



# Targeting blood pressure in the management of total cardiovascular risk

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## KEYWORDS

Hypertension;  
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An overwhelming body of evidence has shown that lowering blood pressure (BP) reduces the risk of cardiovascular events, irrespective of the mechanism of action of the agent. Consistent control of BP is of crucial importance. Treatment should effectively lower BP both in the office and out of the office, and BP control should be achieved throughout the 24-h dosing interval. Agents with long half-lives and long duration of action should be considered for therapy. Tolerability is also an important attribute in anti-hypertensive therapy; both physicians and patients report poor tolerability as a key reason for discontinuing or switching therapy. Telmisartan is an example of an anti-hypertensive agent that provides strong BP reductions and smooth control of 24 h BP. It has greater BP-lowering efficacy than losartan, and also reduces BP towards the end of the dosing interval compared with valsartan. In the Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial, the largest outcome trial with an angiotensin II receptor blocker and with the broadest cross section of cardiovascular high-risk patients, telmisartan was as protective as ramipril in reducing cardiovascular risk but better tolerated. Notably, the discontinuation rate for telmisartan was consistently lower than that for ramipril despite patients being screened for angiotensin-converting enzyme inhibitor tolerance, which suggests that the differences in tolerability may have practical implications for long-term cardiovascular protection.

## Introduction

An overwhelming body of evidence from controlled trials has shown that lowering blood pressure (BP) *per se* reduces the risk of cardiovascular (CV) events, irrespective of the mechanism of action of the drug(s) employed. Much of this literature was incorporated by the Blood Pressure Lowering Treatment Trialists' Collaboration into a meta-regression analysis of data from 29 trials that included over 150 000 patients. The results demonstrated a direct relationship between reduction in BP and reduction

in the incidence of stroke, coronary artery disease (CAD), major CV events, CV death, and total mortality.<sup>1</sup> A subsequent meta-regression analysis of available trials added that this also applies to treatment of heart failure.<sup>2</sup>

In recent years, several new aspects of the relationship between BP and CV risk have emerged, most of which have not been considered in trials. This review will address some of these aspects: the importance of consistent rather than variable BP control by treatment; the BP targets that have shown the closest association with patient protection; and the value of controlling BP throughout the 24-h dosing interval, particularly during the night and early morning periods.

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## Advantages of consistent and tight blood pressure control

Although in a clinical trial the average on-treatment BP may show control, BP values may not be reduced throughout the trial duration. For example, in the European Lacidipine Study on Atherosclerosis (ELSA) study, the proportion of patients with adequately controlled BP at all four annual clinic visits was considerably less than the proportion of patients demonstrating BP control at any single annual visit, indicating BP control was not maintained for many patients in the trial.<sup>3</sup> This is clinically relevant because uniform BP control has been linked to reduced CV risk. In the International Verapamil SR-Trandolapril (INVEST) trial,<sup>4</sup> data from the 22 576 patients were stratified by the proportion of clinic visits in which systolic BP was <140 mmHg and diastolic BP was <80 mmHg (<25%, ≥25% to <50%, ≥50% to <75%, and ≥75% of visits). The primary outcome [first occurrence of death, non-fatal myocardial infarction (MI), or non-fatal stroke] decreased progressively as the proportion of visits in which BP was controlled increased from <25 to ≥75%. A similar pattern of association was noted for outcomes such as MI (fatal and non-fatal) and stroke (fatal and non-fatal) and data were similar for the group of patients with type 2 diabetes. Compared with the group with BP controlled at <25% of visits, the relative risk for patients in the group with BP control at ≥75% of visits was 0.60 for the primary outcome (95% CI 0.53–0.67), 0.58 for all MIs (95% CI 0.48–0.70), and 0.50 for all strokes (95% CI 0.37–0.67).

Tighter BP control (the achievement of lower BP targets using more intensive treatment) has also been recognized as providing a greater CV, cerebrovascular, and renal protection. An early example is the Hypertension in Diabetes Study [a 9-year, multi-centre, randomized, controlled trial embedded within the UK Prospective Diabetes Study (UKPDS) started in 1987] in which patients with type 2 diabetes and hypertension were randomized to a tighter (<150/85 mmHg) or less tight (<180/105 mmHg) BP control by drug treatment. Compared with the latter, in the former group the risk for death related to diabetes and of macrovascular and microvascular complications was significantly reduced.<sup>5</sup> More recently this was also found to be the case when tight BP control reduced BP to values much lower than those seen in the UKPDS study. In the Appropriate Blood Pressure Control in Diabetes (ABCD) trial,<sup>6,7</sup> a BP reduction to <140/80 mmHg was associated with beneficial effects (reduction in stroke and all cause mortality) compared with a reduction that left on-treatment values in the systolic and diastolic BP range between 130–140 and 80–90 mmHg, respectively. Low BP targets (i.e. diastolic BP ≤80 mmHg) were also found to be protective in the Hypertension Optimal Treatment (HOT) trial,<sup>8</sup> the European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease (EUROPA),<sup>9</sup> the Perindopril pROtection aGainst Recurrent Stroke Study (PROGRESS),<sup>10</sup> and the

Comparison of Amlodipine vs. Enalapril to Limit Occurrences of Thrombosis (CAMELOT).<sup>11</sup>

The protection originating from low BP targets has also been found to involve the kidney,<sup>12–14</sup> and to be evident when prospective data from trials are retrospectively analysed in order to compare the event rate at different levels of achieved BP.<sup>15,16</sup> In the PROGRESS study, for example, the incidence of both ischaemic and haemorrhagic stroke decreased progressively as achieved systolic BP was reduced to approximately 120 mmHg.<sup>15</sup>

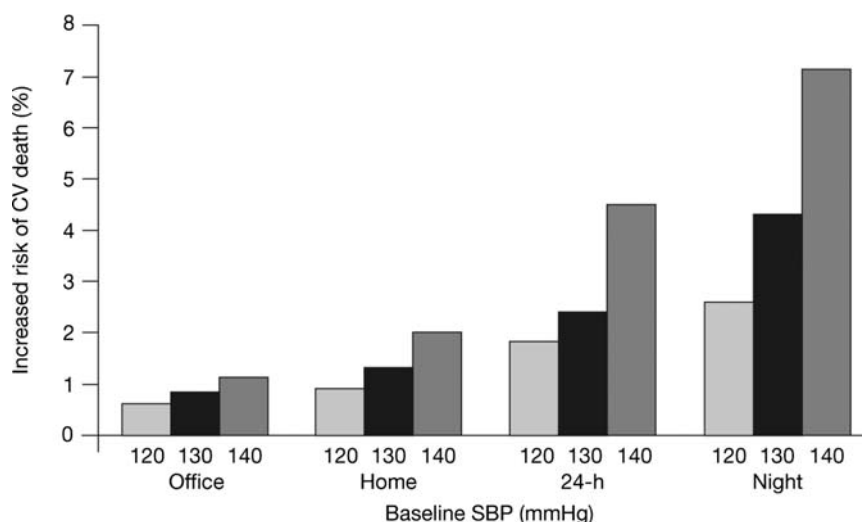
On the basis of this evidence, the current European Society for Hypertension/European Society for Cardiology (ESH/ESC) guidelines recommend that in high-risk patients (those with CAD, CV disease, diabetes, and renal impairment) the target BP is lower (<130/80 mmHg), whereas in hypertensive patients at lower level of risk the less tight target (<140/90 mmHg) remains.<sup>17</sup>

## Twenty-four hours blood pressure control

A growing body of clinical data supports the view that BP measurement outside the office environment (home and ambulatory measurements) has high prognostic value.<sup>18</sup> For example, in the Pressioni Arteriose Monitorate e Loro Associazioni (PAMELA) study, a 10-year observational study of >2000 subjects representative of the general adult population of Monza (Milan, Italy), home and ambulatory BP values along with office BP showed a significant and direct exponential relationship to the risk of CV or all-cause death.<sup>19</sup> The steepest increase in mortality rate was observed with rising 24-h systolic BP compared with the risk associated with increasing home and office systolic BP (Figure 1). Furthermore, mortality rates were highest for patients with elevated BP on all three assessments (office, home, and 24-h mean), followed by patients with two elevated BP measurements. Patients with elevated BP in any one type of assessment were associated with higher mortality than unelevated BP in any of the measurements.<sup>20</sup>

Night-time BP, determined from ambulatory BP monitoring, has particular prognostic significance. As shown in the PAMELA study, a 10-mmHg increase in systolic BP at night-time was associated with greater increases in risk for CV mortality than a corresponding increase in 24-h mean, home, or office BP (Figure 1).<sup>19</sup> A further analysis of the PAMELA data showed that when adjusted for age, sex, 24-h mean BP, and other risk factors, the risk for CV death was inversely related to the difference between daytime and night-time diastolic BP difference ( $\beta$ -coefficient = -0.040;  $P < 0.02$ ), i.e. there was a greater risk in those in whom nocturnal hypotension was less pronounced.<sup>21</sup>

These findings on the prognostic value of night-time BP are consistent with findings that a circadian periodicity exists for the onset of CV events. It seems clear that a minimal-level CV risk occurs during the night, presumably because the lower BP offers protection. In contrast, peak rates of occurrence of acute MI, sudden cardiac death,



**Figure 1** Prognostic significance of office, home, 24-h, and night blood pressure. The greatest increase in risk associated with a 10-mmHg increase in systolic blood pressure was found for the night-time blood pressure followed by 24-h blood pressure – data from the Pressioni Arteriose Monitorate e Loro Associazioni (PAMELA) study.<sup>19</sup> SBP, systolic blood pressure. Reproduced with permission from Segà *et al.*<sup>19</sup>

transient myocardial ischemia, and ischaemic stroke occur in the morning after awakening and before beginning the normal activities of daily living.<sup>22</sup> Finally, BP variability has also been found to have prognostic significance. In the PAMELA study, 24-h BP recordings were subjected to Fourier spectral analysis to identify cyclic and non-cycling components of BP variability, the latter corresponding to short-term BP variations independent on circadian rhythm. The non-cycling or residual components of BP variability showed an independent relationship with risk of CV death ( $\beta$ -coefficient = 0.175,  $P < 0.002$ ).<sup>21</sup>

Overall, these findings support three main concepts for the treatment of hypertension to reduce CV, cerebrovascular, and renal risk:

- (i) BP control is of crucial importance;
- (ii) treatment should effectively lower BP both in the office and out of the office;
- (iii) out-of-office BP control should provide smooth BP reduction throughout the 24-h dosing interval.

### Meta-analysis of 24-h blood pressure reduction with telmisartan and other antihypertensive agents

The angiotensin II receptor blocker (ARB) telmisartan has a long plasma half-life and duration of action.<sup>23</sup> The 24-h BP-lowering efficacy of telmisartan has been demonstrated in several clinical studies and in a pooled analysis. Telmisartan 40 and 80 mg and amlodipine (another antihypertensive characterized by a long half-life and duration of action) provided similar clinical BP reductions in a 12-week clinical trial in patients with mild-to-moderate hypertension (*Figure 2*).<sup>24</sup> However, a greater proportion of telmisartan patients achieved 24 h BP control (mean 24-h diastolic BP  $< 85$  mmHg) than those receiving amlodipine. Furthermore, telmisartan was associated with

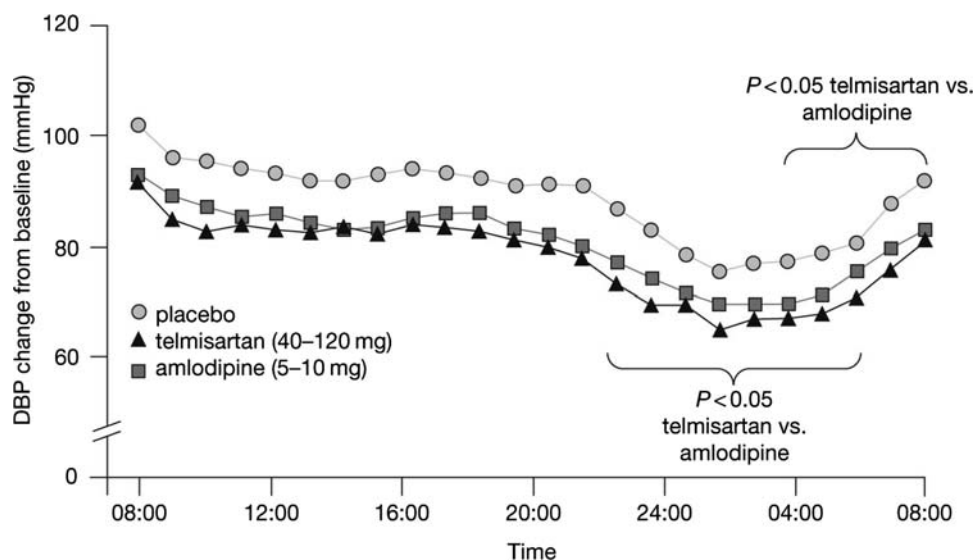
significantly greater decreases in diastolic BP at night-time and during the last 4 h before dosing.

In patients with mild-to-moderate hypertension, telmisartan 80 mg demonstrated significantly greater reductions in systolic and diastolic BP during the last 6 h of the dosing interval with telmisartan compared with valsartan 160 mg.<sup>25</sup> In addition, on the day after a missed dose, telmisartan was associated with greater reductions in early morning and mean 24-h systolic and diastolic BP compared with valsartan.<sup>26</sup>

A meta-analysis of data from the five large, multi-centre clinical trials that assessed 24-h BP control using Ambulatory BP Monitoring (ABPM) from the telmisartan clinical database was conducted by Neutel and Smith.<sup>27</sup> Because the clinical development programme for telmisartan had a strong focus on the use of ABPM, this meta-analysis used the largest ABPM database for an ARB. The five studies included in the meta-analysis, which compared telmisartan 40 and 80 mg, losartan 50 mg, valsartan 80 mg, and amlodipine 5 mg, were chosen because of their consistency regarding criteria for inclusion/exclusion, ABPM, and the type of BP monitor used for measurement.

All of the antihypertensive agents reduced mean 24-h BP from baseline to a greater extent than placebo ( $P < 0.001$ ). The mean change from baseline for 24-h systolic BP was significantly greater for telmisartan 80 mg than telmisartan 40 mg, valsartan 80 mg, and losartan 50 mg ( $P < 0.0125$ ). The mean change in 24-h diastolic BP from baseline with telmisartan 80 mg was significantly greater than that for valsartan 80 mg and losartan 50 mg ( $P < 0.0125$ ). During the early morning period, telmisartan 80 mg was associated with significantly greater mean change from baseline in systolic BP compared with valsartan 80 mg, losartan 50 mg, and telmisartan 40 mg ( $P < 0.0125$  for valsartan and losartan;  $P < 0.05$  for telmisartan).

Another meta-analysis has compared the variability of the 24 h BP effect of treatment with different



**Figure 2** Telmisartan was associated with greater reductions in diastolic blood pressure (DBP) at night and during the early morning hours compared with amlodipine in a direct comparative study.<sup>24</sup> Reproduced with permission from Lacourcière *et al.*<sup>24</sup>

antihypertensives using the smoothness index, which is based on the standard deviation of the effect of treatment on the different hours within a 24-h period.<sup>28</sup> Telmisartan was associated with significantly higher smoothness indices for systolic and diastolic BP, indicating less variability in the antihypertensive effect, compared with valsartan 160 mg ( $P < 0.05$  for both systolic and diastolic BP), valsartan 80 mg ( $P < 0.01$  for systolic BP and  $P < 0.001$  for diastolic BP), ramipril 10 mg ( $P < 0.0001$  for systolic and diastolic BP), and losartan 50 mg ( $P < 0.01$  for systolic and diastolic BP).<sup>29</sup> Thus, telmisartan provides a smoother BP reduction throughout the 24-h interval, with a reflection on BP variability of possible prognostic significance.

## Blood pressure control in clinical practice

A large body of evidence exists to support that the control of BP in hypertensive patients seen in clinical practice is inadequate, despite the availability of effective drugs,<sup>30</sup> and that adequate BP control may be even less common when 24-h BP values are taken into account.<sup>31</sup>

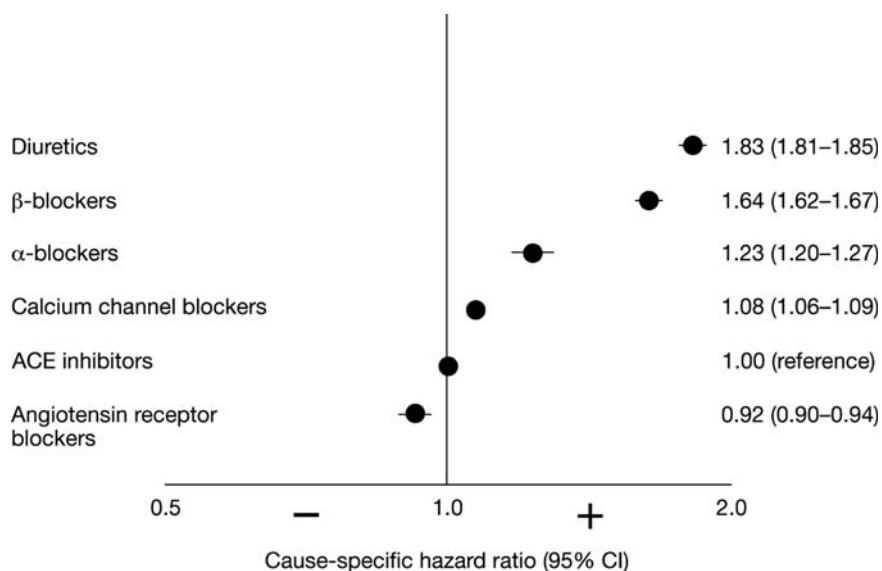
A recent example is that of the ForLife Study,<sup>32</sup> an observational multi-centre study conducted in 2003 and involving 1800 general practitioners (GPs) throughout Italy. The GPs were requested to recruit 10 consecutive patients with essential hypertension, aged 54–84 years, with the aim of enrolling similar numbers of treated and untreated patients. Analysis of BP control in the study population showed that the target BP recommended by ESH/ESC of  $<140/90$  mmHg was achieved in only 18.4% of the treated patients. Furthermore, for patients with diabetes, the BP target of  $<130/80$  mmHg was achieved by only 3%. In a meta-analysis of all available studies, BP control was even rarer for 24-h BP mean values; although in a total of almost 6000

patients, office BP was reduced to  $\sim 140/90$  mmHg, the 24-h mean values remained well above the upper normality values in the population (125/80 mmHg).<sup>31</sup>

There are many reasons for the poor rate of BP control in the hypertensive population. One reason for the poor rate of BP control is a lack of awareness among the general population. A survey study of five European countries, the USA, and Canada using data from the 1990s showed awareness of BP status is low among people with hypertension ranging from 52.7% in Sweden to 88.0% in the USA.<sup>33</sup> Another reason is that discontinuation of initial monotherapy for hypertension is common, and the problem is particularly serious in the real-life setting. In a study by Corrao *et al.*<sup>34</sup> an analysis was made of the Health Service prescription database for Lombardy (Italy), for modifications and switches of initial antihypertensive monotherapy among patients newly prescribed such treatment between 1999 and 2002. The most common modification to treatment was discontinuation; findings on the cumulative incidence of treatment modification revealed that the rate of discontinuation of treatment was 33% at 6 months, 41% at 1 year, and 50% at 5 years. In comparison, the rates of switching and combining other agents, respectively, were 14 and 15% at 6 months, 18 and 17% at 1 year, and 25 and 19% at 5 years.

Hazard ratios (HR) for discontinuation after 1 year for six different classes of anti-hypertensive agents were obtained by Corrao *et al.*<sup>34</sup> using the data on the cumulative treatment modification. The angiotensin-converting enzyme (ACE) inhibitor class was used as the reference (Figure 3). Of the remaining five classes, ARBs were associated with the lowest risk of discontinuation [HR 0.92 (95% CI 0.90–0.94)], and diuretics with the highest risk [HR 1.83 (95% CI 1.81–1.85)].

An earlier Italian epidemiologic study found similarly high rates of discontinuation and switching of initial antihypertensive therapy.<sup>35</sup> The total rate of discontinuation



**Figure 3** Effect of class of drug used for initial antihypertensive treatment on the cumulative incidence of treatment discontinuation.<sup>34</sup> ACE inhibitor, angiotensin-converting enzyme inhibitor.

and switching reported by physicians over a 12-month period was 66%. The most common reasons given for the switches in therapy were inadequate BP control (approximately half of cases) and side effects (in about one-third). In contrast, treatment switching was ascribed to side effects by about half of the patients, whereas inadequate BP control was cited by one-third. A reasonable interpretation is that both physicians and patients consider poor tolerability to be an important reason for switching anti-hypertensive therapy.

### Treatment discontinuation in Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial

Tolerability is, therefore, of primary importance for maintenance anti-hypertensive therapy. The data from the study by Corrao *et al.*<sup>34</sup> showing that the ARBs were associated with the lowest rate of discontinuation are consistent with findings from clinical trials showing a placebo-like tolerability profile for this drug class.<sup>36</sup> Findings from the recently reported Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET), a large (25 620-patient), long-term study comparing telmisartan, ramipril, and combination therapy with telmisartan and ramipril in a broad range of patients at high risk for CV events (either because of established CV disease, or because of diabetes with target organ damage) are also consistent with the premise that the ARBs are particularly well tolerated.<sup>37</sup> ONTARGET showed that telmisartan and ramipril were equally effective on the primary outcome (death from CV causes, MI, stroke, or hospitalization for heart failure). However, despite the fact that patients with known ACE-inhibitor intolerance were excluded from the trial, and despite the fact that all patients underwent a 4-week single-blind run-in period, there was still a

lower cumulative rate of discontinuation throughout the 5 years of follow-up with telmisartan compared with ramipril.

### Summary and conclusions

The CV, cerebrovascular, and renal benefits of BP lowering are supported by a large body of clinical data. Consistent control of BP is critically important, as is consistent BP lowering across the 24-h period. Effective treatment should lower BP both in the office and out of the office, and ideally treatment efficacy should be confirmed by either home or ambulatory BP monitoring.

Tolerability is also an important attribute in anti-hypertensive therapy because it is a key reason for discontinuation and switching of treatment. The ARBs have placebo-like tolerability in clinical trials and a low rate of discontinuation in the real-world setting. Given that protection from CV events is a key goal of anti-hypertensive treatment, the observation in ONTARGET that telmisartan is equally effective in reducing risk as ramipril, while being better tolerated, is particularly interesting. The future of evidence-based hypertension management will increasingly require agents that demonstrate, not only effective BP lowering, but also high levels of tolerability and efficacy on important CV outcomes.

**Conflict of interest:** G.C. has no conflict of interest to declare. G.M. has received speaker or consultancy fees from Boehringer Ingelheim, Novartis, Menarini, Recordati, Servier, Bayer, Takeda, Sankyo, Merck-Sharp-Dohme, and Astra-Zeneca.

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