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The many faces of hypertension in individuals with type 1 diabetes

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ABSTRACT

Several disturbed blood pressure (BP) patterns, including disparities between office and out-of-office BP measurements (such as white-coat and masked hypertension), disturbed circadian BP variability (such as abnormal dipping patterns and nocturnal hypertension) and treatment-resistant hypertension, are common in individuals with type 1 diabetes. Consequently, office or home BP measurements alone may not reflect real BP variation and may lead to inadequate diagnosis and treatment of hypertension. The early detection of these disturbed BP patterns is especially crucial in individuals with type 1 diabetes, as these patterns may indicate future development of adverse cardiovascular and renal outcomes. In this review we will describe these disturbed BP patterns and discuss recent findings on their prevalence and outcomes. We will also address critical areas for future research to determine the true prevalence and prognosis of disturbed BP patterns, and to optimize and improve the knowledge and management of high-risk individuals with type 1 diabetes and disturbed BP patterns.

1. Introduction

Individuals with type 1 diabetes have a high life-time risk of microvascular complications and cardiovascular disease (CVD) [1,2]. Suboptimal control of modifiable risk factors such as hyperglycemia, blood pressure, lipids, BMI, smoking and albuminuria have been shown to be associated with these complications [3–6]. Notably, recent studies have shown the importance of intensive multifactorial interventions targeting all risk markers: the higher the number of risk factors below the target levels, the lower the risk [7,8]. Hypertension is one of the major contributing and modifiable risk factors for microvascular complications and CVD in individuals with type 1 diabetes [3–6]. Hypertension affects approximately one-third of these individuals [9,10]. In contrast to type 2 diabetes, clinical hypertension typically manifests, when the individual with type 1 diabetes develops microalbuminuria [11]. In fact, hypertension is not only a cause, but also a consequence of diabetic kidney disease (DKD). The blood pressure (BP) rises along with the increase of albuminuria, but high BP also accelerates the loss of kidney function [12–14]. Notably, in comparison with the non-diabetic population, type 1 diabetes is associated with higher prevalence of hypertension, also in the absence of DKD [15,16]. In those with type 1 diabetes and normal albumin excretion rate (AER), isolated systolic hypertension is 3 times more common than in non-diabetic controls [15]. Moreover, age-related changes (i.e., increase in systolic BP and decrease in diastolic BP) occur earlier in individuals with type 1 diabetes than in non-diabetic controls [15].

Despite strong evidence that intensive BP control reduces the risk of diabetic complications and improves the prognosis of DKD, a surprisingly low number of individuals with type 1 diabetes reach their BP treatment targets despite regular follow-up visits. A large and representative cohort of individuals with type 1 diabetes from the Finnish Diabetic Nephropathy (FinnDiane) Study ($N = 3678$) showed that over 60% did not reach a BP treatment target of <130/85 mmHg, and the proportion was close to 70% with a target of <130/80 mmHg [17]. This share seemed to increase along the worsening of DKD, even though almost all with advanced kidney disease had antihypertensive drugs in their treatment regimen [17]. Slightly lower numbers have been reported with 24-h and daytime ambulatory BP monitoring (ABPM) from

Abbreviations: ABPM, ambulatory blood pressure monitoring; AER, albumin excretion rate; AHA, American Heart Association; BP, blood pressure; CVD, cardiovascular disease; DKD, diabetic kidney disease; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; FinnDiane, Finnish Diabetic Nephropathy; HBPM, home blood pressure monitoring; MH, masked hypertension; TRH, treatment-resistant hypertension; WCH, white-coat hypertension.

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the Steno Diabetes Center ($N = 569$), showing that 55% to 66% of individuals with type 1 diabetes did not reach the target of <130/80 mmHg [18]. The Scottish Registry Linkage Study ($N = 21,290$), using office-based BP measurements, showed that 60% of men and 53% of women with type 1 diabetes had BP above the target of <130/80 mmHg [19]. Although BP seems to be more difficult to control in those with progression of DKD, it is also sub-optimally controlled in those without or with only early signs of diabetic complications [17]. In the FinnDiane cohort about 60% of those with normal AER or microalbuminuria, and who failed to reach the BP treatment target of <130/85 mmHg, had only one antihypertensive drug in their regimen [17].

In fact, multiple disturbed BP patterns, which may indicate future development of complications, are common in type 1 diabetes [20–22]. These patterns may reflect disparities between office and out-of-office BP measurements (e.g., white-coat or masked hypertension), disturbed circadian BP variability (e.g., abnormal dipping patterns or nocturnal hypertension) or incapability to control BP in spite of multiple antihypertensive therapies (i.e., treatment-resistant hypertension). Thus, office BP measurements based on a limited number of daytime measurements from single occasions alone do not reflect the real BP variation in the individual's usual environment, and may therefore lead to inadequate diagnosis and treatment of hypertension, by focusing the treatment on normalizing office BP [23]. Although out-of-office wake-time self-BP measurements over a longer period of time may better reflect an individual's BP in the usual environment than the office-based BP, they do not typically detect nocturnal hypertension or non-dipping patterns [24,25]. These patterns, may indeed, be especially crucial for the diagnosis and management of hypertension in individuals with type 1 diabetes [26,27]. Therefore, ABPM may offer more accurate estimates than office- or home BP monitoring (HBPM) alone to evaluate, modify and improve BP control [23]. In the present review, we will discuss recent findings on the prevalence and outcomes from studies addressing multiple disturbed BP patterns (e.g., white-coat, masked, nocturnal and treatment-resistant hypertension) in type 1 diabetes. We will also address critical areas for future research to improve knowledge and management of these high-risk individuals with disturbed BP patterns.

2. BP patterns

Four different types of hypertension can be detected by combining office BP and out-of-office BP monitoring (either through HBPM or ABPM): true normotension (normotensive with both), sustained hypertension (hypertensive with both), white-coat hypertension (hypertensive with office BP, but normotensive with HBPM/ABPM) and masked hypertension (normotensive with office BP, but hypertensive with HBPM/ABPM) (Table 1) [28]. The cut-off values for normal BP have been debated for several years, as there are no high-quality data available to guide BP targets in individuals with type 1 diabetes [29]. The current American Diabetes Association guidelines recommend a more stringent office BP goal of <130/80 mmHg for high-risk individuals (i.e., clinically diagnosed CVD or 10-year atherosclerotic CVD-risk ≥15%) and < 140/90 mmHg for low-risk individuals (i.e., 10-year atherosclerotic CVD-risk <15%) with diabetes [29]. It is expected that cut-off values for ABPM should be 5–10 mmHg lower than the office BP [30]. Consequently, the American College of Cardiology and the American Heart Association (AHA) have published corresponding cut-off values for the office BP, HBPM and ABPM (Table 2) [31].

3. White-coat hypertension

Emotional factors, such as anxiety and stress for any reasons can trigger a temporary spike in BP [32]. Individuals with the white-coat effect have been shown to be more prone to higher levels of anxiety compared with normotensive individuals and individuals with persistent high BP [33]. Individuals experiencing anxiety or stress over their doctor's appointment may be at increased risk of white-coat hypertension (WCH) [33]. The white-coat effect illustrates the rise in BP readings, measured by a doctor or a nurse regardless of the daytime BP or antihypertensive therapy [34]. It mainly reflects the pressor response to the clinical setting, that activates the sympathetic nervous system [35]. WCH is diagnosed, when the office BP is repeatedly above the BP threshold, but at normal BP range, when measured out-of-office (i.e., isolated clinic hypertension) [31,36,37]. Originally limited to untreated individuals only, the definition has been extended to encompass also individuals taking antihypertensive drugs (i.e., white-coat uncontrolled hypertension) [38]. Although the white-coat effect can be seen at all grades of hypertension, WCH occurs more often in individuals with newly diagnosed hypertension, who have had a limited number of measurements in the medical environment, and whose hypertension is mild [39]. WCT is also more common with increasing age, in women and in non-smokers, in pregnant women and in individuals without target organ damage [39].

The prevalence of WCH varies substantially, depending on the study population, BP thresholds and the periods (i.e., normality for daytime, nighttime and 24-h periods or daytime only) to define it, and whether treated individuals are also included [40]. In the general population the prevalence of WCH ranges from 15% to 30% [34]. Only small studies have estimated the prevalence of WCH among individuals with diabetes.

Table 2
Corresponding systolic and diastolic BP cut-off values for office, HBPM and ABPM [31].

	High-risk individuals	Low-risk individuals
Office BP	130/80 mmHg	140/90 mmHg
HBPM	130/80 mmHg	135/85 mmHg
Daytime ABPM	130/80 mmHg	135/85 mmHg
Nighttime ABPM	110/65 mmHg	120/70 mmHg
24-h ABPM	125/75 mmHg	130/85 mmHg

BP, blood pressure; HBPM, home blood pressure monitoring; ABPM, ambulatory blood pressure monitoring.

Table 1
The definition and prevalence of different blood pressure patterns in four different cohorts of individuals with type 1 diabetes [18,21,45,61].

BP pattern	Office BP	ABPM	Prevalence (%)			
			FinnDiane[1] $N = 140$	Steno[2] $N = 569$	Brazilian study[3] $N = 188$	Spanish study[4] $N = 85$
Normotension	Normal	Normal	38	18 / 15	47	40
White-coat hypertension	Elevated	Normal	6	27 / 18	10	NA
Masked hypertension	Normal	Elevated	23	10 / 13	7	24
Sustained hypertension	Elevated	Elevated	33	45 / 53	35	NA

BP, blood pressure, ABPM, ambulatory blood pressure monitoring, NA not applicable.
[1] Office <140/90 mmHg and 24-h ABPM <130/80 mmHg.
[2] Office <130/80 mmHg and 24-h ABPM <130/80 mmHg / Daytime ABPM 130/80 mmHg.
[3] Office BP <130/80 mmHg and Daytime ABPM <135/85 mmHg.
[4] Office BP <130/80 mmHg and Daytime ABPM <130/80 mmHg.

Earlier studies reported much higher prevalence rates, reaching up to 51% in type 2 diabetes [41] and even up to 74% in type 1 diabetes [42]. More recent studies have shown, that the prevalence ranges between 7% and 35% in type 2 diabetes [43,44] and between 6% and 27% in type 1 diabetes [18,21,45] (Table 1 and 3). However, the true prevalence rates remain unknown in type 1 diabetes due to the limited number of study participants and differences in cut-off values and time-periods defining WCH in these studies.

Numerous studies have estimated the prognostic significance of WCH in the general population, but the results have been controversial. Findings from the earlier meta-analyses showed that the cardiovascular risk did not differ in those with WCH from those with normal BP [46,47]. In contrast, a more recent meta-analysis reported a slightly greater risk of cardiovascular events and mortality in those with WCH, while no differences were observed for all-cause mortality and stroke, compared with normotensive controls [48]. Another meta-analysis found disparities in risk between antihypertensive drug-treated and untreated individuals [49]. The authors reported higher risk of CVD and mortality only in untreated individuals with WCH, while in treated individuals with WCH no differences in risk were observed compared with normotensive individuals. Similarly, in the most recent meta-analysis, Cohen et al. reported higher cardiovascular risk and mortality in untreated WCH individuals compared to those with normotension, but only when stroke was not included in the definition of cardiovascular events [50]. However, no difference was observed in treated individuals. There is some evidence, that WCH is associated with metabolic abnormalities, such as hyperlipidemia and elevated BMI, that may lead to increased cardiovascular risk and greater tendency for the BP to rise by time and to progress to sustained hypertension [51]. Even though in those with WCH their out-of-office BP values are within the normal range, the BP values tend to be higher than in those with true normotension, which may further explain the increased risk of cardiovascular events [48,51,52]. However, whether pharmacological treatment is beneficial in individuals with WCH needs to be studied with randomized controlled trials [49].

To date, very little is known about the prognostic significance of WCH in type 1 diabetes (Table 3). One study with a limited number of participants estimated the effect of WCH in individuals with type 1 diabetes (20 with WCH and 20 controls with normotension at baseline) on the development of microalbuminuria and sustained hypertension during a 5-year follow-up [53]. In the WCH group, four individuals developed microalbuminuria and only one sustained hypertension, while none in the control group did. Thus, they reported that those with WCH had 25% higher risk of microalbuminuria or sustained hypertension than the controls, and the same individuals had also higher nighttime systolic and diastolic BP at baseline. Previous findings, mainly from the general population, suggest that WCH is not necessarily an innocent clinical condition [51]. Whether that is also the case in type 1 diabetes is not known, and further studies are needed to establish the clinical relevance of this condition. However, close follow-up after a diagnosis of WCH should obviously be recommended for such individuals with type 1 diabetes. Their BP status should be confirmed within 3–6 months and monitored annually with HBPM or ABPM, in order to detect any signs of development of sustained hypertension [54]. In most studies, trained medical staff have measured the office BP with either a mercury sphygmomanometer or an automated oscillometric device. More recently, use of fully automated devices with multiple office BP measurements without an observer present (i.e., unattended clinic BP) have shown to better correlate with daytime BP or ABPM than attended clinic BP [55]. Therefore, it has been suggested, that routine use of unattended BP monitoring may decrease the prevalence of WCH [56].

4. Masked hypertension

Conversely to WCH, masked hypertension (MH) describes individuals with normal office BP but elevated out-of-office BP [57]. Also the prevalence of MH varies considerably, depending on population characteristics, BP measurement technique (HBPM or ABPM) and time-period (i.e., daytime, 24-h or nighttime), and whether or not antihypertensive medication is being used [58]. There is strong evidence that MH is a high-risk BP phenotype, associated with increased risk of target organ damage and cardiovascular events [47,59]. MH is more common in individuals with diabetes and in those with antihypertensive medication than in those without. The population-based International Database on Ambulatory Blood Pressure in Relation to Cardiovascular Outcomes (IDACO) study demonstrated that MH was present in 29% of untreated and in 42% of treated individuals with diabetes (more likely type 2 diabetes), while the corresponding numbers for non-diabetic individuals were 19% and 30% [60]. The authors also reported that untreated individuals with diabetes and MH had similar CVD risk than untreated individuals with stage 1 hypertension (systolic BP 140–159 mmHg and diastolic BP 90–99 mmHg) but lower than in those with stage 2 hypertension (systolic BP $\geq$160 mmHg and diastolic BP $\geq$100 mmHg). In contrast, treated diabetic individuals had similar CVD risk as treated individuals with stage 2 hypertension. The fact that MH is more common in treated individuals may suggest that a subset of those with uncontrolled MH may actually have sustained hypertension [60]. If the treatment has focused on normalizing office BP, ambulatory BP values might still be elevated, and may thus mimic MH [60].

Only a few studies in a limited number of participants and with variable cut-off values and time-periods defining MH, have estimated the prevalence, characteristics, and prognosis of individuals with type 1 diabetes and MH (Table 1 and 3). Findings from a Brazilian study [45] illustrated that the occurrence of MH in adults with type 1 diabetes, who were not treated with antihypertensive therapy, was about 7% of the entire cohort and about 14% among those with normal office BP. Moreover, at baseline about 23% had nocturnal MH. The authors also found an association between nocturnal MH and diabetic retinopathy (odds ratio 3.23 [95% CI 1.29, 8.11], $P = 0.001$). The FinnDiane study ($N = 140$), reported that 23% of adult individuals with type 1 diabetes had MH and about 60% of them were untreated [21]. The same individuals had also higher arterial stiffness (i.e., higher pulse-wave-velocity), a condition that reflects structural and functional changes preceding manifest hypertension and vascular complications, compared with normotensive individuals ($P < 0.001$). In a Spanish study ($N = 85$) 24% of the participants had MH at baseline [61]. During a 7-year follow-up the nocturnal systolic BP was associated with the development of microalbuminuria and the nocturnal diastolic BP with the progression of retinopathy and sustained hypertension [61]. Also a more recent study from Thailand in children and adolescents with type 1 diabetes ($N = 33$) reported that 27% of the cohort had MH [62]. They also found that the presence of unstable glycaemia was related to MH ($P = 0.05$). Basiratnia et al. reported a lower prevalence of MH in 81 children and adolescents with type 1 diabetes: as only 12% fulfilled the definition of MH [63]. Notably, among these nocturnal hypertension was more common than elevated daytime BP (37% vs. 17%) [63].

Several guidelines recommend using daytime HBPM or ABPM to detect MH. Although HBPM can be an alternative method, if ABPM is not available, it is typically unable to evaluate nighttime hypertension, a potentially crucial component of MH, especially in individuals with type 1 diabetes [60,62]. The latest European Society of Hypertension guidelines recommend using 24-h ABPM and nighttime BP rather than daytime BP or HBPM alone to define MH [34]. A recent study in adults without antihypertensive drugs from the New York metropolitan area, reported discordances between ABPM and HBPM; the prevalence of MH was about 11% with HBPM and 26% with ABPM [64]. In line with these findings, we reported that by using daytime ABPM only among individuals with type 1 diabetes, about one-fifth of those affected by MH would have been missed [21]. Consequently, screening strategies, which rely on HBPM, may misclassify many individuals with MH as normotensive [64]. Overall, MH seems to be prevalent in individuals with type 1 diabetes, which highlights the importance of ABPM to effectively

Table 3
Studies reporting the prevalence, risk factors and prognosis of related different disturbed BP patterns in individuals with type 1 diabetes.

Primary (i.e., essential) or/and secondary hypertension				
Study	Definition of hypertension	Cohort	Prevalence of hypertension	Outcomes
de Boer et al., 2008, DCCT/EDIC, US [6]	BP ≥140/90 mmHg or antihypertensive treatment for elevated BP	1441 adults with type 1 diabetes: 733 with conventional and 711 with intensive insulin therapy, 15.8-year follow-up	NA	Intensive therapy →24% reduction in the risk of incident hypertension during EDIC study follow-up (HR 0.76 [95% CI 0.64–0.92])
Chillaron et al., 2011, Spain [10]	BP ≥130/80 mmHg or antihypertensive treatment for elevated BP	291 adults with type 1 diabetes	29.9%, (49.9% in treated individuals)	NA
Lithovius et al., 2014, FinnDiane Study, Finland [17]	BP ≥130/85 mmHg / BP ≥130/80 mmHg	3678 adults with type 1 diabetes	60.9% / 70.3%	NA
Ahmadizar et al., 2018, CPRD, UK [108]	BP ≥140/90 mmHg or antihypertensive treatment	3728 type 1 diabetes children and adolescents (<19 years of age at baseline) in 1988–2014 and 18,513 age-and gender-matched diabetes-free peers, 20-year follow-up	35.2% in type 1 diabetes 11.4% in non-diabetic controls	NA
White-coat hypertension (WCH)				
Study	**Definition of WCH**	**Cohort**	**Prevalence of WCH**	**Outcomes**
Theilade et al., 2012, Steno Diabetes Center, Denmark [18]	Office BP ≥130/80 mmHg and 24-h or daytime ABPM <130/80 mmHg	569 adults with type 1 diabetes	24-h ABPM 27% Daytime ABPM 18%	NA
Lithovius et al., 2018, FinnDiane Study, Finland [21]	Office BP ≥140/90 mmHg and ABPM <130/80 mmHg	140 adults with type 1 diabetes	6%	NA
Flores et al., 2000, Spain [42]	Office BP ≥140/90 mmHg and daytime ABPM ≤135/85 mmHg	47 individuals with type 1 diabetes: 27 newly diagnosed hypertension (defined by office BP) and 20 with normotension	75% in individuals with newly diagnosed hypertension	NA
Flores et al., 2006, Spain [53]	Office BP >140/90 mmHg and daytime BP <135/85 mmHg	40 type 1 diabetes individuals: 20 with WCH and 20 normotensive controls with similar age and normal AER at baseline, 5-year follow-up	NA	Those with WCH had 25% higher risk to develop microalbuminuria or sustained hypertension than controls
Rodriges et al., 2010, Brazil [45]	Office BP >130/80 mmHg and daytime ABPM <135/85 mmHg	188 adults with type 1 diabetes	10.1%	NA
Masked hypertension (MH)				
Study	**Definition of MH**	**Cohort**	**Prevalence of MH**	**Outcomes**
Theilade et al., 2012, Steno Diabetes Center, Denmark [18]	Office BP <130/80 mmHg and 24-h and daytime ABPM ≥130/80 mmHg	569 adults type 1 diabetes	24-h ABPM 10% Daytime ABPM 13%	NA
Lithovius et al., 2014, FinnDiane Study, Finland [21]	Office BP <140/90 mmHg and 24-h ABPM ≥130/80 mmHg	140 adults with type 1 diabetes	23%	NA
Rodrigues et al., 2010, Brazil [45]	Office BP <130/80 mmHg (without antihypertensive treatment) and daytime ABPM ≥135/85 mmHg	188 adults with type 1 diabetes Of them 103 normotensive by office BP measurement	The whole cohort 7.4% Normotensive adults 13.6% Masked nocturnal hypertension 23.3%	Association between masked nocturnal hypertension and diabetic retinopathy (OR 3.23 [95% CI 1.29,8.11], $P = 0.02$)
Mateo-Gavira et al., 2016, Spain [61]	Office BP <130/80 mmHg and 24-h ABPM ≥130/≥80 mmHg	85 adults with type 1 diabetes and normal AER 7-year follow-up	24%	NA
Homhuan et al., 2021, Thailand [62]	Age < 18 years: Office BP <95th percentile by gender, age and height, and ABPM ≥95th percentile by gender and height and BP load (a percentage of readings above the 95th percentile by gender and height over the total readings) ≥ 25% either during awake, sleep, or both periods Age ≥ 18 years: Office BP ≥ 140/90 mmHg and awake	33 children and adolescents (aged 6–21 years) with type 1 diabetes	27%	The presence of unstable glycaemia was related to *MH* ($P = 0.05$).

(*continued on next page*)

Table 3 (*continued*)

Primary (i.e., essential) or/and secondary hypertension				
Study	Definition of hypertension	Cohort	Prevalence of hypertension	Outcomes
	ABPM ≥135/85 mmHg or sleep ABPM ≥120/70 mmHg			
Nocturnal hypertension (NH)				
Study	**Definition of NH**	**Cohort**	**Prevalence of NH**	**Outcomes**
Lithovius et al., 2018, FinnDiane Study, Finland [21]	Increased absolute values of nighttime BP (≥120/≥70 mmHg)	140 adults with type 1 diabetes	51%, half of them not treated One-third had either normal office BP (26% not treated) or normal daytime ABPM (21% not treated) 6% had isolated nocturnal hypertension	NA
Mateo-Gavira et al., 2016, Spain [61]	Increased absolute values of nighttime BP (≥120/≥70 mmHg)	85 adults with type 1 diabetes who had normal albuminuria 7-year follow-up	NA	Nocturnal systolic hypertension was associated with development of microalbuminuria and nocturnal diastolic hypertension to progression of retinopathy and sustained hypertension
Treatment-resistant hypertension (TRH)				
Study	**Definition of TRH**	**Cohort**	**Prevalence of TRH**	**Outcomes**
Lithovius et al., 2014, FinnDiane Study, Finland [17]	Failure to achieve the goal BP (<130/85 mmHg) after using a minimum of 3 anti-hypertensive drugs, from different classes, one of which was a diuretic	3678 adults with type 1 diabetes	21.8%	TRH was associated higher age, lower eGFR and higher weight-to-height ratio, as well as micro- and macroalbuminuria
Lithovius et al., 2020, FinnDiane Study, Finland [22]	Failure to achieve the goal BP (<130/85 mmHg) after using a minimum of 3 anti-hypertensive drugs, from different classes, one of which was a diuretic or controlled BP with ≥4 drugs	1103 adults with type 1 diabetes (those with ESKD excluded) who had antihypertensive treatment at baseline Median follow-up 14.8 years	18.7%	TRH was associated with increased risk of diabetic nephropathy progression (HR 1.95 [95% CI 1.37, 2.79], $P = 0.0002$) compared with the controlled BP group TRH did not predict incident CHD, stroke and all-cause mortality beyond albuminuria and reduced kidney function In those with normal AER or microalbuminuria the risk of stroke was 3.5 higher in those with TRH compared with the controlled BP group

BP, blood pressure; DCCT/EDIC, Diabetes Control and Complications Trial/ Epidemiology of Diabetes Interventions and Complications; CPRD, Clinical Practice Research Datalink; NA, not applicable; HR hazard ratio; ABPM, ambulatory blood pressure monitoring; WCH, white-coat hypertension; FinnDiane, Finnish Diabetic Nephropathy; AER, albumin excretion rate; MH, masked hypertension; OR, odds ratio; NH, nocturnal hypertension; TRH, treatment-resistant hypertension; eGFR, estimated glomerular filtration rate.

identify these high-risk individuals. Moreover, further longitudinal studies are needed to estimate the true prognostic significance of MH, and to assess the effect of pharmacological interventions to reduce the risk of adverse outcomes in individuals with type 1 diabetes and MH [21].

5. Disturbed circadian BP variability

The development of non-invasive ambulatory BP devices have made it possible to follow the BP variation around the clock and to identify several patterns of disturbed diurnal BP variability, such as abnormal dipping patterns or nocturnal hypertension [34]. According to the classic definitions, individuals are designated as dippers, when the nocturnal fall is ≥10% of the daytime values (i.e. normal circadian rhythm), and non-dippers, when the corresponding value is <10% (pathological circadian rhythm) [34]. More recently, this classification has been extended into four categories: extreme-dippers (marked nocturnal BP fall >20% of daytime values), dippers (nocturnal BP fall >10% and ≤ 20% of daytime values), non-dippers (nocturnal fall >0% and < 10% of daytime values) and inverse dippers or risers (nocturnal fall ≤0% of daytime values) [36,39]. Nocturnal hypertension, which could be the first manifestation of hypertension, denotes an increased absolute level of the nighttime BP above the threshold (≥120/70 mmHg) [39,65]. Isolated nocturnal hypertension is often defined as normal office, 24-h and daytime BP control, but elevated nighttime BP only [34].

The prevalence of non-dippers is particularly high in certain subgroups, such as in the elderly [66], in those with chronic kidney disease [67], in those with RH [68] and in those with diabetes [69,70]. In children and adolescents with type 1 diabetes ($N = 2105$), the prevalence of pathological dipping (i.e., nocturnal fall <10%) was about 49% for systolic BP and 17.5% for diastolic BP [69]. In the FinnDiane cohort (N = 140), about 50% of the individuals had elevated nocturnal hypertension, and half of them were not treated with antihypertensive drugs [21]. One-third of them had either normal office BP or normal daytime BP, and 6% of the cohort had isolated nocturnal hypertension. Notably, in those with MH about 12% were non-dippers, and 59% had nocturnal hypertension, while the proportions were 30% and 87% in those with sustained hypertension, respectively [21]. Also 13% of those with true normotension demonstrated a non-dipping pattern [21].

A growing amount of evidence have shown that both non-dippers and those with elevated nighttime BP have higher likelihood for fatal and non-fatal CVD events and target organ damage than those with normal circadian BP pattern [71–73]. There is also compelling evidence that nocturnal BP is a stronger predictor of adverse outcomes and more accurate in cardiovascular risk stratification than daytime BP [39].

Although nocturnal hypertension is a predictor of adverse outcomes, independently of circadian BP pattern, the worst risk profile has been observed in those with both a non-dipping pattern and nocturnal hypertension [74].

In type 1 diabetes, non-dipping pattern was demonstrated as a clinical marker of diabetic autonomic neuropathy [75] and renal damage [76], and thus it emphasizes the importance of characterizing the nocturnal BP profile by ABPM in individuals with type 1 diabetes. Early findings (Table 3), dating back to the early 1990s, already showed an association between a blunted nocturnal fall and microalbuminuria ($N = 90$) [77], as well as between a lower day-night systolic BP variation and cardiovascular autonomic neuropathy ($N = 87$) [78]. Later, in a prospective study ($N = 75$) it was shown that an increased systolic BP during sleep precedes the development of microalbuminuria [27]. However, in those with a normal dipping pattern, progression from normal AER to microalbuminuria appeared to be less likely [27]. Moreover, in a South-Korean study of children and adolescents with type 1 diabetes ($N = 82$), about 37% had elevated BP only during nighttime, and the same participants had also significantly greater carotid intima-media thickness (a measure of subclinical atherosclerosis) than in the normotensive group [79]. More recently, authors from Spain discovered that nocturnal systolic BP was associated with the development of microalbuminuria and nocturnal diastolic BP with progression of retinopathy and sustained hypertension in 85 individuals with type 1 diabetes during a 7-year follow-up [61]. Overall, the findings from these small studies indicate, that nocturnal hypertension may be an early predictor of microvascular complications and sustained hypertension in individuals with type 1 diabetes. Bedtime administration of BP-lowering medication has been proposed for those with nocturnal hypertension [73]. However, very little is known whether the bedtime dosing would improve the prognosis for the individuals with type 1 diabetes with disturbed circadian rhythm.

Apart from day-night BP changes, the number of additional measures derived by ABPM, including 24-h BP variability, postprandial hypertension or morning surge, may have prognostic value for individuals with diabetes, but only a few studies have assessed these phenomena [30]. Both overall 24-h BP variability [80,81] and postprandial hypertension [82] have been shown to indicate autonomic neuropathy. Morning BP surge (BP increase when waking-up in the morning) is a physiological phenomenon, but an exaggerated morning surge may increase the risk of CVD in the general hypertensive population [83]. Only a few studies have demonstrated an association between an exaggerated morning surge and diabetic complications in individuals with diabetes [84–86]. However, up to now, there has been no consensus regarding the definition, threshold, and prognostic impact of the morning surge. Overall, there is still uncertainty about the clinical significance of these measures among individuals with type 1 diabetes.

6. Treatment-resistant hypertension

Certain subgroups of individuals with elevated BP are designated as having treatment-resistant hypertension (TRH). This is a clinical condition, characterized by failure to achieve the target BP even after using a minimum of three antihypertensive drugs at maximum tolerated doses, from different classes, one of which is a diuretic [87]. By extension, also individuals, whose BP requires four or more antihypertensive drugs to be controlled, are considered resistant to treatment [87]. A more recent revision of the AHA Scientific Statement on the definition of TRH recommends, that the antihypertensive regimen should include a long-acting calcium channel blocker, a blocker of the renin-angiotensin system, and a diuretic at maximum or maximally tolerated doses [88]. Moreover, individuals with white-coat effect and non-adherence to medication should be excluded [88]. Therefore, the term apparent TRH would be more precise, especially when information about medication doses, adherence to treatment or out-of-office BP values are missing [88]. Although the definition is arbitrary with respect to the number of medications required, TRH was initially introduced to recognize and improve the management of antihypertensive drug-treated individuals, who may benefit from special diagnostic and therapeutic counseling [88,89]. Since then, a large number of studies have demonstrated the association of TRH with higher risk of cerebrovascular, cardiovascular and kidney disease outcomes compared with non-TRH, underscoring the importance of TRH in clinical practice [88].

The prevalence of TRH is widely reported from both large well-designed observational population-based and clinical-based studies among hypertensive drug-treated adults. The prevalence of TRH have ranged from 12 to 15% in population-based studies [89–92], while slightly higher numbers have been reported in selected populations, such as in individuals with chronic kidney disease [93–95] or type 2 diabetes [96]. A more recent study from Italy reported that 14.9% of individuals with type 2 diabetes had TRH when using the threshold of <130/80 mmHg, and after those with end-stage kidney disease (ESKD) were excluded [97]. Although data are scarce regarding the prevalence of TRH in individuals with type 1 diabetes, it seems that the prevalence of TRH is slightly higher than what has been reported in the general hypertensive population (Table 3). In the FinnDiane cohort the prevalence ranges from 17% (BP threshold of <140/90 mmHg) to 22% (BP threshold of <130/85 mmHg) [17]. When individuals with ESKD were excluded, the prevalence rate was 18.7% with a threshold of <130/85 mmHg [22]. All these studies reflect apparent TRH, and may therefore overestimate the true prevalence of TRH.

Only a few limited studies from the general hypertensive population have reported the prevalence of true TRH. In true TRH, pseudo-RH has to be eliminated by accurate BP measurements and BP targets, by using out-of-office BP monitoring to exclude the white-coat effect and by verifying adherence to antihypertensive medication [98]. In fact, true TRH is present in approximately half of individuals with TRH, who are uncontrolled at the office [89]. There is also some evidence that only 50% of individuals with apparent TRH have optimal antihypertensive therapy, and about 40% might have either WCH or are non-adherent to the treatment [99]. However, in individuals with type 1 diabetes the prevalence of true TRH remains unknown, as previous results reflect only apparent TRH.

Several observational studies in the general population have shown, that apparent TRH is independently associated with increased risk of mortality as well as of adverse cardiovascular and kidney outcomes when compared to those, who have controlled BP [100–103]. Moreover, among individuals with chronic kidney disease TRH is associated with higher risk of all-cause mortality and cardiovascular outcomes compared with those without TRH [104]. Interestingly, in individuals with type 2 diabetes from the Renal Insufficiency And Cardiovascular Events (RIACE) study, TRH did not predict all-cause mortality, when indices of target organ damage were considered [97]. Similarly, a subgroup analysis from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) showed that TRH was associated with all-cause mortality only in non-diabetic individuals, but not in those with diabetes [105]. The authors of the RIACE suggested, that diabetes per se poses a greater risk of mortality, which may mask the risk associated with TRH [97].

DKD is probably one of the most common causes of TRH among individuals with type 1 diabetes. The FinnDiane Study demonstrated, that the presence and severity of CKD increases the likelihood of TRH. While less than one-tenth of those with normal AER or microalbuminuria met the criteria for TRH, the proportion was 40% in those on dialysis [17]. More than a every second of those at the predialytie stage (estimated glomerular filtration rate [eGFR] 15–29 ml/min/1.73 m^2) qualified for the definition of TRH [17]. Several mechanisms, such as overactivation of the renin-angiotensin-aldosterone system, impaired sodium excretion and increased sympathetic nervous system activity, may lower the response to antihypertensive therapy in individuals with impaired kidney function [88]. There are, however, very little published data on the long-term prognosis of the individuals with type 1 diabetes and TRH. In

line with the RIACE and ALLHAT studies, the FinnDiane Study demonstrated, that TRH was associated with all-cause mortality, but not beyond albuminuria and reduced kidney function [22]. Of note, after full adjustment for clinical confounders (including kidney disease markers), TRH was neither associated with incident coronary heart disease nor stroke. In contrast, the risk of progression of DKD remained two-fold increased after full adjustment.

Even before the development of DKD in individuals with type 1 diabetes, the risk of incident stroke was 3.5 times higher in those with TRH compared with those, who had well-controlled BP [22]. This highlights the importance to detect TRH in high-risk individuals, to be able to provide optimal clinical care and counseling as early as possible [104]. However, there are no high-quality data available regarding the optimal BP treatment targets for such individuals [29]. Therefore, clinical trials are needed to find the optimal BP treatment targets (i.e., office BP, HBPM and AMBP), preferred combination of antihypertensive drugs, as well as the efficacy of device-based therapies to optimize the management of TRH throughout the DKD spectrum [104].

7. Conclusions

Several disturbed BP patters are common and may indicate the development of diabetic complications in individuals with type 1 diabetes. ABPM is a crucial and accurate tool to detect nocturnal hypertension and dipping patterns, to reduce the likelihood of false-positive results by detecting WCH, and false-negative results by detecting MH, to confirm the true TRH phenotype, and to ascertain adequate BP control by prescribed antihypertensive therapy throughout the entire 24-h period [25,104]. Numerous studies have shown the superiority of ABPM over office BP or HBPM to detect disturbed BP patterns, including nocturnal and MH, conditions that are an important part of the early diagnosis and management of hypertension in individuals with type 1 diabetes [26,27,106]. In spite of indisputable advantages of ABPM, ABPM is still not available for all individuals, and hence not an integral part of the screening and management of hypertension. However, advances in technology, may provide more validated devices at reduced costs, as well as various software and web-based applications to report the results, all steps that can improve the availability of ABPM in the future, as well as facilitate an accurate diagnosis and management of hypertension in individuals with type 1 diabetes [107]. Meanwhile, there are several key research priorities (Table 4), that need to be explored to determine the true prevalence and prognosis of disturbed BP patterns, and to establish, who would benefit the most from APBM. Furthermore, there is an unmet need for optimization of the diagnosis and management of different disturbed patterns of hypertension in individuals with type 1 diabetes.

Author contributions

R.L. wrote the manuscript, reviewed and edited the manuscript. P.-H. G. contributed to discussion, reviewed and edited the manuscript. P.-H. G. has full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analyses. Both authors gave their final approval of this version of the manuscript.

Duality of interest

P—H.G. has received lecture honoraria from Astellas, Astra Zeneca, Bayer, Boehringer Ingelheim, Eli Lilly, EloWater, Genzyme, Medscape, MSD, Mundipharma, Novartis, Novo Nordisk, Peer Voice, Sanofi and Sciarc. P—H.G. is an advisory board member for AbbVie, Astellas, Astra Zeneca, Bayer, Boehringer Ingelheim, Eli Lilly, Medscape, MSD, Mundipharma, Nestlé, Novartis, Novo Nordisk and Sanofi. P—H.G. has received investigator-initiated grants from Eli Lilly and Roche. No other potential conflicts of interest relevant to this article were reported. The funding sources were not involved in the design or conduct of the study.

Table 4
Suggestions for future areas of research related to different disturbed patters of hypertension in type 1 diabetes.

Pattern	What is already known?	Unresolved issues
White-coat hypertension (WCH)	Findings controversial regarding the prognostic significance of WCH in the general population	What is the most reliable method (i.e., unattended clinic BP, HBPM or ABPM) to define WCH?
		What is the prevalence of WCH in individuals with type 1 diabetes?
		What is the prognosis of the individuals with WCH compared to those who have controlled or sustained hypertension in type 1 diabetes?
		Should individuals with WCH be treated at all?
Masked hypertension (MH)	Individuals with MH have an increased risk of target organ damage compared to those with normotension	Who should be screened for MH?
		What is the true prevalence of MH in type 1 diabetes?
	Up to one-quarter of the individuals with type 1 diabetes have masked hypertension, a pattern that cannot be detected by office-based BP alone	What time-period (daytime, 24-h or nighttime ABPM) and out-of- office BP monitoring (HBPM or ABPM) should be used to diagnose MH?
	Small studies with limited number of participants have found an association between MH and arterial stiffness, MH and retinopathy, MH and unstable glycemia, as well as an association between MH and the development of microalbuminuria and sustained hypertension	Does MH predict diabetic complications in type 1 diabetes?
		What is the prognostic significance of lifestyle and pharmacological interventions in MH?
Nocturnal hypertension (NH)	The prevalence of NH is high among individuals with type 1 diabetes	What is the best pharmacological intervention to decrease NH?
	Individuals with type 1 diabetes and microalbuminuria are more likely to be non-dippers than those without microalbuminuria	Would bedtime dosing decrease the prevalence of NH and improve the prognosis of the individuals with type 1 diabetes with NH?
	Nocturnal systolic BP precedes the development of microalbuminuria	
	NH may be an important early predictor of microvascular complications and sustained hypertension	
Non-dipping pattern	The non-dipping pattern is common in individuals with type 1 diabetes (already in children and adolescents)	Does transformation of non-dippers to dippers prevent or delay the progression of kidney disease and other complications?
	Diabetic autonomic neuropathy and renal damage frequently observed in non-dippers	
Morning surge (MS)	Exaggerated morning BP surge is a risk for CVD events in the general population However, no consensus about the definition, pathological	What is the prevalence and clinical meaning of MS in individuals with type 1 diabetes?

(continued on next page)

Table 4 (*continued*)

Pattern	What is already known?	Unresolved issues
	threshold, and prognostic impact	
Treatment-resistant hypertension (TRH)	The prevalence of apparent TRH is higher in individuals with type 1 diabetes than in the general hypertensive population Apparent TRH is associated with death, CHD and stroke, but not beyond albuminuria and/or reduced kidney function in individuals with type 1 diabetes Before the development of DKD the risk of incident stroke was 3.5 times higher in those with apparent TRH compared with those who had BP in control	What is the prevalence of true TRH based on the latest definition? What is the prognostic significance of true TRH in type 1 diabetes? What is the optimal BP treatment targets (i.e., office BP, HBPM and AMBP), preferred combination of antihypertensive therapy, as well as the efficacy of device-based therapies in RH?

WCH, white-coat hypertension; BP, blood pressure; HBPM, home blood pressure monitoring; ABPM, ambulatory blood pressure monitoring; MH, masked hypertension; NH, nocturnal hypertension; MS, morning surge; CVD, cardiovascular disease; CAD, coronary artery disease; DKD, diabetic kidney disease.

All other authors declare that there is no duality of interest associated with this manuscript.

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References

[1] Harjutsalo V, Pongrac Barlovic D, Groop PH. Long-term population-based trends in the incidence of cardiovascular disease in individuals with type 1 diabetes from Finland: a retrospective, nationwide, cohort study. Lancet Diabetes Endocrinol 2021;9:575–85. https://doi.org/10.1016/S2213-8587(21)00172-8.

[2] Jansson Sigfrids F, Groop PH, Harjutsalo V. Incidence rate patterns, cumulative incidence, and time trends for moderate and severe albuminuria in individuals diagnosed with type 1 diabetes aged 0-14 years: a population-based retrospective cohort study. Lancet Diabetes Endocrinol 2022;10:489–98. https://doi.org/10.1016/S2213-8587(22)00099-7.

[3] Fuller JH, Stevens LK, Wang SL. Risk factors for cardiovascular mortality and morbidity: the WHO Mutinational study of vascular disease in diabetes. Diabetologia 2001;44:S54–64. https://doi.org/10.1007/pl00002940.

[4] Jensen T, Borch-Johnsen K, Kofoed-Enevoldsen A, Deckert T. Coronary heart disease in young type 1 (insulin-dependent) diabetic patients with and without diabetic nephropathy: incidence and risk factors. Diabetologia 1987;30:144–8. https://doi.org/10.1007/BF00274218.

[5] Forrest KY, Becker DJ, Kuller LH, Wolfson SK, Orchard TJ. Are predictors of coronary heart disease and lower-extremity arterial disease in type 1 diabetes the same? A prospective study. Atherosclerosis 2000;148:159–69. https://doi.org/10.1016/s0021-9150(99)00217-8.

[6] de Boer IH, Kestenbaum B, Rue TC, Steffes MW, Cleary PA, Molitch ME, et al. Insulin therapy, hyperglycemia, and hypertension in type 1 diabetes mellitus. Arch Intern Med 2008;168:1867–1873. https://doi.org/10.1001/archinternmed.2008.2.

[7] Sasso FC, Simeon V, Galiero R, Caturano A, De Nicola L, Chiodini P, et al. The number of risk factors not at target is associated with cardiovascular risk in a type 2 diabetic population with albuminuria in primary cardiovascular prevention. Post-hoc analysis of the NID-2 trial. Cardiovasc Diabetol 2022;21:235. https://doi.org/10.1186/s12933-022-01674-7.

[8] Halminen J, Sattar N, Rawshani A, Eliasson B, Eeg-Olofsson K, Bhatt DL, et al. Range of risk factor levels, risk control, and temporal trends for nephropathy and end-stage kidney disease in patients with type 1 and type 2 diabetes. Diabetes Care 2022;45:2326–35. https://doi.org/10.2337/dc22-0926.

[9] Arauz-Pacheco C, Parrott MA, Raskin P. The treatment of hypertension in adult patients with diabetes. Diabetes Care 2002;25:134–47. https://doi.org/10.2337/diacare.27.2007.s65.

[10] Chillaron JJ, Sales MP, Flores-Le-Roux JA, Murillo J, Benaiges D, Castells I, et al. Insulin resistance and hypertension in patients with type 1 diabetes. J Diabetes Complications 2011;25:232–6. https://doi.org/10.1016/j.jdiacomp.2011.03.006.

[11] Mogensen CE. Microalbuminuria and hypertension with focus on type 1 and type 2 diabetes. J Intern Med 2003;254:45–66. https://doi.org/10.1046/j.1365-2796.2003.01157.x.

[12] Hasslacher C, Stech W, Wahl P, Ritz E. Blood pressure and metabolic control as risk factors for nephropathy in type 1 (insulin-dependent) diabetes. Diabetologia 1985;28:6–11. https://doi.org/10.1007/BF00276992.

[13] Mathiesen ER, Ronn B, Jensen T, Storm B, Deckert T. Relationship between blood pressure and urinary albumin excretion in development of microalbuminuria. Diabetes 1990;39:245–9. https://doi.org/10.2337/diab.39.2.245.

[14] Fagerudd JA, Tarnow L, Jacobsen P, Stenman S, Nielsen FS, Pettersson-Fernholm KJ, et al. Predisposition to essential hypertension and development of diabetic nephropathy in IDDM patients. Diabetes 1998;47:439–44. https://doi.org/10.2337/diabetes.47.3.439.

[15] Ronnback M, Fagerudd J, Forsblom C, Pettersson-Fernholm K, Reunanen A, Groop PH, et al. Altered age-related blood pressure pattern in type 1 diabetes. Circulation 2004;110:1076–82. https://doi.org/10.1161/01.CIR.0000139903.29522.8D.

[16] Maahs DM, Kinney GL, Wadwa P, Snell-Bergeon JK, Dabelea D, Hokanson J, et al. Hypertension prevalence, awareness, treatment, and control in an adult type 1 diabetes population and a comparable general population. Diabetes Care 2005;28:301–6. https://doi.org/10.2337/diacare.28.2.301.

[17] Lithovius R, Harjutsalo V, Forsblom C, Saraheimo M, Groop PH, FinnDiane Study Group.. Antihypertensive treatment and resistant hypertension in patients with type 1 diabetes by stages of diabetic nephropathy. Diabetes Care 2014;37:709–17. https://doi.org/10.2337/dc13-2023.

[18] Theilade S, Lajer M, Joergensen C, Persson F, Rossing P. Discrepancy between tonometric ambulatory and cuff-based office blood pressure measurements in patients with type 1 diabetes. J Clin Hypertens Greenwich Conn 2012;14:686–93. https://doi.org/10.1111/j.1751-7176.2012.00689.x.

[19] Livingstone SJ, Looker HC, Hothersall EJ, Wild SH, Lindsay RS, Chalmers J, et al. Risk of cardiovascular disease and total mortality in adults with type 1 diabetes: Scottish registry linkage study. PLoS Med 2012;9(10):e1001321. https://doi.org/10.1371/journal.pmed.1001321.

[20] McFarlane PA. Resistant hypertension in adults with type 1 or 2 diabetes: a structured diagnostic approach. Can J Diabetes 2018;42:173–8. https://doi.org/10.1016/j.jcjd.2018.01.001.

[21] Lithovius R, Gordin D, Forsblom C, Saraheimo M, Harjutsalo V, Groop PH, et al. Ambulatory blood pressure and arterial stiffness in individuals with type 1 diabetes. Diabetologia 2018;61:1935–45. https://doi.org/10.1007/s00125-018-4648-5.

[22] Lithovius R, Harjutsalo V, Mutter S, Gordin D, Forsblom C, Groop PH, et al. Resistant hypertension and risk of adverse events in individuals with type 1 diabetes: a Nationwide prospective study. Diabetes Care 2020;43:1885–92. https://doi.org/10.2337/dc20-0170.

[23] Mancia G, Verdecchia P. Clinical value of ambulatory blood pressure: evidence and limits. Circ Res 2015;116:1034–45. https://doi.org/10.1161/CIRCRESAHA.116.303755.

[24] Shimbo D, Abdalla M, Falzon L, Townsend RR, Muntner P. Role of ambulatory and home blood pressure monitoring in clinical practice: a narrative review. Ann Intern Med 2015;163:691–700. https://doi.org/10.7326/M15-1270.

[25] Hodgkinson J, Mant J, Martin U, Guo B, Hobbs FD, Deeks JJ, et al. Relative effectiveness of clinic and home blood pressure monitoring compared with ambulatory blood pressure monitoring in diagnosis of hypertension: systematic review. BMJ 2011;342:d3621. https://doi.org/10.1136/bmj.d3621.

[26] Stella P, Tabak AG, Zgibor JC, Orchard TJ. Late diabetes complications and non-dipping phenomenon in patients with type 1 diabetes. Diabetes Res Clin Pract 2006;71:14–20. https://doi.org/10.1016/j.diabres.2005.05.001.

[27] Lurbe E, Redon J, Kesani A, Pascual JM, Tacons J, Alvarez V, et al. Increase in nocturnal blood pressure and progression to microalbuminuria in type 1 diabetes. N Engl J Med 2002;347:797–805. https://doi.org/10.1056/NEJMoa013410.

[28] Pickering TG, Eguchi K, Kario K. Masked hypertension: a review. Hypertens Res 2007;30:479–88. https://doi.org/10.1291/hypres.30.479.

[29] American Diabetes Association. Cardiovascular disease and risk management: standards of medical Care in Diabetes-2021. Diabetes Care 2021;44:S125–50. https://doi.org/10.2337/dc21-ad09a.

[30] Parati G, Bilo G. Should 24-h ambulatory blood pressure monitoring be done in every patient with diabetes? Diabetes Care 2009;32:S298–304. https://doi.org/10.2337/dc09-S326.

[31] Whelton PK, Carey RM, Aronow Jr WS, Collins KJ, Himmelfarb CD, 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:e13–115. https://doi.org/10.1161/HYP.0000000000000065.

[32] Herd JA. Cardiovascular response to stress. Physiol Rev 1991;71:305–30. https://doi.org/10.1152/physrev.1991.71.1.305.

[33] Spruill TM, Pickering TG, Schwartz JE, Mostofsky E, Ogedegbe G, Clemow L, et al. The impact of perceived hypertension status on anxiety and the white coat effect. Ann Behav Med 2007;34:1–9. https://doi.org/10.1007/BF02879915.

[34] O'Brien E, Parati G, Stergiou G, Asmar R, Beilin L, Bilo G, et al. European Society of Hypertension position paper on ambulatory blood pressure monitoring.

J Hypertens 2013;31:1731–68. https://doi.org/10.1097/HJH.0b013e328363e964.
[35] Grassi G, Seravalle G, Buzzi S, Magni L, Brambilla G, Quarti-Trevano F, et al. Muscle and skin sympathetic nerve traffic during physician and nurse blood pressure measurement. J Hypertens 2013;31:1131–5. https://doi.org/10.1097/HJH.0b013e3283605c71.
[36] Williams B, Mancia G, Spiering W, Rosei EA, Azizi M, Burnier M, et al. ESC/ESH guidelines for the management of arterial hypertension. The Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension. J Hypertens 2018;36:1953–2041. https://doi.org/10.1097/HJH.0000000000001940.
[37] Mancia G, Zanchetti A. White-coat hypertension: misnomers, misconceptions and misunderstandings. What should we do next? J Hypertens 1996;14:1049–52. https://doi.org/10.1097/00004872-199609000-00001.
[38] Mancia G, Facchetti R, Cuspidi C, Bombelli M, Corrao G, Grassi G. Limited reproducibility of MUCH and WUCH: evidence from the ELSA study. Eur Heart J 2020;41:1565–71. https://doi.org/10.1093/eurheartj/ehz651.
[39] Parati G, Stergiou G, O'Brien E, Asmar R, Beilin L, Bilo G, et al. European Society of Hypertension practice guidelines for ambulatory blood pressure monitoring. J Hypertens 2014;32:1359–66. https://doi.org/10.1097/HJH.0000000000000221.
[40] Gorostidi M, Vinyoles E, Banegas JR, de la Sierra A. Prevalence of white-coat and masked hypertension in national and international registries. Hypertens Res 2015;38:1–7. https://doi.org/10.1038/hr.2014.149.
[41] Puig JG, Ruilope LM, Ortega R. Antihypertensive treatment efficacy in type II diabetes mellitus. Dissociation between casual and 24-hour ambulatory blood pressure. Spanish Multicenter Study Group. Hypertension 1995;26:1093–9. https://doi.org/10.1161/01.hyp.26.6.1093.
[42] Flores L, Recasens M, Gomis R, Esmatjes E. White coat hypertension in type 1 diabetic patients without nephropathy. Am J Hypertens 2000;13:560–3. https://doi.org/10.1016/s0895-7061(00)00232-6.
[43] Gorostidi M, de la Sierra A, Gonzalez-Albarran O, Segura J, de la Cruz JJ, Vinyoles E, et al. Abnormalities in ambulatory blood pressure monitoring in hypertensive patients with diabetes. Hypertens Res 2011;34:1185–9. https://doi.org/10.1038/hr.2011.100.
[44] Kramer CK, Leitao CB, Canani LH, Gross JL. Impact of white-coat hypertension on microvascular complications in type 2 diabetes. Diabetes Care 2008;31:2233–7. https://doi.org/10.2337/dc08-1855.
[45] Rodrigues TC, Canani LH, Viatroski RS, Hoffmann LH, Esteves JF, Gross JL. Masked hypertension, nocturnal blood pressure and retinopathy in normotensive patients with type 1 diabetes. Diabetes Res Clin Pract 2010;87:240–5. https://doi.org/10.1016/j.diabres.2009.10.016.
[46] Fagard RH, Cornelissen VA. Incidence of cardiovascular events in white-coat, masked and sustained hypertension versus true normotension: a meta-analysis. J Hypertens 2007;25:2193–8. https://doi.org/10.1097/HJH.0b013e3282ef6185.
[47] Pierdomenico SD, Cuccurullo F. Prognostic value of white-coat and masked hypertension diagnosed by ambulatory monitoring in initially untreated subjects: an updated meta analysis. Am J Hypertens 2011;24:52–8. https://doi.org/10.1038/ajh.2010.203.
[48] Briasoulis A, Androulakis E, Palla M, Papageorgiou N, Tousoulis D. White-coat hypertension and cardiovascular events: a meta-analysis. J Hypertens 2016;34:593–9. https://doi.org/10.1097/HJH.0b013e3282ef6185.
[49] Huang Y, Huang W, Mai W, Cai X, An D, Liu Z, et al. White-coat hypertension is a risk factor for cardiovascular diseases and total mortality. J Hypertens 2017;35:677–88. https://doi.org/10.1097/HJH.0000000000001226.
[50] Cohen JB, Lotito MJ, Trivedi UK, Denker MG, Cohen DL, Townsend RR. Cardiovascular events and mortality in white coat hypertension: a systematic review and meta-analysis. Ann Intern Med 2019;170:853–62. https://doi.org/10.7326/M19-0223.
[51] Mancia G. Clinical significance of white-coat hypertension. J Hypertens 2016;34:623–6. https://doi.org/10.1097/HJH.0000000000000879.
[52] Mancia G. White-coat hypertension: growing evidence in favour of its adverse prognostic significance. J Hypertens 2017;35:710–2. https://doi.org/10.1097/HJH.0000000000001289.
[53] Flores L, Gimenez M, Esmatjes E. Prognostic significance of the white coat hypertension in patients with type 1 diabetes mellitus. Diabetes Res Clin Pract 2006;74:21–5. https://doi.org/10.1016/j.diabres.2006.03.006.
[54] O'Brien E, Asmar R, Beilin L, Imai Y, Mallion JM, Mancia G, et al. European Society of Hypertension recommendations for conventional, ambulatory and home blood pressure measurement. J Hypertens 2003;21:821–48. https://doi.org/10.1097/00004872-200305000-00001.
[55] Beckett L, Godwin M. The BpTRU automatic blood pressure monitor compared to 24 hour ambulatory blood pressure monitoring in the assessment of blood pressure in patients with hypertension. BMC Cardiovasc Disord 2005;5:18. https://doi.org/10.1186/1471-2261-5-18.
[56] Myers MG, Valdivieso M, Kiss A. Use of automated office blood pressure measurement to reduce the white coat response. J Hypertens 2009;27:280–6. https://doi.org/10.1097/HJH.0b013e32831b9e6b.
[57] Pickering TG, Davidson K, Gerin W, Schwartz JE. Masked hypertension. Hypertension 2002;40:795–6. https://doi.org/10.1161/01.hyp.0000038733.08436.98.
[58] Franklin SS, O'Brien E, Thijs L, Asayama K, Staessen JA. Masked hypertension: a phenomenon of measurement. Hypertension 2015;65:16–20. https://doi.org/10.1161/HYPERTENSIONAHA.114.04522.
[59] Palla M, Saber H, Konda S, Briasoulis A. Masked hypertension and cardiovascular outcomes: an updated systematic review and meta-analysis. Integr Blood Press Control 2018;11:11–24. https://doi.org/10.2147/IBPC.S128947.
[60] Franklin SS, Thijs L, Li Y, Hansen TW, Boggia J, Liu Y, et al. Masked hypertension in diabetes mellitus: treatment implications for clinical practice. Hypertension 2013;61:964–71. https://doi.org/10.1161/HYPERTENSIONAHA.111.00289.
[61] Mateo-Gavira I, Vilchez-Lopez FJ, Garcia-Palacios MV, Laureano FCS, Jimenez-Carmona S, Aguilar-Diosdado M. Nocturnal blood pressure is associated with the progression of microvascular complications and hypertension in patients with type 1 diabetes mellitus. J Diabetes Complications 2016;30:1326–32. https://doi.org/10.1016/j.jdiacomp.2016.05.021.
[62] Homhuan W, Poomthavorn P, Paksi W, Khlairit P, Nongnuch A, Pirojsakul K. Masked hypertension and its associations with glycemic variability metrics in children and adolescents with type 1 diabetes. Pediatr Nephrol Berl Ger 2021;36:379–86. https://doi.org/10.1007/s00467-020-04720-2.
[63] Basiratnia M, Abadi SF, Amirhakimi GH, Karamizadeh Z, Karamifar H. Ambulatory blood pressure monitoring in children and adolescents with type-1 diabetes mellitus and its relation to diabetic control and microalbuminuria. Saudi J Kidney Dis Transplant Off Publ Saudi Cent Organ Transplant Saudi Arab 2012;23:311–5.
[64] Anstey DE, Muntner P, Bello NA, Pugliese DN, Yano Y, Kronish IM, et al. Diagnosing masked hypertension using ambulatory blood pressure monitoring, home blood pressure monitoring, or both? Hypertension 2018;72:1200–7. https://doi.org/10.1161/HYPERTENSIONAHA.118.11319.
[65] Kario K. Nocturnal hypertension: new technology and evidence. Hypertension 2018;71:997–1009. https://doi.org/10.1161/HYPERTENSIONAHA.118.10971.
[66] Hermida RC, Ayala DE, Crespo JJ, Mojon A, Chayan L, Fontao MJ, et al. Influence of age and hypertension treatment-time on ambulatory blood pressure in hypertensive patients. Chronobiol Int 2013;30:176–91. https://doi.org/10.3109/07420528.2012.701131.
[67] Mojon A, Ayala DE, Pineiro L, Otero A, Crespo JJ, Moya A, et al. Comparison of ambulatory blood pressure parameters of hypertensive patients with and without chronic kidney disease. Chronobiol Int 2013;30:145–58. https://doi.org/10.3109/07420528.2012.703083.
[68] Rios MT, Dominguez-Sardina M, Ayala DE, Gomara S, Sineiro E, Pousa L, et al. Prevalence and clinical characteristics of isolated-office and true resistant hypertension determined by ambulatory blood pressure monitoring. Chronobiol Int 2013;30:207–20. https://doi.org/10.3109/07420528.2012.701135.
[69] Dost A, Klinkert C, Kapellen T, Lemmer A, Naeke A, Grabert M, et al. Arterial hypertension determined by ambulatory blood pressure profiles: contribution to microalbuminuria risk in a multicenter investigation in 2,105 children and adolescents with type 1 diabetes. Diabetes Care 2008;31:720–5. https://doi.org/10.2337/dc07-0824.
[70] Ayala DE, Moya A, Crespo JJ, Castineira C, Dominguez-Sardina M, Gomara S, et al. Circadian pattern of ambulatory blood pressure in hypertensive patients with and without type 2 diabetes. Chronobiol Int 2013;30:99–115. https://doi.org/10.3109/07420528.2012.701489.
[71] Clement DL, Buyzere MLD, Bacquer DAD, de Leeuw PW, Duprez DA, Fagard RH, et al. Prognostic value of ambulatory blood-pressure recordings in patients with treated hypertension. N Engl J Med 2003;348:2407–15. https://doi.org/10.1056/NEJMoa022273.
[72] Fagard RH, Celis H, Thijs L, Staessen JA, Clement DL, Buyzere MLD, et al. Daytime and nighttime blood pressure as predictors of death and cause-specific cardiovascular events in hypertension. Hypertension 2008;51:55–61. https://doi.org/10.1161/HYPERTENSIONAHA.107.100727.
[73] Hermida RC, Ayala DE, Fernandez JR, Mojon A, Smolensky MH. Hypertension: new perspective on its definition and clinical management by bedtime therapy substantially reduces cardiovascular disease risk. Eur J Clin Invest 2018;48:e12909. https://doi.org/10.1111/eci.12909.
[74] de la Sierra A, Gorostidi M, Banegas JR, Segura J, de la Cruz JJ, Ruilope LM. Nocturnal hypertension or nondipping: which is better associated with the cardiovascular risk profile? Am J Hypertens 2014;27:680–7. https://doi.org/10.1093/ajh/hpt175.
[75] Spallone V, Maiello MR, Morganti R, Mandica S, Frajese G. Usefulness of ambulatory blood pressure monitoring in predicting the presence of autonomic neuropathy in type I diabetic patients. J Hum Hypertens 2007;21:381–6. https://doi.org/10.1038/sj.jhh.1002162.
[76] Lurbe E, Redon J, Pascual JM, Tacons J, Alvarez V. The spectrum of circadian blood pressure changes in type I diabetic patients. J Hypertens 2001;19:1421–8. https://doi.org/10.1097/00004872-200108000-00010.
[77] Lurbe A, Redon J, Pascual JM, Tacons J, Alvarez V, Batlle DC. Altered blood pressure during sleep in normotensive subjects with type I diabetes. Hypertension 1993;21:227–35. https://doi.org/10.1161/01.hyp.21.2.227.
[78] Spallone V, Gambardella S, Maiello MR, Barini A, Frontoni S, Menzinger G. Relationship between autonomic neuropathy, 24-h blood pressure profile, and nephropathy in normotensive IDDM patients. Diabetes Care 1994;17:578–84. https://doi.org/10.2337/diacare.17.6.578.
[79] Lee SH, Kim JH, Kang MJ, Lee YA, Yang SW, Shin CH. Implications of nocturnal hypertension in children and adolescents with type 1 diabetes. Diabetes Care 2011;34:2180–5. https://doi.org/10.2337/dc11-0830.
[80] Mancia G. Short- and long-term blood pressure variability: present and future. Hypertension 2012;60:512–7. https://doi.org/10.1161/HYPERTENSIONAHA.112.194340.
[81] Ozawa M, Tamura K, Iwatsubo K, Matsushita K, Sakai M, Tsurumi-Ikeya Y, et al. Ambulatory blood pressure variability is increased in diabetic hypertensives. Clin Exp Hypertens 2008;30:213–24. https://doi.org/10.1080/10641960802068477.

[82] Hashizume M, Kinami S, Sakurai K, Izawa KP, Shiotani H. Postprandial blood pressure decrease in patients with type 2 diabetes and mild or severe cardiac autonomic dysfunction. Int J Environ Res Public Health 2019;16:812. https://doi.org/10.3390/ijerph16050812.
[83] Kario K. Morning surge in blood pressure and cardiovascular risk: evidence and perspectives. Hypertension 2010;56:765–73. https://doi.org/10.1161/HYPERTENSIONAHA.110.157149.
[84] Caramori ML, Pecis M, Azevedo MJ. Increase in nocturnal blood pressure and progression to microalbuminuria in diabetes. N Engl Nal Med 2003;348:260–4.
[85] Suzuki H, Kanno Y, Nakamoto H, Okada H, Sugahara S. Decline of renal function is associated with proteinuria and systolic blood pressure in the morning in diabetic nephropathy. Clin Exp Hypertens 2005;27:129–38.
[86] Najafi MT, Khaloo P, Alemi H, Jaafarinia A, Blaha MJ, Mirbolouk M, et al. Ambulatory blood pressure monitoring and diabetes complications: targeting morning blood pressure surge and nocturnal dipping. Medicine (Baltimore) 2018;97:e12185. https://doi.org/10.1097/MD.0000000000012185.
[87] Calhoun DA, Jones D, Textor S, Goff DC, Murphy TP, Toto RD, et al. Resistant hypertension: diagnosis, evaluation, and treatment. A scientific statement from the American Heart Association professional education Committee of the Council for high blood pressure research. Hypertension 2008;51:1403–19. https://doi.org/10.1161/HYPERTENSIONAHA.108.189141.
[88] Carey RM, Calhoun DA, Bakris GL, Brook RD, Daugherty SL, Dennison-Himmelfarb CR, et al. Resistant hypertension: detection, evaluation, and management: a scientific statement from the American Heart Association. Hypertension 2018;72:e53–90. https://doi.org/10.1161/HYP.0000000000000084.
[89] Judd E, Calhoun DA. Apparent and true resistant hypertension: definition, prevalence and outcomes. J Hum Hypertens 2014;28:463–8. https://doi.org/10.1038/jhh.2013.140.
[90] Egan BM, Zhao Y, Axon RN, Brzezinski WA, Ferdinand KC. Uncontrolled and apparent treatment resistant hypertension in the United States, 1988 to 2008. Circulation 2011;124:1046–58. https://doi.org/10.1161/CIRCULATIONAHA.111.030189.
[91] Persell SD. Prevalence of resistant hypertension in the United States, 2003-2008. Hypertension 2011;57:1076–80. https://doi.org/10.1161/HYPERTENSIONAHA.111.170308.
[92] Pimenta E, Calhoun DA. Resistant hypertension: incidence, prevalence, and prognosis. Circulation 2012;125:1594–6. https://doi.org/10.1161/CIRCULATIONAHA.112.097345.
[93] Thomas G, Xie D, Chen HY, Anderson AH, Appel LJ, Bodana S, et al. Prevalence and prognostic significance of apparent treatment resistant hypertension in chronic kidney disease: report from the Chronic Renal Insufficiency Cohort study. Hypertension 2016;67:387–96. https://doi.org/10.1161/HYPERTENSIONAHA.115.06487.
[94] Egan BM, Zhao Y, Li J, Brzezinski WA, Todoran TM, Brook RD, et al. Prevalence of optimal treatment regimens in patients with apparent treatment-resistant hypertension based on office blood pressure in a community-based practice network. Hypertension 2013;62:691–769. https://doi.org/10.1161/HYPERTENSIONAHA.113.01448.
[95] Tanner RM, Calhoun DA, Bell EK, Bowling CB, Gutierrez OM, Irvin MR, et al. Prevalence of apparent treatment-resistant hypertension among individuals with CKD. Clin J Am Soc Nephrol 2013;8:1583–90. https://doi.org/10.2215/CJN.00550113.
[96] Viazzi F, Greco E, Ceriello A, Fioretto P, Giorda C, Guida P, et al. Apparent treatment resistant hypertension, blood pressure control and the progression of chronic kidney disease in patients with type 2 diabetes. Kidney Blood Press Res 2018;43:422–38. https://doi.org/10.1159/000488255.
[97] Solini A, Penno G, Orsi E, Bonora E, Fondelli C, Trevisan R, et al. Is resistant hypertension an independent predictor of all-cause mortality in individuals with type 2 diabetes? A prospective cohort study. BMC Med 2019;17. https://doi.org/10.1186/s12916-019-1313-x. 83-019-1313–x.
[98] Ott C, Schmieder RE. Diagnosis and treatment of arterial hypertension 2021. Kidney Int 2022;101:36–46. https://doi.org/10.1016/j.kint.2021.09.026.
[99] Brambilla G, Bombelli M, Seravalle G, Cifkova R, Laurent S, Narkiewicz K, et al. Prevalence and clinical characteristics of patients with true resistant hypertension in central and Eastern Europe: data from the BP-CARE study. J Hypertens 2013;31:2018–24. https://doi.org/10.1097/HJH.0b013e328363823f.
[100] Daugherty SL, Powers JD, Magid DJ, Tavel HM, Masoudi FA, Margolis KL, et al. Incidence and prognosis of resistant hypertension in hypertensive patients. Circulation 2012;125:1635–42. https://doi.org/10.1161/CIRCULATIONAHA.111.068064.
[101] Irvin MR, Booth 3rd JN, Shimbo D, Lackland DT, Oparil S, Howard G, et al. Apparent treatment-resistant hypertension and risk for stroke, coronary heart disease, and all-cause mortality. J Am Soc Hypertens 2014;8:405–13. https://doi.org/10.1016/j.jash.2014.03.003.
[102] Sim JJ, Bhandari SK, Shi J, Reynolds K, Calhoun DA, Kalantar-Zadeh K, et al. Comparative risk of renal, cardiovascular, and mortality outcomes in controlled, uncontrolled resistant, and nonresistant hypertension. Kidney Int 2015;88:622–32. https://doi.org/10.1038/ki.2015.142.
[103] Holmqvist L, Bostrom KB, Kahan T, Schioler L, Hasselstrom J, Hjerpe P, et al. Cardiovascular outcome in treatment-resistant hypertension: results from the Swedish primary care cardiovascular database (SPCCD). J Hypertens 2018;36:402–9. https://doi.org/10.1097/HJH.0000000000001561.
[104] Rossignol P, Massy ZA, Azizi M, Bakris G, Ritz E, Covic A, et al. The double challenge of resistant hypertension and chronic kidney disease. Lancet 2015;386:1588–98. https://doi.org/10.1016/S0140-6736(15)00418-3.
[105] Muntner P, Davis BR, Cushman WC, Bangalore S, Calhoun DA, Pressel SL, et al. Treatment-resistant hypertension and the incidence of cardiovascular disease and end-stage renal disease: results from the Antihypertensive and Lipid-lowering Treatment to Prevent Heart Attack Trial (ALLHAT). Hypertension 2014;64:1012–21. https://doi.org/10.1161/HYPERTENSIONAHA.114.03850.
[106] Solak Y, Kario K, Covic A, Bertelsen N, Afsar B, Ozkok A, et al. Clinical value of ambulatory blood pressure: is it time to recommend for all patients with hypertension? Clin Exp Nephrol 2016;20:14–22. https://doi.org/10.1007/s10157-015-1184-1.
[107] la Sierra AD. Advantages of ambulatory blood pressure monitoring in assessing the efficacy of antihypertensive therapy. Cardiol Ther 2015;4:5–17. https://doi.org/10.1007/s40119-015-0043-1.
[108] Ahmadizar F, Souverein P, de Boer A, Maitland-van der Zee AH. Undertreatment of hypertension and hypercholesterolaemia in children and adolescents with type 1 diabetes: long-term follow-up on time trends in the occurrence of cardiovascular disease, risk factors and medications use. Br J Clin Pharmacol 2018;84:776–85. https://doi.org/10.1111/bcp.13482.