We reviewed the literature on ambulatory blood pressure (BP) monitoring in type 2 diabetes mellitus (T2DM) (focusing on organ damage progression, prognosis, white coat hypertension, and masked hypertension) and metabolic syndrome (MetS). In the text we reported 21 articles about T2DM and 11 about MetS, part of which were included in meta-analyses. In T2DM, individual studies and meta-analyses indicate that 24-h pulse pressure and reduced night-time BP fall or reverse dipping predict organ damage progression, total cardiovascular events and all-cause mortality. Moreover, white coat hypertension seems to be less frequent in T2DM and its impact on cardiovascular complications remains controversial. In contrast, masked hypertension is more frequent in T2DM and seems to be associated with increased organ damage. Some studies reported higher ambulatory BP in patients with MetS, but these patients were older and had higher clinical BP than those without MetS. With regard to the circadian BP profile, contrasting data have been reported, although pooled data suggest a higher risk of nondipping in patients with MetS. Blood Press Monit 2010, 15:1–7 © 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins.

Keywords: ambulatory blood pressure, dippers, metabolic syndrome, nondippers, organ damage, prognosis, pulse pressure, reverse dippers, type 2 diabetes mellitus

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Introduction
Clinical blood pressure (BP) is variable and it does not always represent true BP throughout the 24-h period. Ambulatory BP monitoring gives the opportunity to evaluate daytime, night-time and 24-h BP, night-time BP pattern, morning BP surge, BP variability, and particular conditions such as white coat hypertension (WCH) and masked hypertension (MH) [1–3].

Although for practical and economical reasons, clinical BP measurement remains the reference method for hypertension management, it has been repeatedly shown that ambulatory BP is superior to clinical BP in predicting prognosis in patients with essential hypertension [4–9].

Type 2 diabetes mellitus (T2DM) is frequently associated with hypertension, which further increases cardiovascular risk. Indeed, clinical trials have emphasized the need for a tight BP control in diabetic patients to improve cardiovascular outcome [10,11].

Metabolic syndrome (MetS) is a cluster of risk factors that confers high cardiovascular risk [12,13]. It has become one of the major public health problems worldwide. MetS has been shown to be frequent in hypertensive populations, although the reported prevalence has been variable probably owing to different populations studied and different definitions used.

As ambulatory BP monitoring provided additional information for risk stratification in patients with essential hypertension, some studies have attempted to evaluate whether it could also be helpful in patients with T2DM and MetS.

The aim of this study was to review the literature to evaluate whether ambulatory BP monitoring adds information for patient evaluation and management in T2DM and MetS.

Methods
Literature search
We searched PubMed for articles on ambulatory BP monitoring in T2DM (focusing on organ damage progression, prognosis, WCH, and MH) and MetS published from 1990 to 2009.

Articles had to be full-text papers in international peer-reviewed journals, in English language, and report ambulatory BP data. Search terms were T2DM (or noninsulin dependent diabetes mellitus) or MetS and ambulatory BP monitoring, daytime, night-time and 24-h BP, daytime, night-time and 24-h pulse pressure, dippers, nondippers, extreme dippers, risers, reverse dippers, night-time BP fall, daytime, night-time and 24-h BP variability, WCH and MH, organ damage or albuminuria or diabetic nephropathy progression, cardiovascular risk, and cardiovascular events. We also searched the reference lists of identified articles. Reasons for article exclusion were patients less than 18-years-old, pregnant women, duplicate publications with similar findings, similar objectives or results.

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incomplete data, type 1 and type 2 diabetes analyzed together, and uncommon patient classification.

**Statistical analysis**
Where feasible (studies reporting data that could be pooled and analyzed together), a meta-analysis was performed. The risk ratio (RR) and 95% confidence interval (CI) were calculated using a random effect model. Statistical significance was defined as P value of less than 0.05. Analyses were done using the Comprehensive Meta-Analysis software version 2 (Biostat, Englewood, New Jersey).

**Ambulatory BP monitoring in T2DM and MetS**
Ambulatory BP and organ damage progression in T2DM

We have identified eight articles: two were excluded, six are reported in the text, and two are analyzed in a meta-analysis.

Two studies [14,15] reported a significant association between urinary albumin excretion increase and 24-h BP increase over time (3–5 years). In a retrospective study, Farmer et al. [16] found that the decline of creatinine clearance was higher in nondippers than in dippers (–7.9 vs. –2.9 ml/min/year, respectively, P < 0.05) over a 6-year period. Palmas et al. [17] reported that ambulatory 24-h pulse pressure, but not office pulse pressure, was independently associated with progression of albuminuria in older patients with T2DM in a 2-year prospective study. The adjusted hazard ratio (95% CI) for each 10-mmHg increment in ambulatory pulse pressure was 1.23 (1.04–1.42). In a further report after 3 years of follow-up, Palmas et al. [18] re-evaluated the impact of ambulatory BP and nocturnal BP pattern on progression of albuminuria. Beyond the 24-h pulse pressure that was confirmed as an independent predictor of albuminuria progression, nocturnal BP rise also resulted independently associated with the progression of albuminuria [hazard ratio (HR) 1.58, 95% CI: 1.02–2.45, P < 0.05]. Knudsen et al. [19] followed their patients with T2DM for 9.5 years. In a Cox regression analysis, independent predictors of nephropathy progression were 24-h pulse pressure, diastolic night/day BP ratio and smoking habit. The adjusted HR for 1 mmHg increment in 24h pulse pressure was 1.04 (95% CI: 1.01–1.07), whereas the adjusted HR for 1% increase in diastolic night/day BP ratio was 1.06 (95% CI: 1.01–1.11).

The main BP characteristics of the last two studies [18,19], according to progression and nonprogression of diabetic nephropathy are reported in Table 1. When they were analyzed together, the overall RR for nephropathy progression in nondippers (nondippers and reverse dippers [18] and those with night/day BP ratio above the median [19]), compared with dippers (dippers [18] and those with night/day BP ratio below the median [19]), was 1.73, 95% CI: 0.97–3.06, P=0.061, and the overall RR for nephropathy progression in those with high pulse pressure (≥65 mmHg [18] and ≥57.5 mmHg [19]), compared with those with low pulse pressure, was 1.92, 95% CI: 1.006–3.649, P=0.048 (Fig. 1).

<table>
<thead>
<tr>
<th>Study name</th>
<th>Risk ratio</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>P value</th>
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<tr>
<td>Knudsen, 2009</td>
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<td>1.916</td>
<td>1.006</td>
<td>3.649</td>
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</table>

Table 1 Baseline blood pressure data in subjects with T2DM with and without diabetic nephropathy progression

<table>
<thead>
<tr>
<th>Study</th>
<th>Clinical BP (mmHg)</th>
<th>Clinical PP (mmHg)</th>
<th>24-h BP (mmHg)</th>
<th>24-h PP (mmHg)</th>
<th>N/D BP (%)</th>
<th>N/D BP (%)</th>
<th>Study FU (years)</th>
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<tr>
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<td>69</td>
<td>131/69</td>
<td>62</td>
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<td>64*</td>
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<td>9.5</td>
</tr>
</tbody>
</table>

BP, blood pressure; FU, follow-up; N/D, night/day ratio; PP, pulse pressure; T2DM, type 2 diabetes mellitus.
*Indicates statistically significant difference in the specific report.

Fig. 1

Risk ratio and 95% confidence interval (CI) for nephropathy progression between diabetic patients with low and high pulse pressure.
Ambulatory blood pressure and prognosis in type 2 diabetes mellitus

We have identified eight articles: one was excluded, seven are reported in the text, and four are analyzed in meta-analyses.

Nakano et al. [20] assessed the significance of reversed circadian BP rhythm as a predictor of cardiovascular events in T2DM. Cox regression analysis showed that patients with reversed circadian BP pattern were at higher risk of both fatal (adjusted RR 10.61, 95% CI: 1.55–72.8) and nonfatal (adjusted RR 4.14, 95% CI: 1.68–10.22) cardiovascular events than those with other night-time BP patterns. In a further analysis [21], the same investigators evaluated whether the diurnal BP pattern was a better predictor of risk than BP level. The rate of various events increased with both reduced nocturnal systolic BP fall and level of all ambulatory BP parameters. Cox regression analysis showed that 24-h pulse pressure and night-time systolic BP predicted fatal and nonfatal cardiovascular events more strongly than nocturnal systolic BP fall. In this report [21], however, an uncommon definition of nondipping was used and reverse dipping was not analyzed separately. In an additional report, Nakano et al. [22] assessed the prognostic role of ambulatory BP only in patients less than 60 years. Cox regression analysis showed that high 24-h pulse pressure independently predicted cardiac, but not cerebrovascular events. Astrup et al. [23] evaluated the prognostic significance of 24-h ambulatory BP for all-cause mortality in patients with T2DM. In Cox regression analysis, beyond other variables, predictors of all-cause mortality were daytime systolic BP (for 1 mmHg increase HR 1.02, 95% CI: 1.01–1.03, P=0.003) and dipping (for 1% increase in dipping HR 0.97, 95% CI: 0.94–0.998, P=0.033). Eguchi et al. [24] studied hypertensive patients with and without T2DM. Daytime, night-time, and 24-h systolic BP predicted cardiovascular risk more strongly than clinical BP, in both groups. Indeed, when clinical and daytime or night-time or 24-h systolic BP were analyzed in the same model, only ambulatory BP parameters resulted in independent predictors of outcome. The riser pattern was associated with about 150% increase of cardiovascular risk, in both groups. Palmas et al. [25], assessed whether ambulatory BP parameters could improve prediction of all-cause and cardiovascular mortality in older people with T2DM. On the basis of different types of analyses, night/ day heart rate ratio, ambulatory arterial stiffness index, 24-h pulse pressure and night-time systolic BP resulted in independent predictors of mortality. Finally, recently Eguchi et al. [26], assessed whether short-term BP variability could predict cardiovascular risk in patients with T2DM. In multivariable analyses, the standard deviations of night-time systolic BP (HR=1.08; 95% CI: 1.01–1.16, P<0.05) and night-time diastolic BP (HR=1.13; 95% CI: 1.04–1.23, P<0.01) were independently associated with incident cardiovascular events.

Four studies [20,23–25] reported data in patients with and without reversed dipping, and their events are shown in Table 2. Two studies [20,24] were analyzed together for total cardiovascular events and two [23,25] for all-cause mortality. The overall RR for total cardiovascular events in reverse dippers, in comparison with other patterns, was 4.9, 95% CI: 2.513–9.546, P=0.0001 (Fig. 2), and the overall RR for all-cause mortality in reverse dippers, in comparison with other patterns, was 1.57, 95% CI: 1.075–2.287, P=0.019 (Fig. 3).

White coat hypertension and masked hypertension in type 2 diabetes mellitus

We have identified 12 articles: four were excluded, eight are reported in the text and four are analyzed in a meta-analysis.

Nielsen et al. [27] reported that the prevalence of WCH (clinical hypertension and daytime BP < 135/85 mmHg) was 23, 8, and 9% in their patients with normo-, micro-, and macro-albuminuria, respectively. The overall prevalence was 12%. Eguchi et al. [28] reported a prevalence of 26% of WCH (clinical hypertension and 24-h BP < 135/80 mmHg) among their patients with T2DM. Moreover, they reported that subjects with WCH and T2DM had higher prevalence of multiple silent cerebral infarcts than those with WCH alone (P<0.05). Kramer et al. [29] reported a prevalence of 23% of WCH (clinical hypertension and daytime BP < 135/85 mmHg) in T2DM. When compared with normotensive patients, those with WCH had more than two-fold higher risk of diabetic nephropathy and retinopathy. However, although in the normal range, 24-h BP was approximately 4 mmHg higher in patients with WCH and it is unclear whether this aspect was taken into account in multivariate analysis.

| Table 2 | Total cardiovascular events and all-cause mortality in T2DM according to night-time blood pressure pattern |
|---------------------------|---------------------------|---------------------------|---------------------------|---------------------------|
| **Patients** | **Total CV events** | **All-cause mortality** | **Patients** | **Total CV events** | **All-cause mortality** | **Study FU (years)** |
| (n) | (n) | (n) | (n) | (n) | (n) |                          |
| Nakano et al. [20] | 201 | 20 | – | 87 | 56 | – | 4 |
| Astrup et al. [23] | 88 | – | 40 | 16 | – | 14 | 9 |
| Eguchi et al. [24] | 274 | 22 | – | 27 | 7 | – | 4 |
| Palmas et al. [25] | 838 | – | 215 | 240 | 72 | – | 6.5 |

BP, blood pressure; CV, cardiovascular; FU, follow-up; T2DM, type 2 diabetes mellitus.
Recently, Eguchi et al. [30] evaluated the occurrence of cardiovascular events in sustained and white coat hypertensive patients with and without T2DM during 4 years of follow-up. Prevalence of WCH in T2DM was about 20%. Cardiovascular risk was significantly lower in patients with WCH and T2DM than in those with sustained hypertension and T2DM, and not significantly different between WCH patients with and without T2DM.

The phenomenon of MH has also been investigated in diabetic patients [31–34]. MH has been defined as clinical BP less than 140/90 mmHg [31,32], less than 130/85 mmHg [33], and less than 130/80 mmHg [34], and daytime BP at least 135 and/or 85 mmHg [31,32,34] or 24-h BP at least 125 and/or 80 mmHg [33]. The prevalence of MH in these studies was 30 [31], 47 [32,33], and 25% [34]. When compared with normotensive individuals, patients with MH had increased urinary albumin excretion and cardiac wall thicknesses [31], higher prevalence of albuminuria and more silent cerebral infarcts [32], and higher left ventricular mass and impaired diastolic function [33]. One study [34] did not find significant differences between diabetic patients with normotension and daytime MH.

BP data and indices of target organ status of these studies [31–34] are reported in Table 3. In addition, age was similar [31–34] and the prevalence of men was not significantly different, except for one study [31], between patients with normotension and MH. When studies were pooled together we found that left ventricular mass index tended to be higher in MH (MH vs. normotension, standard difference in means 0.56, 95% CI: –0.003 to 1.120, $P=0.051$) (Fig. 4).

**Ambulatory blood pressure in metabolic syndrome**

We have identified 18 articles: seven were excluded, 11 are reported in the text, and seven are analyzed in a meta-analysis.
Some studies [35–43] reported that patients with MetS show higher ambulatory BP than those without MetS. In the vast majority of them, however, patients with MetS had higher clinical BP, were older and more frequently smokers. Only two studies [36,40] adjusted BP values for age. Other studies [44,45], including patients with and without MetS with similar age and clinic BP, did not find differences regarding ambulatory BP.

With regard to the night-time BP pattern, some studies [36,37,39,44,45] did not find differences regarding nocturnal BP fall or prevalence of nondipping between patients with and without MetS. Other studies [40–43], in contrast, reported reduced night-time BP fall and/or increased prevalence of nondipping in patients with MetS.

Age, clinical and ambulatory BP of the aforementioned studies are summarized in Table 4. When the majority of these studies [39–45] were analyzed together, the overall RR for nondipping in patients with MetS, in comparison with those without MetS, was 1.29, 95% CI: 1.03–1.58, P=0.018.

**Study limitations**

We used various search terms to retrieve articles. However, it cannot be totally excluded that some papers with uncommon definitions were missed. On account of the characteristics of the studies, only part of them could be included in meta-analyses. For studies on organ damage progression and prognosis, as adjusted hazard ratios were not available or were not reported for various patient groups, we used events and sample size to estimate the effect size. Thus, multivariate analysis in the overall samples could not be performed. However, the prognostic impact of 24-h pulse pressure and reverse dipping was not substantially lessened after adjustment for other variables in the models of the majority of individual studies.

**Summary**

In T2DM, individual studies and meta-analyses indicate that 24-h pulse pressure and reduced night-time BP fall or reverse dipping predict organ damage progression, total cardiovascular events and all-cause mortality. Moreover, WCH seems to be less frequent in T2DM and its impact on cardiovascular complications remains controversial. In contrast, MH is more frequent in T2DM and seems to be associated with increased organ damage.

Some studies reported higher ambulatory BP in patients with MetS, but these individuals were older and had higher clinical BP than those without MetS. With regard...
to the circadian BP profile, contrasting data have been reported in the literature, although pooled data suggest a higher risk of nondipping in patients with MetS.

### References


### Table 4

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Clinical BP (mmHg)</th>
<th>Day BP (mmHg)</th>
<th>Night BP (mmHg)</th>
<th>24-h BP fall (%)</th>
<th>Non-dippers (%)</th>
<th>Clinical BP (mmHg)</th>
<th>Day BP (mmHg)</th>
<th>Night BP (mmHg)</th>
<th>24-h BP fall (%)</th>
<th>Non-dippers (%)</th>
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</table>

BP, blood pressure; MetS, metabolic syndrome.

*Indicates statistically significant difference in the specific report.

**Nondippers plus reverse dippers. All values are rounded to the lower or upper decimal. In papers with available daytime and night-time BP, percentage nocturnal BP fall was calculated when not reported.


