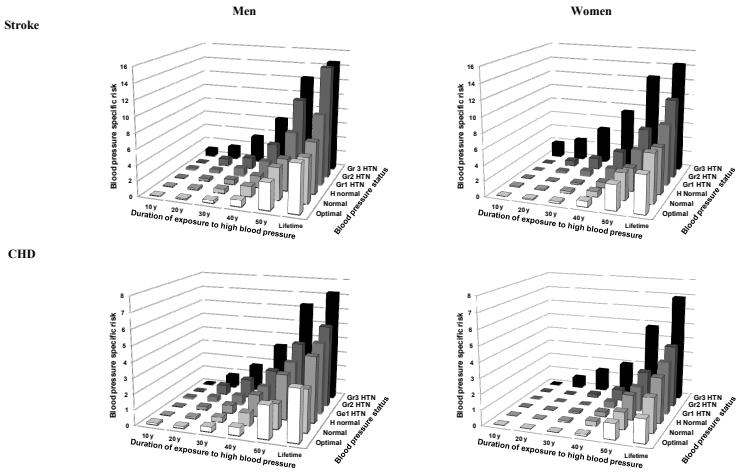
## Long-term consequences of hypertension

### *Epidemiology of hypertension and adverse cardiovascular outcomes*

Epidemiological studies have proven beyond doubt that high BP is associated with adverse cardiovascular outcomes [19]. A study in more than one million adults from 61 observational cohorts determined that each increase in SBP of 20 mmHg, or in DBP of 10 mmHg, was associated with a doubling of the risk of death from ischaemic heart disease and more than doubling of the risk of stroke death, for an individual in middle age (40–69 years) [20]. Another large study in 107,737 individuals participating in observational cohorts in Japan calculated the lifetime risk of death from coronary heart disease or stroke that was attributable to hypertension [21]. The lifetime risks of these adverse outcomes for an individual aged 35 years increased with increasing categories of BP both in men and women, with the excess risk increasing sharply at longer durations of exposure to high BP (Figure 3). This study is important because it stresses the long-term nature of the vascular risk associated with hypertension: for example, the BP-specific risk estimate for stroke death associated with Grade 2 hypertension (160–179/100–109 mmHg, see Table 1) increased from 0.0 at 10 years to 14.5 for men and 10.3 for women across a lifetime.

Calculation of the population-attributable risk (PAR) for a given risk factor allows an estimation of the proportion of cases of a given outcome that were due to the effects of that risk factor. A study in 1,244 community-dwelling subjects in Spain, of whom 35% had hypertension, calculated

**Figure 3 Risks of death from stroke or coronary heart disease (CHD) associated with different levels of blood pressure at 35 years of age [21].**




"GR1 HTN" refers to Grade 1 hypertension (see Table 1 for other definitions). "H Normal" = "high normal". Drawn from data presented in reference [21].

the PAR for cardiovascular disease associated with hypertension [22]. The 13-year risks (95% confidence interval [CI]) of cardiovascular disease associated with hypertension were 1.89 (1.63 to 2.18) in men and 1.71 (1.4 to 2.09) in women, with PARs of 33.1% and 33.8%, respectively.

High BP is associated with a number of other adverse clinical outcomes besides coronary heart disease and stroke, as described below.

**Heart failure:** The relationship between BP and outcomes in people with heart failure is complex, higher SBP is associated with improved prognosis once heart failure is established. However, hypertension has been described as the predominant risk factor for future heart failure [23]. Conversely, most people with heart failure have a history of hypertension [24]. The observational study described above demonstrated a PAR for heart failure associated with hypertension of 57% in men and 69% in women [22]. Data from the Framingham Heart Study in the USA found that hypertension accounted for 39% of cases of heart failure in men and 59% of cases in women [25].

**Chronic kidney disease (CKD):** Renal dysfunction is usually associated with the development of hypertension [26]. Elevated SBP

was the strongest risk factor for renal death among those studied in a meta-analysis of 35 studies incorporating >500,000 subjects; each increase in SBP of 19 mmHg was associated with an increase in the risk of renal death of >80% [27]. A systematic review of studies that enrolled a total of more than 2 million subjects found that hypertension (SBP >140 mmHg vs <120 mmHg) was associated with a relative risk of incident CKD or end-stage renal disease (ESRD) of 1.56 (95% CI, 1.39 to 1.75) in women and 2.06 (95% CI, 1.64 to 2.60) in men [28]. Analysis of a health insurance population in the USA found that the risk of ESRD increased in line with increasing severity of hypertension, but that even modest increases in BP to 120–129/80–84 mmHg (vs <120/80 mmHg) were associated with a significantly increased risk of ESRD [29].

**Cognitive decline:** The results of several observational studies have confirmed associations between arterial hypertension, especially in midlife, and cognitive impairment or dementia later in life [30–32]. Moreover, the results of the CARDIA study (Coronary Artery Risk Development in Young Adults), a community-based cohort of young individuals followed over 30 years, suggested that not only hypertension but also higher cumulative systolic BP levels were associated with lower cognitive performance in the executive, memory and global domains, and higher cumulative diastolic BP was associated with lower cognitive performance in the memory domain, in midlife [33]. Notably, the results of meta-analyses of fourteen randomised clinical trials (96,158 participants) have documented that BP lowering with antihypertensive agents, compared with the control group, was associated with a significantly lower risk of incident dementia or cognitive impairment [34].

**Other adverse clinical outcomes:** Epidemiological studies have demonstrated significant associations between high BP and a range of other adverse clinical outcomes, including cardiomyopathy, atrial fibrillation, erectile dysfunction, and peripheral arterial disease [19].

## *Proven outcome benefits from antihypertensive therapy*

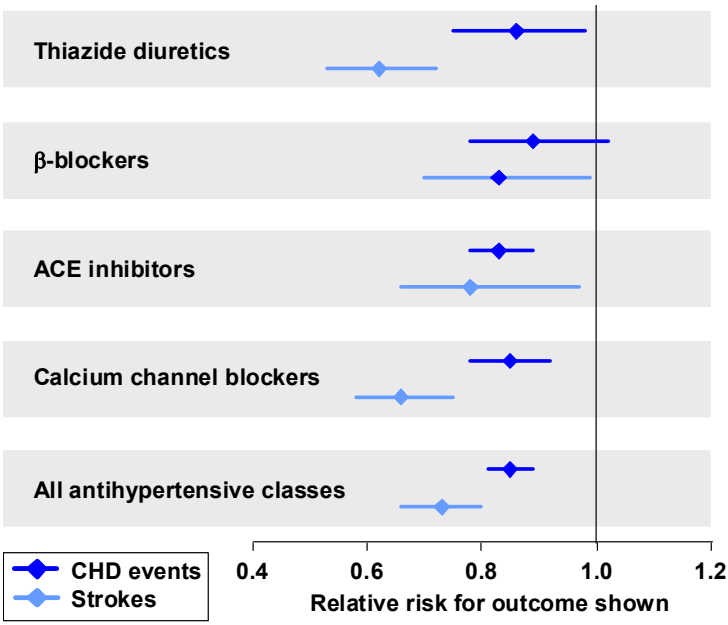
Randomised evaluations of antihypertensive therapies have been conducted, and these provide another source of evidence relating to the association between high BP and adverse clinical outcomes. Many clinical trials of this type have been conducted, and this section will consider large systematic reviews and meta-analyses in this area. In general, the significant reductions in the risk of adverse cardiovascular outcomes within pooled randomised trial populations was consistent with the magnitude of benefit expected from epidemiological studies of the excess risk of these outcomes associated with high BP, and the main results of three principal meta-analyses are summarised below [35–37].

**Law et al** demonstrated significant benefit for antihypertensive therapy on cardiovascular outcomes (relative risks vs control groups of 0.84 [95% CI, 0.81 to 0.88] for coronary heart disease events and 0.70 [95% CI, 0.65 to 0.76] for stroke) [37]. Importantly, similar benefits were seen whether or not patients had a history of cardiovascular disease. This analysis also demonstrated that the effects of different classes of antihypertensive therapies on coronary heart disease outcomes was broadly similar, apart from a modest additional efficacy of calcium channel blockers for preventing strokes (Figure 4).

**Bundy et al** compared outcomes between randomised treatment groups that achieved different levels of SBP, compared with an achievement of 120–124 mmHg [35]. The hazard ratios (95% CI) for major cardiovascular disease events in this group were 0.71 (0.60 to 0.83) versus mean achieved SBP of 130–134 mmHg, 0.58 (0.48 to 0.72) versus mean achieved SBP of 140–144 mmHg, 0.46 (0.34 to 0.63) versus mean achieved SBP of 150–154 mmHg, and 0.36 (0.26 to 0.51) versus mean achieved SBP of 160 mmHg. Comparable reductions in the risk of all-cause mortality were seen that also increased in line with the differences in achieved SBP.

In the meta-analysis from **Ettehad et al** [36], each 10 mmHg reduction in SBP associated with antihypertensive therapy was associated with reduced relative risks (95% CI) of coronary heart disease

**Figure 4 Effects of different classes of antihypertensive agents on clinical cardiovascular outcomes from a large meta-analysis of randomised trials in populations with hypertension [37].**




Relative risks are for antihypertensive drug classes versus placebo or control. Excludes trials of β-blockers in patients with a history of coronary heart disease (CHD). Angiotensin receptor blockers are omitted as only 4 trials were included in the original meta-analysis, with 378 CHD events (relative risk 0.86 [95% CI, 0.53 to 1.40]) and 0 stroke events.
Drawn from data presented in reference [37]. ACE: angiotensin converting enzyme.

(0.83 [0.78 to 0.88]), stroke (0.73 [0.68 to 0.77]), heart failure (0.72 [0.67 to 0.78]) and all-cause mortality (0.87 [0.84 to 0.91]) [36].

Thus, evidence from randomised trials of BP lowering agents adds to the evidence from observational studies on the relationship between high BP and an increased risk of adverse cardiovascular outcomes.

## Conclusions

Hypertension is a common condition, occurring in about one-quarter of individuals worldwide, with a markedly higher prevalence in some countries. The severe burden of morbidity and premature mortality imposed by high BP is proven beyond doubt, and a large database of clinical trials and meta-analyses has confirmed that reducing BP delivers statistically and clinically significant reductions in the risk of cardiovascular events. As a result, pharmacological antihypertensive therapy is firmly established as evidence-based care for hypertension. The following chapter considers the place of each class of currently available antihypertensive agents in the management of hypertension.

## References


1 Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, et al. 2018 ESC/ESH guidelines for the management of arterial hypertension. Eur Heart J. 2018;39:3021–104. https://doi.org/10.1093/eurheartj/ehy339.

2 Whelton PK, Carey RM, Aronow WS, Casey DE, Jr., Collins KJ, Dennison Himmelfarb C, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. Hypertension. 2018;71:e13–e115. https://doi.org/10.1161/hyp.0000000000000065.

3 National Institute for Health and Care Excellence. Hypertension in adults: diagnosis and management: NICE guideline [NG136]. 2019. Available from: https://www.nice.org.uk/guidance/ng136. Accessed May 2022.

4 NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in hypertension prevalence and progress in treatment and control from 1990 to 2019: a pooled analysis of 1201 population-representative studies with 104 million participants. Lancet. 2021;398:957–80. https://doi.org/10.1016/s0140-6736(21)01330-1.

5 Mills KT, Stefanescu A, He J. The global epidemiology of hypertension. Nat Rev Nephrol. 2020;16:223–37. https://doi.org/10.1038/s41581-019-0244-2.

6 NCD Risk Factor Collaboration (NCD-RisC). Long-term and recent trends in hypertension awareness, treatment, and control in 12 high-income countries: an analysis of 123 nationally representative surveys. Lancet. 2019;394:639–51. https://doi.org/10.1016/s0140-6736(19)31145-6.

7 Katsimardou A, Imprialos K, Stavropoulos K, Sachinidis A, Doumas M, Athyros V. Hypertension in metabolic syndrome: novel insights. Curr Hypertens Rev. 2020;16:12–8. https://doi.org/10.2174/1573402115666190415161813.

8 Center for Disease Control and Prevention (CDC). The facts, stats, and impacts of diabetes. 2022. Available from: https://www.cdc.gov/diabetes/library/spotlights/diabetes-facts-stats.html Accessed June 2022.

9 Salameh AB, Hyassat D, Suhail A, Makahleh Z, Khader Y, El-Khateeb M, et al. The prevalence of hypertension and its progression among patients with type 2 diabetes in Jordan. Ann Med Surg (Lond). 2022;73:103162. https://doi.org/10.1016/j.amsu.2021.103162.

**10** Akalu Y, Belsti Y. Hypertension and its associated factors among type 2 diabetes mellitus patients at Debre Tabor General Hospital, Northwest Ethiopia. Diabetes Metab Syndr Obes. 2020;13:1621–31. https://doi.org/10.2147/dmso.S254537.
**11** Sreedevi A, Krishnapillai V, Menon VB, Mathew MM, Nair RR, Pillai GS, et al. Uncontrolled blood pressure and associated factors among persons with diabetes: a community based study from Kerala, India. Front Public Health. 2021;9:778235. https://doi.org/10.3389/fpubh.2021.778235.
**12** Colosia AD, Palencia R, Khan S. Prevalence of hypertension and obesity in patients with type 2 diabetes mellitus in observational studies: a systematic literature review. Diabetes Metab Syndr Obes. 2013;6:327–38. https://doi.org/10.2147/dmso.S51325.
**13** Aronow WS. Association of obesity with hypertension. Ann Transl Med. 2017;5:350. https://doi.org/10.21037/atm.2017.06.69.
**14** Atiim GA, Elliott SJ. The global epidemiologic transition: noncommunicable diseases and emerging health risk of allergic disease in Sub-Saharan Africa. Health Educ Behav. 2016;43:37s–55s. https://doi.org/10.1177/1090198115606918.
**15** Ciccacci F, Orlando S, Majid N, Marazzi C. Epidemiological transition and double burden of diseases in low-income countries: the case of Mozambique. Pan Afr Med J. 2020;37:49. https://doi.org/10.11604/pamj.2020.37.49.23310.
**16** Mendoza W, Miranda JJ. Global shifts in cardiovascular disease, the epidemiologic transition, and other contributing factors: toward a new practice of global health cardiology. Cardiol Clin. 2017;35:1–12. https://doi.org/10.1016/j.ccl.2016.08.004.
**17** Juma K JP, Shumba C, Otieno P, Asiki G. Non-communicable diseases and urbanization in African cities: a narrative review. In: Public Health in Developing Countries: Challenges and Opportunities. Anugwom EE and Awofeso Ns: Anugwom EE and Awofeso N. Published by: Intech Open Publishing. 2019.
**18** Gupta R, Xavier D. Hypertension: the most important non communicable disease risk factor in India. Indian Heart J. 2018;70:565–72. https://doi.org/10.1016/j.ihj.2018.02.003.
**19** Fuchs FD, Whelton PK. High blood pressure and cardiovascular disease. Hypertension. 2020;75:285-92. https://doi.org/10.1161/hypertensionaha.119.14240.
**20** Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet. 2002;360:1903–13. https://doi.org/10.1016/s0140-6736(02)11911-8.
**21** Satoh M, Ohkubo T, Asayama K, Murakami Y, Sugiyama D, Yamada M, et al. Lifetime risk of stroke and coronary heart disease deaths according to blood pressure level: EPOCH-JAPAN (Evidence for Cardiovascular Prevention from Observational Cohorts in Japan). Hypertension. 2019;73:52–9. https://doi.org/10.1161/hypertensionaha.118.11635.
**22** Ruiz-Hernandez A, Tellez-Plaza M, Dominguez-Lucas A, Pichler G, Martin-Escudero JC, Martinez-Garcia F, et al. Population attributable risk for cardiovascular disease associated with hypertension: results from the Hortega follow-up study. Journal of Hypertension. 2018;36:e27. https://doi.org/10.1097/01.hjh.0000539035.92296.a3.
**23** Tackling G, Borhade MB. Hypertensive heart disease. In: StatPearls. Published by: Treasure Island (FL): StatPearls Publishing. 2021.
**24** Messerli FH, Rimoldi SF, Bangalore S. The transition from hypertension to heart failure: contemporary update. JACC Heart Fail. 2017;5:543–51. https://doi.org/10.1016/j.jchf.2017.04.012.
**25** Levy D, Larson MG, Vasan RS, Kannel WB, Ho KK. The progression from hypertension to congestive heart failure. JAMA. 1996;275:1557–62. https://doi.org/10.1001/jama.1996.03530440037034.
**26** Taddei S, Bruno RM, Masi S, Solini A. Epidemiology and pathophysiology of hypertension. In: The ESC Textbook of Cardiovascular Medicine (online edition). Third edn. Camm AJ, Lüscher TF, Maurer G, Serruys PW (eds). Oxford; ESC Family 2018 [cited 27 July 2022]. Available from: https://academic.oup.com/esc/book/35489/chapter-abstract/312428514?redirectedFrom=fulltext.

**27** O'Seaghdha CM, Perkovic V, Lam TH, McGinn S, Barzi F, Gu DF, et al. Blood pressure is a major risk factor for renal death: an analysis of 560 352 participants from the Asia-Pacific region. Hypertension. 2009;54:509–15. https://doi.org/10.1161/hypertensionaha.108.128413.
**28** Weldegiorgis M, Woodward M. The impact of hypertension on chronic kidney disease and end-stage renal disease is greater in men than women: a systematic review and meta-analysis. BMC Nephrol. 2020;21:506. https://doi.org/10.1186/s12882-020-02151-7.
**29** Hsu CY, McCulloch CE, Darbinian J, Go AS, Iribarren C. Elevated blood pressure and risk of end-stage renal disease in subjects without baseline kidney disease. Arch Intern Med. 2005;165:923–8. https://doi.org/10.1001/archinte.165.8.923.
**30** Whitmer RA, Sidney S, Selby J, Johnston SC, Yaffe K. Midlife cardiovascular risk factors and risk of dementia in late life. Neurology. 2005;64:277–81. https://doi.org/10.1212/01.Wnl.0000149519.47454.F2.
**31** Launer LJ, Ross GW, Petrovitch H, Masaki K, Foley D, White LR, et al. Midlife blood pressure and dementia: the Honolulu-Asia aging study. Neurobiol Aging. 2000;21:49–55. https://doi.org/10.1016/s0197-4580(00)00096-8.
**32** Skoog I, Lernfelt B, Landahl S, Palmertz B, Andreasson LA, Nilsson L, et al. 15-year longitudinal study of blood pressure and dementia. Lancet. 1996;347:1141–5. https://doi.org/10.1016/s0140-6736(96)90608-x.
**33** Mahinrad S, Kurian S, Garner CR, Sedaghat S, Nemeth AJ, Moscufo N, et al. Cumulative blood pressure exposure during young adulthood and mobility and cognitive function in midlife. Circulation. 2020;141:712–24. https://doi.org/10.1161/circulationaha.119.042502.
**34** Hughes D, Judge C, Murphy R, Loughlin E, Costello M, Whiteley W, et al. Association of blood pressure lowering with incident dementia or cognitive impairment: a systematic review and meta-analysis. JAMA. 2020;323:1934–44. https://doi.org/10.1001/jama.2020.4249.
**35** Bundy JD, Li C, Stuchlik P, Bu X, Kelly TN, Mills KT, et al. Systolic blood pressure reduction and risk of cardiovascular disease and mortality: a systematic review and network meta-analysis. JAMA Cardiol. 2017;2:775–81. https://doi.org/10.1001/jamacardio.2017.1421.
**36** Ettehad D, Emdin CA, Kiran A, Anderson SG, Callender T, Emberson J, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. Lancet. 2016;387:957–67. https://doi.org/10.1016/s0140-6736(15)01225-8.
**37** Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. BMJ. 2009;338:b1665. https://doi.org/10.1136/bmj.b1665.

# Chapter 2

# Current Guideline Recommendations on Different Classes of Antihypertensive Agents

**Felix Mahfoud**
Clinic for Internal Medicine III, Cardiology, Angiology and Internal Intensive Care, University Hospital, Saarland University, Homburg, Germany

**This chapter reviews recommendations in current guidelines that relate to the five major classes of antihypertensive therapy (angiotensin converting enzyme inhibitors [ACEI], angiotensin II receptor blockers [ARB], β-blockers, calcium channel blockers [CCB] and thiazide-like diuretics). European guidelines recommend that most patients with hypertension begin with a combination of an ACEI or ARB with a CCB or a diuretic. However, other comorbidities often influence the prescribing decision: for example, β-blockers and CCBs are evidence-based treatments for heart failure with reduced ejection fraction and stable coronary artery disease, post-myocardial infarction (MI), and are also useful for ameliorating the symptoms of angina.**

# Introduction

There are many antihypertensive agents available currently for therapeutic use. For this reason, guidelines for the management of hypertension consider the therapeutic evidence base for five major classes of antihypertensive agents, as well as for individual agents within those classes. This chapter considers current recommendations from major guidelines relating to the use of antihypertensive classes for the management of arterial hypertension in adults. Table 1 provides a list of the guidelines reviewed in this chapter [1–7], and Table 2 gives an overview of the five antihypertensive drug classes, with examples of the more commonly used individual drugs within them [8]. In each case, these tables define the commonly used acronyms for these drug classes and the guidelines that will be used throughout this chapter.

**Table 1 Hypertension guidelines summarised in this chapter with names of their sponsoring organisations.**

| Guideline | Year of publication |
|---|---|
| Guideline for the management of arterial hypertension from the European Society of Cardiology (ESC)/European Society of Hypertension (ESH) [1] | 2018 |
| Guideline on the prevention of cardiovascular disease from the ESC and 12 additional expert societies [2] | 2021 |
| Guideline on the management of high BP in adults from the American College of Cardiology (ACC), the American Heart Association (AHA) and 9 other expert societies [3] | 2018 |
| International Society of Hypertension (ISH) global hypertension practice guideline [4] | 2020 |
| National Institute for Health and Care Excellence (NICE) guideline on hypertension management in adults [5] | 2022 |
| ESC guideline for the management of heart failure [6] | 2021 |
| ESC guideline for the management of chronic coronary syndromes [7] | 2019 |

BP: blood pressure.

**Table 2 Major classes of antihypertensive agents [2].**

| Antihypertensive class | Examples of commonly used individual drugs within each class[d] |
|---|---|
| ACEI | Captopril, enalapril, fosinopril, imidapril, lisinopril, perindopril, quinapril, ramipril, trandolapril |
| ARB | Azilsartan medoxomil, candesartan cilexetil, eprosartan, irbesartan, losartan, olmesartan medoxomil, telmisartan, valsartan |
| β-blocker | *$\beta_1$-selective*: acebutolol, atenolol, betaxolol, bisoprolol, celiprolol, esmolol, metoprolol, nebivolol[a]<br>*Not $\beta_1$-selective*: carvedilol,[b] labetolol,[b] levobunolol, nadolol, pindolol, propranolol, sotalol, timolol |
| CCB | *Dihydropyridine*: amlodipine, felodipine, lacidipine, lercanidipine, nicardipine, nifedipine, nimodipine<br>*Non-dihydropyridine*: verapamil, diltiazem |
| Diuretic[c] | Bendroflumethiazide, chlorthalidone, hydrochlorothiazide, indapamide |

ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin II receptor blocker; CCB: calcium channel blocker.
[a]Also inhibits phosphodiesterase-5.
[b]Also blocks $\alpha_1$-adrenoceptors.
[c]Particularly thiazide and thiazide-like diuretics, listed here.
[d]The lists of drugs of each class serves to provide examples only, and are not intended to be exhaustive. Compiled from information presented in reference [2].

# General recommendations on the use of antihypertensive therapy

## *Importance of lifestyle interventions*

Adverse lifestyle behaviours, such as physical inactivity and poor diet leading to weight gain are associated with higher levels of blood pressure (BP) [9]. Conversely, lifestyle intervention—improving the diet and undertaking increased levels of physical activity—improves multiple cardiovascular risk factors, including reducing BP in people with hypertension [10–12]. A recent large, observational study from the United Kingdom (UK) showed that a healthier lifestyle (compared with a very unhealthy lifestyle) was associated with increased life expectancy of up to about 6 years in men and about 8 years in women [13]. All guidelines agree on the central importance of encouraging patients with hypertension to improve their lifestyle. It is important to note that all guideline recommendations on the pharmacological management of hypertension discussed here are considered in addition to lifestyle modification.

## *Initiation of antihypertensive pharmacotherapy*

Table 3 summarises the main recommendations relating to the initiation of antihypertensive pharmacotherapy from major guidelines for the management of hypertension. It should be noted that lifestyle improvement should be undertaken by all patients, as described above.

The classical approach to the pharmacological management of hypertension has been to start with monotherapy, followed by sequential addition of other drugs if BP is not controlled adequately. Observations of a high prevalence of uncontrolled hypertension and high rates of non-adherence in drug-treated patients have prompted reconsideration of this approach. For example, one study from the United States (US) found that 38% of patients taking antihypertensive monotherapy had BP >140/90 mmHg [14]. Accordingly, guidelines proposed by the European Society of Cardiology (ESC) and the European Society of Hypertension (ESH) recommends starting pharmacological antihypertensive treatment with a 2-drug combination for most patients (possible exceptions being patients with SBP <150 mmHg and low cardiovascular risk, the very elderly and frail patients) [3]. A blocker of the renin-angiotensin system (RAS), such as an ACEI or ARB, given with a CCB or diuretic is preferred. A more recent guideline on cardiovascular disease (CVD) prevention from the ESC and 12 other expert societies provide similar recommendations on the initiation of antihypertensive pharmacotherapy, but also state that a combination of any of the five classes of antihypertensive therapies can be used instead of the preferred ACEI/ARB + CCB or diuretic combination [2].

The 2018 ESC guideline for the management of hypertension [2] (but not the 2021 guideline for cardiovascular risk reduction [3]) provides support for pharmacological management of high-normal BP, especially in very high-risk patients with coronary artery disease. The US guideline from 2018 (proposed by the American College of Cardiology [ACC] and American Heart Association [AHA]) also supports pharmacological intervention to prevent recurrent CVD in patients with BP ≥130/80 mmHg and either prior CVD or 10-year CVD risk ≥10%. Antihypertensive medication is proposed for patients at lower cardiovascular risk if their BP is

**Table 3 Overview of recommendations on initiation of antihypertensive pharmacotherapy.**

| Sponsor(s) | Summary of recommendations[c] |
|---|---|
| ESC/ESH (2018) [1][a] | Initiate pharmacotherapy for patients with Grade I hypertension at low-to-moderate CV risk if a 3–6-month trial of lifestyle intervention is unsuccessful<br>Initiate pharmacotherapy immediately for patients with Grade I hypertension and high or very high CV risk (with CV or renal disease or target organ damage) and for all patients with Grade 2 or 3 hypertension<br>Start with a 2-drug combination for most patients (ACEI/ARB + CCB or diuretic preferred) |
| ESC (2021) [2][b] | Similar recommendations as above for initiation of antihypertensive pharmacotherapy, including preference for ACEI/ARB + CCB or diuretic<br>Support for alternative combination of any two drugs from the five major classes |
| ACC/AHA (2018) [3] | Prescribe antihypertensive therapy if BP is ≥130/80 mmHg and CVD is already present or 10-year CV risk is ≥10%<br>Prescribe antihypertensive therapy if BP is ≥140/90 mmHg for patients at lower risk<br>Consider initial combination of drugs with complementary mechanisms of action for patients with BP ≥140/90 mmHg |
| ISH (2020) [4] | Initiate pharmacotherapy for patients with Grade I hypertension at low-to-moderate CV risk if a 3–6-month trial of lifestyle intervention is unsuccessful<br>Initiate pharmacotherapy immediately for patients with Grade I hypertension and high or very high CV risk (with CV or renal disease, target organ damage or diabetes) and for all patients with Grade 2 or 3 hypertension<br>Use ACEI/ARB + CCB or diuretic initially ("optimal" recommendation) or use whatever drugs are available if they have as many of the following characteristics as possible: evidence-based improvement in outcomes, effective given once daily, affordable and cost effective, well tolerated, and shown to be effective in the population in which they are to be used ("essential" recommendation) |
| NICE (2022) [5] | "Discuss" pharmacological antihypertensive therapy for patients with Stage 1 hypertension if they have one or more target organs with damage, established CV or renal disease, diabetes, or 10-year CV risk ≥10%<br>"Consider" pharmacological antihypertensive therapy for patients with Stage 1 hypertension and lower CV risk<br>Initiate pharmacological antihypertensive therapy for patients with Stage 2 hypertension<br>Use clinical judgement with regards to patient issues such as comorbidities, frailty, etc.<br>ACEI/ARB favoured for patients with type 2 diabetes or age <55 years who are not of African-Caribbean heritage<br>CCB favoured for age >55 years without diabetes or patients of African-Caribbean heritage |

BP: blood pressure; CV: cardiovascular; CVD: cardiovascular disease. See Table 1 for definitions of acronyms for expert societies.
[a]Guideline for the management of arterial hypertension.
[b]Guideline for CV risk reduction.
[c]All recommendations for pharmacological therapy are in addition to lifestyle interventions. Applies to patients without contraindications of compelling indications for a particular class of therapy (see text).

≥140/90 mmHg, which is consistent with the ESC recommendations, described above. Physicians are invited to consider the use of a combination of antihypertensive agents with complementary mechanisms of action as initial antihypertensive pharmacotherapy for patients with BP ≥140/90 mmHg; it should be noted that the US guideline identifies this level of BP as "Stage 2 hypertension", which differs from the European approach summarised in Box 1.

With regard to other guidelines, the approach of the International Society of Hypertension (ISH) towards initiation of antihypertensive pharmacotherapy is broadly similar to that of the ESC, with combination treatment preferred in all but the lowest-risk and very elderly patients. "Optimal" recommendations favour the use of an ACEI/ARB + CCB or diuretic at therapy initiation, but "essential" recommendations for areas with limited access to healthcare support the use of any available combination, which ideally satisfies five criteria. The most recent (2022) guideline considered here, from the National Institute for Health and Care Excellence (NICE) in the UK, takes a very different approach to that of other expert groups [7]. There is no absolute recommendation for the use of antihypertensive drug treatment for patients with Grade 1 hypertension, even those at high risk. The choice of initial drug treatment is based on a patient's medical history or ethnicity, with either ACEI/ARB or CCB preferred as initial therapy. There is no focus on the application of antihypertensive combination therapy at diagnosis in this guideline.

**Box 1. Grading of severity of hypertension (European definition).**

| Grade | Systolic BP (mmHg) | Diastolic BP (mmHg) |
|---|---|---|
| **High normal** | 130–139 | 85–89 |
| **Grade 1** | 140–159 | 90–99 |
| **Grade 2** | 160–179 | 100–109 |
| **Grade 3** | ≥180 | ≥110 |

BP: blood pressure. Compiled from information presented in reference [3].

### *Elderly patients*

The ESC/ESH guideline supports the use of antihypertensive pharmacotherapy for patients with Grade I hypertension who are aged between 65 and 80 years. Older patients may receive antihypertensive pharmacotherapy if their SBP is ≥160 mmHg. Other guidelines take a broadly similar approach.

### *Further intensification of antihypertensive therapy*

Approximately one-third of patients with hypertension will remain sub-optimally controlled despite treatment with two antihypertensive agents [15]. The ESC/ESH guideline favours a triple combination of ACEI/ARB + diuretic + CCB as the usual mode of treatment for these patients [2, 3]. Addition of spironolactone is recommended if not contraindicated, or other classes of diuretic, β-blocker, α-blocker or centrally acting agents for patients unable to receive spironolactone. The ACC/AHA guideline acknowledges the need for a third antihypertensive for some patients, and notes the existence of single-tablet combinations containing ACEI/ARB/CCB [3]. NICE and the ISH also favour the use of this triple combination, followed where required by addition of low-dose spironolactone (where not contraindicated) [5, 6].

## Antihypertensive therapy for special populations

Hypertension often appears alongside other long-term, non-communicable diseases that may influence the choice of antihypertensive therapy. Table 4 summarises European guideline recommendations on the management of hypertension in patients with comorbidities. In some cases, the recommendations cited are a synthesis of those given in guidelines for hypertension and the specific comorbidity, e.g. heart failure or chronic coronary syndrome.

**Table 4 Use of classes of antihypertensive agents in populations with a comorbidity.**

| Comorbidity | Include in the regimen |
|---|---|
| **Heart failure with reduced ejection fraction** | ACEI/ARB (or sacubitril/valsartan)<br>β-blocker<br>MRA<br>SGLT2 inhibitor<br>Loop diuretic (for fluid retention)<br>Consider CCB if BP target not achieved |
| **Heart failure with preserved ejection fraction** | SGLT2 inhibitor<br>Consider β-blocker, long-acting nitrates, CCB, ivabradine, ranolazine, trimetazidine, nicorandil (alone or in combination) for angina relief but there is no evidence base for improved outcomes |
| **CCS (post-MI)** | ACEI and β-blocker or CCB (history of myocardial infarction)<br>β-blocker and/or CCB (for symptomatic angina) |
| **Diabetes** | ACEI/ARB + CCB or diuretic |
| **Chronic kidney disease** | ACEI/ARB + CCB or diuretic<br>SGLT2 inhibitor |
| **Atrial fibrillation** | β-blocker or non-dihydropyridine CCB if rate control is needed |
| **Prior ischaemic stroke or TIA** | ACEI/ARB + CCB or diuretic |
| **COPD** | ACEI/ARB + CCB<br>Consider $\beta_1$-selective β-blocker or diuretic if BP goal not met |

ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin II receptor blocker; BP: blood pressure; CCB: calcium channel blocker; CCS: chronic coronary syndrome; COPD: chronic obstructive pulmonary disease; MI: myocardial infarction; MRA: mineralocorticoid receptor antagonist; SGLT2: sodium glucose co-transporter 2; TIA: transient ischaemic attack.
Compiled from information presented in European guidelines for the management of hypertension, heart failure or chronic coronary syndromes [2, 6, 7].

## *Heart failure*

### *Heart failure with reduced left ventricular ejection fraction (HFrEF)*

ACEI/ARBs [16] (or sacubitril/valsartan [17]), β-blockers [18] and mineralocorticoid receptor antagonists (MRAs) [19] are evidence-based therapies for improving clinical outcomes in people with HFrEF, and guidelines recommend that they should be included in the therapeutic regimen of these patients. Sodium glucose co-transporter 2 inhibitors (SGLT2i) have shown large and consistent reductions in hospitalisations and mortality due to HFrEF, which led to guideline recommendations to include them in treatment regimens for heart failure [20]. Moreover, SGLT2i produce reductions in SBP of about 2–4 mmHg [21, 22], which may contribute to the overall management of BP in patients with hypertension and

HFrEF (or indeed, chronic kidney disease [CKD], see below). A recent meta-analysis found a combination of sacubitril/valsartan, β-blocker, mineralocorticoid receptor antagonists (MRA) and SGLT2i to be the most effective combination for reducing the risk of mortality in patients with heart failure [23]. Non-dihydropyridines should not be given to patients with decompensated heart failure.

## *Heart failure with preserved left ventricular ejection fraction (HFpEF)*

HFpEF is usually defined as heart failure with a left ventricular ejection fraction (LVEF) >50%, although patients with LVEF 40–50% have been included in many studies [7]. As many as half of community-dwelling patients with heart failure have HFpEF [24]. Prognosis is poor, with one study reporting an average life expectancy of 2.1 years and 75% mortality over 5 years from diagnosis [25].

Blockers of the RAS or sacubitril/valsartan, which are effective in improving mortality outcomes in HFrEF (see above), have not been shown to reduce mortality in HFpEF [26, 27]. MRA appear to reduce hospitalisations for HFpEF, but not mortality [25]. Meta-analyses have reported that treatment with a β-blocker reduced the risk of cardiovascular mortality in patients with HFpEF [25, 26]. A further meta-analysis found a mortality benefit for β-blockade in patients with LVEF 40–49%, but not in a small group with LVEF ≥50% [17]. These findings are intriguing, and suggest the need for further research on the effects of β-blockers in HFpEF. However, the limited and *post-hoc* nature of this evidence does not support a role for the use of β-blockers in the management of HFpEF currently, in the absence of an additional reason for their use.

Guidelines for HFpEF recommend the use of diuretics to improve heart failure symptoms [7]. The Emperor-Preserved trial demonstrated recently that treatment with an SGLT2i (empagliflozin) significantly reduced the risk of hospitalisation for heart failure in patients with HFpEF [28]. A large meta-analysis, which included patients with LVEF >50%, added support to this finding [29]. In future, SGLT2i may become part of the standard management of HFpEF, with some implications for BP management, as for HFrEF.

## *Chronic coronary syndrome (post-MI)*

As with HFrEF, RAS blockers and β-blockers are evidence-based therapy for improving clinical outcomes in patients with a prior history of MI [30, 31]. Patients with symptomatic angina pectoris may benefit from a combination of a β-blocker with a CCB.

## *Other comorbidities and contraindications*

The recommended initial pharmacotherapy for a patient with hypertension and diabetes, CKD, prior stroke or transient ischaemic attack, or chronic obstructive pulmonary disease (COPD), is a blocker of the RAS combined with a CCB or a thiazide-like diuretic. An exception is atrial fibrillation, where a β-blocker or non-dihydropyridine CCB may be useful in controlling both BP and the ventricular rate.

SGLT2i have been shown to improve clinical outcomes in patients with CKD, and some agents now have an indication for this condition. Future guidelines for the management of hypertension may include a compelling indication for these agents in the management of patients with CKD and hypertension.

The 2018 ESC/ESH guideline for the management of hypertension includes "compelling" and "possible" contraindications to the use of the five main classes of antihypertensive agents. These are discussed briefly here as they will impact on the use of these drugs in patients with specific comorbidities.

**Diabetes or metabolic syndrome:** These conditions are listed as "possible" contraindications for β-blockers and thiazide-like diuretics. Diuretics may also be considered contraindicated in patients who are athletes or physically active. It should be noted that β-blockers are a highly heterogeneous class of drugs, including individual agents with or without selectivity for the $\beta_1$-adrenoceptor, intrinsic sympathomimetic activity or additional vasodilator properties, among other attributes [32]. The potentially adverse metabolic effects of β-blockers are largely associated with blockade of $\beta_2$-adrenoceptors, and such effects have not been observed with highly selective $\beta_1$-adrenoceptor blockers (cardioselective agents), such as bisoprolol [33–36]. Metabolic disturbances

with thiazides are less marked at low dosages, consistent with those delivered in fixed-dose combinations with other antihypertensive agents [37].

**COPD/asthma:** Asthma is listed as a compelling contraindication for β-blockers. Again, $\beta_2$-adrenoceptor blockade accounts for most or all of the adverse effects on bronchial tone in people with asthma, or with interference with the action of $\beta_2$-agonists taken to manage an asthma attack [38]. Observational data have shown no increased risk of asthma exacerbations in patients receiving a selective $\beta_1$-adrenoceptor, compared with clearly increased risk with a non-selective agent, even at lower dosages [39]. The European Summary of Product Characteristics lists only "severe bronchial asthma" as a contraindication for bisoprolol (a highly selective $\beta_1$-adrenoceptor blocker), compared with "a history of bronchospasm or asthma" for the non–cardio-selective β-blocker, propranolol. These observations are important, as β-blockers may be underused in patients with airways disease [40].

**Sinoatrial block or bradycardia:** Neither β-blockers nor non-dihydropyridine CCBs should be used in patients with high-grade atrioventricular block or severe bradycardia.

**Pregnancy:** ACEI and ARBs should not be taken during pregnancy and being a "woman of childbearing potential without reliable contraception" is given as a contraindication for these agents. Pregnancy is also a contraindication for thiazide-like diuretics.

**Other compelling contraindications:** ACEI or ARB may cause hyperkalaemia [41]. Accordingly, hyperkalaemia (serum $K^+$ >5.5 mmol/L) is listed among the compelling contraindications to the use of these agents. ACEI or ARBs should not be used in patients with bilateral renal artery stenosis, as they may precipitate acute renal failure in this setting. This arises because the maintenance of glomerular pressure and filtration becomes dependent on angiotensin II-mediated constriction of the efferent arteriole when flow though the renal afferent arteriole is limited (as in renal artery stenosis). Removing the effect of angiotensin II collapses glomerular pressure and effectively switches off glomerular filtration [42]. ACEI use also rarely causes angioneurotic oedema, associated with accumulation of bradykinin, which would

normally be metabolised by ACE; this is another compelling contraindication for this class of antihypertensive [43]. Finally, gout is a compelling contraindication for thiazide-like diuretics, associated with increased circulating levels of uric acid [44].

## Discussion

Perhaps the main take-home message from current major guidelines for the management of hypertension, especially those from Europe, is that almost all patients will need combination therapy with at least two drugs to achieve adequate control of BP. The most common recommendation for initial antihypertensive therapy in the guidelines is for a blocker of the RAS (ACEI or ARB), together with a CCB or thiazide-like diuretic, which fulfils the requirement of choosing two agents with different, and potentially complementary, mechanisms of action. The role of β-blockers has diminished in guidelines in recent years, due in part to concerns over adverse metabolic effects (likely attributable to lack of $\beta_1$-adrenoceptor selectivity of some β-blockers, as described above), or lower potential to reduce the risk of adverse coronary events than newer classes in some meta-analyses [45, 46], although this was not seen in a large meta-analysis that incorporated data from 464,000 patients [47]. These meta-analyses also suggested that CCBs tend to be more effective in preventing strokes than other antihypertensive classes. Combining a highly selective β-blocker with a CCB therefore remains a rational approach to the management of hypertension, especially for patients with HFrEF, prior MI or stroke, atrial fibrillation or hypertension driven by high sympathetic tone [48, 49]. Chapter 4 of this book will consider the mechanism of action of this combination.

# References


1 Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, et al. 2018 ESC/ESH guidelines for the management of arterial hypertension. Eur Heart J. 2018;39:3021–104. https://doi.org/10.1093/eurheartj/ehy339.

2 Visseren FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC, Bäck M, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J. 2021;42:3227–337. https://doi.org/10.1093/eurheartj/ehab484.

3 Whelton PK, Carey RM, Aronow WS, Casey DE, Jr., Collins KJ, Dennison Himmelfarb C, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. Hypertension. 2018;71:e13–e115. https://doi.org/10.1161/hyp.0000000000000065.

4 Unger T, Borghi C, Charchar F, Khan NA, Poulter NR, Prabhakaran D, et al. 2020 International Society of Hypertension global hypertension practice guidelines. Hypertension. 2020;75:1334–57. https://doi.org/10.1161/hypertensionaha.120.15026.

5 National Institute for Health and Care Excellence. Hypertension in adults: diagnosis and management: NICE guideline [NG136] 2019. Available from: https://www.nice.org.uk/guidance/ng136 Accessed May 2022.

6 McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) with the special contribution of the Heart Failure Association (HFA) of the ESC [published correction appears in Eur Heart J. 2021 Dec 21;42(48):4901]. Eur Heart J. 2021;42:3599–726. https://doi.org/10.1093/eurheartj/ehab670.

7 Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, et al. 2019 ESC guidelines for the diagnosis and management of chronic coronary syndromes: The Task Force for the diagnosis and management of chronic coronary syndromes of the European Society of Cardiology (ESC) [published correction appears in Eur Heart J. 2020 Nov 21;41(44):4242]. Eur Heart J. 2020;41:407–77. https://doi.org/10.1093/eurheartj/ehz425.

8 National Institute for Health and Care Excellence. British National Formulary. Available from: https://bnf.nice.org.uk/ Accessed May 2022.

9 Yang MH, Kang SY, Lee JA, Kim YS, Sung EJ, Lee KY, et al. Correction: The effect of lifestyle changes on blood pressure control among hypertensive patients. Korean J Fam Med. 2017;38:311–2. https://doi.org/10.4082/kjfm.2017.38.5.311.

10 Paula TP, Viana LV, Neto AT, Leitão CB, Gross JL, Azevedo MJ. Effects of the DASH diet and walking on blood pressure in patients with type 2 diabetes and uncontrolled hypertension: a randomized controlled trial. J Clin Hypertens (Greenwich). 2015;17:895–901. https://doi.org/10.1111/jch.12597.

11 Higashino R, Miyaki A, Kumagai H, Choi Y, Akazawa N, Ra SG, et al. Effects of lifestyle modification on central blood pressure in overweight and obese men. Blood Press Monit. 2013;18:311–5. https://doi.org/10.1097/mbp.0000000000000006.

12 Appel LJ, Champagne CM, Harsha DW, Cooper LS, Obarzanek E, Elmer PJ, et al. Effects of comprehensive lifestyle modification on blood pressure control: main results of the PREMIER clinical trial. JAMA. 2003;289:2083–93. https://doi.org/10.1001/jama.289.16.2083.

13 Chudasama YV, Khunti K, Gillies CL, Dhalwani NN, Davies MJ, Yates T, et al. Healthy lifestyle and life expectancy in people with multimorbidity in the UK Biobank: a longitudinal cohort study. PLoS Med. 2020;17:e1003332. https://doi.org/10.1371/journal.pmed.1003332.

14 Derington C, King J, Herrick J, Dixon D, Cohen JB, Shimbo D, et al. Factors associated with antihypertensive monotherapy among US adults with treated and uncontrolled blood pressure, NHANES 2005–2016. J Hypertens. 2021;39:p e241. https://doi.org/10.1097/01.hjh.0000747184.27176.5a

**15** Wald DS, Law M, Morris JK, Bestwick JP, Wald NJ. Combination therapy versus monotherapy in reducing blood pressure: meta-analysis on 11,000 participants from 42 trials. Am J Med. 2009;122:290-300. https://doi.org/10.1016/j.amjmed.2008.09.038.

**16** Flather MD, Yusuf S, Køber L, Pfeffer M, Hall A, Murray G, et al. Long-term ACE-inhibitor therapy in patients with heart failure or left-ventricular dysfunction: a systematic overview of data from individual patients. ACE-inhibitor myocardial infarction collaborative group. Lancet. 2000;355:1575–81. https://doi.org/10.1016/s0140-6736(00)02212-1.

**17** Nielsen EE, Feinberg JB, Bu FL, Hecht Olsen M, Raymond I, Steensgaard-Hansen F, et al. Beneficial and harmful effects of sacubitril/valsartan in patients with heart failure: a systematic review of randomised clinical trials with meta-analysis and trial sequential analysis. Open Heart. 2020;7(2):e001294. https://doi.org/10.1136/openhrt-2020-001294.

**18** Cleland JGF, Bunting KV, Flather MD, Altman DG, Holmes J, Coats AJS, et al. Beta-blockers for heart failure with reduced, mid-range, and preserved ejection fraction: an individual patient-level analysis of double-blind randomized trials. Eur Heart J. 2018;39:26–35. https://doi.org/10.1093/eurheartj/ehx564.

**19** Berbenetz NM, Mrkobrada M. Mineralocorticoid receptor antagonists for heart failure: systematic review and meta-analysis. BMC Cardiovasc Disord. 2016;16:246. https://doi.org/10.1186/s12872-016-0425-x.

**20** Zannad F, Ferreira JP, Pocock SJ, Anker SD, Butler J, Filippatos G, et al. SGLT2 inhibitors in patients with heart failure with reduced ejection fraction: a meta-analysis of the EMPEROR-Reduced and DAPA-HF trials. Lancet. 2020;396:819–29. https://doi.org/10.1016/s0140-6736(20)31824-9.

**21** Johnston R, Uthman O, Cummins E, Clar C, Royle P, Colquitt J, et al. Canagliflozin, dapagliflozin and empagliflozin monotherapy for treating type 2 diabetes: systematic review and economic evaluation. Health Technol Assess. 2017;21:1–218. https://doi.org/10.3310/hta21020.

**22** Zaccardi F, Webb DR, Htike ZZ, Youssef D, Khunti K, Davies MJ. Efficacy and safety of sodium-glucose co-transporter-2 inhibitors in type 2 diabetes mellitus: systematic review and network meta-analysis. Diabetes Obes Metab. 2016;18:783–94. https://doi.org/10.1111/dom.12670.

**23** Tromp J, Ouwerkerk W, van Veldhuisen DJ, Hillege HL, Richards AM, van der Meer P, et al. A systematic review and network meta-analysis of pharmacological treatment of heart failure with reduced ejection fraction. JACC Heart Fail. 2022;10:73–84. https://doi.org/10.1016/j.jchf.2021.09.004.

**24** Dunlay SM, Roger VL, Redfield MM. Epidemiology of heart failure with preserved ejection fraction. Nat Rev Cardiol. 2017;14:591–602. https://doi.org/10.1038/nrcardio.2017.65.

**25** Shah KS, Xu H, Matsouaka RA, Bhatt DL, Heidenreich PA, Hernandez AF, et al. Heart failure with preserved, borderline, and reduced ejection fraction: 5-year outcomes. J Am Coll Cardiol. 2017;70:2476–86. https://doi.org/10.1016/j.jacc.2017.08.074.

**26** Martin N, Manoharan K, Davies C, Lumbers RT. Beta-blockers and inhibitors of the renin-angiotensin aldosterone system for chronic heart failure with preserved ejection fraction. Cochrane Database Syst Rev. 2021;5:Cd012721. https://doi.org/10.1002/14651858.CD012721.pub3.

**27** Zheng SL, Chan FT, Nabeebaccus AA, Shah AM, McDonagh T, Okonko DO, et al. Drug treatment effects on outcomes in heart failure with preserved ejection fraction: a systematic review and meta-analysis. Heart. 2018;104:407–15. https://doi.org/10.1136/heartjnl-2017-311652.

**28** Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med. 2015;373:2117–28. https://doi.org/10.1056/NEJMoa1504720.

**29** Tsampasian V, Elghazaly H, Chattopadhyay R, Ali O, Corballis N, Chousou PA, et al. Sodium glucose co-transporter 2 inhibitors in heart failure with preserved ejection fraction: a systematic review and meta-analysis. Eur J Prev Cardiol. 2022;29:e227–e9. https://doi.org/10.1093/eurjpc/zwab189.

**30** Bangalore S, Fakheri R, Wandel S, Toklu B, Wandel J, Messerli FH. Renin angiotensin system inhibitors for patients with stable coronary artery disease without heart failure: systematic review and meta-analysis of randomized trials. BMJ. 2017;356:j4. https://doi.org/10.1136/bmj.j4.

**31** Freemantle N, Cleland J, Young P, Mason J, Harrison J. Beta blockade after myocardial infarction: systematic review and meta regression analysis. BMJ. 1999;318:1730–7. https://doi.org/10.1136/bmj.318.7200.1730.

**32** Pathak A, Mrabeti S. β-blockade for patients with hypertension, ischemic heart disease or heart failure: where are we now? Vasc Health Risk Manag. 2021;17:337–48. https://doi.org/10.2147/vhrm.S285907.

**33** Cruickshank JM. Are we misunderstanding beta-blockers. Int J Cardiol. 2007;120:10–27. https://doi.org/10.1016/j.ijcard.2007.01.069.

**34** National Institute for Health and Care Excellence. Bisoprolol fumarate. British National Formulary. Available from: https://bnf.nice.org.uk/drug/bisoprolol-fumarate.html#sideEffects Accessed June 2018.

**35** Hirst JA, Farmer AJ, Feakins BG, Aronson JK, Stevens RJ. Quantifying the effects of diuretics and β-adrenoceptor blockers on glycaemic control in diabetes mellitus - a systematic review and meta-analysis. Br J Clin Pharmacol. 2015;79:733–43. https://doi.org/10.1111/bcp.12543.

**36** Janka HU, Ziegler AG, Disselhoff G, Mehnert H. Influence of bisoprolol on blood glucose, glucosuria, and haemoglobin A1 in noninsulin-dependent diabetics. J Cardiovasc Pharmacol. 1986;8 Suppl 11:S96–9. https://doi.org/10.1097/00005344-198511001-00018.

**37** Scheen AJ. Type 2 diabetes and thiazide diuretics. Curr Diab Rep. 2018;18:6. https://doi.org/10.1007/s11892-018-0976-6.

**38** Lipworth B, Wedzicha J, Devereux G, Vestbo J, Dransfield MT. Beta-blockers in COPD: time for reappraisal. Eur Respir J. 2016;48:880–8. https://doi.org/10.1183/13993003.01847-2015.

**39** Morales DR, Lipworth BJ, Donnan PT, Jackson C, Guthrie B. Respiratory effect of beta-blockers in people with asthma and cardiovascular disease: population-based nested case control study. BMC Med. 2017;15:18. https://doi.org/10.1186/s12916-017-0781-0.

**40** Lim KP, Loughrey S, Musk M, Lavender M, Wrobel JP. Beta-blocker under-use in COPD patients. Int J Chron Obstruct Pulmon Dis. 2017;12:3041–6. https://doi.org/10.2147/copd.S144333.

**41** Raebel MA. Hyperkalemia associated with use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers. Cardiovasc Ther. 2012;30:e156–66. https://doi.org/10.1111/j.1755-5922.2010.00258.x.

**42** Schoolwerth AC, Sica DA, Ballermann BJ, Wilcox CS. Renal considerations in angiotensin converting enzyme inhibitor therapy: a statement for healthcare professionals from the Council on the Kidney in Cardiovascular Disease and the Council for High Blood Pressure Research of the American Heart Association. Circulation. 2001;104:1985–91. https://doi.org/10.1161/hc4101.096153.

**43** Montinaro V, Cicardi M. ACE inhibitor-mediated angioedema. Int Immunopharmacol. 2020;78:106081. https://doi.org/10.1016/j.intimp.2019.106081.

**44** Hainer BL, Matheson E, Wilkes RT. Diagnosis, treatment, and prevention of gout. Am Fam Physician. 2014;90:831–6.

**45** Wiysonge CS, Bradley HA, Volmink J, Mayosi BM, Opie LH. Beta-blockers for hypertension. Cochrane Database Syst Rev. 2017;1:Cd002003. https://doi.org/10.1002/14651858.CD002003.pub5.

**46** Lindholm LH, Carlberg B, Samuelsson O. Should beta blockers remain first choice in the treatment of primary hypertension? A meta-analysis. Lancet. 2005;366:1545–53. https://doi.org/10.1016/s0140-6736(05)67573-3.

**47** Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. BMJ. 2009;338:b1665. https://doi.org/10.1136/bmj.b1665.

**48** Grassi G. Sympathetic overdrive in hypertension: clinical and therapeutic relevance. ESC Council for Cardiology Practice. 2015. Available from: https://www.escardio.org/Journals/

E-Journal-of-Cardiology-Practice/Volume-13/sympathetic-overdrive-in-hypertension-clinical-and-therapeutic-relevance (Accessed July 2022)

**49** Santilli F, Simeone P, D'Ardes D, Davì G. The deadly line linking sympathetic overdrive, dipping status and vascular risk: critical appraisal and therapeutic implications. Hypertens Res. 2016;39:404–6. https://doi.org/10.1038/hr.2016.27.

# Chapter 3

# Medical Need for Combination Treatment in Hypertension

**Luciano F Drager**
Heart Institute (InCor), University Hospital HCFMUSP, University of São Paulo, São Paulo, Brazil

**Blood pressure (BP) is not optimally controlled in half or more patients with hypertension in most countries. Current guidelines call for more intensive management of hypertension, including use of combination treatment from diagnosis for most patients. These guidelines strongly support the use of single-tablet combinations from diagnosis for most patients, as this approach is more effective and better tolerated than titration of monotherapies, helps to avoid clinical inertia, and supports good adherence to the treatment regimen.**

## Sub-optimal control of hypertension is common

### *Prevalence of sub-optimal BP control in hypertension*

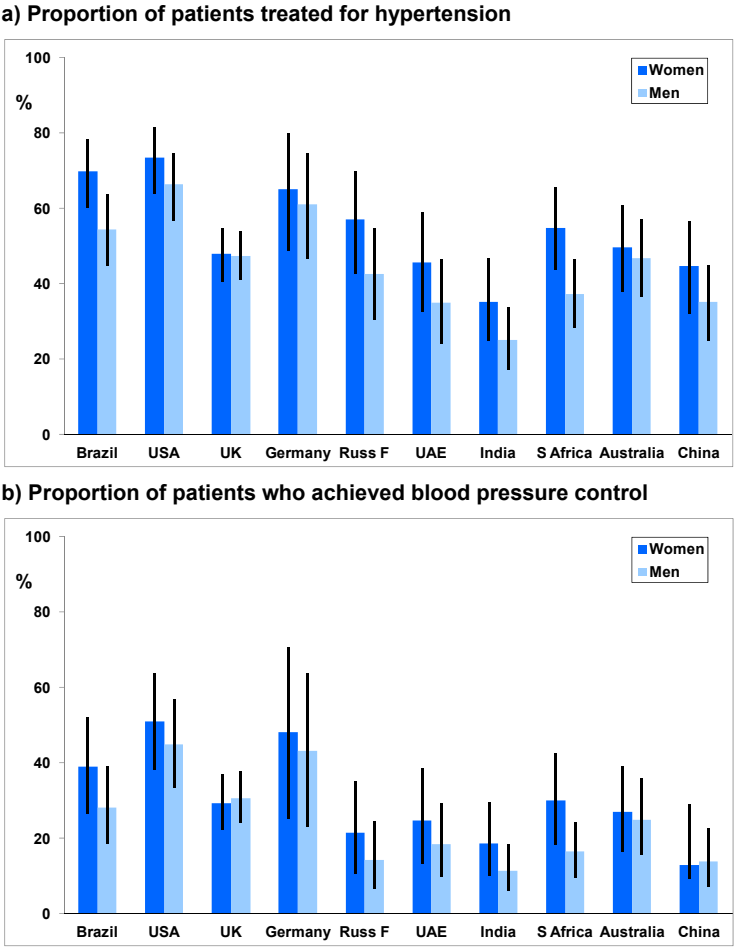
We have seen in the preceding chapters of this book that hypertension is prevalent world-wide, and that uncontrolled hypertension is associated with a major burden of premature cardiovascular morbidity and

mortality. We have also seen that major international guidelines provide targets for BP control in people with hypertension that, if achieved, will help to preserve cardiovascular health and reduce the risk of major adverse cardiovascular events.

So, how well are we doing? The Non-Communicable Disease Risk Factor Collaboration undertook a global survey of hypertension that included data from a total of 104 million individuals, with BP data from 1,204 individual studies [1]. The survey reported that, overall, 47% (95% confidence interval [CI], 43 to 51%) of women and 38% (95% CI, 35 to 41%) of men received treatment for hypertension, and hypertension was controlled in 23% (95% CI, 20 to 27%) of women and 18% (95% CI, 16 to 21%) of men in 2019. Figure 1 summarises some of these data from selected countries from different regions of the world. The proportions treated and controlled were highly variable between countries. Also, the rates of treatment and control were higher for women than for men in most of the countries, consistent with the results of the overall analysis.

Other published data support these findings. Data from the nationally representative National Health and Nutrition Survey (NHANES) 2015–2018 cohort in the United States of America (USA) reported that only 22.3% of women and 18.2% of men with hypertension had their BP controlled [2]. This was even lower than the global survey, although it should be noted that these data were generated using the US BP target of <130/80 mmHg (see Chapter 2 of this book), rather than the <140/90 mmHg cut-off used in the global survey. A 2017 survey using data from 6,546 individuals across ten countries and three continents found that treatment and BP control rates (<140/90 mmHg) were 48.0% (range, 33.5 to 74.1%) and 38.6% (range, 10.1 to 55.3%), respectively [3]. The World Health Organization has reported that 42.0% of adults with hypertension are diagnosed and treated, and only 21.0% achieve BP control [4]. Elsewhere, control of hypertension was achieved in 38.1% (95% CI, 37.8 to 38.4%) of 100,000 treated hypertensive patients in the United Kingdom (UK) (<140/90 mmHg, 2021) [5]; in 47.3% (standard deviation, 1.17) of 3,969 hypertensive patients in Korea (<140/90 mmHg, 2016–2017) [6]; in 51.6% of treated patients with hypertension in Ireland (<140/90 mmHg, 2009–2011) [7]; in 64.6%

**Figure 1 Proportion of patients with hypertension who (a) received treatment and (b) achieved adequate blood pressure control (<140/90 mmHg) from a global survey on hypertension [1].**




Russ F: Russian Federation; S Africa: South Africa; UAE: United Arab Emirates; UK: United Kingdom; USA: United States of America.

of hypertensive patients in Canada (<140/90 mmHg, 2009) [8]; and in 49.9% of treated hypertensive patients in Guinea-Bissau, West Africa (<140/90 mmHg, 2021) [9].

## Need for combination therapy in hypertension

### *Superior clinical efficacy of antihypertensive combinations versus monotherapy*

The clinical evidence summarised above confirms that a substantial proportion of people with hypertension are under treated. Three strategies are available for increasing the effectiveness of antihypertensive therapy: (1) switching to another drug (i.e. sequential antihypertensive monotherapy); (2) titrating the dose of another drug; or (3) adding one or more new drugs to the regimen.

A randomised trial compared all three strategies during 9 months of treatment. More patients with hypertension achieved BP <140/90 mmHg following initial treatment with a single-tablet, low-dose combination of perindopril (an angiotensin-converting enzyme inhibitor), a thiazide, and indapamide, compared with sequential monotherapy with atenolol (a β-blocker), losartan, and amlodipine (a calcium channel blocker), or 'stepped care' where monotherapy with valsartan (an angiotensin II receptor blocker [ARB]) was titrated and a thiazide added if required (Table 1) [10]. A second randomised trial in 605 patients with previously untreated hypertension compared strategies (1) and (3) directly [11]. Patients in two study arms received the ARB losartan or the thiazide diuretic hydrochlorothiazide for 8 weeks, followed by crossing over to the other monotherapy for a further 8 weeks. Patients in a third study arm received both drugs together for the 16-week treatment period. The mean change in clinic BP was –23.8/–13.4 mmHg for combination therapy versus –13.7/–7.1 mmHg for sequential monotherapy (mean treatment difference –10.1/–6.31 mmHg, $p<0.001$). Thus, initial combination therapy is more effective than sequential monotherapy for controlling high BP. A third randomised trial, where perindopril plus indapamide were given as initial antihypertensive therapy to drug-naïve

**Table 1 Greater antihypertensive efficacy with a single-tablet combination of two antihypertensive agents compared with sequential monotherapies or a stepped care approach during 9 months of treatment in patients with hypertension [10].**

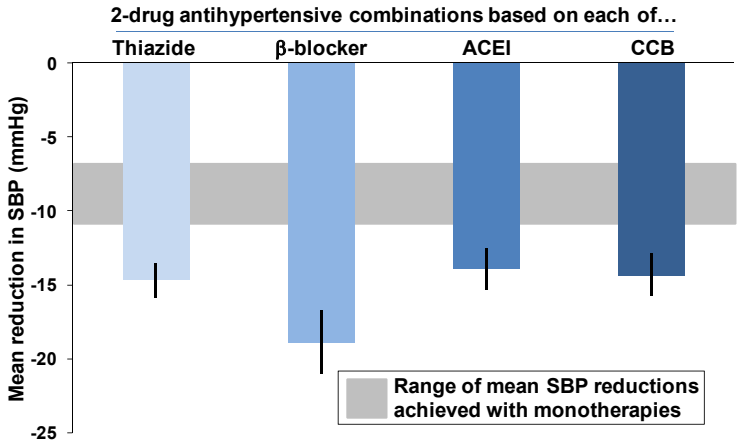
| | Mean change in systolic/diastolic blood pressure (mmHg) | Percent of patients with blood pressure <140/90 mmHg |
|---|---|---|
| **Initial single-tablet combination approach** (indapamide + perindopril[a]) | –26.6*/–13.6 | 62* |
| **Sequential monotherapy approach** (atenolol → losartan → amlodipine[b]) | –22.6/–12.5 | 49 |
| **Stepped care approach** (valsartan 40–80 mg + additional hydrochlorothiazide if needed[c]) | –21.5/–12.1 | 47 |

[a]For the initial combination tablet approach, the dose of the combination could be titrated if required.
[b]In the sequential monotherapy approach, monotherapies were replaced if blood pressure remained uncontrolled.
[c]For the stepped care approach, valsartan monotherapy could be titrated followed by addition of hydrochlorothiazide if needed.
*p<0.05 or better vs. both other treatment groups.
Data are from the end of the study (9 months of treatment).
Compiled from data presented in Mourad et al. [10]

patients, or to uncontrolled hypertensive patients as replacement for a monotherapy or in addition to an existing monotherapy, reported control rates for hypertension of 67–70% across the three groups, which is higher than expected in usual routine care, as described above [12].

A meta-analysis of 42 clinical trials (including 10,968 participants), which compared two-drug combinations with one or more of their components as monotherapy, showed that addition of a second antihypertensive drug to a thiazide diuretic produced reductions in BP that were clearly larger than those obtained with monotherapies (Figure 2) [13]. This study also showed that adding an additional antihypertensive agent delivered BP reduction that was five-fold higher than titrating an existing monotherapy. Another meta-analysis showed that patients with hypertension taking combination antihypertensive therapy were more likely to achieve their BP goal compared with monotherapy [14]. Finally, a real-world evidence study compared strategies of single-tablet combination therapy, a free combination of antihypertensive agents, and monotherapy during the first treatment year [15]. The likelihood of achieving BP control was higher for the single-tablet or free combination versus monotherapy

**Figure 2 Mean reduction in systolic blood pressure in patients receiving two-drug combination therapy compared with monotherapy [13].**




Bars represent 95% confidence intervals.
ACEI: angiotensin converting enzyme inhibitor; CCB: calcium channel blocker; SBP: systolic blood pressure.

(hazard ratio, 1.53 [95% CI, 1.47 to 1.58] and 1.34 [95% CI, 1.31 to 1.37]), respectively.

A number of other randomised trials have confirmed the superior efficacy of initial combination therapy for increasing BP control rates in populations with hypertension [16]. These data further confirm the superior efficacy of the combination therapy approach for increasing the effectiveness of antihypertensive treatment, compared with monotherapy.

## *Experience from clinical trials of intensive BP control*

Several clinical trials have evaluated the effects on outcomes of intensive BP control in various populations, in order to explore the clinical validity of guideline BP targets. These trials have required the use of multiple antihypertensive agents to achieve their intensive BP control targets. For example, patients in the intensive control arm of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) BP trial (in people with type 2 diabetes and hypertension) received an average of 3.4 antihypertensive

agents (compared with an average of 2.1 agents for the standard control group) [17]. Similar findings came from the intensive and standard control groups in the Systolic Blood Pressure Intervention Trial (SPRINT) in hypertensive patients at elevated cardiovascular risk (2.8 versus 1.8 agents, respectively) [18], and the Strategy of Blood Pressure Intervention in the Elderly Hypertensive Patients (STEP) trial in older patients with hypertension (1.9 versus 1.5 agents, respectively) [19].

## Advantages of single-tablet combinations

### *Overcoming clinical inertia in hypertension*

The definition of therapeutic inertia is a "*failure of healthcare providers to initiate or intensify therapy according to current guidelines*" [20, 21]. In the setting of hypertension management this means a failure to initiate or to intensify antihypertensive therapy despite a patient's BP being above the current guideline goal.

Therapeutic inertia is common in the management of hypertension, for reasons related to the healthcare provider, the patients themselves, and the healthcare system [22]. A recent (2021) cohort study in the Netherlands found that this applied to 87% of a population of hypertensive patients above their guideline BP goal while receiving one or two antihypertensive drugs [23]. Older age, having BP close to the goal, and comorbid diabetes were associated with therapeutic inertia in this study. Physicians cited a preference for optimising lifestyle intervention and waiting for the next set of results among the reasons for not intensifying therapy. The prevalence of therapeutic inertia in the standard and intensive BP management arms of the randomised SPRINT trial varied between 56–60%, with some evidence of differences according to ethnicity [24]. Almost half of the patients with Stage 1 or 2 hypertension remained on monotherapy over 8 years in Belgium and Luxembourg, despite uncontrolled BP [25]. A systematic review suggested that a range of interventions designed to reduce therapeutic inertia increased the likelihood of achieving BP control by 19% [20].

Modelling studies have also addressed this issue. A therapeutic inertia score, based on disparities between expected and actual changes in medication, predicted a reduction in BP (patients in the lowest quartile of the score) or an increase in BP (patients in the highest quartile) [26]. Reproducing routine clinical practice in a Monte Carlo simulation suggested that therapeutic inertia may be responsible for as many as half of all hypertensive patients failing to meet their BP target during 10 years of follow-up [27].

The American Medical Association recommends four strategies for reducing therapeutic inertia in the management of hypertension [28]:

- Using single-tablet combinations (to simplify the regimen).
- Paying careful attention to dosages prescribed (so that a second agent can be prescribed before titrating a monotherapy to its maximum dosage thereby reducing the potential for side effects).
- Identifying barriers to adherence (e.g. side effects, forgetting to take medication).
- Encouraging patients to self-monitor their BP (to ensure adequate BP readings are available to support good prescribing decisions).

## *Supporting good adherence to the therapeutic regimen*

People with hypertension, especially older patients, often have additional comorbidities leading to a need for polypharmacy, which is a risk factor for sub-optimal adherence to the therapeutic regimen [29–31]. Simplifying the regimen improves adherence; clinical studies have reported better adherence to once-daily, single-tablet combinations, compared with free combinations of two or more agents [32–35], twice-daily treatment [36], or antihypertensive monotherapy [37, 38].

A systematic review reported improved adherence to a single-tablet combination compared with a free, co-administered combination, and that this was associated with a larger decrease in BP (treatment difference –4.0/1.5 mmHg) [39]. Another systematic review not only reported better antihypertensive goal achievement with single-tablet versus free combinations, but also reported a significantly reduced need for outpatient visits, emergency room visits and hospitalisations for patients with

hypertension and/or dyslipidaemia [40]. Better adherence to antihypertensive therapy has also been significantly associated with a lower risk of adverse cardiovascular outcomes in a large database study from the USA [41]. The improved adherence associated with single-tablet combinations therefore has functional significance for patients.

### *Maximising efficacy while minimising side-effects*

Titrating an antihypertensive therapy beyond half of its maximum indicated dose is unlikely to produce marked additional BP lowering efficacy, instead increasing the potential for side effects [42]. Combination tablets are more effective for BP control than monotherapy from therapy initiation, as described above, while the low dose of each individual component of the combination tablet supports good tolerability. For example, single-tablet antihypertensive combination therapy was better tolerated than either sequential monotherapy or stepped care in one of the randomised trials reviewed above. The number of patients achieving BP <140/90 mmHg without side effects was 66% for the single-tablet combination, compared with 42% for sequential monotherapy or stepped care ($p=0.001$ and $p=0.004$, respectively) [10].

## What the guidelines say

The current European guideline for the management of hypertension provides strong support for the prescription of combination antihypertensive therapy [43], especially using a combination of agents within a single tablet, for the majority of patients at the time of diagnosis of hypertension. This is to "*improve the speed, efficiency, and predictability of BP control*". Antihypertensive monotherapy is reserved in this guideline for patients with systolic BP <150 mmHg, patients with high-normal BP who are at very high cardiovascular risk, or frail or very elderly patients. US guidelines recommend consideration of antihypertensive combination therapy for patients with BP ≥140/90 mmHg (Stage 2 hypertension) [44].

The use of additional antihypertensive drugs beyond a two-drug combination is also supported strongly in this guideline, with recommendations on the appropriate use of a third or fourth agent, if needed. These recommendations are consistent with the observation that multi-drug combinations were needed to control BP in the intensive control arms of large outcomes trials, as described above.

The European guideline for the management of hypertension considers that insufficient use of combination therapy is likely a contributing factor to the low rates of hypertension control described above. The guideline writers did not provide evidence for this, but several recent studies suggest that a majority of patients across various countries with newly diagnosed hypertension have been prescribed antihypertensive monotherapy, rather than combination therapy [45–48].

## Conclusions

BP is controlled to guideline targets in less than half of the people treated for hypertension in most countries, leaving millions of people with hypertension at an unnecessarily increased risk of adverse cardiovascular outcomes. Under-treatment of hypertension, associated with clinical inertia, contributes to low rates of treatment and control of high BP. Current guidelines for the management of hypertension recommend that most patients should receive combination antihypertensive therapies, usually from the time of diagnosis of hypertension. Antihypertensive combinations, delivered by single tablets, are an effective approach to the delivery of combination antihypertensive therapy in a way that is convenient for patients, better tolerated than high doses of monotherapy, and supports good adherence to the antihypertensive regimen.

# References


1 NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in hypertension prevalence and progress in treatment and control from 1990 to 2019: a pooled analysis of 1201 population-representative studies with 104 million participants. Lancet. 2021;398:957–80. https://doi.org/10.1016/s0140-6736(21)01330-1.

2 Department of Health and Human Services. Estimated hypertension prevalence, treatment, and control among U.S. adults. 2021. Available from: https://millionhearts.hhs.gov/data-reports/hypertension-prevalence.html Accessed June 2022.

3 Melgarejo JD, Maestre GE, Thijs L, Asayama K, Boggia J, Casiglia E, et al. Prevalence, treatment, and control rates of conventional and ambulatory hypertension across 10 populations in 3 continents. Hypertension. 2017;70:50–8. https://doi.org/10.1161/hypertensionaha.117.09188.

4 World Health Organization (WHO). Hypertension. 2021. Available from: https://www.who.int/news-room/fact-sheets/detail/hypertension. Accessed June 2022.

5 Tapela N, Collister J, Clifton L, Turnbull I, Rahimi K, Hunter DJ. Prevalence and determinants of hypertension control among almost 100 000 treated adults in the UK. Open Heart. 2021;8(1):e001461. https://doi.org/10.1136/openhrt-2020-001461.

6 Kim KI, Ji E, Choi JY, Kim SW, Ahn S, Kim CH. Ten-year trends of hypertension treatment and control rate in Korea. Sci Rep. 2021;11:6966. https://doi.org/10.1038/s41598-021-86199-x.

7 Murphy CM, Kearney PM, Shelley EB, Fahey T, Dooley C, Kenny RA. Hypertension prevalence, awareness, treatment and control in the over 50s in Ireland: evidence from the Irish longitudinal study on ageing. J Public Health (Oxf). 2016;38:450–8. https://doi.org/10.1093/pubmed/fdv057.

8 McAlister FA, Wilkins K, Joffres M, Leenen FH, Fodor G, Gee M, et al. Changes in the rates of awareness, treatment and control of hypertension in Canada over the past two decades. CMAJ. 2011;183:1007–13. https://doi.org/10.1503/cmaj.101767.

9 Turé R, Damasceno A, Djicó M, Lunet N. Prevalence, awareness, treatment, and control of hypertension in Bissau, Western Africa. J Clin Hypertens (Greenwich). 2022;24:358–61. https://doi.org/10.1111/jch.14443.

10 Mourad JJ, Waeber B, Zannad F, Laville M, Duru G, Andréjak M. Comparison of different therapeutic strategies in hypertension: a low-dose combination of perindopril/indapamide versus a sequential monotherapy or a stepped-care approach. J Hypertens. 2004;22:2379–86. https://doi.org/10.1097/00004872-200412000-00021.

11 MacDonald TM, Williams B, Webb DJ, Morant S, Caulfield M, Cruickshank JK, et al. Combination therapy is superior to sequential monotherapy for the initial treatment of hypertension: a double-blind randomized controlled trial. J Am Heart Assoc. 2017;6(11):e006986. https://doi.org/10.1161/jaha.117.006986.

12 Mourad JJ, Nguyen V, Lopez-Sublet M, Waeber B. Blood pressure normalization in a large population of hypertensive patients treated with perindopril/indapamide combination: results of the OPTIMAX trial. Vasc Health Risk Manag. 2007;3:173–80.

13 Wald DS, Law M, Morris JK, Bestwick JP, Wald NJ. Combination therapy versus monotherapy in reducing blood pressure: meta-analysis on 11,000 participants from 42 trials. Am J Med. 2009;122:290–300. https://doi.org/10.1016/j.amjmed.2008.09.038.

14 Bakris G, Sarafidis P, Agarwal R, Ruilope L. Review of blood pressure control rates and outcomes. J Am Soc Hypertens. 2014;8:127–41. https://doi.org/10.1016/j.jash.2013.07.009.

15 Egan BM, Bandyopadhyay D, Shaftman SR, Wagner CS, Zhao Y, Yu-Isenberg KS. Initial monotherapy and combination therapy and hypertension control the first year. Hypertension. 2012;59:1124–31. https://doi.org/10.1161/hypertensionaha.112.194167.

16 Shina S. Monotherapy versus combination therapy for the initial treatment of hypertension. J Clin Prev Cardiol. 2020;9:78–83. https://doi.org/10.4103/jcpc.Jcpc_27_20.

17 Cushman WC, Evans GW, Byington RP, Goff DC, Jr., Grimm RH, Jr., Cutler JA, et al. Effects of intensive blood-pressure control in type 2 diabetes mellitus. N Engl J Med. 2010;362:1575–85. https://doi.org/10.1056/NEJMoa1001286.

**18** Wright JT, Jr., Williamson JD, Whelton PK, Snyder JK, Sink KM, Rocco MV, et al. A randomized trial of intensive versus standard blood-pressure control. N Engl J Med. 2015;373:2103–16. https://doi.org/10.1056/NEJMoa1511939.

**19** Zhang W, Zhang S, Deng Y, Wu S, Ren J, Sun G, et al. Trial of intensive blood-pressure control in older patients with hypertension. N Engl J Med. 2021;385:1268–79. https://doi.org/10.1056/NEJMoa2111437.

**20** Rakugi H. Step for breaking free from clinical inertia. Hypertens Res. 2022;45:5–7. https://doi.org/10.1038/s41440-021-00767-2.

**21** Milman T, Joundi RA, Alotaibi NM, Saposnik G. Clinical inertia in the pharmacological management of hypertension: a systematic review and meta-analysis. Medicine (Baltimore). 2018;97:e11121. https://doi.org/10.1097/md.0000000000011121.

**22** Shawahna R. Scoping and bibliometric analysis of promoters of therapeutic inertia in hypertension. Am J Manag Care. 2021;27:e386–e94. https://doi.org/10.37765/ajmc.2021.88782.

**23** Ali DH, Kiliç B, Hart HE, Bots ML, Biermans MCJ, Spiering W, et al. Therapeutic inertia in the management of hypertension in primary care. J Hypertens. 2021;39:1238–45. https://doi.org/10.1097/hjh.0000000000002783.

**24** Zheutlin AR, Mondesir FL, Derington CG, King JB, Zhang C, Cohen JB, et al. Analysis of therapeutic inertia and race and ethnicity in the systolic blood pressure intervention trial: a secondary analysis of a randomized clinical trial. JAMA Netw Open. 2022;5:e2143001. https://doi.org/10.1001/jamanetworkopen.2021.43001.

**25** De Backer T, Van Nieuwenhuyse B, De Bacquer D. Antihypertensive treatment in a general uncontrolled hypertensive population in Belgium and Luxembourg in primary care: therapeutic inertia and treatment simplification. The SIMPLIFY study. PLoS One. 2021;16:e0248471. https://doi.org/10.1371/journal.pone.0248471.

**26** Okonofua EC, Simpson KN, Jesri A, Rehman SU, Durkalski VL, Egan BM. Therapeutic inertia is an impediment to achieving the Healthy People 2010 blood pressure control goals. Hypertension. 2006;47:345–51. https://doi.org/10.1161/01.HYP.0000200702.76436.4b.

**27** Augustin A, Coutts L, Zanisi L, Wierzbicki AS, Shankar F, Chowienczyk PJ, et al. Impact of therapeutic inertia on long-term blood pressure control: a Monte Carlo simulation study. Hypertension. 2021;77:1350–9. https://doi.org/10.1161/hypertensionaha.120.15866.

**28** Berg S. 4 ways to reduce therapeutic inertia in patients with high BP. 2021. American Medical Association. Available from: https://www.ama-assn.org/delivering-care/hypertension/4-ways-reduce-therapeutic-inertia-patients-high-bp. Accessed June 2022.

**29** Burnier M, Egan BM. Adherence in hypertension. Circ Res. 2019;124:1124–40. https://doi.org/10.1161/circresaha.118.313220.

**30** Mukete BN, Ferdinand KC. Polypharmacy in older adults with hypertension: a comprehensive review. J Clin Hypertens (Greenwich). 2016;18:10–8. https://doi.org/10.1111/jch.12624.

**31** Sheppard JP, Albasri A, Gupta P, Patel P, Khunti K, Martin U, et al. Measuring adherence to antihypertensive medication using an objective test in older adults attending primary care: cross-sectional study. J Hum Hypertens. 2021. https://doi.org/10.1038/s41371-021-00646-w.

**32** Rea F, Savaré L, Corrao G, Mancia G. Two-drug fixed-dose combination as initial antihypertensive treatment strategy confers higher medication adherence compared to monotherapy. J Hypertens. 2021;39:e43. https://doi.org/10.1097/01.hjh.0000744812.30266.80.

**33** Kim SJ, Kwon OD, Cho B, Oh SW, Lee CM, Choi HC. Effects of combination drugs on antihypertensive medication adherence in a real-world setting: a Korean nationwide study. BMJ Open. 2019;9:e029862. https://doi.org/10.1136/bmjopen-2019-029862.

**34** Ishida T, Oh A, Hiroi S, Shimasaki Y, Nishigaki N, Tsuchihashi T. Treatment patterns and adherence to antihypertensive combination therapies in Japan using a claims database. Hypertens Res. 2019;42:249–56. https://doi.org/10.1038/s41440-018-0127-0.

**35** Du LP, Cheng ZW, Zhang YX, Li Y, Mei D. The impact of fixed-dose combination versus free-equivalent combination therapies on adherence for hypertension: a meta-analysis. J Clin Hypertens (Greenwich). 2018;20:902–7. https://doi.org/10.1111/jch.13272.

**36** Hassanein M. Adherence to antihypertensive fixed-dose combination among Egyptian patients presenting with essential hypertension. Egypt Heart J. 2020;72:10. https://doi.org/10.1186/s43044-020-00044-6.
**37** Patel BV, Remigio-Baker RA, Thiebaud P, Preblick R, Plauschinat C. Improved persistence and adherence to diuretic fixed-dose combination therapy compared to diuretic monotherapy. BMC Fam Pract. 2008;9:61. https://doi.org/10.1186/1471-2296-9-61.
**38** Rea F, Savaré L, Franchi M, Corrao G, Mancia G. Adherence to treatment by initial antihypertensive mono and combination therapies. Am J Hypertens. 2021;34:1083–91. https://doi.org/10.1093/ajh/hpab083.
**39** Parati G, Kjeldsen S, Coca A, Cushman WC, Wang J. Adherence to single-pill versus free-equivalent combination therapy in hypertension: a systematic review and meta-analysis. Hypertension. 2021;77:692–705. https://doi.org/10.1161/hypertensionaha.120.15781.
**40** Weisser B, Predel HG, Gillessen A, Hacke C, Vor dem Esche J, Rippin G, et al. Single pill regimen leads to better adherence and clinical outcome in daily practice in patients suffering from hypertension and/or dyslipidemia: results of a meta-analysis. High Blood Press Cardiovasc Prev. 2020;27:157–64. https://doi.org/10.1007/s40292-020-00370-5.
**41** Lee H, Yano Y, Cho SMJ, Heo JE, Kim DW, Park S, et al. Adherence to antihypertensive medication and incident cardiovascular events in young adults with hypertension. Hypertension. 2021;77:1341–9. https://doi.org/10.1161/hypertensionaha.120.16784.
**42** DiPette DJ, Skeete J, Ridley E, Campbell NRC, Lopez-Jaramillo P, Kishore SP, et al. Fixed-dose combination pharmacologic therapy to improve hypertension control worldwide: clinical perspective and policy implications. J Clin Hypertens (Greenwich). 2019;21:4–15. https://doi.org/10.1111/jch.13426.
**43** Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, et al. 2018 ESC/ESH guidelines for the management of arterial hypertension. Eur Heart J. 2018;39:3021–104. https://doi.org/10.1093/eurheartj/ehy339.
**44** Whelton PK, Carey RM, Aronow WS, Casey DE, Jr., Collins KJ, Dennison Himmelfarb C, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. Hypertension. 2018;71:e13–e115. https://doi.org/10.1161/hyp.0000000000000065.
**45** Abegaz TM, Tefera YG, Abebe TB. Antihypertensive drug prescription patterns and their impact on outcome of blood pressure in Ethiopia: a hospital-based cross-sectional study. Integr Pharm Res Pract. 2017;6:29–35. https://doi.org/10.2147/iprp.S124047.
**46** Venkataraman R, Rashid M, Shashikantha B, Soumya A, Vijayan G, Manuel GG, et al. Prescribing pattern of antihypertensive medication and adherence to Joint National Commission-8 guidelines in a rural tertiary care Indian teaching hospital. J Basic Clin Physiol Pharmacol. 2019;31. https://doi.org/10.1515/jbcpp-2019-0133.
**47** Ahmed A, Saqlain M, Tanveer M, Nawaz MS, Rehman K, Safdar A, et al. Prescribing patterns of antihypertensive drugs in patients attending tertiary care hospitals in Pakistan. SN Comprehensive Clinical Medicine. 2021;3:176–82. https://doi.org/10.1007/s42399-020-00696-0.
**48** Kim SH, Shin DW, Kim S, Han K, Park SH, Kim YH, et al. Prescribing patterns of antihypertensives for treatment-naïve patients in South Korea: from Korean NHISS claim data. Int J Hypertens. 2019;2019:4735876. https://doi.org/10.1155/2019/4735876.

Chapter 4

# Mode of Action of a Combination of Bisoprolol and Amlodipine

**Ningling Sun**
Department of Cardiovascular & Hypertension Center,
Peking University People's Hospital, Beijing, China

**Cardioselective ($\beta_1$-adrenoceptor selective) β-blockade reduces blood pressure (BP) in hypertension mainly via reductions in heart rate and cardiac output, and suppression of the renin-angiotensin-aldosterone system. Calcium channel blockers (CCBs) reduce BP by peripheral arteriolar vasodilatation. Bisoprolol, a highly $\beta_1$-selective β-blocker, and amlodipine, a long-acting dihydropyridine calcium channel blocker, represent an effective choice of antihypertensive combination therapy due to these complementary antihypertensive mechanisms.**

## Introduction

Current guidelines for the management of hypertension provide strong support for the use of antihypertensive combination therapy to achieve adequate control of BP in people with hypertension [1, 2]. The guidelines also emphasise the use of combinations using agents from different

classes of antihypertensive drugs, as this approach is likely to provide (at least) additive effects on BP. This chapter will consider the mode of action of two established antihypertensive therapies supported by a substantial evidence base: the selective $\beta_1$-adrenoceptor antagonist, bisoprolol, and the dihydropyridine CCB, amlodipine. The early parts of the chapter will focus on the properties of these two agents individually, followed by consideration of how these agents work together in combination.

# Therapeutic properties of bisoprolol and amlodipine

## *Overview of the β-blocker class*

### *Main subtypes of β-blockers*

Although there are many β-blockers approved for clinical use, this is a very diverse and heterogeneous class of drugs. Individual members of the class vary in terms of their selectivity for subtypes of the β-adrenoceptor, their potential for acting as partial agonists at the $\beta_1$-adrenoceptor (intrinsic sympathomimetic activity [ISA]), actions at other receptors present in the heart and/or vasculature, and their lipophilicity (Table 1) [3–11].

### *Cardioselective agents without ISA*

All β-blockers reduce BP by reducing activation of the sympathetic nervous system and suppression of the renin-angiotensin-aldosterone system [4, 12]. The degree of selectivity for $\beta_1$-adrenoceptors and the presence or absence of ISA are important features that distinguish between β-blockers. Cardioselective, or $\beta_1$-adrenoceptor selective β-blockers, reduce BP by reducing heart rate and cardiac output, with limited effect on the peripheral vasculature [4, 13]. Non-selective β-blockers, by contrast, increase peripheral resistance by opposing $\beta_2$-adrenoceptor-mediated vasodilatation [13, 14].

Bisoprolol, metoprolol, atenolol, and esmolol, have all been described as $\beta_1$-selective, without ISA (Table 1). A study in animal tissues *in vitro* reported that nebivolol was highly selective for $\beta_1$- versus $\beta_2$-adrenoceptors [15], and studies in human myocardium [16, 17] and a study involving administration of a $\beta_1$-agonist to human volunteers [18] demonstrated greater $\beta_1$- versus $\beta_2$-adrenoceptor selectivity for nebivolol versus bisoprolol. However, a head-to-head comparison of this agent and bisoprolol in human myocardium *in vitro* showed that bisoprolol had 16–20-fold greater selectivity for $\beta_1$- versus $\beta_2$-adrenoceptors, compared with only 3–4-fold selectivity for nebivolol; similar results were obtained using a cultured cell line [19]. The usual dose of bisoprolol (10 mg/day) has been reported to avoid significant blockade of $\beta_2$-adrenoceptors, while atenolol blocks about one-quarter of $\beta_2$-adrenoceptors at its usual dose of 100 mg/day [20]. Another experimental study demonstrated greater $\beta_1$-selectivity for bisoprolol versus atenolol [21]. Studies using cloned human β-adrenoceptors also showed that bisoprolol was more $\beta_1$-selective than atenolol or metoprolol. Finally, esmolol is a very short-acting agent used mainly intravenously in the emergency setting for the control of heart rate during supraventricular tachycardia or atrial fibrillation, and is not used clinically for the management of hypertension [22].

The data as a whole confirm that bisoprolol is highly $\beta_1$-selective, although, the relative $\beta_1$-selectivity of bisoprolol and nebivolol is unclear, and bisoprolol is more $\beta_1$-selective than atenolol or metoprolol. There is no clear evidence for additional clinical benefits associated with enhanced nitric oxide release by nebivolol, which occurs secondary to stimulation of $\beta_2$- and $\beta_3$-adrenoceptors [23].

## *Cardioselective agents with ISA*

Xamoterol, acebutolol, celiprolol and nevibolol are $\beta_1$-selective agents with ISA (Table 1). ISA tends to limit reductions in heart rate and cardiac output during β-blockade and can limit adverse metabolic effects associated with a pack of cardioselectivity (see below) [24]. However, the presence of ISA appears to blunt the beneficial outcomes seen in several studies with cardioselective β-blockers in patients with heart failure [23].

**Table 1 Overview of the mechanistic properties of the β-blocker class [3–11].**

| | $\beta_1$-selective? | ISA? | Other clinically significant actions? | Lipophilicity? |
|---|---|---|---|---|
| **Bisoprolol** | **Yes** | **No** | **–** | **Moderate** |
| Metoprolol | Yes | No | – | High |
| Atenolol | Yes | No | – | Low |
| Esmolol | Yes | No | Short-acting | Low |
| Xamoterol | Yes | Yes | – | Low |
| Acebutolol | Yes | Yes | $\beta_2$ agonist | Moderate |
| Celiprolol | Yes | Yes | $\beta_2$ agonist<br>$\alpha_1$ antagonist | Low |
| Nevibolol | Yes | Yes | Activates NO synthesis[a] | Moderate |
| Propranolol | No | No | – | High |
| Sotalol | No | No | Class III antiarrhythmic | Low |
| Timolol | No | No | – | High |
| Carvedilol | No | No | $\alpha_1$ antagonist | Moderate |
| Pindolol | No | No | $\beta_2$ agonist | Moderate |
| Oxprenolol | No | No | – | High |
| Labetolol | No | No | $\alpha_1$ antagonist | Low |
| Bucindolol | No | Mild | $\alpha_1$ antagonist | High |

ISA: intrinsic sympathomimetic activity; NO: nitric oxide.
[a]Via activation of $\beta_2$-and $\beta_3$-adrenoceptors.
Compiled from information presented in references [3–11].

## *Non-cardioselective agents*

Blockade of $\beta_2$-adrenoceptors by non- (or less) cardioselective β-blockers is more likely than by cardioselective agents to induce potentially serious side effects such as bronchospasm, compared with non- (or less) cardioselective agents [25]. As an example, current European prescribing information states that bisoprolol (highly $\beta_1$-selective) must be used with caution in patients with bronchial asthma or obstructive airways diseases, while propranolol (non-selective) is formally contraindicated in patients with a history of bronchial asthma or bronchospasm. The use of a cardioselective agent may reduce the risk of other side effects commonly attributed to β-blockade, such as cold extremities, metabolic disturbances and erectile dysfunction in men [8].

### *Lipophilicity/hydrophilicity*

The lipophilicity of a β-blocker determines its ability to cross the blood-brain barrier, and consequently the possibility for it to exert an effect in the central nervous system (CNS). However, the lipophilicity of a β-blocker per se does not predict the extent to which its therapeutic actions will be mediated by an effect in the CNS, as has been described for hydrophilic β-blockers such as atenolol [3].

## Therapeutic properties of amlodipine

### *Overview of the CCB class*

CCBs are also a heterogeneous class of drugs [26–28]. There are three classes of CCBs: most agents in use are dihydropyridines (including amlodipine), while the phenylalkylamine and benzothiazepine classes are each represented by a single agent in current clinical use (verapamil and diltiazem, respectively). All CCBs block the L-type calcium channel, although verapamil and diltiazem interact with the channel at different sites than dihydropyridine CCBs. Blockade of these channels reduces the influx of calcium into smooth muscle cells that is required to maintain contractility. The net result of this action in the vascular system is vasodilatation. All CCBs reduce BP by inducing peripheral arteriolar vasodilatation, with the dihydropyridines more potent in this regard [29]. Dihydropyridines have little potential for reducing cardiac contractility in clinical use, although this may occur during treatment with the other CCB classes, especially verapamil [27].

The duration of action of CCBs (Table 2) varies widely from nifedipine (plasma elimination half-life 2–5 h) to amlodipine (plasma elimination half-life 30–50 h) [26–28]. A number of agents employ sustained release tablets to prolong their action and reduce the number of tablet intakes/day, while amlodipine is administered once daily without the need for use of a sustained release preparation. The long duration of action of amlodipine has clinical significance, in that superior control of BP

**Table 2 Overview of calcium channel blockers [26–28].**

| | DHP? | Cardiac contractility | Heart rate | Peripheral vasodilatation | Plasma half-life (h)[a] |
|---|---|---|---|---|---|
| **Amlodipine** | **Yes** | **–** | **–** | **+++** | **30–50** |
| Felodipine | Yes | – | – | +++ | 11–16 |
| Lacidipine | Yes | – | – | +++ | 13–19 |
| Lercanidipine | Yes | – | – | +++ | 8–10 |
| Nicardipine | Yes | – | – | +++ | 2–4 |
| Nifedipine | Yes | – | –[b] | +++ | 2–5 |
| Nimodipine | Yes | – | – | +++ | 1–2 |
| Isradipine | Yes | – | – | +++ | 8 |
| Verapamil | No[c] | ↓↓ | ↓↓ | ++ | 3–7 |
| Diltiazem | No[d] | ↓ | ↓ | ++ | 3–6 |

DHP: dihydropyridine; h: hour.
[a]For immediate-release formulations.
[b]Short-acting agents such as nifedipine may cause reflex tachycardia, but this is mitigated by the use of prolonged-release formulations; higher doses of all agents may increase heart rate.
[c]Phenylalkylamine.
[d]Benzothiazepine.
'–' indicates little or no effect.
'++' and '↓' indicate moderate effect.
'+++' and '↓↓' indicate strong effect.
Compiled from information presented in references [26–28] and the Summaries of Product Characteristics at www.medicines.org.uk/emc (June 2022).

throughout the 24-hour dosing interval has been reported for amlodipine versus agents with a shorter duration of action administered once daily [30]. In addition, the long duration of action of amlodipine provides a sustained antihypertensive effect even in the common setting of one or two missed doses, in contrast to a shorter-acting antihypertensive agent [31]. Short-acting CCBs administered without a sustained-release formulation may induce reflex tachycardia [27].

Verapamil (especially) and diltiazem reduce heart rate via an action on the atrioventricular node and verapamil can be useful in controlling the ventricular rate during episodes of supraventricular tachycardia or atrial fibrillation when administered intravenously. For this reason, these agents are contraindicated in patients with second- or third-degree atrioventricular block, or severe bradycardia. Dihydropyridine CCBs do not have a clinically significant action at the atrioventricular node.

## Amlodipine and bisoprolol together: implications for clinical practice

Current European guidelines for the management of arterial hypertension give strong support to the use of two-drug combinations of antihypertensive agents from the time of diagnosis of hypertension [1]. Use of combination therapies with distinct modes of action facilitates additive effects on BP. Indeed, a large meta-analysis of studies evaluating antihypertensive combination therapies of different classes found that the effects of two-drug combinations on BP were close to that predicted from adding together the expected effects of each agent had they been used as monotherapy [32].

Several factors identify amlodipine and bisoprolol as suitable for co-administration in a combination tablet:

**Proven efficacy in the management of hypertension:** Both bisoprolol and amlodipine have been used in the management of hypertension for about 30 years, and are indicated for this purpose. Both agents are also indicated for the management of angina. Numerous clinical studies have confirmed the efficacy of these agents in these conditions (reviewed elsewhere [8, 33, 34]). The efficacy of bisoprolol and amlodipine in combination is described in Chapter 6.

**Complementary mechanisms of BP reduction:** Bisoprolol is a non-vasodilatory β-blocker, while amlodipine is a CCB that induces peripheral vasodilation. A study in 78 patients with hypertension showed that markers of sympathetic nervous activation were elevated in about 70% of patients. Bisoprolol and a CCB, verapamil, reduced different markers of sympathetic activity, consistent with an action involving distinct, but complementary, mechanisms [35]. Therefore, β-blockade and calcium channel blockade fulfil the key criterion for inclusion within a combination of being from distinct pharmacological classes.

**Once-daily dosing:** Once-daily dosing is required for the management of hypertension, to limit the complexity of the treatment regimen. The elimination half-life of amlodipine is 30–50 h, as described above, and that of bisoprolol is 9–12 h, and the antihypertensive effect of each agent is maintained over the 24-hour dosing interval [36]. Both

of these drugs are therefore suitable for once-daily dosing, and are used once daily in the routine management of hypertension (and angina pectoris). Chapter 5 describes pharmacokinetic studies with the bisoprolol-amlodipine combination tablet in more detail.

## Conclusions

Rational partners for antihypertensive combination therapy should act via complementary mechanisms. Cardioselective ($\beta_1$-adrenoceptor selective) β-blockade reduces BP mainly via actions on the heart (reductions in heart rate and cardiac output) and via suppression of the renin-angiotensin-aldosterone system and sympathetic nervous activity. CCBs are peripheral arteriolar vasodilators. Together, these are potent mechanisms for controlling hypertension, and bisoprolol, a highly $\beta_1$-selective β-blocker, and amlodipine, a long-acting dihydropyridine CCB, represent an effective choice of antihypertensive combination therapy.

## References


1 Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, et al. 2018 ESC/ESH guidelines for the management of arterial hypertension. Eur Heart J. 2018;39:3021–104. https://doi.org/10.1093/eurheartj/ehy339.

2 Whelton PK, Carey RM, Aronow WS, Casey DE, Jr., Collins KJ, Dennison Himmelfarb C, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. Hypertension. 2018;71:e13–e115. https://doi.org/10.1161/hyp.0000000000000065.

3 Drayer DE. Lipophilicity, hydrophilicity, and the central nervous system side effects of beta blockers. Pharmacotherapy. 1987;7:87–91. https://doi.org/10.1002/j.1875-9114.1987.tb04029.x.

4 Poirier L, Tobe SW. Contemporary use of β-blockers: clinical relevance of subclassification. Can J Cardiol. 2014;30:S9–s15. https://doi.org/10.1016/j.cjca.2013.12.001.

5 Kendall MJ, John VA. Oxprenolol: clinical pharmacology, pharmacokinetics, and pharmacodynamics. Am J Cardiol. 1983;52:27d–33d. https://doi.org/10.1016/0002-9149(83)90639-2.

6 Smart NA, Kwok N, Holland DJ, Jayasighe R, Giallauria F. Bucindolol: a pharmacogenomic perspective on its use in chronic heart failure. Clin Med Insights Cardiol. 2011;5:55–66. https://doi.org/10.4137/cmc.S4309.

7 Pathak A, Mrabeti S. β-blockade for patients with hypertension, ischemic heart disease or heart failure: where are we now? Vasc Health Risk Manag. 2021;17:337–48. https://doi.org/10.2147/vhrm.S285907.

**8** AlHabeeb W, Mrabeti S, Abdelsalam AAI. Therapeutic properties of highly selective β-blockers with or without additional vasodilator properties: focus on bisoprolol and nebivolol in patients with cardiovascular disease. Cardiovasc Drugs Ther. 2021. https://doi.org/10.1007/s10557-021-07205-y.

**9** Nawarskas JJ, Cheng-Lai A, Frishman WH. Celiprolol: a unique selective adrenoceptor modulator. Cardiol Rev. 2017;25:247–53. https://doi.org/10.1097/crd.0000000000000159.

**10** MacNeil DJ. The side effect profile of class III antiarrhythmic drugs: focus on d,l-sotalol. Am J Cardiol. 1997;80:90g–8g. https://doi.org/10.1016/s0002-9149(97)00718-2.

**11** Oliver E, Mayor F, Jr., D'Ocon P. Beta-blockers: historical perspective and mechanisms of action. Rev Esp Cardiol (Engl Ed). 2019;72:853–62. https://doi.org/10.1016/j.rec.2019.04.006.

**12** Blumenfeld JD, Sealey JE, Mann SJ, Bragat A, Marion R, Pecker MS, et al. Beta-adrenergic receptor blockade as a therapeutic approach for suppressing the renin-angiotensin-aldosterone system in normotensive and hypertensive subjects. Am J Hypertens. 1999;12:451–9. https://doi.org/10.1016/s0895-7061(99)00005-9.

**13** Kelbaek H, Godtrfedsen J. Effects of acute cardioselective and non-selective beta-adrenergic blockade on left-ventricular volumes and vascular resistance at rest and during exercise. Scand J Clin Lab Invest. 1991;51:161–6.

**14** Wollam GL, Cody RJ, Jr., Tarazi RC, Bravo EL. Acute hemodynamic effects and cardioselectivity of acebutolol, practolol, and propranolol. Clin Pharmacol Ther. 1979;25:813–20. https://doi.org/10.1002/cpt1979256813.

**15** Van de Water A, Janssens W, Van Neuten J, Xhonneux R, De Cree J, Verhaegen H, et al. Pharmacological and hemodynamic profile of nebivolol, a chemically novel, potent, and selective beta 1-adrenergic antagonist. J Cardiovasc Pharmacol. 1988;11:552–63. https://doi.org/10.1097/00005344-198805000-00007.

**16** Brixius K, Bundkirchen A, Bölck B, Mehlhorn U, Schwinger RH. Nebivolol, bucindolol, metoprolol and carvedilol are devoid of intrinsic sympathomimetic activity in human myocardium. Br J Pharmacol. 2001;133:1330–8. https://doi.org/10.1038/sj.bjp.0704188.

**17** Bundkirchen A, Brixius K, Bölck B, Nguyen Q, Schwinger RH. Beta 1-adrenoceptor selectivity of nebivolol and bisoprolol. A comparison of [3H]CGP 12.177 and [125I]iodocyanopindolol binding studies. Eur J Pharmacol. 2003;460:19–26. https://doi.org/10.1016/s0014-2999(02)02875-3.

**18** Nuttall SL, Routledge HC, Kendall MJ. A comparison of the beta1-selectivity of three beta1-selective beta-blockers. J Clin Pharm Ther. 2003;28:179–86. https://doi.org/10.1046/j.1365-2710.2003.00477.x.

**19** Maack C, Tyroller S, Schnabel P, Cremers B, Dabew E, Südkamp M, et al. Characterization of beta(1)-selectivity, adrenoceptor-G(s)-protein interaction and inverse agonism of nebivolol in human myocardium. Br J Pharmacol. 2001;132:1817–26. https://doi.org/10.1038/sj.bjp.0703992.

**20** Brodde OE. The pharmacology of bisoprolol. Rev Contemp Pharmacother. 1997;8:21–33.

**21** Baker JG. The selectivity of beta-adrenoceptor antagonists at the human beta1, beta2 and beta3 adrenoceptors. Br J Pharmacol. 2005;144:317–22. https://doi.org/10.1038/sj.bjp.0706048.

**22** Garnock-Jones KP. Esmolol: a review of its use in the short-term treatment of tachyarrhythmias and the short-term control of tachycardia and hypertension. Drugs. 2012;72:109–32. https://doi.org/10.2165/11208210-000000000-00000.

**23** Cruickshank JM. Are we misunderstanding beta-blockers. Int J Cardiol. 2007;120:10–27. https://doi.org/10.1016/j.ijcard.2007.01.069.

**24** Jaillon P. Relevance of intrinsic sympathomimetic activity for beta blockers. Am J Cardiol. 1990;66:21c–3c. https://doi.org/10.1016/0002-9149(90)90758-s.

**25** Kubota Y, Asai K, Furuse E, Nakamura S, Murai K, Tsukada YT, et al. Impact of β-blocker selectivity on long-term outcomes in congestive heart failure patients with chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis. 2015;10:515–23. https://doi.org/10.2147/copd.S79942.

**26** Elliott WJ, Ram CV. Calcium channel blockers. J Clin Hypertens (Greenwich). 2011;13:687–9. https://doi.org/10.1111/j.1751-7176.2011.00513.x.
**27** Sica DA. Pharmacotherapy review: calcium channel blockers. J Clin Hypertens (Greenwich). 2006;8:53–6. https://doi.org/10.1111/j.1524-6175.2005.04140.x.
**28** Horowitz BZ. What are the pharmacokinetics of calcium channel blockers (CCBs)? 2021. MedScape. Available from: https://www.medscape.com/answers/2184611-167308/what-are-the-pharmacokinetics-of-calcium-channel-blockers-ccbs. Accessed June 2022.
**29** Godfraind T. Discovery and development of calcium channel blockers. Front Pharmacol. 2017;8:286. https://doi.org/10.3389/fphar.2017.00286.
**30** Eguchi K, Kario K, Hoshide Y, Hoshide S, Ishikawa J, Morinari M, et al. Comparison of valsartan and amlodipine on ambulatory and morning blood pressure in hypertensive patients. Am J Hypertens. 2004;17:112–7. https://doi.org/10.1016/j.amjhyper.2003.09.008.
**31** de Leeuw PW, Fagard R, Kroon AA. The effects of missed doses of amlodipine and losartan on blood pressure in older hypertensive patients. Hypertens Res. 2017;40:568–72. https://doi.org/10.1038/hr.2016.190.
**32** Wald DS, Law M, Morris JK, Bestwick JP, Wald NJ. Combination therapy versus monotherapy in reducing blood pressure: meta-analysis on 11,000 participants from 42 trials. Am J Med. 2009;122:290–300. https://doi.org/10.1016/j.amjmed.2008.09.038.
**33** Kaplan NM. Amlodipine in the treatment of hypertension. Postgrad Med J. 1991;67 Suppl 5:S15–9.
**34** Jeffers BW, Robbins J, Bhambri R, Wajsbrot D. A systematic review on the efficacy of amlodipine in the treatment of patients with hypertension with concomitant diabetes mellitus and/or renal dysfunction, when compared with other classes of antihypertensive medication. Am J Ther. 2015;22:322–41. https://doi.org/10.1097/mjt.0000000000000202.
**35** Sun N, Hong T, Zhang R, Yang X. The effects of verapamil SR and bisoprolol on reducing the sympathetic nervous system's activity. Hypertens Res. 2000;23:537–40. https://doi.org/10.1291/hypres.23.537.
**36** Davidov ME, Singh SP, Vlachakis ND, Blumenthal JB, Simon JS, Bryzinski BS, et al. Bisoprolol, a once-a-day beta-blocking agent for patients with mild to moderate hypertension. Clin Cardiol. 1994;17:263–8. https://doi.org/10.1002/clc.4960170509.

Chapter 5

# Pharmacokinetic Properties of a Combination of Bisoprolol and Amlodipine

**Rohit Khurana**
The Harley Street Heart and Vascular Centre, Gleneagles Hospital, Singapore, Singapore

**The duration of action of bisoprolol and amlodipine exceeds 24 hours after dosing. The bisoprolol and amlodipine components of the single-tablet combination meet formal criteria for bioequivalence with a co-administered combination of leading proprietary formulations of these agents. This simplifies a switch from a co-administered bisoprolol and amlodipine combination to the single-tablet formulation. Overall, bisoprolol and amlodipine have complementary pharmacokinetic properties consistent with inclusion in a combination tablet.**

## General pharmacokinetics of bisoprolol and amlodipine

Table 1 provides an overview of key pharmacokinetic parameters for bisoprolol and amlodipine [1–4]. Both drugs are extensively absorbed,

and have a plasma half-life consistent with once-daily dosing, with the duration of action of amlodipine being especially long, consistent with its large volume of distribution and extensive binding to plasma proteins. Neither drug is susceptible to clinically significant first-pass metabolism, and neither generates active metabolites.

The balanced renal/hepatic elimination of bisoprolol has clinical significance. For example, the elimination half-life of bisoprolol was increased by 1.96 fold in patients with versus without severe renal dysfunction, with similar plasma levels of bisoprolol in patients with severe renal dysfunction or receiving renal dialysis [4]. Therefore, it is unlikely that severe accumulation of the drug would occur in this setting (Chapter 8 of this book addresses the safety and tolerability of this combination). Amlodipine should be used with caution in the setting of hepatic impairment consistent with the liver being its principal site of metabolism; no dose adjustments are required for renal dysfunction, however.

The pharmacokinetic profiles of these agents suggests that they are suitable for co-administration (duration of action is consistent with once-daily dosing, and there are no major restrictions according to renal or hepatic function). However, regulatory requirements mean that dedicated studies need to be conducted to ensure that bisoprolol and amlodipine, delivered by a combination tablet, are bioequivalent with

**Table 1 Overview of the pharmacokinetics of bisoprolol and amlodipine [1–4].**

| | Bisoprolol | Amlodipine |
|---|---|---|
| Bioavailability | 90% | 60–65% |
| Elimination | Balanced between hepatic metabolism and renal excretion as unchanged drug | Mainly hepatic metabolism with 5% excreted as unchanged drug |
| Active metabolites? | No | No |
| First pass metabolism | Very low/absent | Very low/absent |
| Time to peak plasma concentration after dosing | 2 hours | 6–8 hours |
| Elimination half life | 10–11 hours | 30–50 hours |
| Volume of distribution | 3.5 L | 21 L |
| Recommended dosing schedule | Once daily | Once daily |
| Plasma protein binding | 30% | 98% |

Compiled from information presented in references [1–4].

marketed formulations of these agents. This chapter summarises the results of these studies.

# Pharmacokinetic evaluation of a single-tablet combination of bisoprolol and amlodipine

## *Overview of pharmacokinetic studies*

Four pharmacokinetic studies, (three bioequivalence studies and one drug-drug interaction study, Table 2), have evaluated the bisoprolol-amlodipine combination tablet in comparison with proprietary reference formulations of bisoprolol (Concor™, Merck Healthcare KGaA) and amlodipine (Norvasc®, Pfizer) [5]. All were randomised, crossover studies conducted in healthy volunteers. Three studies (A, B and C in Table 2), compared a bisoprolol 10 mg/amlodipine 10 mg tablet with the respective monotherapies, either after a single dose or after 5 days of dosing. The fourth study (D in Table 2), compared single administrations of the bisoprolol 5 mg/amlodipine 5 mg combination tablet with a co-administered combination of the corresponding proprietary reference products. The studies took place in Canada, China and Brazil in order to confirm the results of the studies in different populations.

## *Bioequivalence studies in fasted subjects*

The mean maximal plasma concentration ($C_{max}$), mean area under the concentration-time curve over the 24-hour dosing interval (AUC), and the time to $C_{max}$ of each drug after ingestion ($T_{max}$) are shown in Table 3. Within each study, these parameters were similar for bisoprolol and amlodipine proprietary reference products and the combination tablet. $C_{max}$ and AUC were higher for the multiple-dose study (study C), compared with the single-dose study (study A). This would be expected as these drugs have durations of action that exceed 24 hours. Plasma concentrations of drugs started at zero at the time of drug administration in the single-dose study, whereas the last administration of drug in the multiple-dose study added to the steady-state trough drug concentration

**Table 2 Pharmacokinetic evaluations of a single-tablet combination of bisoprolol and amlodipine [5]*.**

| Study | Design | N | Subjects | Treatments | Duration |
|---|---|---|---|---|---|
| **A** (Canada) | R, X, OL | 28 | Healthy male or female volunteers (fasted) | Amlodipine 10 mg[a]<br>Bisoprolol 10 mg[b]<br>Amlodipine 10 mg/bisoprolol 10 mg combination tablet | Single dose |
| **B** (Brazil) | R, X, OL, SB | 28 | Healthy male volunteers (fasted) | Amlodipine 10 mg[a]<br>Bisoprolol 10 mg[b]<br>Amlodipine 10 mg/bisoprolol 10 mg combination tablet | Single dose |
| **C** (Canada) | R, X, OL | 22 | Healthy male or female volunteers (fasted) | Amlodipine 10 mg[a]<br>Bisoprolol 10 mg[b]<br>Amlodipine 10 mg/bisoprolol 10 mg combination tablet | 5 days |
| **D** (China) | R, X, OL | 32 | Healthy male or female volunteers (fasted and fed) | Amlodipine 5 mg[a]<br>Bisoprolol 5 mg[b]<br>Amlodipine 5 mg/bisoprolol 5 mg combination tablet | Single dose |

OL: open-label; R: randomised; SB: single (laboratory) blind; X: crossover.
Proprietary reference formulations: [a]Novasc® (Pfizer); [b]Concor™ (Merck Healthcare KGaA), or equivalent local brands.
*Also includes information from original clinical study reports (Merck Healthcare KGaA).

**Table 3 Key pharmacokinetic evaluation of the bisoprolol 10 mg/amlodipine 10 mg combination tablet in fasted subjects compared with proprietary reference formulations of the individual components [5]*.**

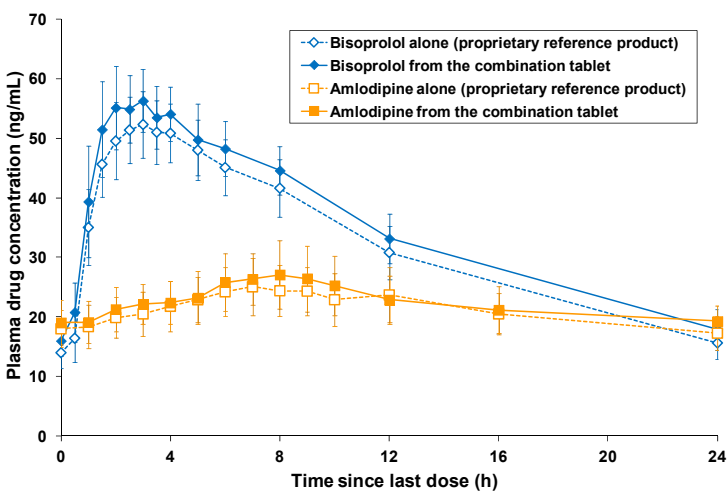
| | Mean $C_{max}$ [ng/mL (CV(%)] | Mean $AUC_{\tau}$ [ng·h/mL (CV(%)] | Median $T_{max}$ (hours) |
|---|---|---|---|
| **Single dose (Study A)[a]** | | | |
| Bisoprolol 10 mg (combination tablet) | 43.4 (19.0) | 719.0 (19.2) | 2.5 |
| Bisoprolol 10 mg (reference) | 42.8 (17.7) | 703.6 (21.1) | 2.0 |
| Amlodipine 10 mg (combination tablet) | 5.9 (25.9) | 315.5 (29.6) | 8.0 |
| Amlodipine 10 mg (reference) | 5.5 (28.3) | 286.1 (34.9) | 8.0 |
| **Multiple doses (5 days, Study C)[a]** | | | |
| Bisoprolol 10 mg (combination tablet) | 58.5 (8.7) | 838.7 (10.7) | 2.50 |
| Bisoprolol 10 mg (reference) | 53.6 (9.7) | 771.0 (11.7) | 2.75 |
| Amlodipine 10 mg (combination tablet) | 28.6 (18.7) | 534.4 (16.1) | 8.0 |
| Amlodipine 10 mg (reference) | 26.2 (18.2) | 506.7 (16.6) | 7.0 |

$AUC_{\tau}$: mean area under the concentration-time curve over a 24-hour dosing interval; $C_{max}$: mean maximal plasma drug concentration; CV: coefficient of variation; $T_{max}$: time to maximal plasma drug concentration after ingestion.
[a]See Table 2 for details of studies and proprietary reference products; studies B and D did not provide data for arithmetic means for these parameters and are thus omitted here.
*Also includes information from original clinical study reports (Merck Healthcare KGaA).

in each case. This can be seen clearly in Figure 1, where the concentrations of bisoprolol and amlodipine at time zero of the last day of the multiple-dose study were about 15 ng/mL and 18 ng/ML, respectively. Values of $T_{max}$ were also similar for bisoprolol or amlodipine from the proprietary or combination tablets, and similar to published values (Table 1).

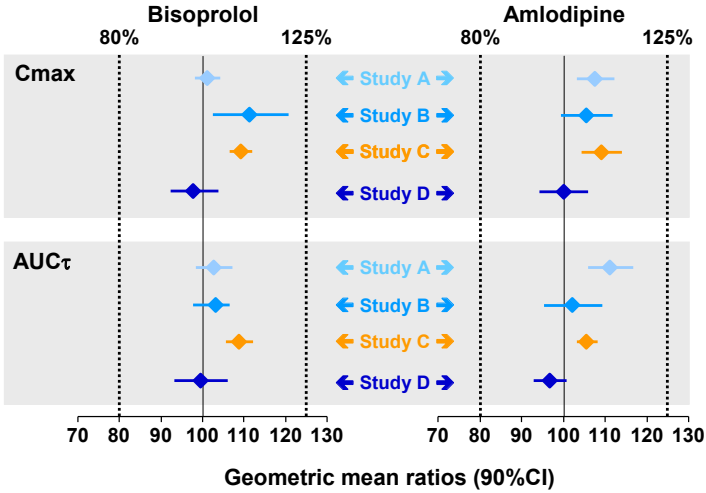
The formal demonstration of bioequivalence requires geometric mean ratios of pharmacokinetic parameters, and their 90% confidence intervals (90% CI), determined after administration of the test versus reference drug to lie between 80% and 125% [6]. Figure 2 shows the data on bioequivalence from the three studies in fasted volunteers. The geometric mean ratios and their 90% CI for both bisoprolol and amlodipine were well within the 80–125% criteria. This applied to single-dose administration (Studies A, B and D), multiple-dose administration (Study C), and to administration of combination tablet strengths of 5 mg/5 mg (Study D) and 10 mg/10 mg (Studies A, B and C). Therefore,

**Figure 1 Plasma concentrations of bisoprolol and amlodipine during a 24-hour dosing interval from a crossover study in healthy volunteers treated once daily for 5 days with amlodipine 10 mg or bisoprolol 10 mg monotherapy, or a single-tablet combination containing these treatments [5]*.**




*Also includes information from original clinical study reports (Merck Healthcare KGaA). Proprietary reference products were as per Table 1. h: hour.

**Figure 2 Demonstration of bioequivalence between the bisoprolol and amlodipine components of a combination tablet and proprietary reference formulations of these agents [5]*.**



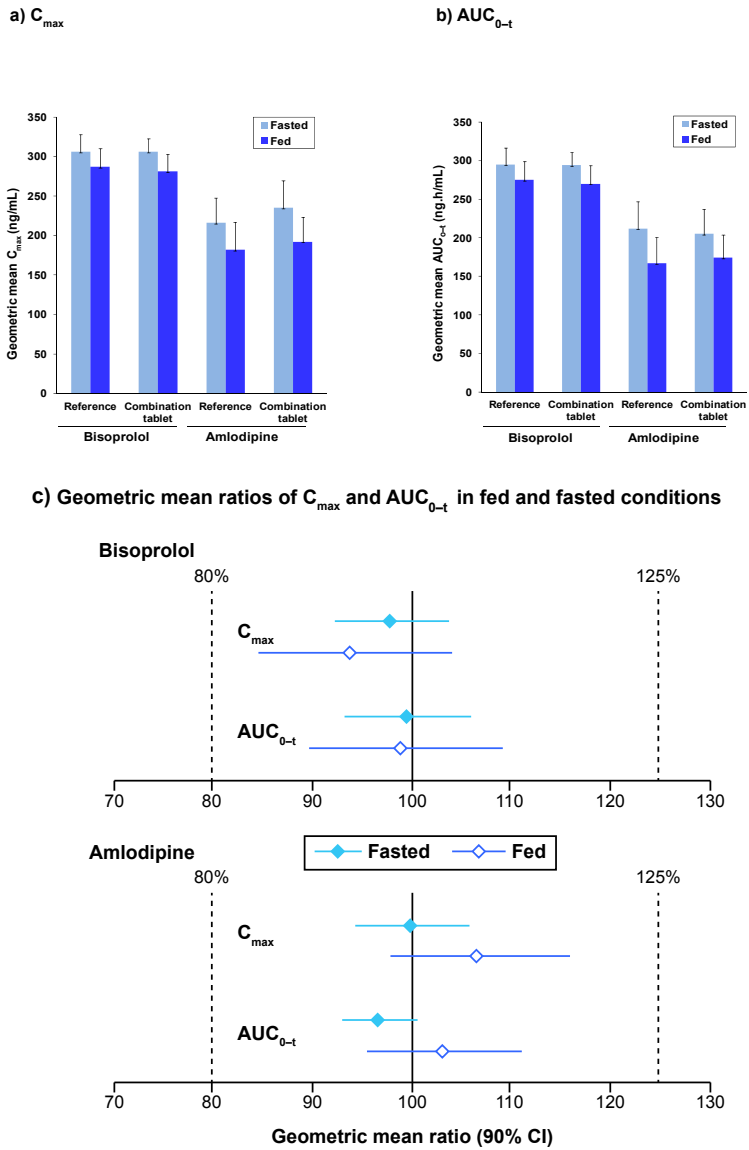

$AUC_\tau$: mean area under the concentration-time curve over a 24-hour dosing interval; CI: confidence interval; $C_{max}$: mean maximal plasma drug concentration.
*Also includes information from original clinical study reports (Merck Healthcare KGaA).
Formal bioequivalence is demonstrated when the geometric mean ratios and their 90% CI for $C_{max}$ or AUC fall between 80% and 125%.
Studies A, C and D were single-dose studies; Study C was a multiple-dose study.

the bisoprolol-amlodipine combination tablet is fully bioequivalent with previously marketed formulations of these agents.

## *Effects of food on the pharmacokinetics of the single-tablet combination of bisoprolol and amlodipine*

Study D evaluated the effects of food on the pharmacokinetics of bisoprolol and amlodipine delivered from the combination tablet or from a co-administered combination of proprietary reference products. Mean $C_{max}$ (Figure 3a) and mean $AUC_{0-t}$ (Figure 3b) were slightly lower in fed versus fasted subjects, but not to a clinically significant extent. Importantly, bioequivalence was maintained between the formulations irrespective of fed or fasted status (Figure 3c). Accordingly, the combination tablet can be taken with food.

**Figure 3 Effects of food on the pharmacokinetics of the bisoprolol 5 mg/amlodipine 5 mg combination tablet (Study D) [5]*.**




$AUC_{0-t}$: mean area under the concentration-time curve from 0 to t hours; CI: confidence interval; $C_{max}$: mean maximal plasma drug concentration; CV: coefficient of variation.
*Also includes information from original clinical study reports (Merck Healthcare KGaA).
Bars in panel (a) represent CV (%).

$T_{max}$ for bisoprolol was 1.0 hour (95% CI, 1.0 to 3.0 for combination tablet and 0.5 to 2.0 for co-administration) for both formulations in the fasted state and was 3.0 hours (95% CI, 1.0 to 6.0 for combination tablet and 2.0 to 6.0 for co-administration) for both formulations in the fed state. Corresponding $T_{max}$ values for amlodipine were 6.0 hours (95% CI, 4.0 to 8.0 for combination tablet and 4.0 to 12.0 for co-administration) and 6.0 hours (95% CI, 4.0 to 15.0 for combination tablet and 4.0 to 10.0 for co-administration) for both formulations. $T_{max}$ was minimally affected by food, apart from the possibility of a slight delay to absorption of bisoprolol with food.

## Physical properties of the bisoprolol-amlodipine combination tablet

### *Solubility*

The dissolution of the combination tablets in aqueous medium was assessed according to *a priori* quality control criteria set by the European and United States (US) regulators and the pharmaceutical sponsor of the treatment. On average, ≥85% of the bisoprolol content and ≥75% of the bisoprolol and amlodipine content, respectively, were required to be released within 30 minutes, with no individual findings of <70% (bisoprolol) or <65% (amlodipine) active ingredient release [7]. The average release ranged between 98.4–101.6% for bisoprolol and 95.9–101.9% for amlodipine; corresponding minimum amounts were ≥86.1% and ≥82.4%. The combination tablet therefore exceeded the minimum standards required for dissolution in an aqueous medium.

### *Breaking combination tablets for flexibility of dosage and administration*

The bisoprolol-amlodipine combination tablet is scored to facilitate breaking the tablet in half, whether to provide a lower dosage or to reduce the size of the tablet for easier ingestion. It is important to establish

that tablets broken to halve the dose provide consistent dosages of the active ingredients, as it is possible that tablets may break unevenly. This was tested in an analytical study on samples from three batches each of the amlodipine/bisoprolol 5/5 mg and 5/10 mg tablet strengths [7]. Both the mass of each half of broken tablet, and the amount of active ingredient contained within each half, passed criteria set by the European [8] and the US Pharmacopeia [9].

These findings are important for the routine administration of this combination tablet. Some physicians have preferred to start bisoprolol at a dosage below the lower adult dose of 5 mg/day, especially for vulnerable populations [10]. The scored tablet containing bisoprolol 5 mg provides flexibility to do this. In addition, difficulty swallowing tablets is an important cause of poor adherence to therapy, and halved tablets are easier for patients to swallow [11].

## Conclusions

The bisoprolol and amlodipine components of the single-tablet combination met formal criteria for bioequivalence with a co-administered combination of leading proprietary formulations of these agents. Accordingly, a switch from a co-administered bisoprolol and amlodipine combination to the combination tablet can be made at equivalent doses, thereby simplifying the regimen without expectation of a marked change in antihypertensive effect. Alternatively, intensification of the regimen by using the combination tablet in place of either of the components would be expected to provide additional antihypertensive efficacy. The analytical data on the solubility of the tablet is consistent with the findings on bioequivalence. In addition, the analytical data on the effective dose delivered by halved tablets adds to the flexibility of dosing with the combination tablet, where the physician wishes to administer bisoprolol at a dose of 2.5 mg. Overall, bisoprolol and amlodipine have complementary pharmacokinetic properties consistent with their inclusion in a combination tablet for the management of hypertension.

# References


1 Leopold G. Balanced pharmacokinetics and metabolism of bisoprolol. J Cardiovasc Pharmacol. 1986;8 Suppl 11:S16–20. https://doi.org/10.1097/00005344-198511001-00003.

2 Tjandrawinata RR, Setiawati E, Yunaidi DA, Santoso ID, Setiawati A, Susanto LW. Bioequivalence study of two formulations of bisoprolol fumarate film-coated tablets in healthy subjects. Drug Des Devel Ther. 2012;6:311–6. https://doi.org/10.2147/dddt.S36567.

3 Meredith PA, Elliott HL. Clinical pharmacokinetics of amlodipine. Clin Pharmacokinet. 1992;22:22–31. https://doi.org/10.2165/00003088-199222010-00003.

4 Payton CD, Fox JG, Pauleau NF, Boulton-Jones JM, Ioannides C, Johnston A, et al. The single dose pharmacokinetics of bisoprolol (10 mg) in renal insufficiency: the clinical significance of balanced clearance. Eur Heart J. 1987;8 Suppl M:15–22. https://doi.org/10.1093/eurheartj/8.suppl_m.15.

5 Gottwald-Hostalek U, Gaikwad S. Pharmacokinetic properties of a fixed-dose combination of bisoprolol and amlodipine. EC Cardiology. 2018;5:523–32.

6 Davit B, Braddy AC, Conner DP, Yu LX. International guidelines for bioequivalence of systemically available orally administered generic drug products: a survey of similarities and differences. AAPS J. 2013;15:974–90. https://doi.org/10.1208/s12248-013-9499-x.

7 Krüger P, Gottwald-Hostalek U, Sun N. Divisibility of Bisoprolol and Amlodipine Fixed-dose Combination Tablets. EC Cardio. 2019;6:917–23.

8 Council of Europe, European Directorate for the Quality of Medicine. Subdivision of tablets in European Pharmacopeia 9.4. 2018. Strasbourg. Available from https://www.edqm.eu/en/. Accessed June 2022.

9 United States Pharmacopeial Convention Inc. Quality attributes of tablets having a functional score. 2018. United States Pharmacopeia 41–National Formulary 36. Available from: https://doi.usp.org/USPNF/USPNF_M7826_01_01.html Accessed June 2022.

10 Mion D, Jr., Ortega KC, Gomes MA, Kohlmann O, Jr., Oigman W, Nobre F. Amlodipine 2.5 mg once daily in older hypertensives: a Brazilian multi-centre study. Blood Press Monit. 2004;9:83–9. https://doi.org/10.1097/00126097-200404000-00005.

11 Fields J, Go JT, Schulze KS. Pill properties that cause dysphagia and treatment failure. Curr Ther Res Clin Exp. 2015;77:79–82. https://doi.org/10.1016/j.curtheres.2015.08.002.

Chapter 6

# Clinical Efficacy of a Combination of Bisoprolol and Amlodipine

**Zbigniew Gaciong**
Department of Internal Medicine, Hypertension and Vascular Diseases, Medical University of Warsaw, Warsaw, Poland

**Randomised and real-world evaluations of a bisoprolol/amlodipine combination tablet have shown this treatment to be more effective than monotherapy and to support good adherence to therapy in patients with hypertension. A consistent reduction in heart rate (HR) with this treatment is a further potential benefit likely to improve long-term clinical outcomes in this population.**

## Therapeutic efficacy of the bisoprolol/amlodipine combination tablet in patients with hypertension

### *Overview of studies that have evaluated the efficacy of bisoprolol/amlodipine combination tablets in patients with hypertension*

A series of randomised and observational studies have evaluated single-tablet combinations of bisoprolol and amlodipine in patients with

hypertension with or without other comorbidities. These are summarised in Table 1 [1–12] and described below.

**Table 1 Details of studies that evaluated the bisoprolol/amlodipine combination tablet in patients with hypertension.**

| Design (1st author) | N | Duration | Key details |
|---|---|---|---|
| Randomised (*Gottwald-Hostalek et al [1]*) | 200 | 18 weeks | Study of the efficacy, tolerability and safety of the combination tablet in patients with BP previously sub-optimally controlled on bisoprolol 5 mg or amlodipine 5 mg monotherapy |
| Randomised (*Jędrusik et al [2]*) | 367 | 8 weeks | Comparison of amlodipine 5 mg and bisoprolol/amlodipine 5/5 mg in patients uncontrolled on amlodipine 5 mg |
| Randomised (*Shirure et al [3]*) | 60 | 1 month | Comparison of bisoprolol/amlodipine 5/5 mg with bisoprolol 5 mg and amlodipine 5 mg monotherapies in patients with WHO Stage 2 hypertension |
| Randomised (*Fendrikova et al [4] Tarlovskaya et al [5]*) | 61 | 12 weeks | Study of effects of the bisoprolol/amlodipine combination tablet vs a free combination of bisoprolol and amlodipine (each added to enalapril) on BP and aortic pulse wave velocity in patients with sub-optimally controlled hypertension and coronary heart disease; a pharmacoeconomic evaluation was also conducted |
| Observational (modelled) (*Foch et al [6]*) | 260 | 8 weeks | Anchored, simulated treatment comparison of effects on BP of the bisoprolol/amlodipine 5/5 mg combination with up titration of amlodipine monotherapy from 5 mg to 10 mg based on the results of two randomised trials |
| Observational (*Gottwald-Hostalek, et al [7]*) | 12,424 | 6 months | Non-interventional cohort study of patients with hypertension switched from a co-administered combination of bisoprolol and amlodipine to the combination tablet ≥4 weeks in 6 countries in eastern Europe |
| Observational (*Mehta et al [8]*) | 106 | 8 weeks | Observational, non-comparative study of the effects on BP of a bisoprolol/amlodipine 2.5/5 mg combination tablet in patients with moderate hypertension |
| Observational (*Rana et al [9]*) | 801 | 4 weeks | Observational, non-comparative evaluation of the effects on BP of a bisoprolol/amlodipine 5/5 mg combination tablet in patients with Stage 2 hypertension |

| | | | |
|---|---|---|---|
| Observational (*Chesnikova et al [10]*) | 100 | 4 weeks | Study of the effects of the bisoprolol/amlodipine combination tablet on BP and signs of cardiac ischaemia in patients with sub-optimally controlled hypertension and coronary heart disease |
| Observational (clin pharm) (*Bogomaz et al [11]*) | 15 | 8 weeks | Study of peripheral (brachial) and central (aortic) haemodynamics in patients treated with bisoprolol/amlodipine 5/5 mg combination tablet (5/10 mg or 10/10 mg) |
| Observational (clin pharm) (*Zapesochnaya et al [12]*) | 140 | 6 months | Study of the effects of a bisoprolol/amlodipine combination tablet on BP and on the structural and functional status of the myocardium in patients with hypertension |

BP: blood pressure; Clin pharm: clinical pharmacy; WHO: World Health Organization.

## *Effects on blood pressure*

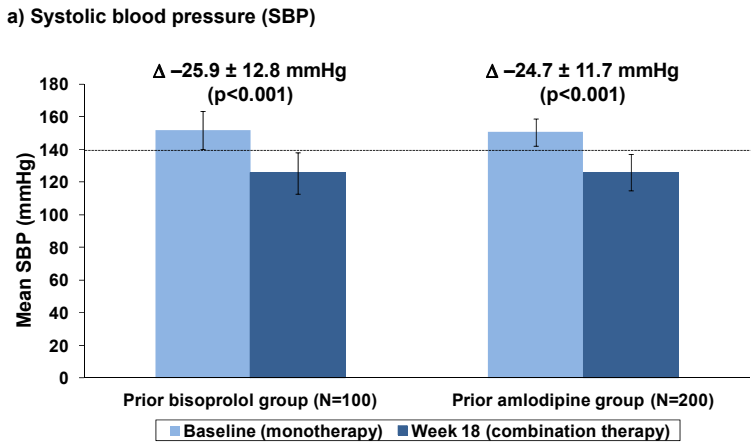
### *Randomised trials in patients with blood pressure (BP) uncontrolled on monotherapy with bisoprolol or amlodipine*

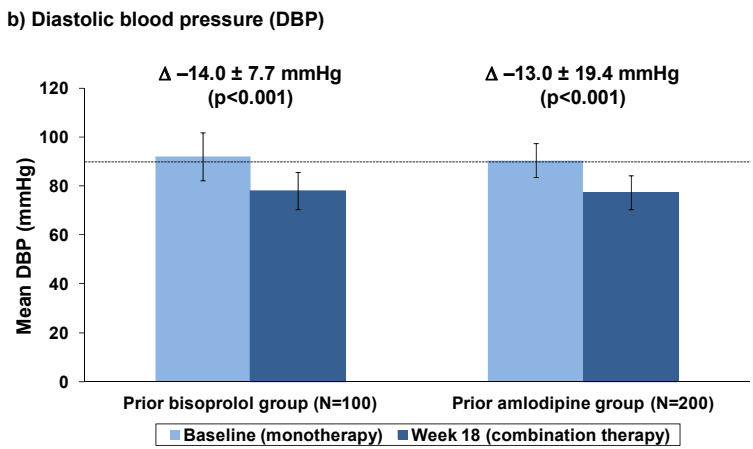
A randomised clinical trial evaluated the single-tablet combination of bisoprolol/amlodipine in 200 patients with hypertension sub-optimally controlled by monotherapy with either amlodipine 5 mg or bisoprolol 5 mg [1]. Initially patients were randomised into two groups ("A" and "B") and all received bisoprolol/amlodipine 5/5 mg for 6 weeks. Patients with sub-optimally controlled BP (≥140/≥90 mmHg) at week 6 in group A were up-titrated to bisoprolol/amlodipine 5/10 mg, while sub-optimally controlled patients in group B were up-titrated to the 10/5 mg dosage strength. BP control was evaluated again at week 12, when patients with sub-optimal control of BP received the 10/10 mg combination tablet for another 6 weeks. Patients with well-controlled BP (<140/<90 mmHg) continued on their previous treatment at each stage.

The primary outcome of the trial was the mean change in systolic BP (SBP) from baseline (when patients were receiving antihypertensive monotherapy) to week 18. Mean changes in SBP were substantial, clinically and statistically ($p<0.001$) significant, and essentially identical

in patients from both the prior bisoprolol and prior amlodipine groups (–26 mmHg and –25 mmHg, respectively; Figure 1a). Substantial reductions in diastolic BP (DBP) were also seen (–14 mmHg and –13 mmHg, respectively; Figure 1b). The majority of patients (74%) had achieved

**Figure 1 Effect of treatment with a bisoprolol/amlodipine combination tablet on blood pressure in patients with hypertension sub-optimally controlled by monotherapy with bisoprolol 5 mg or amlodipine 5 mg.**



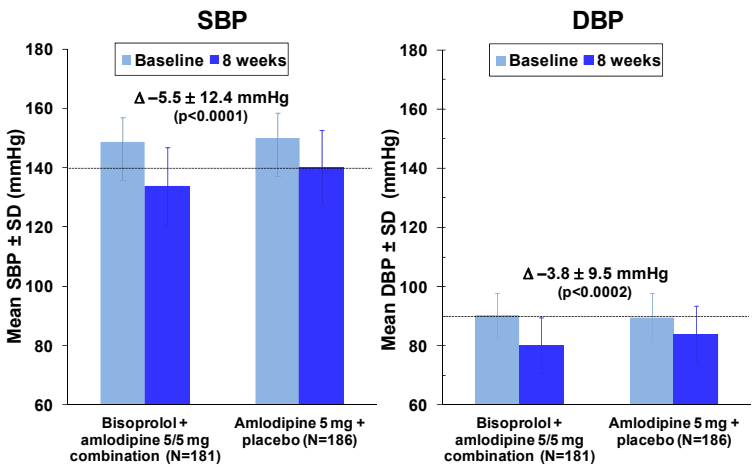




Δ: mean change. The mean change in SBP from baseline to week 18 was the primary endpoint of the trial; mean change in DBP was a pre-specified secondary endpoint.
Dotted lines show targets for BP control of 140 mmHg (SBP) and 90 mmHg (DBP).
Drawn from data presented in reference [1].

control of BP on the 5/5 mg combination tablet at study end. Up titration of therapy, where required, increased the proportion of patients with well-controlled BP to 88% by the end of the study. Control rates were similar for patients in each prior therapy group.

The AMCOR trial involved randomisation of 367 patients with BP sub-optimally controlled by amlodipine 5 mg to the same treatment with additional placebo or to treatment with a combination of bisoprolol and amlodipine 5/5 mg, for 8 weeks [2]. Mean SBP and DBP were reduced in both groups (Figure 2). There was a statistically and clinically significant treatment difference in favour of the combination of –5.5 ± 12.4 mmHg for SBP ($p<0.0001$) and of –3.8 ± 9.5 mmHg for DBP ($p<0.0002$).

**Figure 2 Effects of bisoprolol/amlodipine 5/5 mg combination treatment vs. amlodipine 5 mg and placebo on BP in patients uncontrolled on amlodipine 5 mg monotherapy: data from the AMCOR trial.**




BP: blood pressure; DBP: diastolic blood pressure; SBP: systolic blood pressure; SD: standard deviation.
Dotted lines show targets for BP control of 140 mmHg (SBP) and 90 mmHg (DBP).
Drawn from data presented in reference [2].

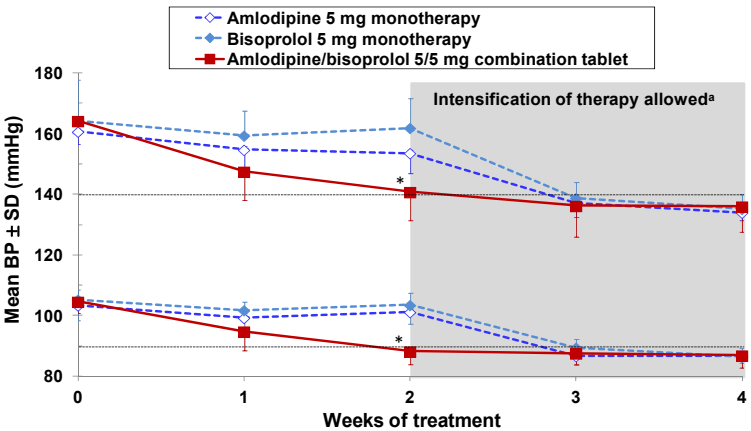
## *Other randomised evaluations of bisoprolol/amlodipine combination tablets*

Sixty patients with Stage 2 hypertension (SBP ≥160 mmHg or DBP ≥100 mmHg[a]) were randomised to receive bisoprolol 5 mg, amlodipine 5 mg, or the bisoprolol/amlodipine 5/5 mg combination tablet for 1 month [3]. After 2 weeks of treatment, patients with sub-optimal BP (target <140/<90 mmHg) on monotherapy were switched to the bisoprolol/amlodipine 5/5 mg combination tablet; enalapril was added at 2 weeks for patients uncontrolled on the combination tablet. The combination tablet was significantly more effective than either monotherapy over the first 2 weeks of treatment (Figure 3). Thereafter, mean SBP and DBP became similar as antihypertensive therapy was intensified where required; 80% of the amlodipine monotherapy group and 90% of the bisoprolol monotherapy group required a switch to the combination tablet due to sub-optimal BP control, compared with only 5% of the combination tablet group requiring additional enalapril.

Another randomised trial conducted in Russia employed ambulatory BP recording to study the effects of the bisoprolol/amlodipine combination tablet versus a free combination of bisoprolol and amlodipine (each added to enalapril) in 61 patients with sub-optimally controlled hypertension and pre-existing coronary heart disease [4]. Daytime and nighttime BP was reduced in both groups, becoming well controlled in 97% of the combination tablet group and in 87% of the free combination group. Aortic pulse wave velocity, aortic augmentation index and aortic DBP improved significantly only in the combination therapy group. A pharmacoeconomic evaluation derived from these data (from the Russian healthcare system perspective) found lower costs per unit of reduction of SBP, DBP and HR for the combination tablet versus the free combination approach [5].

a. See Chapter 1 of this book for details of classifications of hypertension.

**Figure 3 Changes in blood pressure in a randomised comparison of the bisoprolol 5 mg/amlodipine 5 mg combination tablet with bisoprolol 5 mg or amlodipine 5 mg monotherapy in patients with Stage 2 hypertension.**




BP: blood pressure; DBP: diastolic blood pressure; SBP: systolic blood pressure; SD: standard deviation.
[a]If BP was >140/90 mmHg, patients randomised to either monotherapy could be switched to the combination tablet and enalapril could be added to the regimen of patients randomised to the combination tablet.
Some SD bars have been omitted for clarity.
*p<0.001 vs. either monotherapy at week 2.
Dotted lines show targets for BP control of 140 mmHg (SBP) and 90 mmHg (DBP).
Drawn from data presented in reference [3].

## *Model-derived analysis based on data from randomised clinical trials*

No randomised clinical trial to date has compared the effects of up titration of amlodipine with a switch to bisoprolol/amlodipine combination therapy in patients sub-optimally controlled on monotherapy with amlodipine 5 mg. A modelling approach was used to simulate this treatment comparison, based on data from two randomised clinical trials in patients with hypertension sub-optimally controlled on amlodipine 5 mg monotherapy [6]:

**Study 1:** randomised comparison of bisoprolol/amlodipine 5/5 mg combination versus amlodipine 5 mg plus placebo [2];

**Study 2:** the amlodipine monotherapy arms of a randomised comparison of amlodipine 5 mg, amlodipine 10 mg, and two strengths of a telmisartan/amlodipine tablet [13].

This was an anchored, simulated treatment comparison; the term "anchored" refers to the amlodipine 5 mg arm, which was present in both studies. Briefly, the analysis used individual patient data from Study 1 to construct a model that adjusted its study population to resemble that of Study 2, based on the baseline characteristics of each trial. This enabled the model to make predictions of average changes in BP that would be expected to occur had the two studies had the same patient populations. In this way, the model enabled a comparison of the predicted effect on BP of a switch from amlodipine 5 mg monotherapy to an amlodipine/bisoprolol 5 mg/5 mg combination (evaluated in Study 1) with the observed effect of up titrating amlodipine 5 mg to amlodipine 10 mg (evaluated in Study 2).

Baseline and follow-up measures of BP were available from 261 patients in the combination therapy arm and 255 patients in the amlodipine 10 mg monotherapy arm, and these patients were included in the analysis population. The analysis was based on 8 weeks of treatment. The predicted reduction in BP with the bisoprolol/amlodipine 5/5 mg combination (modelled to the population of Study 2) was larger than the effect of amlodipine 5 mg monotherapy (mean treatment difference [standard deviation (SD)] –6.5 [1.8]/–5.5 [1.2] mmHg), as was the observed effect of up titration of amlodipine from 5 mg to 10 mg in Study 2 (mean treatment difference [SD] –4.9 [1.0]/–2.2 [0.7] mmHg). The estimated mean difference for effects on BP between the combination tablet and amlodipine 10 mg was –1.6 [1.9]/–3.3 [1.3] mmHg.

The combination tablet, therefore, induced larger reductions in BP than either amlodipine 5 mg or amlodipine 10 mg in this analysis, though the magnitude of the difference between treatments was clinically meaningful only for DBP. It should be noted that 27% of patients in Study 2 reported peripheral oedema as a side-effect of amlodipine 10 mg, compared with 4–9% of patients in study arms that included amlodipine 5 mg [2]. Only 1–2% of patients in Study 1 reported peripheral oedema with regimens that included amlodipine 5 mg. Thus, in this analysis, the bisoprolol/amlodipine 5/5 mg combination tablet was more effective than amlodipine 5 mg, and at least as effective as amlodipine 10 mg, with less potential for oedema-related side-effects.

## *Real-world study that involved switching from a free combination of bisoprolol and amlodipine to the bisoprolol/amlodipine combination tablet*

This study enrolled a population of 12,242 patients with hypertension who had been switched from a free combination of bisoprolol and amlodipine to bisoprolol/amlodipine combination tablets at least 4 weeks previously [7]. Patients were followed up for 6 months. Substantial reductions were observed for:

**SBP** – reduced from 147.6 ± 16 mmHg at baseline to 131.2 ± 10 mmHg at 6 months (mean difference ± SD: –16.5 ± 15 mmHg);

**DBP** – reduced from 88.3 ± 10 mmHg at baseline to 78.9 ± 7 mmHg at 6 months (mean difference: –9.5 ± 11 mmHg);

**Pulse pressure** – reduced from 59.3 ± 13 mmHg at baseline to 52.3 ± 10 mmHg at 6 months (mean difference: –7.1 ± 14 mmHg).

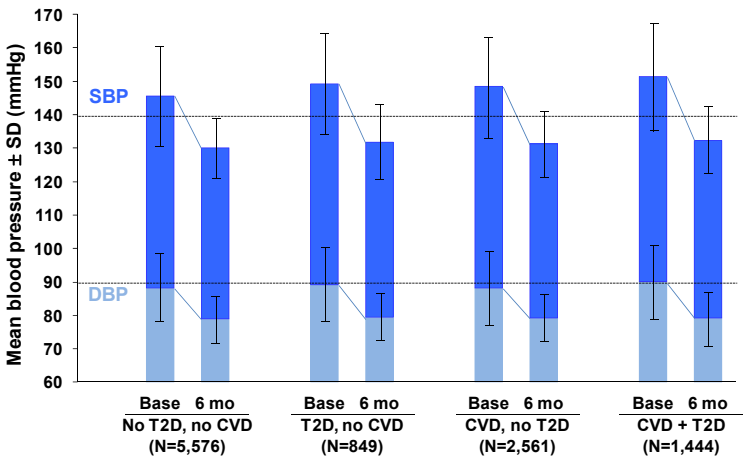
Effects on BP were studied after stratification of patients at baseline for normal body mass index (BMI; 19–25 kg/m$^2$), overweight (>25–30 kg/m$^2$) or obesity (>30 kg/m$^2$). Mean BP values at 6 months differed slightly across these BMI categories (130.3 ± 10/78.5 ± 7 mmHg, 131.1 ± 10/78.9 mmHg, and 131.8 ± 10/79.3 ± 7 mmHg, respectively), and were consistent with achievement of good BP control for most patients.

These BP reductions were achieved despite patients receiving similar average doses of bisoprolol and amlodipine before the switch (5.5 mg and 6.1 mg, respectively) and after the switch (5.8 mg and 6.3 mg, respectively); about 80% of patients received the same dose of the therapies before and after the switch. The improvement in BP was likely associated, at least in part, with good adherence to the combination therapy regimen. Adherence (measured as proportion of prescribed medication received in this study) was “good” or “excellent” in 99% of patients.

This real-world population contained patients with a range of comorbidities, and a subsequent analysis from the same patient population focussed on the impact of cardiovascular comorbidities in more detail [14]. Patients were stratified for the presence of cardiovascular disease without type 2 diabetes (N=2,561 [25% of the population]); type 2 diabetes without cardiovascular disease (N=849 [8%]); both cardiovascular

disease and type 2 diabetes (N=1,444 [14%]); or none of these (N=5,576 [53%]). Higher mean values of SBP were observed in patients with cardiovascular disease (148.5 mmHg), diabetes (149.3 mmHg), or both (151.5 mmHg) at baseline, compared with 145.5 mmHg for patients without these comorbidities (DBP was similar between these groups). BP was >140/90 mmHg in 28% of patients with no comorbidities, compared with 31% (cardiovascular disease), 33% (type 2 diabetes), and 38% (both comorbidities), consistent with this observation. These differences were no longer evident at study end, as mean SBP ranged between 130.0 mmHg and 132.2 mmHg across the four groups (Figure 4).

**Figure 4 Changes in blood pressure according to the presence or absence at baseline of predefined comorbidities in a large cohort of patients with hypertension previously treated with a free combination of bisoprolol and amlodipine who received 6 months' treatment with bisoprolol/amlodipine combination tablets.**




Base: baseline; CVD: cardiovascular disease; DBP: diastolic blood pressure; mo: months; SBP: systolic blood pressure; SD: standard deviation; T2D: type 2 diabetes.
Dotted lines show targets for BP control of 140 mmHg (SBP) and 90 mmHg (DBP).
Drawn from data presented in reference [14].

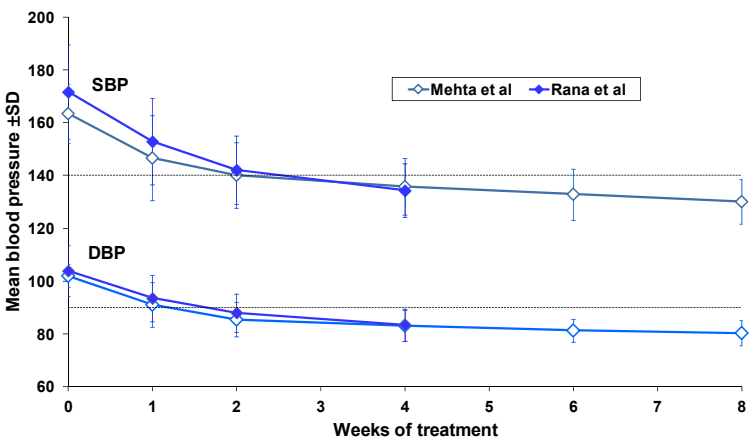
## *Other real-world analyses*

Two real-world analyses evaluated the effects of bisoprolol/amlodipine 2.5/5 mg [8] or 5/5 mg [9] combination tablets in patients with Stage 2 hypertension in India, over 8 weeks (N=106) and 4 weeks (N=801) of treatment, respectively. Marked reductions in BP occurred in both studies (Figure 5), from 163/102 mmHg to 130/80 mmHg (8-week study) and from 172/104 mmHg to 134/83 mmHg (4-week study). The majority of patients in the 8-week study (89%) achieved BP <140/90 mmHg with the bisoprolol/amlodipine 2.5/5 mg tablet.

Three other real-world analyses (from Russia) are briefly summarised below:

- Mean BP was reduced from 163/93 mmHg to 128/77 mmHg during 4 weeks of treatment with bisoprolol/amlodipine combination tablets in an observational study in 100 patients with uncontrolled hypertension and coronary heart disease [10]. SBP and DBP goals were achieved by 90% and 97%, respectively.

**Figure 5 Changes in mean blood pressure during treatment with bisoprolol/amlodipine 5/5 mg combination tablets in patents with Stage 2 hypertension in India.**




DBP: diastolic blood pressure; SBP: systolic blood pressure; SD: standard deviation.
Dotted lines show targets for BP control of 140 mmHg (SBP) and 90 mmHg (DBP).
Drawn from data presented by Mehta et al [8] and Rana et al [9].

- The second study was conducted in 15 previously antihypertensive-drug naïve patients with BP not adequately controlled by a 4-week trial of bisoprolol 5–10 mg monotherapy [11]. Mean peripheral (brachial) BP decreased from 157/98 mmHg at baseline to 148/95 mmHg after 4 weeks of bisoprolol 10 mg, and to 133/81 mmHg after a further 4 weeks of treatment with bisoprolol/amlodipine. During treatment with bisoprolol monotherapy, central BP decreased slightly (from 145 mmHg to 140 mmHg), with little change in pulse pressure (from 48.2 to 47.1 mmHg) and a slight increase in Augmentation Index (from 32.8% to 34.7%). Treatment with the bisoprolol/amlodipine 5/5 mg combination tablet markedly reduced central SBP (to 121 mmHg), pulse pressure (to 41.2 mmHg) and Augmentation Index (to 22.5%). Thus, bisoprolol alone was less effective on central versus brachial BP, while addition of amlodipine overcame this limitation.
- A study in two groups of 72 and 68 patients with hypertension (stratified according to shift work patterns) used echocardiography to explore changes in left ventricular structure during 6 months of treatment with bisoprolol/amlodipine tablets [12]. A reduction in mean BP (93% and 88% of the two groups achieved goal BP) was accompanied by increases in the proportions of patients with normal left ventricular geometry (from 38% to 45% in one group and from 24% to 33% in the other) and a decrease in the proportions of patients with concentric left ventricular hypertrophy (from 31% to 24% in one group and from 46% to 38% in the other).

## *Effects on HR*

Table 2 shows the effects of bisoprolol/amlodipine 5/5 mg combination tablets on HR, where reported. Variable, but substantial, reductions in HR occurred in all randomised or real-world studies, with average reductions in HR ranging from about –6 bpm to about –19 bpm in populations receiving bisoprolol/amlodipine combination tablets.

**Table 2 Effects of bisoprolol/amlodipine combination tablets on heart rate in randomised and real-world studies.**

| Ref | Heart rate (bpm) + SD at | | Δ | P-value |
|---|---|---|---|---|
| | Baseline | Study end | | |
| ***Randomised trials*** | | | | |
| [1] | 71.7 ± 9.7 | 62.7 ± 9.5 | –9.0 ± 9.5 | <0.001 |
| [2] | 66.7 ± 9.78 | 74.2 ± 9.38 | –6.3 ± 9.3 | <0.0001 |
| ***Real-world studies*** | | | | |
| [7] | 75.8 ± 10 | 68.4 ± 7 | –7.7 ± 10 | NR |
| [8] | 87.3 ± 11.0 | 68.4 ± 8.1 | –18.9[a] | NR |
| [9] | 83.3 ± 9.6 | 74.6 ± 6.8 | –8.7[a] | NR |
| [10] | 80.1 ± 9.6 | 63.0 ± 5.4 | –17.1[a] | NR |
| [11] | 74.3 ± 5.8 | 62.4 ± 4.2 | –11.9[a] | <0.05 |

bpm: beats per minute; NR: not reported; Ref: reference.
Δ: mean difference in heart rate between baseline and study end ([a]or difference in mean values where this was not reported).

# Other clinical evidence

## *Studies with combinations of β-blockers and calcium channel blockers (CCBs)*

Studies with other $\beta_1$-selective β-blockers in combination with amlodipine will be described briefly here, in the absence of randomised trials that specifically evaluated co-administered (free) combinations of bisoprolol and amlodipine. Trials for inclusion here were identified using a PubMed search for "*(atenolol OR metoprolol OR acebutolol OR nebivolol OR bisoprolol OR Xamoterol OR Acebutolol OR Celiprolol) AND amlodipine*", limited to "*Randomised controlled trial*". Relevant articles were identified by inspection of abstracts of the resulting 187 search hits.

Low-dose atenolol 25 mg/amlodipine 2.5 mg combination therapy was superior for effects on BP compared with atenolol 25 mg or amlodipine 2.5 mg alone in patients with hypertension [15]. A similar benefit for the combination was seen in patients who needed higher doses of combination therapy (atenolol 50 mg/amlodipine 5 mg) versus these doses of monotherapy in this study. Addition of amlodipine to atenolol reduced 24-hour BP significantly in patients with BP uncontrolled

by atenolol alone [16]. The highest dose of a single-tablet combination of metoprolol and amlodipine induced a numerically larger fall in BP than a lower-dose combination of these agents or the constituent monotherapies, although the difference did not achieve statistical significance [17]. The efficacy of a metoprolol extended release/amlodipine combination was similar to that of a losartan/amlodipine combination in another study [18]. A thiazide diuretic induced a larger reduction in BP than atenolol in patients with hypertension already receiving amlodipine and lisinopril [19].

A combination of atenolol and amlodipine reduced BP and arterial stiffness (measured using pulse wave velocity [PWV]) to a similar extent compared with a valsartan/amlodipine combination in patients with hypertension [20]. Reductions in BP and HR accounted largely for the reduced PWV in the β-blocker-amlodipine group. Another study showed that a valsartan/amlodipine combination induced comparable reductions in brachial BP versus an atenolol/amlodipine combination, although the valsartan/amlodipine combination reduced central BP more effectively [21]. Addition of valsartan, but not amlodipine, to atenolol suppressed indices of intracardiac conduction, consistent with the mechanisms of these drugs (see Chapter 4) [22].

Both cardioselective β-blockers and amlodipine are indicated for the management of angina pectoris, and studies evaluating combinations of these mechanisms in these patients are included briefly here for completeness. Results of trials that evaluated $\beta_1$-blockers in combination with amlodipine in patients with angina have been conflicting. Bisoprolol plus amlodipine was not more effective than bisoprolol alone in two studies that used treadmill exercise tolerance as its main outcome [23, 24], but reduced the occurrence of chest pain on exercise in two other studies [25, 26], and during exercise testing and in the ambulatory setting in a fifth [27]. Elsewhere, addition of atenolol to amlodipine was more effective in suppressing ischaemic episodes in ambulatory patients, compared with amlodipine alone [28]. Amlodipine was more effective than diltiazem added to atenolol in suppressing ischaemic symptoms in patients sub-optimally controlled by atenolol alone, and was better tolerated [29]. Finally, addition of amlodipine to

atenolol was haemodynamically safe 15 days after an acute myocardial infarction for normotensive patients without severe left ventricular dysfunction [30].

### *Comparisons of bisoprolol or amlodipine with other monotherapies*

Large meta-analyses have confirmed that the BP-lowering efficacy of β-blockers and CCBs are comparable to that provided by other antihypertensive classes [31, 32]. A number of randomised, head-to-head trials have demonstrated that bisoprolol and amlodipine each have similar antihypertensive efficacy to other antihypertensive agents within their class, and to agents from the four other classes (Table 3).

## Conclusions

Numerous randomised clinical trials have shown that bisoprolol and amlodipine monotherapies are as effective as members of other antihypertensive classes (Table 3). The effects on BP of combining two antihypertensive agents is essentially additive [32]. The results of the randomised and real-world studies that evaluated single-tablet combinations of these agents, summarised in this chapter, have confirmed the greater efficacy of this treatment for controlling BP compared with monotherapies. The consistent reductions in HR observed with the bisoprolol/amlodipine tablet is another potential source of clinical benefit, as higher versus lower HR has been identified as a predictor of adverse cardiac outcomes, especially (but not only) in people with coronary heart disease or heart failure [33–35].

The principle of applying combination antihypertensive therapy in the management of hypertension is well established in current European guidelines (see also Chapter 2 of this book) [36, 37]. Moreover, these guidelines recognise the valuable role of single-tablet combinations in simplifying the antihypertensive regimen and supporting good adherence to therapy [38, 39], which in turn helps to optimise long-term patient outcomes [40]. The large, real-world studies summarised here

**Table 3 Overview of head-to-head randomised trials of bisoprolol and amlodipine vs antihypertensive agents from other classes.**

| | Effects of bisoprolol on BP vs other antihypertensive agents | Effects of amlodipine on BP vs other antihypertensive agents |
|---|---|---|
| **β-blockers** | | |
| Acebutolol | Comparable [41] | Comparable [42] |
| Atenolol | Comparable [43–47]<br>or larger effect [48–51]<br>Lower effect on central BP [43] | Comparable [52–56] |
| Celiprolol | Less effective on central BP [57] | – |
| Metoprolol | Comparable [58]<br>More effective during exercise [59] | Comparable (obstructive sleep apnoea) [60] |
| Nebivolol | Comparable [61] | Comparable [62] |
| **Renin-angiotensin-aldosterone system blockers** | | |
| Captopril | Comparable [63] | Comparable [64] or more effective [65] |
| Enalapril | Comparable (office- [66, 67] and 24-hour [66] BP) | Comparable [42, 68–72]<br>Larger effect on trough BP [73] |
| Zofenopril | – | Comparable [74] |
| Lisinopril | Comparable (ambulatory [75] or office [76] BP) | Comparable [77–82] or larger effect [83] |
| Benazepril | – | Comparable [84] or larger [85] effect |
| Quinapril | – | Comparable [86, 87] |
| Ramipril | – | Larger effect (ambulatory) [88, 89] |
| Irbesartan | – | Comparable [90] |
| Losartan | Comparable (office BP) [91, 92]<br>Less effective on central BP [91] | Larger [93] or comparable [71, 82, 94–100] incl. post-renal transplant [101] and in NASH [102] |
| Valsartan | – | Comparable [103–105] or larger [106] |
| Telmisartan | – | Comparable (ambulatory) [89] |
| Candesartan | – | Comparable [107–109] |
| **Calcium channel blockers** | | |
| Amlodipine | Comparable (haemodialysis) [110] | – |
| Manidipine | – | Comparable [111] |
| SR nifedipine | Comparable [67, 112, 113] | – |
| **Diuretics** | | |
| Thiazides | Comparable [114] | Comparable [42, 68, 71, 77, 78, 115–117] |
| Spironolactone | Larger effect of spironolactone (drug-resistant hypertension) [118] | – |

BP: blood pressure; incl.: including; NASH: non-alcoholic steatohepatitis; SR: sustained release.
Randomised head-to-head trials designed to measure efficacy of monotherapies in people with hypertension were included from a PubMed search for "*amlodipine AND ([list of drugs of interest]) AND hypertension*".
Comparisons are from the perspective of bisoprolol or amlodipine: for example, a "larger effect" means a larger effect of those drugs vs. the stated comparator.

confirmed that adherence rates to regimens based on the bisoprolol/amlodipine tablet were high.

In conclusion, these studies have shown that the bisoprolol/amlodipine tablet is an effective option for the management of hypertension that supports good adherence to therapy. This tablet has a place in the management of hypertension, particularly for people with a compelling indication for β-blockade (such as coronary heart disease, post-myocardial infarction or atrial fibrillation), or in younger women planning a family [37].

## References


1 Gottwald-Hostalek U, Li L, Montenegro P. Bisoprolol/amlodipine combination therapy improves blood pressure control in patients with essential hypertension following monotherapy failure. Curr Med Res Opin. 2016;32:1735–43. https://doi.org/10.1080/03007995.2016.1205573

2 Jędrusik P, Placha G, Gaciong Z, AMCOR trial investigators. Efficacy and safety of bisoprol 5 mg plus amlodipine 5 mg in patients with hypertension uncontrolled on monotherapy with 5 mg of amlodipine, a phase III multicentre, randomized, double-blind, placebo-controlled clinical trial – the AMCOR study. Curr Med Res Opin 2022;Submitted.

3 Shirure PA, Tadvi NA, Bajait CS, Baig MS, Gade PR. Comparative effect of fixed dose combination of amlodipine + bisoprolol versus amlodipine and bisoprolol alone on blood pressure in stage-2 essential hypertensive patients. Int J Med Res Health Sci 2012;1:13–9.

4 Fendrikova A, Skibitsky V. Effectiveness of fixed-dose combination of bisoprolol and amlodipine in patients with arterial hypertension and coronary heart disease. J Hypertens 2015;(eSuppl):e322.

5 Tarlovskaya E, Malchikova S, Skibitskyi V, Fendrikova A, Skibitskyi A, Sirotenko D. Economy of antianginal and antihypertensive efficacy of the fixed combination of bisoprolol/amlodipine in patients with arterial hypertension and coronary heart disease. J Hypertens. 2015;(eSuppl):e328–e9.

6 Foch C, Feifel J, Gottwald-Hostalek U. An anchored simulated treatment comparison of uptitration of amlodipine compared with a low-dose combination treatment with amlodipine 5 mg/bisoprolol 5 mg for patients with hypertension suboptimally controlled by amlodipine 5 mg monotherapy. Curr Med Res Opin. 2022;38:587–93. https://doi.org/10.1080/03007995.2022.2030112.

7 Hostalek U, EMW K. Treatment of hypertension with a fixed-dose combination of bisoprolol and amlodipine in daily practice: results of a multinational non-investigational study. Cardiovasc Disord Med 2016;1:10. https://doi.org/10.15761/CDM.1000118.

8 Mehta S, Shah M, Shah A. Efficacy and tolerability of a fixed dose combination of amlodipine and bisoprolol in essential hypertension. Indian Pract. 2005;58:751–9.

9 Rana R, Patil A. Efficacy and safety of bisoprolol plus amlodipine fixed dose combination in essential hypertension. Indian Pract. 2008;61:225–34.

10 Chesnikova AI, Safronenko VA, Kolomatskaia OE. Evaluating the effectiveness of a fixed combination of amlodipine and bisoprolol in ambulatory patients with arterial hypertension and ischemic heart disease. Kardiologiia. 2014;54:17–23. https://doi.org/10.18565/cardio.2014.9.17–23.

11 Bogomaz A, Kotovskaya Y, Kobalava Z. Combination with amlodipine eliminates adverse effect of a beta-blocker on aortic pulse pressure augmentation. J Hypertens. 2015;33:e326. https://doi.org/10.1097/01.hjh.0000468379.55561.95.

**12** Zapesochnaya IL, Avtandilov AG. Dynamics of structural and functional status of myocardium due to combination therapy with amlodipine and bisoprolol in patients with arterial hypertension. Rational Pharmacother Cardiol 2014;10:606–11. https://doi.org/10.20996/1819-6446-2014-10-6-606-611.

**13** Neldam S, Lang M, Jones R. Telmisartan and amlodipine single-pill combinations vs amlodipine monotherapy for superior blood pressure lowering and improved tolerability in patients with uncontrolled hypertension: results of the TEAMSTA-5 study. J Clin Hypertens (Greenwich). 2011;13:459–66. https://doi.org/10.1111/j.1751-7176.2011.00468.x.

**14** Hostalek U, Czarnecka D, Kurzeja A, Koch E. Efficacy of and adherence to a fixed-dose combination of bisoprolol and amlodipine in hypertensive patients with and without type 2 diabetes mellitus or coronary artery disease. J Heart Health 2015b. 2015. https://doi.org/10.16966/2379-769X.114.

**15** Pareek A, Salkar H, Mulay P, Desai S, Chandurkar N, Redkar N. A randomized, comparative, multicentric evaluation of atenolol/amlodipine combination with atenolol alone in essential hypertensive patients. Am J Ther. 2010;17:46–52. https://doi.org/10.1097/MJT.0b013e3181a9db74.

**16** Mettimano M, Pichetti F, Fazzari L, Migneco A, Specchia L, Romano Spica V, et al. Combination therapy with beta-adrenergic blockade and amlodipine as second line treatment in essential hypertension. Int J Clin Pract. 2000;54:424–8.

**17** Devi P, Xavier D, Sigamani A, Pandey S, Thomas T, Murthy S, et al. Effect of fixed dose combinations of metoprolol and amlodipine in essential hypertension: MARS--a randomized controlled trial. Blood Press Suppl. 2011;2:5–12. https://doi.org/10.3109/08037051.2011.617040.

**18** Pareek A, Chandurkar NB, Sharma R, Tiwari D, Gupta BS. Efficacy and tolerability of a fixed-dose combination of metoprolol extended release/amlodipine in patients with mild-to-moderate hypertension: a randomized, parallel-group, multicentre comparison with losartan plus amlodipine. Clin Drug Investig. 2010;30:123–31. https://doi.org/10.2165/11531770-000000000-00000.

**19** Antonios TF, Cappuccio FP, Markandu ND, Sagnella GA, MacGregor GA. A diuretic is more effective than a beta-blocker in hypertensive patients not controlled on amlodipine and lisinopril. Hypertension. 1996;27:1325–8. https://doi.org/10.1161/01.hyp.27.6.1325.

**20** Boutouyrie P, Beaussier H, Achouba A, Laurent S. Destiffening effect of valsartan and atenolol: influence of heart rate and blood pressure. J Hypertens. 2014;32:108–14. https://doi.org/10.1097/hjh.0000000000000014.

**21** Boutouyrie P, Achouba A, Trunet P, Laurent S. Amlodipine-valsartan combination decreases central systolic blood pressure more effectively than the amlodipine-atenolol combination: the EXPLOR study. Hypertension. 2010;55:1314–22. https://doi.org/10.1161/hypertensionaha.109.148999.

**22** Santarelli P, Biscione F, Natale A, Manzoli A, Lanza GA. Electrophysiologic effects of amlodipine vs. diltiazem in patients with coronary artery disease and beta-blocking therapy. Cardiovasc Drugs Ther. 1994;8:653–8. https://doi.org/10.1007/bf00877419.

**23** Ferguson JD, Ormerod O, Lenox-Smith AJ. Bisoprolol alone and in combination with amlodipine or nifedipine in the treatment of chronic stable angina. Int J Clin Pract. 2000;54:360–3.

**24** Pehrsson SK, Ringqvist I, Ekdahl S, Karlson BW, Ulvenstam G, Persson S. Monotherapy with amlodipine or atenolol versus their combination in stable angina pectoris. Clin Cardiol. 2000;23:763–70. https://doi.org/10.1002/clc.4960231014.

**25** Woodmansey PA, Stewart AG, Morice AH, Channer KS. Amlodipine in patients with angina uncontrolled by atenolol. A double blind placebo controlled cross over trial. Eur J Clin Pharmacol. 1993;45:107–11. https://doi.org/10.1007/bf00315489.

**26** Dunselman PH, van Kempen LH, Bouwens LH, Holwerda KJ, Herweijer AH, Bernink PJ. Value of the addition of amlodipine to atenolol in patients with angina pectoris despite adequate beta blockade. Am J Cardiol. 1998;81:128–32. https://doi.org/10.1016/s0002-9149(97)00877-1.

**27** Davies RF, Habibi H, Klinke WP, Dessain P, Nadeau C, Phaneuf DC, et al. Effect of amlodipine, atenolol and their combination on myocardial ischemia during treadmill exercise and ambulatory monitoring. Canadian Amlodipine/Atenolol in Silent Ischemia Study (CASIS) Investigators. J Am Coll Cardiol. 1995;25:619–25. https://doi.org/10.1016/0735-1097(94)00436-t.

**28** Frishman WH, Glasser S, Stone P, Deedwania PC, Johnson M, Fakouhi TD. Comparison of controlled-onset, extended-release verapamil with amlodipine and amlodipine plus atenolol on exercise performance and ambulatory ischemia in patients with chronic stable angina pectoris. Am J Cardiol. 1999;83:507–14. https://doi.org/10.1016/s0002-9149(98)00904-7.

**29** Knight CJ, Fox KM. Amlodipine versus diltiazem as additional antianginal treatment to atenolol. Centralised European Studies in Angina Research (CESAR) Investigators. Am J Cardiol. 1998;81:133–6. https://doi.org/10.1016/s0002-9149(97)00893-x.

**30** Rocha P, Pathé M, Bernaud C, Zannier D, Baron B, Marchand X, et al. Acute hemodynamic effects of amlodipine 15 days after a myocardial infarction in normotensive patients treated with atenolol. Cardiovasc Drugs Ther. 1997;11:139–47. https://doi.org/10.1023/a:1007732830753.

**31** Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. BMJ. 2009;338:b1665. https://doi.org/10.1136/bmj.b1665.

**32** Wald DS, Law M, Morris JK, Bestwick JP, Wald NJ. Combination therapy versus monotherapy in reducing blood pressure: meta-analysis on 11,000 participants from 42 trials. Am J Med. 2009;122:290–300. https://doi.org/10.1016/j.amjmed.2008.09.038.

**33** Diaz A, Bourassa MG, Guertin MC, Tardif JC. Long-term prognostic value of resting heart rate in patients with suspected or proven coronary artery disease. Eur Heart J. 2005;26:967–74. https://doi.org/10.1093/eurheartj/ehi190.

**34** Hsia J, Larson JC, Ockene JK, Sarto GE, Allison MA, Hendrix SL, et al. Resting heart rate as a low tech predictor of coronary events in women: prospective cohort study. BMJ. 2009;338:b219. https://doi.org/10.1136/bmj.b219.

**35** Böhm M, Swedberg K, Komajda M, Borer JS, Ford I, Dubost-Brama A, et al. Heart rate as a risk factor in chronic heart failure (SHIFT): the association between heart rate and outcomes in a randomised placebo-controlled trial. Lancet. 2010;376:886–94. https://doi.org/10.1016/s0140-6736(10)61259-7.

**36** Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, et al. 2018 ESC/ESH guidelines for the management of arterial hypertension. Eur Heart J. 2018;39:3021–104. https://doi.org/10.1093/eurheartj/ehy339.

**37** Visseren FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC, Bäck M, et al. 2021 ESC guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J. 2021;42:3227–337. https://doi.org/10.1093/eurheartj/ehab484.

**38** Parati G, Kjeldsen S, Coca A, Cushman WC, Wang J. Adherence to single-pill versus free-equivalent combination therapy in hypertension: a systematic review and meta-analysis. Hypertension. 2021;77:692–705. https://doi.org/10.1161/hypertensionaha.120.15781.

**39** Weisser B, Predel HG, Gillessen A, Hacke C, Vor dem Esche J, Rippin G, et al. Single pill regimen leads to better adherence and clinical outcome in daily practice in patients suffering from hypertension and/or dyslipidemia: results of a meta-analysis. High Blood Press Cardiovasc Prev. 2020;27:157–64. https://doi.org/10.1007/s40292-020-00370-5.

**40** Lee H, Yano Y, Cho SMJ, Heo JE, Kim DW, Park S, et al. Adherence to antihypertensive medication and incident cardiovascular events in young adults with hypertension. Hypertension. 2021;77:1341–9. https://doi.org/10.1161/hypertensionaha.120.16784.

**41** Bouvier JM, Rabot D, Herrero G. Effect of bisoprolol and acebutolol on resting blood pressure and on exercise blood pressure profile in hypertensive patients: a comparative, single-blind study. J Cardiovasc Pharmacol. 1990;16 Suppl 5:S179–83.

**42** Neaton JD, Grimm RH, Jr., Prineas RJ, Stamler J, Grandits GA, Elmer PJ, et al. Treatment of mild hypertension study. Final results. Treatment of mild hypertension study research group. Jama. 1993;270:713–24. https://doi.org/10.1001/jama.1993.03510060059034.

**43** Zhou WJ, Wang RY, Li Y, Chen DR, Chen EZ, Zhu DL, et al. A randomized controlled study on the effects of bisoprolol and atenolol on sympathetic nervous activity and central aortic pressure in patients with essential hypertension. PLoS One. 2013;8:e72102. https://doi.org/10.1371/journal.pone.0072102.

**44** Wheeldon NM, MacDonald TM, Prasad N, Maclean D, Peebles L, McDevitt DG. A double-blind comparison of bisoprolol and atenolol in patients with essential hypertension. Qjm. 1995;88:565–70.

**45** Leeman M, van de Borne P, Collart F, Vandenhoven G, Peeters L, Mélot C, et al. Bisoprolol and atenolol in essential hypertension: effects on systemic and renal hemodynamics and on ambulatory blood pressure. J Cardiovasc Pharmacol. 1993;22:785–91. https://doi.org/10.1097/00005344-199312000-00002.

**46** Neutel JM, Smith DH, Ram CV, Lefkowitz MP, Kazempour MK, Weber MA. Comparison of bisoprolol with atenolol for systemic hypertension in four population groups (young, old, black and nonblack) using ambulatory blood pressure monitoring. Bisoprolol Investigators Group. Am J Cardiol. 1993;72:41–6. https://doi.org/10.1016/0002-9149(93)90216-y.

**47** Lithell H, Selinus I, Hosie J, Frithz G, Weiner L. Efficacy and safety of bisoprolol and atenolol in patients with mild to moderate hypertension: a double-blind, parallel group international multicentre study. Eur Heart J. 1987;8 Suppl M:55–64. https://doi.org/10.1093/eurheartj/8.suppl_m.55-a.

**48** Neutel JM, Smith DH, Ram CV, Kaplan NM, Papademetriou V, Fagan TC, et al. Application of ambulatory blood pressure monitoring in differentiating between antihypertensive agents. Am J Med. 1993;94:181–7. https://doi.org/10.1016/0002-9343(93)90181-n.

**49** Lewis R, Maclean D, Ioannides C, Johnston A, McDevitt DG. A comparison of bisoprolol and atenolol in the treatment of mild to moderate hypertension. Br J Clin Pharmacol. 1988;26:53–9. https://doi.org/10.1111/j.1365-2125.1988.tb03363.x.

**50** Bühler FR, Berglund G, Anderson OK, Brunner HR, Scherrer U, van Brummelen P, et al. Double-blind comparison of the cardioselective beta-blockers bisoprolol and atenolol in hypertension: the Bisoprolol International Multicenter Study (BIMS). J Cardiovasc Pharmacol. 1986;8 Suppl 11:S122–7. https://doi.org/10.1097/00005344-198511001-00022.

**51** Dixon MS, Thomas P, Sheridan DJ. A randomized double-blind study of bisoprolol versus atenolol in mild to moderate essential hypertension. Eur J Clin Pharmacol. 1990;38:21–4. https://doi.org/10.1007/bf00314797.

**52** Schiffrin EL, Pu Q, Park JB. Effect of amlodipine compared to atenolol on small arteries of previously untreated essential hypertensive patients. Am J Hypertens. 2002;15:105–10. https://doi.org/10.1016/s0895-7061(01)02290-7.

**53** Frishman WH, Brobyn R, Brown RD, Johnson BF, Reeves RL, Wombolt DG. Amlodipine versus atenolol in essential hypertension. Am J Cardiol. 1994;73:50a–4a. https://doi.org/10.1016/0002-9149(94)90275-5.

**54** Tham TC, Herity N, Guy S, Silke B. Haemodynamic comparison of amlodipine and atenolol in essential hypertension using the quantascope. Br J Clin Pharmacol. 1993;36:555–60. https://doi.org/10.1111/j.1365-2125.1993.tb00414.x.

**55** Johnson BF, Frishman WH, Brobyn R, Brown RD, Reeves RL, Wombolt DG. A randomized, placebo-controlled, double-blind comparison of amlodipine and atenolol in patients with essential hypertension. Am J Hypertens. 1992;5:727–32. https://doi.org/10.1093/ajh/5.10.727.

**56** Frishman WH, Brobyn R, Brown RD, Johnson BF, Reeves RL, Wombolt DG. A randomized placebo-controlled comparison of amlodipine and atenolol in mild to moderate systemic hypertension. J Cardiovasc Pharmacol. 1988;12 Suppl 7:S103–6. https://doi.org/10.1097/00005344-198812007-00023.

**57** Eguchi K, Hoshide S, Kario K. Effects of celiprolol and bisoprolol on blood pressure, vascular stiffness, and baroreflex sensitivity. Am J Hypertens. 2015;28:858–67. https://doi.org/10.1093/ajh/hpu245.

**58** Yang T, Jiang Y, Hao Y, Zhou S, Xu X, Qu B, et al. Comparison of bisoprolol to a metoprolol CR/ZOK tablet for control of heart rate and blood pressure in mild-to-moderate

hypertensive patients: the CREATIVE study. Hypertens Res. 2017;40:79–86. https://doi.org/10.1038/hr.2016.101.

**59** Haasis R, Bethge H. Exercise blood pressure and heart rate reduction 24 and 3 hours after drug intake in hypertensive patients following 4 weeks of treatment with bisoprolol and metoprolol: a randomized multicentre double-blind study (BISOMET). Eur Heart J. 1987;8 Suppl M:103–13. https://doi.org/10.1093/eurheartj/8.suppl_m.103.

**60** Shi J, Yuan Y, Deng X, Pan Y, He M, Liu G, et al. Metoprolol has a similar therapeutic effect as amlodipine on BP lowering in hypertensive patients with obstructive sleep apnea. Sleep Breath. 2019;23:227–33. https://doi.org/10.1007/s11325-018-1688-5.

**61** Czuriga I, Riecansky I, Bodnar J, Fulop T, Kruzsicz V, Kristof E, et al. Comparison of the new cardioselective beta-blocker nebivolol with bisoprolol in hypertension: the Nebivolol, Bisoprolol Multicenter Study (NEBIS). Cardiovasc Drugs Ther. 2003;17:257–63. https://doi.org/10.1023/a:1026180325278.

**62** Mazza A, Gil-Extremera B, Maldonato A, Toutouzas T, Pessina AC. Nebivolol vs amlodipine as first-line treatment of essential arterial hypertension in the elderly. Blood Press. 2002;11:182–8. https://doi.org/10.1080/080370502760050421.

**63** Bracchetti D, Gradnik R, Alberti A, Brunelli A, Orselli L, Leonardi G, et al. A double-blind comparison of bisoprolol and captopril for treatment of essential hypertension in the elderly. Cardiovasc Drugs Ther. 1990;4:261–4. https://doi.org/10.1007/bf01857642.

**64** Velasco M, Urbina A, Silva H, Fonseca R, Guevara J, Hernandez R, et al. A double-blind, parallel, comparative evaluation of amlodipine vs. captopril in the monotherapeutic treatment of mild and moderate essential hypertension. J Cardiovasc Pharmacol. 1991;17 Suppl 1:S19–21. https://doi.org/10.1097/00005344-199117001-00007.

**65** Lacourcière Y, Poirier L, Provencher P. Comparison of the effects of amlodipine and captopril on clinic and ambulatory blood pressure. J Hum Hypertens. 1992;6 Suppl 1:S25–8.

**66** Gosse P, Roudaut R, Herrero G, Dallocchio M. Beta-blockers vs. angiotensin-converting enzyme inhibitors in hypertension: effects on left ventricular hypertrophy. J Cardiovasc Pharmacol. 1990;16 Suppl 5:S145–50.

**67** Liu G, Li M, Shi X, et al. Efficacy of domestic bisoprolol, enalapril and nifedipine retard in mild to moderate hypertension: a randomized double-blind multicenter clinical trial in China. Zhonghua Nei Ke Za Zhi. 2002;41:450–2.

**68** Rasmussen S, Borrild N, Vang Andersen J. Efficacy and safety of 24 weeks of therapy with bendroflumethiazide 1.25 mg/day or 2.5 mg/day and potassium chloride compared with enalapril 10 mg/day and amlodipine 5 mg/day in patients with mild to moderate primary hypertension : a multicentre, randomised, open study. Clin Drug Investig. 2006;26:91–101. https://doi.org/10.2165/00044011-200626020-00004.

**69** Webster J, Fowler G, Jeffers TA, Lyons D, Witte K, Crichton WA, et al. A comparison of amlodipine with enalapril in the treatment of isolated systolic hypertension. Br J Clin Pharmacol. 1993;35:499–505. https://doi.org/10.1111/j.1365-2125.1993.tb04176.x.

**70** Fowler G, Webster J, Lyons D, Witte K, Crichton WA, Jeffers TA, et al. A comparison of amlodipine with enalapril in the treatment of moderate/severe hypertension. Br J Clin Pharmacol. 1993;35:491–8. https://doi.org/10.1111/j.1365-2125.1993.tb04175.x.

**71** Kraiczi H, Hedner J, Peker Y, Grote L. Comparison of atenolol, amlodipine, enalapril, hydrochlorothiazide, and losartan for antihypertensive treatment in patients with obstructive sleep apnea. Am J Respir Crit Care Med. 2000;161:1423–8. https://doi.org/10.1164/ajrccm.161.5.9909024.

**72** Omvik P, Thaulow E, Herland OB, Eide I, Midha R, Turner RR. A double-blind, long-term, comparative study on quality of life, safety, and efficacy during treatment with amlodipine or enalapril in mild or moderate hypertensive patients: a multicenter study. J Cardiovasc Pharmacol. 1993;22 Suppl A:S13–9.

**73** Tomlinson B, Woo J, Thomas GN, Chau YM, Critchley JA. Randomized, controlled, parallel-group comparison of ambulatory and clinic blood pressure responses to amlodipine or enalapril during and after treatment in adult chinese patients with hypertension. Clin Ther. 2004;26:1292–304. https://doi.org/10.1016/s0149-2918(04)80145-0.

**74** Farsang C. Blood pressure control and response rates with zofenopril compared with amlodipine in hypertensive patients. Blood Press Suppl. 2007;2:19–24. https://doi.org/10.1080/08038020701561737.

**75** Vaïsse B, Herpin D, Asmar R, Battistella P, Zannad F, Boutelant S, et al. Assessment of antihypertensive effect by blood pressure monitoring: applications to bisoprolol and lisinopril in a double-blind study. J Cardiovasc Pharmacol. 1997;29:612–7. https://doi.org/10.1097/00005344-199705000-00008.

**76** Saku K, Liu K, Takeda Y, Jimi S, Arakawa K. Effects of lisinopril and bisoprolol on lipoprotein metabolism in patients with mild-to-moderate essential hypertension. Clin Ther. 1995;17:1136–46. https://doi.org/10.1016/0149-2918(95)80092-1.

**77** Reisin E, Graves JW, Yamal JM, Barzilay JI, Pressel SL, Einhorn PT, et al. Blood pressure control and cardiovascular outcomes in normal-weight, overweight, and obese hypertensive patients treated with three different antihypertensives in ALLHAT. J Hypertens. 2014;32:1503–13; discussion 13. https://doi.org/10.1097/hjh.0000000000000204.

**78** Cushman WC, Ford CE, Einhorn PT, Wright JT, Jr., Preston RA, Davis BR, et al. Blood pressure control by drug group in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). J Clin Hypertens (Greenwich). 2008;10:751–60. https://doi.org/10.1111/j.1751-7176.2008.00015.x.

**79** Stanton AV, Chapman JN, Mayet J, Sever PS, Poulter NR, Hughes AD, et al. Effects of blood pressure lowering with amlodipine or lisinopril on vascular structure of the common carotid artery. Clin Sci (Lond). 2001;101:455–64.

**80** Terpstra WF, May JF, Smit AJ, de Graeff PA, Havinga TK, van den Veur E, et al. Long-term effects of amlodipine and lisinopril on left ventricular mass and diastolic function in elderly, previously untreated hypertensive patients: the ELVERA trial. J Hypertens. 2001;19:303–9. https://doi.org/10.1097/00004872-200102000-00018.

**81** Ranieri G, Andriani A, Lamontanara G, De Cesaris R. Effects of lisinopril and amlodipine on microalbuminuria and renal function in patients with hypertension. Clin Pharmacol Ther. 1994;56:323–30. https://doi.org/10.1038/clpt.1994.143.

**82** Wu SC, Liu CP, Chiang HT, Lin SL. Prospective and randomized study of the antihypertensive effect and tolerability of three antihypertensive agents, losartan, amlodipine, and lisinopril, in hypertensive patients. Heart Vessels. 2004;19:13–8. https://doi.org/10.1007/s00380-003-0724-x.

**83** Lorimer AR, Lyons D, Fowler G, Petrie JC, Rothman MT. Differences between amlodipine and lisinopril in control of clinic and twenty-four hour ambulatory blood pressures. J Hum Hypertens. 1998;12:411–6. https://doi.org/10.1038/sj.jhh.1000620.

**84** Frishman WH, Ram CV, McMahon FG, Chrysant SG, Graff A, Kupiec JW, et al. Comparison of amlodipine and benazepril monotherapy to amlodipine plus benazepril in patients with systemic hypertension: a randomized, double-blind, placebo-controlled, parallel-group study. The Benazepril/Amlodipine Study Group. J Clin Pharmacol. 1995;35:1060–6. https://doi.org/10.1002/j.1552-4604.1995.tb04027.x.

**85** Stergiou GS, Makris T, Papavasiliou M, Efstathiou S, Manolis A. Comparison of antihypertensive effects of an angiotensin-converting enzyme inhibitor, a calcium antagonist and a diuretic in patients with hypertension not controlled by angiotensin receptor blocker monotherapy. J Hypertens. 2005;23:883–9. https://doi.org/10.1097/01.hjh.0000163159.22116.ab.

**86** Ding YA, Chang SM, Chou TC. Comparison of amlodipine and quinapril on ambulatory blood pressure and platelet function in hypertension. J Hum Hypertens. 1995;9:637–41.

**87** Rajzer M, Klocek M, Kawecka-Jaszcz K. Effect of amlodipine, quinapril, and losartan on pulse wave velocity and plasma collagen markers in patients with mild-to-moderate arterial hypertension. Am J Hypertens. 2003;16:439–44. https://doi.org/10.1016/s0895-7061(03)00052-9.

**88** Perticone F, Pugliese F, Ceravolo R, Mattioli PL. Amlodipine versus ramipril in the treatment of mild to moderate hypertension: evaluation by 24-hour ambulatory blood pressure monitoring. Cardiology. 1994;85:36–46. https://doi.org/10.1159/000176644.

**89** Poirier L, de Champlain J, Larochelle P, Lamarre-Cliche M, Lacourcière Y. A comparison of the efficacy and duration of action of telmisartan, amlodipine and ramipril in patients with confirmed ambulatory hypertension. Blood Press Monit. 2004;9:231–6. https://doi.org/10.1097/00126097-200410000-00001.

**90** Neutel JM, Germino FW, Smith D. Comparison of monotherapy with irbesartan 150 mg or amlodipine 5 mg for treatment of mild-to-moderate hypertension. J Renin Angiotensin Aldosterone Syst. 2005;6:84–9. https://doi.org/10.3317/jraas.2005.014.

**91** Radchenko GD, Sirenko YM, Kushnir SM, Torbas OO, Dobrokhod AS. Comparative effectiveness of a fixed-dose combination of losartan + HCTZ versus bisoprolol + HCTZ in patients with moderate-to-severe hypertension: results of the 6-month ELIZA trial. Vasc Health Risk Manag. 2013;9:535–49. https://doi.org/10.2147/vhrm.S44568.

**92** Parrinello G, Paterna S, Torres D, Di Pasquale P, Mezzero M, La Rocca G, et al. One-year renal and cardiac effects of bisoprolol versus losartan in recently diagnosed hypertensive patients: a randomized, double-blind study. Clin Drug Investig. 2009;29:591–600. https://doi.org/10.2165/11315250-000000000-00000.

**93** Phillips RA, Kloner RA, Grimm RH, Jr., Weinberger M. The effects of amlodipine compared to losartan in patients with mild to moderately severe hypertension. J Clin Hypertens (Greenwich). 2003;5:17–23. https://doi.org/10.1111/j.1524-6175.2003.01416.x.

**94** Yasuda G, Ando D, Hirawa N, Umemura S, Tochikubo O. Effects of losartan and amlodipine on urinary albumin excretion and ambulatory blood pressure in hypertensive type 2 diabetic patients with overt nephropathy. Diabetes Care. 2005;28:1862–8. https://doi.org/10.2337/diacare.28.8.1862.

**95** Volpe M, Junren Z, Maxwell T, Rodriguez A, Gamboa R, Gomez-Fernandez P, et al. Comparison of the blood pressure-lowering effects and tolerability of losartan- and amlodipine-based regimens in patients with isolated systolic hypertension. Clin Ther. 2003;25:1469–89. https://doi.org/10.1016/s0149-2918(03)80133-9.

**96** Lee JW, Choi E, Son JW, Youn YJ, Ahn SG, Ahn MS, et al. Comparison of blood pressure variability between losartan and amlodipine in essential hypertension (COMPAS-BPV). Am J Hypertens. 2020;33:748–55. https://doi.org/10.1093/ajh/hpaa060.

**97** Ishimitsu T, Minami J, Yoshii M, Suzuki T, Inada H, Ohta S, et al. Comparison of the effects of amlodipine and losartan on 24-hour ambulatory blood pressure in hypertensive patients. Clin Exp Hypertens. 2002;24:41–50. https://doi.org/10.1081/ceh-100108714.

**98** Wilson TW, Lacourcière Y, Barnes CC. The antihypertensive efficacy of losartan and amlodipine assessed with office and ambulatory blood pressure monitoring. Canadian Cozaar Hyzaar Amlodipine Trial Study Group. CMAJ. 1998;159:469–76.

**99** Dahlöf B, Lindholm LH, Carney S, Pentikäinen PJ, Ostergren J. Main results of the losartan versus amlodipine (LOA) study on drug tolerability and psychological general well-being. LOA Study Group. J Hypertens. 1997;15:1327–35. https://doi.org/10.1097/00004872-199715110-00018.

**100** Oparil S, Barr E, Elkins M, Liss C, Vrecenak A, Edelman J. Efficacy, tolerability, and effects on quality of life of losartan, alone or with hydrochlorothiazide, versus amlodipine, alone or with hydrochlorothiazide, in patients with essential hypertension. Clin Ther. 1996;18:608–25. https://doi.org/10.1016/s0149-2918(96)80212-8.

**101** Fogari R, Maffioli P, Mugellini A, Zoppi A, Lazzari P, Derosa G. Effects of losartan and amlodipine alone or combined with simvastatin in hypertensive patients with nonalcoholic hepatic steatosis. Eur J Gastroenterol Hepatol. 2012;24:164–71. https://doi.org/10.1097/MEG.0b013e32834ba188.

**102** Formica RN, Jr., Friedman AL, Lorber MI, Smith JD, Eisen T, Bia MJ. A randomized trial comparing losartan with amlodipine as initial therapy for hypertension in the early post-transplant period. Nephrol Dial Transplant. 2006;21:1389–94. https://doi.org/10.1093/ndt/gfk058.

**103** Eguchi K, Imaizumi Y, Kaihara T, Hoshide S, Kario K. Comparison of valsartan and amlodipine on ambulatory blood pressure variability in hypertensive patients. Clin Exp Hypertens. 2016;38:721–4. https://doi.org/10.1080/10641963.2016.1200609.

**104** Katada E, Uematsu N, Takuma Y, Matsukawa N. Comparison of effects of valsartan and amlodipine on cognitive functions and auditory p300 event-related potentials in elderly hypertensive patients. Clin Neuropharmacol. 2014;37:129–32. https://doi.org/10.1097/wnf.0000000000000042.

**105** Delles C, Klingbeil AU, Schneider MP, Handrock R, Weidinger G, Schmieder RE. Direct comparison of the effects of valsartan and amlodipine on renal hemodynamics in human essential hypertension. Am J Hypertens. 2003;16:1030–5. https://doi.org/10.1016/j.amjhyper.2003.07.017.

**106** Eguchi K, Kario K, Hoshide Y, Hoshide S, Ishikawa J, Morinari M, et al. Comparison of valsartan and amlodipine on ambulatory and morning blood pressure in hypertensive patients. Am J Hypertens. 2004;17:112–7. https://doi.org/10.1016/j.amjhyper.2003.09.008.

**107** Zhang Y, Agnoletti D, Safar ME, Blacher J. Effect of antihypertensive agents on blood pressure variability: the Natrilix SR versus candesartan and amlodipine in the reduction of systolic blood pressure in hypertensive patients (X-CELLENT) study. Hypertension. 2011;58:155–60. https://doi.org/10.1161/hypertensionaha.111.174383.

**108** Kloner RA, Weinberger M, Pool JL, Chrysant SG, Prasad R, Harris SM, et al. Comparative effects of candesartan cilexetil and amlodipine in patients with mild systemic hypertension. Comparison of Candesartan and Amlodipine for Safety, Tolerability and Efficacy (CASTLE) Study Investigators. Am J Cardiol. 2001;87:727–31. https://doi.org/10.1016/s0002-9149(00)01491-0.

**109** Imbs JL, Nisse-Durgeat S. Efficacy and tolerability of candesartan cilexetil vs. amlodipine as assessed by home blood pressure in hypertensive patients. Int J Clin Pract. 2005;59:78–84. https://doi.org/10.1111/j.1742-1241.2005.00296.x.

**110** Youssef AM, Elghoneimy HA, Helmy MW, Abdelazeem AM, El-Khodary NM. Effect of amlodipine versus bisoprolol in hypertensive patients on maintenance hemodialysis: a randomized controlled trial. Medicine (Baltimore). 2021;100:e28322. https://doi.org/10.1097/md.0000000000028322.

**111** Zanchetti A, Omboni S, La Commare P, De Cesaris R, Palatini P. Efficacy, tolerability, and impact on quality of life of long-term treatment with manidipine or amlodipine in patients with essential hypertension. J Cardiovasc Pharmacol. 2001;38:642–50. https://doi.org/10.1097/00005344-200110000-00017.

**112** Oliván Martinez J, Garcia MJ, Rodriguez Botaro A, Pizarro JL, Carretero J, Garrido M. Bisoprolol and nifedipine SR in the treatment of hypertension in the elderly. J Cardiovasc Pharmacol. 1990;16 Suppl 5:S95–9.

**113** Amabile G, Serradimigni A. Comparison of bisoprolol with nifedipine for treatment of essential hypertension in the elderly: comparative double-blind trial. Eur Heart J. 1987;8 Suppl M:65–9. https://doi.org/10.1093/eurheartj/8.suppl_m.65.

**114** Bueno J, Amiguet JA, Carasusan J, Cebollada J, Carretero J. Bisoprolol vs. chlorthalidone: a randomized, double-blind, comparative study in arterial hypertension. J Cardiovasc Pharmacol. 1990;16 Suppl 5:S189–92.

**115** Adolphe AB, Vlachakis ND, Rofman BA, Brescia D, Zellner SR. Long-term open evaluation of amlodipine vs hydrochlorothiazide in patients with essential hypertension. Int J Clin Pharmacol Res. 1993;13:203–10.

**116** Burris JF, Ames RP, Applegate WB, Ram CV, Davidov ME, Mroczek WJ. Double-blind comparison of amlodipine and hydrochlorothiazide in patients with mild to moderate hypertension. J Cardiovasc Pharmacol. 1988;12 Suppl 7:S98–102. https://doi.org/10.1097/00005344-198812007-00022.

**117** Rofman BA. Long-term open evaluation of amlodipine versus hydrochlorothiazide in patients with essential hypertension. J Cardiovasc Pharmacol. 1988;12 Suppl 7:S94–7. https://doi.org/10.1097/00005344-198812007-00021.

**118** Williams B, MacDonald TM, Morant S, Webb DJ, Sever P, McInnes G, et al. Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomised, double-blind, crossover trial. Lancet. 2015;386:2059–68. https://doi.org/10.1016/s0140-6736(15)00257-3.

Chapter 7

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

**Danuta Czarnecka[a], Katarzyna Stolarz-Skrzypek[a]**
[a]Jagiellonian University Medical College, First Department of Cardiology, Interventional Electrocardiology and Hypertension, Krakow, Poland

**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].

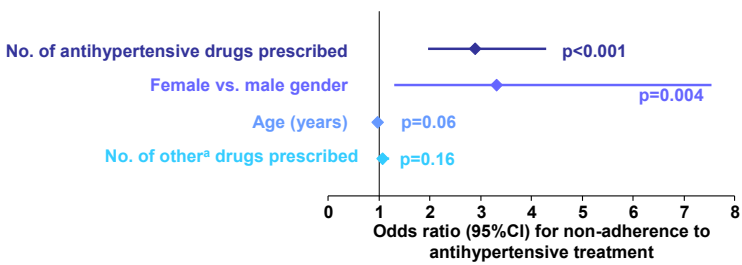
## *Scale of the problem of non-adherence*

### *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

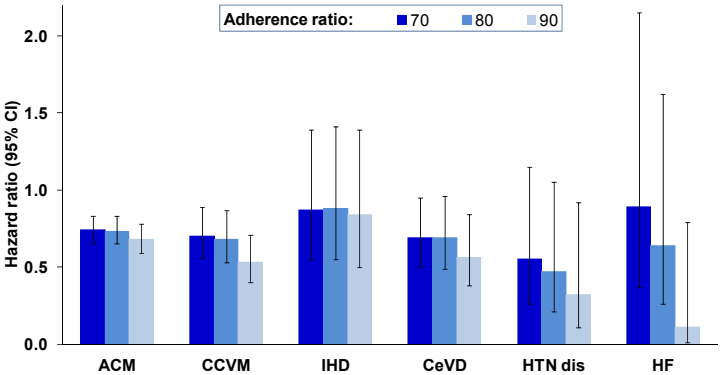
**Table 2 Overview of studies that associated sub-optimal adherence to antihypertensive medications with clinical outcomes.**

| 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*

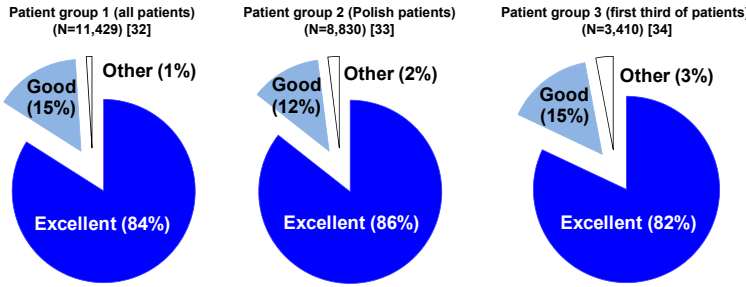
Adherence to therapy was the primary study outcome for a 6-month observational, non-interventional study on the effects of bisoprolol/amlodipine combination tablets in patients with hypertension. Tablet counting was used to measure adherence to therapy in each study [32–34]. For the study, patients with 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].

## References


1 Parati G, Kjeldsen S, Coca A, Cushman WC, Wang J. Adherence to single-pill versus free-equivalent combination therapy in hypertension: a systematic review and meta-analysis. Hypertension. 2021;77:692–705. https://doi.org/10.1161/hypertensionaha.120.15781.

2 Prieto-Merino D, Mulick A, Armstrong C, Hoult H, Fawcett S, Eliasson L, et al. Estimating proportion of days covered (PDC) using real-world online medicine suppliers' datasets. J Pharm Policy Pract. 2021;14:113. https://doi.org/10.1186/s40545-021-00385-w.

3 Burnier M, Egan BM. Adherence in hypertension. Circ Res. 2019;124:1124–40. https://doi.org/10.1161/circresaha.118.313220.

4 Tang KL, Quan H, Rabi DM. Measuring medication adherence in patients with incident hypertension: a retrospective cohort study. BMC Health Serv Res. 2017;17:135. https://doi.org/10.1186/s12913-017-2073-y.

**5** Dhar L, Dantas J, Ali M. A systematic review of factors influencing medication adherence to hypertension treatment in developing countries. Open J Epidemiol 2017;7:73018. https://doi.org/10.4236/ojepi.2017.73018

**6** Gupta P, Patel P, Štrauch B, Lai FY, Akbarov A, Marešová V, et al. Risk factors for nonadherence to antihypertensive treatment. Hypertension. 2017;69:1113–20. https://doi.org/10.1161/hypertensionaha.116.08729.

**7** Tomaszewski M, White C, Patel P, Masca N, Damani R, Hepworth J, et al. High rates of non-adherence to antihypertensive treatment revealed by high-performance liquid chromatography-tandem mass spectrometry (HP LC-MS/MS) urine analysis. Heart. 2014;100:855–61. https://doi.org/10.1136/heartjnl-2013-305063.

**8** Avataneo V, De Nicolò A, Rabbia F, Perlo E, Burrello J, Berra E, et al. Therapeutic drug monitoring-guided definition of adherence profiles in resistant hypertension and identification of predictors of poor adherence. Br J Clin Pharmacol. 2018;84:2535–43. https://doi.org/10.1111/bcp.13706.

**9** Kulkarni S, Rao R, Goodman JDH, Connolly K, O'Shaughnessy KM. Nonadherence to antihypertensive medications amongst patients with uncontrolled hypertension: a retrospective study. Medicine (Baltimore). 2021;100:e24654. https://doi.org/10.1097/md.0000000000024654.

**10** Peacock E, Joyce C, Craig LS, Lenane Z, Holt EW, Muntner P, et al. Low medication adherence is associated with decline in health-related quality of life: results of a longitudinal analysis among older women and men with hypertension. J Hypertens. 2021;39:153–61. https://doi.org/10.1097/hjh.0000000000002590.

**11** Bourque G, Ilin JV, Ruzicka M, Davis A, Hundemer G, Hiremath S. The prevalence of non-adherence in patients with resistant hypertension: a systematic review and meta-analysis. MedRxiv Preprint Server for Health Sciences. 2020. https://doi.org/10.1101/2020.08.14.20175125.

**12** Feng Y, Zhao Y, Yang X, Li Y, Han M, Qie R, et al. Adherence to antihypertensive medication and cardiovascular disease events in hypertensive patients: a dose-response meta-analysis of 2 769 700 participants in cohort study. QJM. 2022;115:279–86. https://doi.org/10.1093/qjmed/hcaa349.

**13** Van Alsten SC, Harris JK. Cost-related nonadherence and mortality in patients with chronic disease: a multiyear investigation, national health interview survey, 2000–2014. Prev Chronic Dis. 2020;17:E151. https://doi.org/10.5888/pcd17.200244.

**14** Shin S, Song H, Oh SK, Choi KE, Kim H, Jang S. Effect of antihypertensive medication adherence on hospitalization for cardiovascular disease and mortality in hypertensive patients. Hypertens Res. 2013;36:1000–5. https://doi.org/10.1038/hr.2013.85.

**15** Lee H, Yano Y, Cho SMJ, Heo JE, Kim DW, Park S, et al. Adherence to antihypertensive medication and incident cardiovascular events in young adults with hypertension. Hypertension. 2021;77:1341–9. https://doi.org/10.1161/hypertensionaha.120.16784.

**16** Kim S, Shin DW, Yun JM, Hwang Y, Park SK, Ko YJ, et al. Medication adherence and the risk of cardiovascular mortality and hospitalization among patients with newly prescribed antihypertensive medications. Hypertension. 2016;67:506–12. https://doi.org/10.1161/hypertensionaha.115.06731.

**17** Corrao G, Parodi A, Nicotra F, Zambon A, Merlino L, Cesana G, et al. Better compliance to antihypertensive medications reduces cardiovascular risk. J Hypertens. 2011;29:610–8. https://doi.org/10.1097/HJH.0b013e328342ca97.

**18** Kim CL, Do YS, Kim BJ, Lee KS, Nah MA, Kim U, et al. Clinical impact of medication adherence on 10-year cardio-cerebrovascular mortality in newly diagnosed hypertensive patients. J Clin Hypertens (Greenwich). 2021;23:1695–702. https://doi.org/10.1111/jch.14320.

**19** Ma LY, He F, Liu S, Wang XD, Gao Y, Shi Z, et al. The association between the prevalence, medication adherence and control of hypertension and the prevalence of mild cognitive impairment in rural northern China: a cross-sectional study. Patient Prefer Adherence. 2022;16:493–502. https://doi.org/10.2147/ppa.S351588.

**20** Khatib R, Schwalm JD, Yusuf S, Haynes RB, McKee M, Khan M, et al. Patient and healthcare provider barriers to hypertension awareness, treatment and follow up: a systematic review and meta-analysis of qualitative and quantitative studies. PLoS One. 2014;9:e84238. https://doi.org/10.1371/journal.pone.0084238.

**21** Macquart de Terline D, Kane A, Kramoh KE, Ali Toure I, Mipinda JB, Diop IB, et al. Factors associated with poor adherence to medication among hypertensive patients in twelve low and middle income Sub-Saharan countries. PLoS One. 2019;14:e0219266. https://doi.org/10.1371/journal.pone.0219266.

**22** Al-Noumani H, Wu JR, Barksdale D, Sherwood G, AlKhasawneh E, Knafl G. Health beliefs and medication adherence in patients with hypertension: a systematic review of quantitative studies. Patient Educ Couns. 2019;102:1045–56. https://doi.org/10.1016/j.pec.2019.02.022.

**23** Buckley L, Labonville S, Barr J. A systematic review of beliefs about hypertension and its treatment among African Americans. Curr Hypertens Rep. 2016;18:52. https://doi.org/10.1007/s11906-016-0662-5.

**24** Marshall IJ, Wolfe CD, McKevitt C. Lay perspectives on hypertension and drug adherence: systematic review of qualitative research. BMJ. 2012;345:e3953. https://doi.org/10.1136/bmj.e3953.

**25** Tan JP, Cheng KKF, Siah RC. A systematic review and meta-analysis on the effectiveness of education on medication adherence for patients with hypertension, hyperlipidaemia and diabetes. J Adv Nurs. 2019;75:2478–94. https://doi.org/10.1111/jan.14025.

**26** Cheema E, Sutcliffe P, Singer DR. The impact of interventions by pharmacists in community pharmacies on control of hypertension: a systematic review and meta-analysis of randomized controlled trials. Br J Clin Pharmacol. 2014;78:1238–47. https://doi.org/10.1111/bcp.12452.

**27** Machado M, Bajcar J, Guzzo GC, Einarson TR. Sensitivity of patient outcomes to pharmacist interventions. Part II: systematic review and meta-analysis in hypertension management. Ann Pharmacother. 2007;41:1770–81. https://doi.org/10.1345/aph.1K311.

**28** Brownstein JN, Chowdhury FM, Norris SL, Horsley T, Jack L, Jr., Zhang X, et al. Effectiveness of community health workers in the care of people with hypertension. Am J Prev Med. 2007;32:435–47. https://doi.org/10.1016/j.amepre.2007.01.011.

**29** Li R, Liang N, Bu F, Hesketh T. The effectiveness of self-management of hypertension in adults using mobile health: systematic review and meta-analysis. JMIR Mhealth Uhealth. 2020;8:e17776. https://doi.org/10.2196/17776.

**30** Zhang W, Cheng B, Zhu W, Huang X, Shen C. Effect of telemedicine on quality of care in patients with coexisting hypertension and diabetes: a systematic review and meta-analysis. Telemed J E Health. 2021;27:603–14. https://doi.org/10.1089/tmj.2020.0122.

**31** Hassanein M. Adherence to antihypertensive fixed-dose combination among Egyptian patients presenting with essential hypertension. Egypt Heart J. 2020;72:10. https://doi.org/10.1186/s43044-020-00044-6.

**32** Hostalek U, Koch EMW. Treatment of hypertension with a fixed-dose combination of bisoprolol and amlodipine in daily practice: results of a multinational non-investigational study. Cardiovasc Disord Med 2016. https://doi.org/10.15761/CDM.1000118.

**33** Hostalek U, Czarnecka D, Koch EM. Treatment of hypertensive patients with a fixed-dose combination of bisoprolol and amlodipine: results of a cohort study with more than 10,000 patients. Cardiol Ther. 2015;4:179–90. https://doi.org/10.1007/s40119-015-0045-z.

**34** Czarnecka D, Koch EM, Gottwald-Hostalek U. Benefits of a fixed-dose combination of bisoprolol and amlodipine in the treatment of hypertension in daily practice: results of more than 4000 patients. Curr Med Res Opin. 2015;31:875–81. https://doi.org/10.1185/03007995.2015.1027676.

**35** Hostalek U, Czarnecka D, Kurzeja A, Koch E. Efficacy of and adherence to a fixed-dose combination of bisoprolol and amlodipine in hypertensive patients with and without type 2 diabetes mellitus or coronary artery disease. J Heart Health 2015b. 2015.

**36** Du LP, Cheng ZW, Zhang YX, Li Y, Mei D. The impact of fixed-dose combination versus free-equivalent combination therapies on adherence for hypertension: a meta-analysis. J Clin Hypertens (Greenwich). 2018;20:902–7. https://doi.org/10.1111/jch.13272.

**37** Kawalec P, Holko P, Gawin M, Pilc A. Effectiveness of fixed-dose combination therapy in hypertension: systematic review and meta-analysis. Arch Med Sci. 2018;14:1125–36. https://doi.org/10.5114/aoms.2018.77561.

**38** Morrissey EC, Durand H, Nieuwlaat R, Navarro T, Haynes RB, Walsh JC, et al. Effectiveness and content analysis of interventions to enhance medication adherence and blood pressure control in hypertension: A systematic review and meta-analysis. Psychol Health. 2017;32:1195–232. https://doi.org/10.1080/08870446.2016.1273356.

**39** Mallat SG, Tanios BY, Itani HS, Lotfi T, Akl EA. Free versus fixed combination antihypertensive therapy for essential arterial hypertension: a systematic review and meta-analysis. PLoS One. 2016;11:e0161285. https://doi.org/10.1371/journal.pone.0161285.

# Chapter 8

# Safety and Tolerability of a Single-Tablet Combination of Bisoprolol and Amlodipine

**Ulrike Gottwald-Hostalek**
Merck Healthcare KGaA, Darmstadt, Germany

**Bisoprolol and amlodipine have been available for therapeutic use in the management of hypertension for more than three decades and their safety and tolerability profiles are well understood. Clinical evaluations of treatment with bisoprolol/amlodipine combinations, including within randomised trials and using real-world evidence, have revealed tolerability profiles consistent with clinical experience from this long period of therapeutic use with both agents, and add further support for a role for this treatment in the management of hypertension.**

## Introduction

Bisoprolol and amlodipine have been available for therapeutic use for the management of hypertension for more than 30 years. The safety and tolerability profiles of these drugs, and the patients in whom they

should and should not be used, are well understood (see Chapter 2 of this book for a summary of the place of bisoprolol and amlodipine in current guidelines for the management of hypertension). This chapter reviews the safety and tolerability of these agents, with respect to both clinical evaluations of bisoprolol/amlodipine combination tablets in patients with hypertension, and their individual therapeutic properties as described in the clinical literature.

## General tolerability and safety profiles of bisoprolol and amlodipine

### *Most common side effects*

The all-cause side effects for bisoprolol and amlodipine, listed in the European Summary of Product Characteristics (SmPC) for the bisoprolol/amlodipine combination tablet are shown in Table 1. Most of the side effects listed in Table 1 are "uncommon" (occurring in <1% of patients; less frequent side-effects were omitted from the table for conciseness and clarity). Among "common" side-effects of bisoprolol (occurring in at least 1% but <10% of patients), dizziness, headache, and fatigue are described as occurring mainly early in treatment. A similar statement is made for dizziness and fatigue for amlodipine. Other "common" side-effects are gastrointestinal symptoms (both agents), cold/numb extremities (bisoprolol), fatigue/asthenia, symptoms associated with vasodilatation (palpitation, manifestations of peripheral oedema, flushing), dyspnoea, muscle symptoms, and visual disturbances (amlodipine). Oedema is the only "very common" adverse event (occurring in at least 10% of patients treated with a combination of bisoprolol and amlodipine).

It has been suggested that a nocebo effect may apply to some side effects of β-blockers, where patients prescribed one of these drugs are willing to ascribe the presence of some pre-existing symptoms to the new treatment after being briefed by the prescribing physician on the possibility of it occurring [1, 2]. A systematic review found that, of 100 patients reporting stated side effects, a majority of cases were unlikely to be

**Table 1 Summary of all-cause 'Uncommon', 'Common', and '*Very common*' side effects of bisoprolol/amlodipine combination tablets from European prescribing documentation.**

| Body system | Related to bisoprolol | Related to amlodipine |
|---|---|---|
| **Psychiatric** | Depression, sleep disorders | Mood changes (incl. anxiety), depression, insomnia |
| **Nervous system** | **Dizziness[a], headache[a]** | Tremor, dysgeusia, syncope, hypoesthesia, paraesthesia, **somnolence, dizziness, headache[a]** |
| **Eye** | – | **Visual disturbances, incl. diplopia** |
| **Ear and labyrinth** | – | Tinnitus |
| **Cardiac** | Atrioventricular conduction disorders, deterioration of existing heart failure, bradycardia | Arrhythmia[b], **palpitation** |
| **Vascular** | Hypotension, **cold/numb extremities** | Hypotension, **flushing** |
| **Respiratory, thoracic and mediastinal** | Bronchospasm in patients with history of bronchial asthma or COPD | Cough, rhinitis, **dyspnoea** |
| **Gastrointestinal** | **GI disturbances, e.g. nausea, vomiting, diarrhoea, constipation** | Vomiting, dry mouth, **GI disturbances, e.g. abdominal pain, nausea, dyspepsia, altered bowel habits** |
| **Skin and subcutaneous tissues** | – | Alopecia, purpura, skin discoloration, hyperhydrosis, pruritis, rash, exanthema, urticaria |
| **Musculoskeletal and connective tissue** | Muscle weakness, cramps | Arthralgia, myalgia, back pain, **ankle swelling, muscle cramps** |
| **Renal and urinary** | – | Micturition disorder, nocturia, increased urinary frequency |
| **Reproductive system and breast** | – | Impotence, gynaecomastia |
| **General/ administration site conditions** | Asthenia[a], **fatigue[a]** | Chest pain, pain, malaise, **fatigue, asthenia, *oedema*** |

GI: gastrointestinal; incl.: including.
[a]Especially at the beginning of treatment.
[b]Including bradycardia, ventricular tachycardia, atrial fibrillation.
Uncommon = prevalence in ≥0.1% and <1% of patients; Common = prevalence in ≥1% and <10% of patients; Very common = prevalence in ≥10% of patients.
Less common side effects: Rare = ≥0.01% and <0.1% of patients; Very rare = ≥0.001% and <0.01% of patients. These side effects are not shown here for conciseness – see the full Summary of Product Characteristics for more details.
Data source: Summary of Product Characteristics for Concor AMLO tablets (Merck Healthcare KGaA, Darmstadt, Germany).

associated with β-blockade, e.g. for dizziness, 81% of cases (95% confidence interval [CI], 73 to 89%) were likely to have developed it on placebo, for diarrhoea 82% (95% CI, 70 to 95%), and for hyperglycaemia 83% (95% CI, 68 to 98%) [3]. Six commonly cited side effects of β-blockers were less common with β-blockers compared to placebo. Bradycardia (33% of cases [95% CI, 21 to 44%]) and intermittent claudication (41% [95% CI, 2 to 81%]) were more clearly associated with β-blockade, though it should be noted that this analysis was not limited to cardioselective $\beta_1$-adrenoceptor blockers. Some of the more common side effects of these agents are considered in more detail below:

**Peripheral oedema** is a well-known side-effect of calcium channel blockers, including dihydropyridines such as amlodipine [4]. Oedema is the only side effect of bisoprolol/amlodipine combination tablets that is listed as "very common" in Table 1. A meta-analysis of 22 trials, including 7,226 patients, showed that the risk of peripheral oedema with amlodipine was 2.9-fold higher versus placebo ($p<0.0001$); however, further analysis suggested that 37% of these events were unrelated to amlodipine treatment [5]. The incidence of oedema on amlodipine was dose related, with a 2.0-fold increase versus placebo at a dose of 2.5–5 mg, compared with a 3.1-fold increase at a dose of 10 mg ($p<0.0001$ for each). Bisoprolol is not associated with peripheral oedema.

**Headache** is a common symptom of bisoprolol and amlodipine that is described as occurring more frequently at the beginning of treatment and tends to disappear on continued treatment (Table 1). Headache of varying aetiology is a common symptom of hypertension and may be driven in part by activation of the renin-angiotensin-aldosterone system [6, 7]. A systematic review in this area described a reduction in the frequency of headache with several antihypertensive drug classes, with β-blockers being most effective in this regard [8]. Indeed, β-blockers, including bisoprolol, may reduce the frequency of headache of different aetiologies [9–11]. Channel blockers were ineffective on headache frequency in the meta-analysis described above [5]. However, another recent meta-analysis stratified patients by the dose of amlodipine [2]. The incidence of headache was not increased for amlodipine 10 mg versus placebo in the meta-analysis described above (risk ratio: 0.92

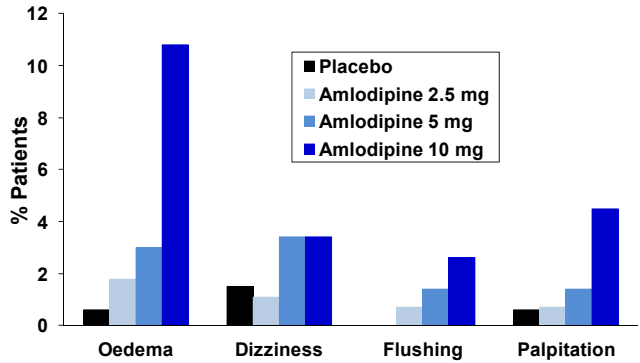
[95% CI, 0.74 to 1.15]), and was reduced versus placebo at a dose of 2.5–5 mg (risk ratio: 0.52 (95% CI, 0.40 to 0.69) [2].

**Dizziness** is another common side effect associated with antihypertensive therapy, as well as many other causes [12]. A review of spontaneous reports of adverse events to a pharmacovigilance database found associations with dizziness for all antihypertensive classes except β-blockers [13]. However, this side effect is known to occur with bisoprolol and amlodipine, typically early in therapy (Table 1). It is important to identify and intervene to correct more severe presentations of dizziness, as this is associated much more strongly with serious adverse outcomes such as falls in older, vulnerable individuals [9]. As a highly selective $\beta_1$-adrenoceptor blocker, bisoprolol does not cause marked peripheral vasodilatation [14, 15]. In one retrospective study in patients with heart failure, for whom it was not possible to increase the dose of a vasodilating β-blocker (carvedilol), all 13 patients with dizziness as a limiting factor, and 9/15 patients with hypotension as a limiting factor, could be safely switched to bisoprolol [16].

## *Dose-relationship of side effects*

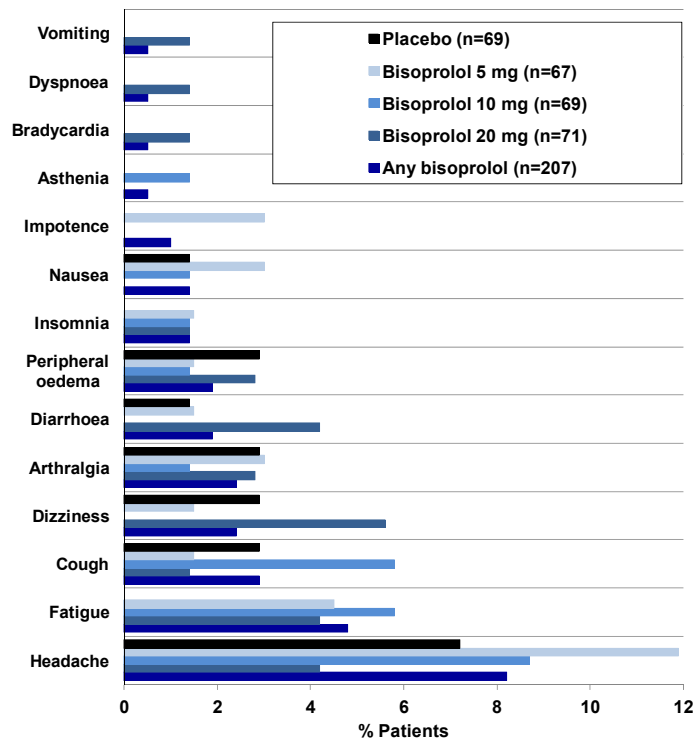
Figure 1 shows the incidence of dose-related side effects with amlodipine from clinical trials that compared amlodipine directly with placebo using the United States (US) label of a marketed formulation of this drug (N=1,750 and N=1,250, respectively) [17]. The incidence of oedema and palpitation rose steeply at a dose of amlodipine 10 mg, while the incidence of the other side effects remained relatively low. A systematic review of the tolerability of different doses of bisoprolol within the permitted dosage range in Europe is not available. The side effects of bisoprolol were not clearly dose related in a randomised comparison of bisoprolol 5–20 mg versus placebo (Figure 2) [18]. This is especially the case for bisoprolol dosages of 5–10 mg, which is the range of bisoprolol doses used in the bisoprolol/amlodipine combination tablets, and 10 mg is the usual maximum dose of bisoprolol. The data for bisoprolol 20 mg is shown here for completeness, and to help highlight any dose-relationship of side effects that may have been present.

**Figure 1 Dose-relationship of side effects of amlodipine [14].**




Drawn from data presented in the US label of a marketed formulation. These were the only side effects considered to be dose-related in this analysis.

**Figure 2 Dose relationship of side effects of bisoprolol [15].**




Drawn from data presented in reference [15].

## Contraindications and precautions when prescribing bisoprolol/amlodipine combination tablets

Contraindications and precautions relating to the therapeutic use of bisoprolol/amlodipine combination tablets are summarised in Table 2. Contraindications for bisoprolol relate mainly to exacerbation of acute or decompensated heart failure, bradycardia or intracardiac conduction block, or use in severe bronchial asthma. Contraindications to amlodipine mostly reflect concern over exacerbation of heart failure and also situations where blood pressure (BP) may become dangerously low (hypotension, shock, and aortic stenosis).

Precautions for the use of these agents reflect similar potential concerns (uncontrolled heart failure for both, and atrioventricular conduction block for bisoprolol). Additionally, bisoprolol should be used with caution where there is a high risk of hypoglycaemia, as sympathetic activation is an important part of the counter regulatory response to low blood glucose [19]. Other precautions include situations where any level of $\beta_2$-adrenoceptor blockade would be harmful (peripheral artery occlusive disease and obstructive airways disease). With regard to the latter, the use of bisoprolol is supported for patients with less severe obstructive airways disease where there is a compelling indication for its use (e.g. angina, post-myocardial infarction, or heart failure), as bisoprolol's highly selective $\beta_1$-adrenoceptor blockade would not be expected to constrict the bronchi (a $\beta_2$-adrenoceptor-mediated effect) at usual therapeutic doses [12]. Consistent with these observations, a network meta-analysis of 14 randomised trials and 23 observational studies found that among seven β-blockers evaluated, only propranolol (a non-cardioselective β-blocker) reduced forced expiratory volume in 1 second significantly, while bisoprolol, atenolol, labetalol, celiprolol, metoprolol, and carvedilol did not [20].

**Table 2 Contraindications and precautions relating to the use of bisoprolol/amlodipine combination tablets from European prescribing information.**

| | Related to the bisoprolol component | Related to the amlodipine component |
|---|---|---|
| **Contraindications** | Acute HF<br>Episodes of decompensated HF requiring inotropic therapy<br>Sick sinus syndrome<br>Sinoatrial block<br>Symptomatic bradycardia<br>Symptomatic hypotension<br>Severe bronchial asthma<br>Severe peripheral occlusive disease (incl. severe forms of Raynaud's syndrome)<br>Untreated pheochromocytoma<br>Metabolic acidosis | Severe hypotension<br>Shock (incl. cardiogenic shock)<br>Left ventricular outflow obstruction (e.g. high grade aortic stenosis)<br>Haemodynamically unstable HF |
| **Warnings and precautions** | | |
| **Patients with heart failure** | Use with caution in hypertension angina associated with HF | Use with caution (pulmonary oedema has been observed with amlodipine in patients with severe HF). |
| **Patients with IHD** | Do not withdraw therapy abruptly<br>Use with caution in Prinzmetal's angina | – |
| **Hepatic impairment** | – | Use with caution (elimination is prolonged but dose adjustments have not been established in these patients) |
| **Renal impairment** | – | -- |
| **Elderly** | – | Use caution when increasing the dose |
| **Diabetes** | Use with caution where glucose levels fluctuate severely (may mask symptoms of hypoglycaemia) | – |
| **Obstructive airway diseases** | Avoid unless compelling indication (then use with caution) | – |
| **Other areas requiring cautious use** | 1st degree AV block<br>Peripheral occlusive artery disease<br>Psoriasis<br>Hyperthyroidism (may mask symptoms)<br>Concomitant allergen desensitisation<br>Potential for interactions with other drugs in the peri-operative period (promotion of bradycardia or reflexes to compensate for blood loss) | – |

AV: atrioventricular; HF: heart failure; IHD: ischaemic heart disease.
Hypersensitivity to any component of the tablet is also a contraindication; omitted from the table for conciseness.
Contents of the table are paraphrased: please see the full Summary of Product Characteristics before prescribing.
Data source: Summary of Product Characteristics for Concor AMLO tablets (Merck Healthcare KGaA, Darmstadt, Germany).

## Tolerability and safety in clinical evaluations of bisoprolol/amlodipine combination tablets

Three randomised trials and three observational studies have provided data on the tolerability and safety of bisoprolol/amlodipine combination tablets (Table 3) [21–26]. One of these studies compared a free combination of bisoprolol and amlodipine with placebo and amlodipine in patients with BP sub-optimally controlled on amlodipine monotherapy [22]. As the bisoprolol and amlodipine components of the combination tablet have been shown to be bioequivalent with commercial formulations of these agents, the tolerability findings are directly comparable with the findings of studies that evaluated bisoprolol/amlodipine combination tablets.

The incidence of side effects was low in these studies. The more common side effects reported included those typical of a β-blocker and vasodilatory calcium channel blocker, (e.g. bradycardia, headache, and oedema), as described above. The low incidence of side effects in these studies likely reflects the prior treatment received by the populations of most of the trials with bisoprolol and/or amlodipine.

## Conclusions

Bisoprolol and amlodipine have been effective and well tolerated therapeutic options within the management of hypertension for decades. Their side effect profiles, contraindications, and precautions for use are well known and understood. Clinical evaluations of treatment with bisoprolol/amlodipine combinations have revealed tolerability profiles consistent with clinical experience from this long period of therapeutic use with both agents. Moreover, this evidence was from both randomised, controlled trials (the 'gold standard' for clinical evidence) and from real-world evaluations (that add valuable information on the therapeutic profile of a drug in routine clinical practice, away from the often restrictive inclusion and exclusion criteria of randomised trials [27]). These studies confirm that patients can be switched safely to the bisoprolol/amlodipine combination tablets from either monotherapy with either

**Table 3 Overview of safety and tolerability findings reported in clinical evaluations of bisoprolol plus amlodipine combinations.**

| | Prior therapy | Any AE (%) | Most common AE | Serious AE (%) | Discont. for AE (%) | Deaths |
|---|---|---|---|---|---|---|
| ***Randomised trials*** | | | | | | |
| 21 | Bisoprolol 5 mg or amlodipine 5 mg | 74.5[a] | **B + A combination tablets[a]:** Sinus bradycardia (27.5%)[b] Other bradycardia (14.5%)[b] Peripheral oedema (8.5%)[b] | 1.5 | 3 | 2 deaths[c] |
| 22 | Amlodipine 5 mg QD | B+A[d]: 12.7 Placebo[d]: 11.8 | **B + A free combination[a,e]:** Oedema (2.2%) Headache (1.6%) **Placebo**: No individual AE occurred in >2 patients | B+A[d]: 6.6 Plac[d]: 3.2 | B+A[d]: 6.6 Plac[d]: 3.20 | No deaths |
| 23 | None | Not reported | No significant impact on laboratory parameters | Not reported | Not reported | Not reported |
| ***Observational studies*** | | | | | | |
| 24 | Bisoprolol + amlodipine (free combination) | Not reported (total of 101 AE) | **B + A combination tablets[f]:** Swelling (0.2%) Joint swelling (0.1%) Bradycardia (0.04%) Dizziness (0.04%) Headache (0.04%) | 0.1 | 0.1 | 1 death[c] |
| 25 | Not reported | Not reported | **B + A combination tablets[e,f]:** Oedema (7.5%)[e] Headache (3.8%)[e] Fatigue (2.8%)[e] Leg cramps (2.8%) | 0 | 0 | No deaths |
| 26 | Amlodipine, ramipril or atenolol | Not reported | **B + A combination tablets[e,f]:** Oedema (8%) Headache (4%) Fatigue (3%) Leg cramps (3%) | 0 | 0 | No death |

A: amlodipine; AE: adverse event; B: bisoprolol; discont.: discontinued; QD: daily.
[a]There was no active comparator in this trial, patients were randomised to combination tablets incorporating different dosage strengths of amlodipine and bisoprolol (see Chapter 6 for more details).
[b]Treatment-related AE.
[c]Unrelated to treatment.
[d]Patients uncontrolled on amlodipine 5 mg were randomised to additional placebo or additional amlodipine
[e]Occurring in at least 3 patients.
[f]Observational study with no comparator group.

agent (for increased efficacy, see Chapter 6 of this book) or from pre-existing free combinations of bisoprolol and amlodipine (to simplify regimens to support good adherence to therapy, see Chapter 7), depending on the local label. The data on the tolerability profile of bisoprolol/amlodipine combination therapy summarised in this Chapter adds further support for the role of this treatment in the management of hypertension.

## References


1 Arnaout MS, Almahmeed W, Ibrahim M, Ker J, Khalil MT, Van Wyk CT, et al. Hypertension and its management in countries in Africa and the Middle East, with special reference to the place of β-blockade. Curr Med Res Opin. 2011;27:1223–36. https://doi.org/10.1185/03007995.2011.576239.

2 Silvestri A, Galetta P, Cerquetani E, Marazzi G, Patrizi R, Fini M, et al. Report of erectile dysfunction after therapy with beta-blockers is related to patient knowledge of side effects and is reversed by placebo. Eur Heart J. 2003;24:1928–32. https://doi.org/10.1016/j.ehj.2003.08.016.

3 Barron AJ, Zaman N, Cole GD, Wensel R, Okonko DO, Francis DP. Systematic review of genuine versus spurious side-effects of beta-blockers in heart failure using placebo control: recommendations for patient information. Int J Cardiol. 2013;168:3572–9. https://doi.org/10.1016/j.ijcard.2013.05.068.

4 Liang L, Kung JY, Mitchelmore B, Cave A, Banh HL. Comparative peripheral edema for dihydropyridines calcium channel blockers treatment: a systematic review and network meta-analysis. J Clin Hypertens (Greenwich). 2022;24:536–54. https://doi.org/10.1111/jch.14436.

5 Vukadinović D, Scholz SS, Messerli FH, Weber MA, Williams B, Böhm M, et al. Peripheral edema and headache associated with amlodipine treatment: a meta-analysis of randomized, placebo-controlled trials. J Hypertens. 2019;37:2093–103. https://doi.org/10.1097/hjh.0000000000002145.

6 Mohammadi M, Ayoobi F, Khalili P, Soltani N, La Vecchia C, Vakilian A. Relation of hypertension with episodic primary headaches and chronic primary headaches in population of Rafsanjan cohort study. Sci Rep. 2021;11:24071. https://doi.org/10.1038/s41598-021-03377-7.

7 Parfenov V.A., Ostroumova T.M., Ostroumova O.D. Hypertension and headache: the effect of antihypertensive drugs. Ration Pharmacother Cardiol. 2019;15:416–23. https://doi.org/doi.org/10.20996/1819-6446-2019-15-3-416-423.

8 Webb AJ, Rothwell PM. The effect of antihypertensive treatment on headache and blood pressure variability in randomized controlled trials: a systematic review. J Neurol. 2012;259:1781–7. https://doi.org/10.1007/s00415-012-6449-y.

9 Sándor PS, Afra J, Ambrosini A, Schoenen J. Prophylactic treatment of migraine with beta-blockers and riboflavin: differential effects on the intensity dependence of auditory evoked cortical potentials. Headache. 2000;40:30–5. https://doi.org/10.1046/j.1526-4610.2000.00005.x.

10 Ha H, Gonzalez A. Migraine headache prophylaxis. Am Fam Physician. 2019;99:17–24.

11 Jackson JL, Cogbill E, Santana-Davila R, Eldredge C, Collier W, Gradall A, et al. A comparative effectiveness meta-analysis of drugs for the prophylaxis of migraine headache. PLoS One. 2015;10:e0130733. https://doi.org/10.1371/journal.pone.0130733.

12 Kammerlind AS, Ernsth Bravell M, Fransson EI. Prevalence of and factors related to mild and substantial dizziness in community-dwelling older adults: a cross-sectional study. BMC Geriatr. 2016;16:159. https://doi.org/10.1186/s12877-016-0335-x.

**13** Chimirri S, Aiello R, Mazzitello C, Mumoli L, Palleria C, Altomonte M, et al. Vertigo/dizziness as a drugs' adverse reaction. J Pharmacol Pharmacother. 2013;4:S104–9. https://doi.org/10.4103/0976-500x.120969.
**14** Wollam GL, Cody RJ, Jr., Tarazi RC, Bravo EL. Acute hemodynamic effects and cardioselectivity of acebutolol, practolol, and propranolol. Clin Pharmacol Ther. 1979;25:813–20. https://doi.org/10.1002/cpt1979256813.
**15** Poirier L, Tobe SW. Contemporary use of β-blockers: clinical relevance of subclassification. Can J Cardiol. 2014;30:S9–s15. https://doi.org/10.1016/j.cjca.2013.12.001.
**16** Taniguchi T, Ohtani T, Mizote I, Kanzaki M, Ichibori Y, Minamiguchi H, et al. Switching from carvedilol to bisoprolol ameliorates adverse effects in heart failure patients with dizziness or hypotension. J Cardiol. 2013;61:417–22. https://doi.org/10.1016/j.jjcc.2013.01.009.
**17** Food and Drug Administration. Amlodipine besylate: highlights of prescribing information. 2007. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2007/019787s042lbl.pdf Accessed June 2022.
**18** Davidov ME, Singh SP, Vlachakis ND, Blumenthal JB, Simon JS, Bryzinski BS, et al. Bisoprolol, a once-a-day beta-blocking agent for patients with mild to moderate hypertension. Clin Cardiol. 1994;17:263–8. https://doi.org/10.1002/clc.4960170509.
**19** Hoffman RP. Sympathetic mechanisms of hypoglycemic counterregulation. Curr Diabetes Rev. 2007;3:185–93. https://doi.org/10.2174/157339907781368995.
**20** Gulea C, Zakeri R, Alderman V, Morgan A, Ross J, Quint JK. Beta-blocker therapy in patients with COPD: a systematic literature review and meta-analysis with multiple treatment comparison. Respir Res. 2021;22:64. https://doi.org/10.1186/s12931-021-01661-8.
**21** Gottwald-Hostalek U, Li L, Montenegro P. Bisoprolol/amlodipine combination therapy improves blood pressure control in patients with essential hypertension following monotherapy failure. Curr Med Res Opin. 2016;32:1735–43. https://doi.org/10.1080/03007995.2016.1205573.
**22** Jedrusik P, Placha G, Gaciong Z. Efficacy and safety of bisoprolol 5 mg plus amlodipine 5 mg in patients with hypertension uncontrolled on monotherapy with 5 mg of amlodipine, a phase III multicentre, randomized, double-blind, placebo-controlled clinical trial—the AMCOR study. In press
**23** Shirure PA, Tadvi NA, Bajait CS, Baig MS, Gade PR. Comparative effect of fixed dose combination of Amlodipine + Bisoprolol versus Amlodipine and Bisoprolol alone on blood pressure in stage-2 essential hypertensive patients. Int J Med Res Health SCi 2012;1(1):12–9.
**24** Hostalek U, Koch EMW. Treatment of hypertension with a fixed-dose combination of bisoprolol and amlodipine in daily practice: results of a multinational non-investigational study. Cardiovasc Disord Med 2016;1. https://doi.org/10.15761/CDM.1000118.
**25** Mehta S, Shah M, Shah A. Efficacy and tolerability of a fixed dose combination of amlodipine and bisoprolol in essential hypertension. Indian Pract. 2005;58:751–9.
**26** Rana R, Patil A. Efficacy and safety of bisoprolol plus amlodipine fixed dose combination in essential hypertension. Indian Pract. 2008;61:225–34.
**27** Blonde L, Khunti K, Harris SB, Meizinger C, Skolnik NS. Interpretation and impact of real-world clinical data for the practicing clinician. Adv Ther. 2018;35:1763–74. https://doi.org/10.1007/s12325-018-0805-y.

# Chapter 9

# Clinical Outcomes with Bisoprolol and Amlodipine: Current Status and Future Prospects

**Yi-Heng Li**
Division of Cardiology, National Cheng Kung University Hospital, Tainan, Taiwan

**Both β-blockade and calcium channel blockade has been shown to improve clinical outcomes in hypertension and other cardiovascular conditions. Most people with hypertension receive combination antihypertensive therapy, and β-blockers and calcium channel blockers will play an important role in the combination regimens of many patients with hypertension.**

## Introduction

The goal of antihypertensive treatment is to reduce the risk of the long-term, adverse cardiovascular outcomes associated with high blood pressure (BP), such as myocardial infarctions (MIs), strokes, and chronic kidney disease, among others. Chapter 1 of this book details the association between hypertension and its cardiovascular complications. The purpose of this chapter is to review the strengths and limitations of β-blockers

and calcium channel blockers (CCBs) with regard to improving clinical outcomes in people with hypertension.

# Clinical evidence for improved clinical outcomes with β-blockers and CCBs

## *β-blockers (including bisoprolol)*

### *β-blockers in hypertension*

Bisoprolol has never been evaluated in a randomised outcome trial in people with hypertension. Accordingly, this section will review the evidence for the effects of β-blockers as a class on outcomes in populations with hypertension, followed by a summary of indirect evidence relating to bisoprolol itself and cardiovascular outcomes.

Multiple meta-analyses have compared β-blockers with placebo (or no treatment) or members of other antihypertensive classes and Table 1 shows recent examples of these, published since 2015 [1–7]. Overall, there is clear evidence for a reduction in the risk of major adverse cardiovascular events and other adverse outcomes with β-blockers versus placebo or no treatment. Evidence for an effect on mortality was conflicting, and several analyses suggested that CCBs were more effective in preventing strokes than β-blockers (although β-blockers themselves reduced the risk of stroke compared with placebo). Another meta-analysis, not shown in Table 1, showed that members of any class of antihypertensive agent reduced the risk of stroke in patients at high risk of adverse cardiovascular outcomes (mostly due to the presence of pre-existing cardiovascular disease) [8].

There was no significant difference in effects on all-cause or cardiovascular mortality, or all-cause or cardiovascular hospitalisation between bisoprolol (highly selective $\beta_1$-adrenoceptor blocker) and nebivolol (a "third generation" $\beta_1$-adrenoceptor blocker, i.e. with additional vasodilator actions) in a head-to-head randomised comparison involving 1 year of treatment [9]. Consistent with these findings, a large database analysis found no significant differences in the risk of acute MI, stroke

**Table 1 Overview of large, recent meta-analyses that compared the effects of β-blockers with placebo or no treatment, or members of other antihypertensive classes.**

| Author [Ref] | Trials | Patients | Main findings |
|---|---|---|---|
| Thomopoulos et al [1] | 67 | 68,478 | Benefit vs. placebo[a] for stroke (RR 0.77 [0.61 to 0.97]), HF (RR 0.57 [0.35 to 0.91]), stroke + CHD (RR 0.84 [0.74 to 0.95]), stroke + CHD + HF (RR 0.78 [0.64 to 0.96]) in populations with hypertension; no significant effect vs. placebo[a] on CHD or CV or all-cause mortality. |
| Wiysonge et al [2,3] | 4[b] | 23,613 | β-blockers were more effective vs. placebo[a] for CVE (RR 0.88 [0.79 to 0.97]) and stroke (RR 0.80 [0.66 to 0.96]); no significant benefit for all-cause mortality or CHD.<br>CCBs more effective vs. β-blockers for preventing stroke (RR 1.07 [1.0 to 1.14]), CVE (RR 1.18 [1.08 to 1.29]) and all-cause mortality (RR 1.07 [1.0 to 1.14]); no significant difference for CHD.<br>RAAS blockers more effective vs. β-blockers for preventing stroke (RR 1.30 [1.11 to 1.53]); no significant benefit for all-cause mortality, CVE or CHD.<br>No significant difference between β-blockers and diuretics for all outcomes. |
| Emdin et al [4] | 45[c] | 100,354 | Similar effects of members of different antihypertensive classes on outcomes in people with T2D except for apparent benefit for CCBs on stroke (higher risk with β-blocker), and lower risk of HF with diuretics or ARBs. |
| Ettehad et al [5] | 123 | 613,815 | β-blockers were less effective than other antihypertensive classes for prevention of MACE, stroke, and renal failure.<br>Calcium channel blockers were superior to other drugs for the prevention of stroke. |
| Thomopoulos et al [6] | 50 | 247,006 | β-blockers were less effective for reducing stroke vs. CCBs, ARBs or all RAAS blockers (there was no comparison between β-blockers and ACEI).<br>No significant differences between β-blockers and other antihypertensive classes or effects on CHD, HF, stroke + CHD, stroke + CHD + HF, CV mortality, or all-cause mortality. |
| Vögele et al [7] | 5[d] | 8,019 | No significant difference between β-blockers and placebo[a] on a composite outcome of death, MI or stroke (RR 0.89 [0.75–1.05]).<br>Benefit for β-blockers vs. placebo[a] on nonfatal stroke (RR 0.78 [0.63 to 0.98]) and HF (RR 0.54 [0.37 to 0.81]); no difference for death or nonfatal MI.<br>β-blockers less effective than other antihypertensive classes (pooled) for nonfatal stroke (RR 1.18, [1.07–1.30]); no difference for death, nonfatal MI, HF. |

[a]Or no treatment. [b]Evaluations of β-blockers vs. placebo or no treatment for the first-line treatment of hypertension. [c]Studies in people with type 2 diabetes. [d]Evaluated effects in patients aged ≥65 y. ACEI: angiotensin-converting enzyme inhibitors; ARB: angiotensin receptor blockers; CCB: calcium channel blocker(s); CHD: coronary heart disease; CV: cardiovascular; CVE: CV events; HF: heart failure; MACE: major adverse cardiac events; MI: myocardial infarction; RAAS: renin-angiotensin-aldosterone system; Ref: reference; RR: risk ratio; T2D: type 2 diabetes; vs.: versus; y: year. Numbers in square parentheses are 95% confidence intervals.

or hospitalisation for heart failure between two third-generation β-blockers (nebivolol and carvedilol) and atenolol, a cardioselective β-blocker with lower selectivity for $\beta_1$- versus $\beta_2$-adrenoceptors than bisoprolol (see Chapter 4 of this book for a discussion of cardioselectivity) [10]. Evidence for an additional beneficial effect on clinical outcomes associated with the additional vasodilator properties (stimulation of nitric oxide production for nebivolol and α-adrenoceptor blockade for carvedilol) is lacking [11, 12].

## *β-blockers in other cardiovascular diseases*

The clinical evidence for improved clinical outcomes with β-blockers in patients with stable heart failure or ischaemic heart disease (IHD) is well established [12]. Indeed, β-blockers are recommended as part of the therapeutic regimen for these patients in international guidelines [13–15].

The evidence base for bisoprolol in the management of heart failure was established by the three randomised Cardiac Insufficiency Bisoprolol Study (CIBIS) trials [16–18]. CIBIS I demonstrated symptomatic improvement in patients with heart failure randomised to bisoprolol or to placebo, but had insufficient power to evaluate effects on hard clinical endpoints [16]. CIBIS II was larger, and demonstrated statistically and clinically significant improvements for bisoprolol versus placebo in all-cause mortality (hazard ratio [HR] 0.66, 95% confidence interval [95% CI] 0.54 to 0.81, $p<0.0001$) and sudden deaths (HR 0.56 [95% CI 0.39 to 0.80], $p=0.0011$) [17]. These were interim findings, as the study was stopped early, as routine data monitoring indicated that its primary endpoint (reduction in mortality) had been met. Finally, CIBIS III demonstrated that clinical outcomes did not differ importantly whether bisoprolol was administered before or after an angiotensin converting enzyme (ACE) inhibitor [18].

Meta-analysis supports the benefit of β-blockers in patients with IHD, including after application of percutaneous coronary intervention and in patients receiving an ACE inhibitor [19–23]. The Total Ischemic Burden Bisoprolol Study involved randomisation of 330 patients with stable angina, a positive exercise test and ≥2 documented episodes of

myocardial ischaemia during the previous 2 days to bisoprolol or nifedipine (a short-acting CCB) [24, 25]. Patients randomised to bisoprolol versus nifedipine demonstrated fewer episodes of ischaemia and a lower risk of a composite cardiac outcome at 1 year.

## *Amlodipine*

### *Amlodipine in hypertension*

Table 2 summarises three major randomised cardiovascular outcomes trials that evaluated amlodipine in patients with hypertension [26–29]. All of these trials enrolled populations at elevated cardiovascular risk due to the presence of hypertension and one or more risk factors for adverse cardiovascular outcomes.

The large **Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) trial** randomised more than 30,000 people with hypertension to amlodipine, a thiazide diuretic, or an ACE inhibitor [26]. There were no significant differences between treatments in the incidence of the primary cardiovascular endpoint in ALLHAT.

**The Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial** involved randomisation of a hypertensive patient population to either amlodipine or to an angiotensin receptor blocker (ARB), valsartan [27]. There was no significant difference between treatments in the incidence of the primary composite cardiovascular endpoint at the end of the trial. However, there were fewer MIs in the amlodipine versus valsartan groups (HR 1.19, p=0.02), with a trend towards a lower risk of stroke with amlodipine (HR 1.15, p=0.08). Differences in BP lowering between the study arms, in particular during the first year, has been advanced as a possible explanation for these observations [30].

**The Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA)** was a randomised comparison of the effects on clinical outcomes of treatment based on amlodipine versus atenolol in high-risk hypertensive subjects [28]. This trial differed from ALLHAT and VALUE, as an element of combination therapy was factored into the design of the study: patients uncontrolled on

**Table 2 Principal randomised evaluations of the effects of amlodipine on clinical outcomes.**

| Trial (year[a]) | Study arms | Follow-up (y)[b] | Primary outcome | Main findings |
|---|---|---|---|---|
| ALLHAT (2002) [10] (N=33,357) | Amlodipine Chlorthalidone Lisinopril[c] | 4.9 | Composite: fatal CHD + nonfatal MI | No significant differences in the primary outcome (RR vs chlorthalidone was 0.98 [0.90 to 1.07] for amlodipine and 0.99 [0.91 to 1.08] for lisinopril. Also no differences between groups for mortality (secondary outcome). |
| VALUE (2004) [27] (N=15,245) | Amlodipine Valsartan | 4.5 | Cardiac morbidity/ mortality[f] | No difference overall between treatment groups for the primary endpoint (HR 1.04 [94 to 1.15]). An apparent early excess of MI events in the valsartan arm is unexplained but has been attributed to slower BP lowering vs amlodipine. |
| ASCOT-BPLA (2005) [28] (N=19,257) | Amlodipine[d] Atenolol[d] | 5.5[e] | Composite: fatal CHD + nonfatal MI | Trend in favour of amlodipine- vs atenolol-based therapy for primary outcome (HR 0.90 [79 to 1.02]). Benefit for amlodipine in terms of fewer strokes (HR 0.77 [0.66 to 0.89]), total CV events and procedures (HR 0.84 [0.78 to 0.90]), and deaths (HR 0.89 [0.81 to 0.99]). |
| ACCOMPLISH (2008) [29] (N=11,506) | Amlodipine Hydrochloro-thiazide (each added to benazepril) | 3 y | Composite: CV death, MI, stroke, other cardiac morbidity[g] | Benefit for amlodipine for primary endpoint (HR 0.80 [0.72 to 0.90]) and secondary composite of CV death, MI or stroke (HR 0.79 [0.67 to 0.92]). |

[a]Of main publication. [b]Mean or median. [c]A doxazosin arm was discontinued during the study and will not be discussed here. [d]Perindopril could be added to amlodipine and bendro-flumethiazide to atenolol, as required. [e]Trial terminated prematurely as recommended by routine trial data monitoring. [f]Interventional procedures, hospitalisation for heart failure, nonfatal MI, fatal CHD. [g]Primary composite was CV death, nonfatal MI, nonfatal stroke, hospitalisation for angina, resuscitation after sudden cardiac arrest, coronary revascularisation.
BP: blood pressure; CHD: coronary heart disease; CV: cardiovascular; HR: hazard ratio; MI: myocardial infarction; RR: relative risk; y: year. Numbers in square parentheses are 95% confidence intervals.

amlodipine or atenolol could receive additional per-protocol treatment with perindopril or a thiazide diuretic, respectively. The trial was terminated early due to a likelihood of benefit in the amlodipine arm; while the reduction in the primary endpoint with amlodipine did not achieve statistical significance, there were benefits for amlodipine versus atenolol in multiple secondary cardiovascular outcomes.

**The Avoiding Cardiovascular Events Through Combination Therapy in Patients Living With Systolic Hypertension (ACCOMPLISH) trial** was a randomised comparison of two antihypertensive combination regimens (amlodipine or a thiazide diuretic added to an ACE inhibitor in high-risk hypertensive patients) [29]. Amlodipine-based treatment was associated with a lower risk of a broad primary cardiovascular composite outcome as well as a secondary composite that resembles the primary outcome used in the other trials discussed here (cardiovascular death + nonfatal MI or stroke).

Accordingly, amlodipine was equivalent to, or superior to, other evidence-based treatments for hypertension for improving long-term clinical outcomes. Meta-analyses suggest comparable efficacy for CCBs versus other antihypertensive classes in reducing the risk of major adverse cardiovascular outcomes, with a greater effect on stroke compared with other antihypertensive classes, as described above [2–6]. A meta-analysis published in 2014 that included these and smaller trials shows that the risk of most adverse clinical outcomes was lower or similar for amlodipine compared with a β-blocker or diuretic, or with an ACE inhibitor or ARB [31].

## *Amlodipine in other cardiovascular diseases*

Several outcomes trials have evaluated amlodipine in patients with stable coronary artery disease, and these are reviewed briefly below.

**The Comparison of Amlodipine vs Enalapril to Limit Occurrences of Thrombosis (CAMELOT) study** compared the effectiveness of these agents with placebo for reducing the risk of cardiovascular events over 2 years of treatment in 1,991 patients with angiographically documented coronary artery disease [32]. The broad primary endpoint employed by this trial included cardiovascular death,

nonfatal MI, resuscitated cardiac arrest, coronary revascularisation, hospitalization for angina or for congestive heart failure, stroke, transient ischemic attack, or peripheral vascular disease. The frequency of the primary endpoint was reduced during treatment with both amlodipine (HR 0.69 [95% CI 0.54 to 0.88]) and enalapril (HR 0.85 [95% CI 0.67 to 1.07]), with no significant difference between treatments (HR 0.81 [95% CI 0.63 to 1.04]). There was a trend towards slowing of atherosclerosis regression in the amlodipine group, compared with the other treatments.

**The Prospective Randomized Evaluation of the Vascular Effects of Norvasc Trial (PREVENT)** was a randomised, placebo-controlled trial in 825 patients with angiographically confirmed coronary artery disease [33]. The study was designed to test the hypothesis that treatment with amlodipine might slow the progression of coronary atherosclerosis, determined using quantitative angiography. The primary endpoint (change in coronary luminal diameter) was not met in this study, although there was significant reduction of atherosclerosis progression for amlodipine versus placebo when measured using ultrasound techniques. There was also no difference between treatments for mortality or major adverse cardiovascular events. However, there were fewer episodes of angina or heart failure, or of revascularisation procedures, in the amlodipine versus placebo group.

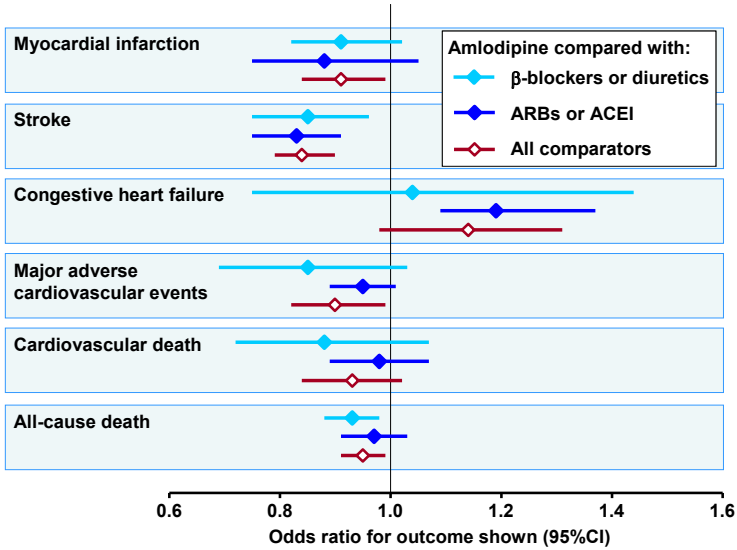
**The Coronary AngioPlasty Amlodipine REStenosis Study (CAPARES) study** evaluated the rate of restenosis following percutaneous transluminal coronary angioplasty (PTCA) in a population of 661 patients randomised to amlodipine or placebo [34]. The primary endpoints were loss in minimal lumen diameter (quantitative coronary angiography) and a major adverse cardiovascular events composite of death, MI, coronary artery bypass graft surgery and repeat PTCA, measured during the 4 months following the original PTCA procedure. There was no difference between treatments for the angiographic outcome, but there was a clinical benefit for amlodipine versus placebo in terms of reduced need for repeat PTCA (relative risk ratio [RRR] 0.45 [95% CI 0.22 to 0.91]), and a reduced frequency of the cardiovascular composite outcome (RRR 0.65 [95% CI 0.43 to 0.99]).

An outcomes trial was conducted in patients with severe heart failure—**the Prospective Randomized Amlodipine Survival Evaluation (PRAISE)** [35]. A total of 1153 patients with left ventricular ejection fraction (LVEF) <30% were randomised to amlodipine or placebo, in addition to their usual therapy, for 6–33 months. The risk of the primary cardiovascular composite outcome (death or hospitalisation for coronary events) was reduced by 16% (95% CI 10 to 24) for amlodipine versus placebo. A subgroup analysis suggested that benefit was only seen in patients with heart failure of non-ischaemic aetiology, with no significant effect in patients with heart failure of ischaemic aetiology. A second study (**PRAISE-2**) tested this hypothesis by randomising a population of 1,654 patients with non-ischaemic cardiomyopathy and LVEF <30% to amlodipine or placebo for a median of 33 months [36]. In this trial, there was no benefit for amlodipine versus placebo (HR 1.09 [95% CI 0.92 to 1.29]). The effects of amlodipine therefore, appear to be neutral in patients with heart failure [36].

## The clinical evidence base for bisoprolol and amlodipine—limitations and future prospects

Guidelines have downgraded the place of β-blockers as a class in the management of hypertension in recent years, and these agents are favoured for use in patients with special indications for their use, such as heart failure or IHD [13]. The effects of combination therapy approaches on hypertension-mediated clinical outcomes remains largely unstudied, especially with regard to the β-blocker class. For example, the ASCOT-BPLA [28] and ACCOMPLISH [29] trials, described above, were cardiovascular outcomes trials that set out to evaluate antihypertensive combinations. Both evaluated amlodipine in combination with an ACE inhibitor, but only ASCOT-BPLA included a β-blocker, atenolol, that has lower $\beta_1$-adrenoceptor selectivity (cardioselectivity) than bisoprolol. Indeed, the ASCOT-BPLA trial was described by one of its principal investigators as a comparison of “older” and “newer”

**Figure 1 Comparison of clinical outcomes for amlodipine versus other antihypertensive agents from a meta-analysis.**




Odds ratios <1 indicate lower frequency/risk for amlodipine vs. comparator. ARB: angiotensin receptor blocker; ACEI: angiotensin-converting enzyme inhibitor; CI: confidence interval. Drawn from data presented in reference [31].

antihypertensive therapies [37], a strategy which seemed likely to preclude evaluation of β-blockers in combination with "newer" antihypertensive therapies.

The reduction in emphasis on the use of the β-blocker class in people with hypertension is due to a perception of lower efficacy in reducing hypertension-mediated target organ damage, associated in turn with a lesser effect of β-blockers on central BP, compared with some other antihypertensive classes [13, 38, 39]. However, consideration of the clinical pharmacology of antihypertensive agents as though given as monotherapy is discordant with the call from the current European guideline for the management of hypertension for the use of combination antihypertensive therapy from the time of diagnosis of hypertension [13]. Complementary mechanisms of action of components of combination regimens can, in principle, provide complementary mechanisms of cardiovascular protection. For example, a study in hypertensive patients showed that addition

of amlodipine to bisoprolol markedly reduced both central BP and pulse pressure, in addition to brachial BP, thus overcoming one of the clinical limitations of β-blockade when used as monotherapy [40].

Current European guidelines for the management of hypertension are very clear in their recommendation that most people with hypertension who require pharmacotherapy should receive rational combination treatments, rather than monotherapy [13]. In future, the therapeutic evaluation of antihypertensive treatments should focus more strongly on comparing rational antihypertensive combinations with complementary mechanisms of action, rather than monotherapies. This approach would build on the substantial evidence base for improved outcomes that we have with existing antihypertensive agents, in a way that reflects more closely actual current practice in the management of hypertension.

## Conclusions

Bisoprolol and amlodipine have been in clinical use for the management of hypertension (and other cardiovascular conditions) for decades, and their efficacy and safety profiles when used as monotherapy are well understood. These drugs have complementary mechanisms of action and have each been shown to improve clinical outcomes in this population. This combination, prescribed appropriately and supported by delivery within a single tablet, has a place in the management of hypertension.

## References


1 Thomopoulos C, Bazoukis G, Tsioufis C, Mancia G. Beta-blockers in hypertension: overview and meta-analysis of randomized outcome trials. J Hypertens. 2020;38:1669–81. https://doi.org/10.1097/HJH.0000000000002523.

2 Wiysonge CS, Bradley HA, Volmink J, Mayosi BM, Opie LH. Beta-blockers for hypertension. Cochrane Database Syst Rev. 2017;1:Cd002003. https://doi.org/10.1002/14651858.CD002003.pub5.

3 Wiysonge CS, Bradley HA, Volmink J, Mayosi BM. Cochrane corner: beta-blockers for hypertension. Heart. 2018;104:282–3. https://doi.org/10.1136/heartjnl-2017-311585.

4 Emdin CA, Rahimi K, Neal B, Callender T, Perkovic V, Patel A. Blood pressure lowering in type 2 diabetes: a systematic review and meta-analysis. JAMA. 2015;313:603–15. https://doi.org/10.1001/jama.2014.18574.

**5** Ettehad D, Emdin CA, Kiran A, Anderson SG, Callender T, Emberson J, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. Lancet. 2016;387:957–67. https://doi.org/10.1016/s0140-6736(15)01225-8.

**6** Thomopoulos C, Parati G, Zanchetti A. Effects of blood pressure-lowering on outcome incidence in hypertension: 5. Head-to-head comparisons of various classes of antihypertensive drugs—overview and meta-analyses. J Hypertens. 2015;33:1321–41. https://doi.org/10.1097/HJH.0000000000000614.

**7** Vögele A, Johansson T, Renom-Guiteras A, Reeves D, Rieckert A, Schlender L, et al. Effectiveness and safety of beta blockers in the management of hypertension in older adults: a systematic review to help reduce inappropriate prescribing. BMC Geriatr. 2017;17:224. https://doi.org/10.1186/s12877-017-0575-4.

**8** Thomopoulos C, Parati G, Zanchetti A. Effects of blood-pressure-lowering treatment on outcome incidence. 12. Effects in individuals with high-normal and normal blood pressure: overview and meta-analyses of randomized trials. J Hypertens. 2017;35:2150–60. https://doi.org/10.1097/HJH.0000000000001547.

**9** Kumar R, Mal K, Begum J, Shaukat F. Comparison of Nebivolol and Bisoprolol for Cardiovascular Mortality in Hypertensive Patients. Cureus. 2019;11:e6453. https://doi.org/10.7759/cureus.6453.

**10** Chan You S, Krumholz HM, Suchard MA, Schuemie MJ, Hripcsak G, Chen R, et al. Comprehensive Comparative Effectiveness and Safety of First-Line beta-Blocker Monotherapy in Hypertensive Patients: A Large-Scale Multicenter Observational Study. Hypertension. 2021;77:1528–38. https://doi.org/10.1161/HYPERTENSIONAHA.120.16402.

**11** AlHabeeb W, Mrabeti S, Abdelsalam AAI. Therapeutic properties of highly selective β-blockers with or without additional vasodilator properties: focus on bisoprolol and nebivolol in patients with cardiovascular disease. Cardiovasc Drugs Ther. 2021. https://doi.org/10.1007/s10557-021-07205-y.

**12** Pathak A, Mrabeti S. β-blockade for patients with hypertension, ischemic heart disease or heart failure: where are we now? Vasc Health Risk Manag. 2021;17:337–48. https://doi.org/10.2147/vhrm.S285907.

**13** Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, et al. 2018 ESC/ESH guidelines for the management of arterial hypertension. Eur Heart J. 2018;39:3021–104. https://doi.org/10.1093/eurheartj/ehy339.

**14** McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) with the special contribution of the Heart Failure Association (HFA) of the ESC [published correction appears in Eur Heart J. 2021 Dec 21;42(48):4901]. Eur Heart J. 2021;42:3599–726. https://doi.org/10.1093/eurheartj/ehab670.

**15** Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, et al. 2019 ESC guidelines for the diagnosis and management of chronic coronary syndromes: The Task Force for the diagnosis and management of chronic coronary syndromes of the European Society of Cardiology (ESC) [published correction appears in Eur Heart J. 2020 Nov 21;41(44):4242]. Eur Heart J. 2020;41:407–77. https://doi.org/10.1093/eurheartj/ehz425.

**16** A randomized trial of beta-blockade in heart failure. The Cardiac Insufficiency Bisoprolol Study (CIBIS). CIBIS Investigators and Committees. Circulation. 1994;90:1765–73. https://doi.org/10.1161/01.cir.90.4.1765.

**17** The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. Lancet. 1999;353:9–13.

**18** Willenheimer R, van Veldhuisen DJ, Silke B, Erdmann E, Follath F, Krum H, et al. Effect on survival and hospitalization of initiating treatment for chronic heart failure with bisoprolol followed by enalapril, as compared with the opposite sequence: results of the randomized Cardiac Insufficiency Bisoprolol Study (CIBIS) III. Circulation. 2005;112:2426–35. https://doi.org/10.1161/CIRCULATIONAHA.105.582320.

**19** Freemantle N, Cleland J, Young P, Mason J, Harrison J. Beta blockade after myocardial infarction: systematic review and meta regression analysis. BMJ. 1999;318:1730–7. https://doi.org/10.1136/bmj.318.7200.1730.

**20** Andersson C, Shilane D, Go AS, Chang TI, Kazi D, Solomon MD, et al. beta-blocker therapy and cardiac events among patients with newly diagnosed coronary heart disease. J Am Coll Cardiol. 2014;64:247–52. https://doi.org/10.1016/j.jacc.2014.04.042.

**21** Sorbets E, Steg PG, Young R, Danchin N, Greenlaw N, Ford I, et al. beta-blockers, calcium antagonists, and mortality in stable coronary artery disease: an international cohort study. Eur Heart J. 2019;40:1399–407. https://doi.org/10.1093/eurheartj/ehy811.

**22** Brugts JJ, Bertrand M, Remme W, Ferrari R, Fox K, MacMahon S, et al. The Treatment Effect of an ACE-Inhibitor Based Regimen with Perindopril in Relation to Beta-Blocker use in 29,463 Patients with Vascular Disease: a Combined Analysis of Individual Data of ADVANCE, EUROPA and PROGRESS Trials. Cardiovasc Drugs Ther. 2017;31:391–400. https://doi.org/10.1007/s10557-017-6747-9.

**23** Peyracchia M, Errigo D, Raposeiras Rubin S, Conrotto F, DiNicolantonio JJ, Omede P, et al. Beta-blocker therapy reduces mortality in patients with coronary artery disease treated with percutaneous revascularization: a meta-analysis of adjusted results. J Cardiovasc Med (Hagerstown). 2018;19:337–43. https://doi.org/10.2459/JCM.0000000000000662.

**24** Von Arnim T. Prognostic significance of transient ischemic episodes: response to treatment shows improved prognosis. Results of the Total Ischemic Burden Bisoprolol Study (TIBBs) follow-up. J Am Coll Cardiol. 1996;28:20–4. https://doi.org/10.1016/0735-1097(96)00122-2.

**25** von Arnim T. Medical treatment to reduce total ischemic burden: total ischemic burden bisoprolol study (TIBBS), a multicenter trial comparing bisoprolol and nifedipine. The TIBBS Investigators. J Am Coll Cardiol. 1995;25:231–8. https://doi.org/10.1016/0735-1097(94)00345-q.

**26** ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). JAMA. 2002;288:2981–97. https://doi.org/10.1001/jama.288.23.2981.

**27** Julius S, Kjeldsen SE, Weber M, Brunner HR, Ekman S, Hansson L, et al. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. Lancet. 2004;363:2022–31. https://doi.org/10.1016/S0140-6736(04)16451-9.

**28** Dahlöf B, Sever PS, Poulter NR, Wedel H, Beevers DG, Caulfield M, et al. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. Lancet. 2005;366:895–906. https://doi.org/10.1016/S0140-6736(05)67185-1.

**29** Jamerson K, Weber MA, Bakris GL, Dahlof B, Pitt B, Shi V, et al. Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. N Engl J Med. 2008;359:2417–28. https://doi.org/10.1056/NEJMoa0806182.

**30** Sever P. The VALUE trial: a commentary. J Renin Angiotensin Aldosterone Syst. 2004;5:99–101. https://doi.org/10.3317/jraas.2004.033.

**31** Lee SA, Choi HM, Park HJ, Ko SK, Lee HY. Amlodipine and cardiovascular outcomes in hypertensive patients: meta-analysis comparing amlodipine-based versus other antihypertensive therapy. Korean J Intern Med. 2014;29:315–24. https://doi.org/10.3904/kjim.2014.29.3.315.

**32** Nissen SE, Tuzcu EM, Libby P, Thompson PD, Ghali M, Garza D, et al. Effect of antihypertensive agents on cardiovascular events in patients with coronary disease and normal blood pressure: the CAMELOT study: a randomized controlled trial. JAMA. 2004;292:2217–25. https://doi.org/10.1001/jama.292.18.2217.

**33** Pitt B, Byington RP, Furberg CD, Hunninghake DB, Mancini GB, Miller ME, et al. Effect of amlodipine on the progression of atherosclerosis and the occurrence of clinical events. PREVENT Investigators. Circulation. 2000;102:1503–10. https://doi.org/10.1161/01.cir.102.13.1503.

**34** Jørgensen B, Simonsen S, Endresen K, Forfang K, Vatne K, Hansen J, et al. Restenosis and clinical outcome in patients treated with amlodipine after angioplasty: results from the Coronary AngioPlasty Amlodipine REStenosis Study (CAPARES). J Am Coll Cardiol. 2000;35:592–9. https://doi.org/10.1016/s0735-1097(99)00599-9.

**35** Packer M, O'Connor CM, Ghali JK, Pressler ML, Carson PE, Belkin RN, et al. Effect of amlodipine on morbidity and mortality in severe chronic heart failure. Prospective Randomized Amlodipine Survival Evaluation Study Group. N Engl J Med. 1996;335:1107–14. https://doi.org/10.1056/NEJM199610103351504.

**36** Packer M, Carson P, Elkayam U, Konstam MA, Moe G, O'Connor C, et al. Effect of amlodipine on the survival of patients with severe chronic heart failure due to a nonischemic cardiomyopathy: results of the PRAISE-2 study (prospective randomized amlodipine survival evaluation 2). JACC Heart Fail. 2013;1:308–14. https://doi.org/10.1016/j.jchf.2013.04.004.

**37** Sever PS. The Anglo-Scandinavian Cardiac Outcomes Trial: implications and further outcomes. Hypertension. 2012;60:248–59. https://doi.org/10.1161/HYPERTENSIONAHA.111.187070.

**38** Epstein BJ, Anderson S. Discordant effects of beta-blockade on central aortic systolic and brachial systolic blood pressure: considerations beyond the cuff. Pharmacotherapy. 2007;27:1322–33. https://doi.org/10.1592/phco.27.9.1322.

**39** Jeon KH, Kim HL, Lim WH, Seo JB, Kim SH, Zo JH, et al. Associations between measurements of central blood pressure and target organ damage in high-risk patients. Clin Hypertens. 2021;27:23. https://doi.org/10.1186/s40885-021-00179-x.

**40** Bogomaz A, Kotovskaya Y, Kobalava Z. Combination with amlodipine eliminates adverse effect of a betablocker on aortic pulse pressure augmentation [abstract PP.21.27]. J Hypertens. 2015;33:e326. https://doi.org/10.1097/01.hjh.0000468379.55561.95.

MHKDELM400104