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Ambulatory Blood Pressure Monitoring and its Importance in the Management of Diabetic Patients

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**Summary**

Numerous independent studies have shown that the average BP during Sleep is a better marker of CV risk than clinical BP and activity measures or of 24 hours derived from the ABPM. The prevalence of an altered circadian BP pattern and noctur- nal hypertension is very high in patients with diabetes, so in these patients, the diagnosis of hypertension and its therapeutic control are frequently inadequate in the absence of 24-h BP assessment using ABPM. For all these reasons, ABPM should be the tool of choice in patients with diabetes for the correct diagnosis of hypertension and to establish the scheme most appro- priate therapeutic that allows the control of elevated nocturnal BP, which could result in a significant reduction in CV events.

**Keywords:** Diabetic Patients; Ambulatory Blood Pressure Monitoring; Arterial hypertension; Acute Myocardial Infarction; Cardiovascular

**Acronyms and Abbreviations**

ABPM = Ambulatory Blood Pressure Monitoring; HTA = Arterial hypertension; BP = Blood pressure; AMI = Acute My- ocardial Infarction; CV = Cardiovascular; SBP = Systolic blood pressure; DBP = Diastolic blood pressure; PP = Pulse

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Pressure; ACEI = Angiotensin-converting enzyme inhibitor; ARA II = Angiotensin II receptor antagonists; RAAS = Renin Angiotensin Aldosterone System; HR = Heart Rate; HR = Hazard Ratio; AMPA = Self-Measurement of Blood Pressure; CVD = Cardiovascular Disease; CKD = Chronic Kidney Disease; ACV = Cerebrovascular Accidents; IMC = Body Mass Index

# Introduction

The concept of cardiovascular risk factor comes from the 1960s. Between 1930 and 1950, studies began to be published in which it was observed that People who suf- fered from Acute Myocardial Infarction (AMI) were prefer- ably men and had a higher cholesterol concentration and blood pressure higher than those who did not suffer from it. However, given the case-control design of these studies, no unequivocal causal relationships could be established. This motivated the setting the first large prospective study, the Framingham study, which began in 1948 with the recruit- ment of more than 4,000 men and women between 39 and 59 years old. The first analysis was carried out in 1957, after 4 years of complete follow-up of 90% of the included popula- tion, and demonstrated that the occurrence of coronary heart disease was more common in men and was favored by the presence of high blood pressure (HTA), obesity and hy- percholesterolemia. Smoking should have waited a second analysis of the data, which was carried out 2 years later, to demonstrate their association with cardiovascular disease. These predictor variables of AMI were I would call risk fac- tors [1,2]. Based on successive analyzes of the data. From the Framingham study, more risk factors were identified such as diabetes, which later demonstrated its unequivocal association with cardiovascular disease in different popula- tions. These classic factors can divided into modifiable and

non-modifiable (Table 1) [3,4].

The Framingham is a prospective popula- tion-based study that began in Framingham and that for the last 75 years has allowed researchers collect data on cardio- vascular diseases and their predisposing factors. One of the myths that the Framingham study helped debunk was that hypertension. Diastolic blood pressure was more dangerous than systolic blood pressure in terms of cardiovascular risk. In fact, among their conclusions are that systolic HBP has a stronger with coronary disease than diastolic. Two other ar- ticles related the Systolic HBP with strokes and heart fail- ure, which did not happen with diastolic HBP Contributed to modifying medical practice, disease treatment cardiovas- cular disease to work actively on prevention and identifica- tion of people at risk. Factors such as hypertension, dyslipi- demia, and diabetes increase the risk of suffering a cardio- vascular event and are recognized as risk factors. Risk from Kannel's original article in his publication \\"Factors of Risk in the Development of Coronary Heart Disease. Six year fol- low-up experience. The Framingham study\\", in Annals of Internal Medicine in 1961.

Diabetes has currently become one of the modifi- able risk factors most prevalent worldwide and establish the most appropriate therapeutic scheme that allowing BP con- trol is something that is essential.

**Table1:** Classic cardiovascular risk factors

|  |  |
| --- | --- |
| **Not Modifiable** | **Modifiable** |
| Sex | Arterial Hypertension |
| Age | Smoking |
| Family History (1st Grade) | Diabetes Mellitus |
| Premature coronary heart disease |  |
| Men <45 years |  |
| Women <55 years |  |

## Development of the Topic

Numerous independent studies have shown that the average rest period (period of sleep) of BP is a better marker of CV risk than conventional clinical BP and then the activity or 24-h averages derived from ABPM [5-7], also in patients with diabetes [8-10]. In general, these studies show that, when analyzed jointly the averages of activity and rest adjusted by variables of significant influences (in- cluding sex, age, diabetes, chronic kidney disease, smoking, previous CV event, etc.), only the average of rest, but not the average of activity, It is a significant and independent marker of CV morbidity and mortality. There are new Emerging perspectives on alterations in the circadian pat- tern of BP in patients with diabetes and its potential normal- ization through timing (chronotherapy) of antihypertensive treatment at bedtime with the double objective of increase BP control and reduce CV risk [5,8,11,12].

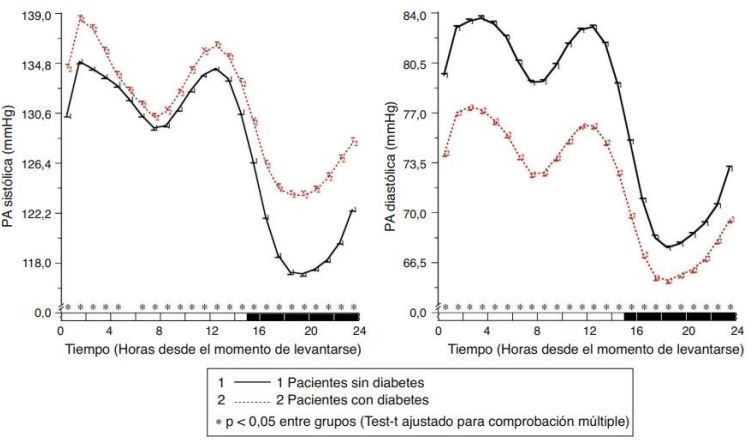
## Ambulatory Blood Pressure Pattern in Patients with Diabetes

Patients with diabetes constitute one of the groups of greatest interest when it comes to evaluate the potential

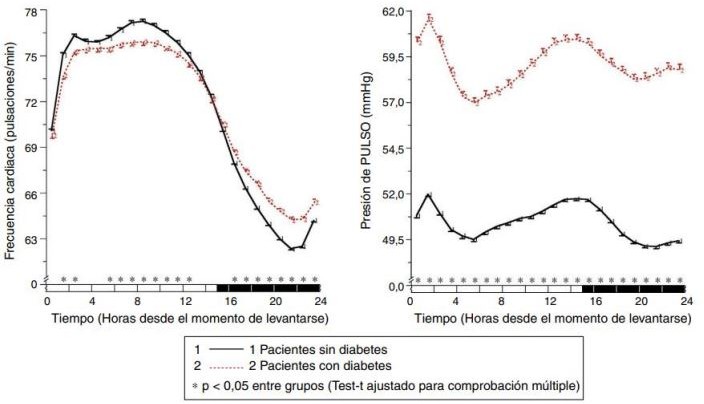
of ABPM as a diagnostic tool, due to the strong association between this disease and increased risk of damage to target organs, stroke and CV morbidity and mortality. The no-dip- per pattern and nocturnal hypertension, conditions that ne- cessarily require ABPM for diagnosis, are common in dia- betes [13-16].

Patients with diabetes constitute one of the groups of greatest interest when it comes to evaluate the potential of ABPM as a diagnostic tool, due to the strong association between this disease and increased risk of damage to target organs, stroke and CV morbidity and mortality. The no-dip- per pattern and nocturnal hypertension, conditions that ne- cessarily require ABPM for diagnosis, are common in dia- betes [13-16].

Ayala et al. [17] in a prospective and controlled multicenter study investigated the influence of diabetes on the circadian BP profile among patients hypertensive. In pa- tients with diabetes, ambulatory SBP was significantly high- er elevated (p < 0.001), mainly during the hours of night rest and early hours of the activity cycle, regardless of the presence/absence of treatment.



**Figure 1:** Circadian Pattern of SBP (left) and DBP (right) in hypertensive patients without (solid line) and with diabetes (dashed line) as- sessed through 48-hour ambulatory blood pressure monitoring. The shaded bar on the horizontal axis of the graphs indicates the average nighttime hours of patient sleep.



**Figure 2**: Circadian pattern of heart rate (left) and pulse pressure (PP) (right) in hypertensive patients without (solid line) and with diabetes (dashed line) assessed through 48-hour ambulatory blood pressure monitoring (ABPM). The shaded bar on the horizontal axis of the graphs indicates the average nighttime rest period of the patients.

Antihypertensive (figure 1, left panel). Ambulato- ry DBP, however, was significantly lower (p < 0.001) in pa- tients with diabetes, mainly during the hours of daytime ac- tivity (figure 1, right panel). As a consequence of these dif- ferences in SBP and DBP, ambulatory PP was significantly higher (p < 0.001) in patients with diabetes throughout the 24 hours of the day (Figure 2, right panel). The proportion of patients with a 48-h mean PP >53 mmHg, a threshold as- sociated with increased CV risk [18] was significantly high- er in patients with diabetes (63 vs. 34%; p < 0.001). Heart rate was significantly higher during the hours of nocturnal rest and minor during most of the cycle of activity in pa- tients with diabetes than without (figure 2, left panel). The prevalence of the no-dipper pattern was significantly higher in patients with diabetes (62.1 vs. 45.9%; p < 0.001), as has already been recently corroborated [19]. The biggest differ- ence between groups was in the prevalence of the riser pat- tern (SBP depth < 0.001). The main factor in the diagnosis of hypertension or inadequate BP control in patients with di- abetes it was high BP during sleep; thus, 89.2% of hyperten-

sive patients with uncontrolled diabetes had nocturnal hy- pertension [17].

Additionally, Ayala et al.17 used the data collected from the 12,765 participants in their cross-sectional study to investigate possible influencing factors on the profile no- dipper in hypertensive patients. The logistic regression anal- ysis indicated that the profile no-dipper (as a categorical variable) was simultaneously and significantly associated, in order of importance, with reduced estimated glomerular fil- tration rate, advanced age, presence of diabetes, low HDL-c- holesterol, not smoking (due to the expected increase in ac- tivity BP associated with the pressor effect of tobacco), low triglycerides, mass index elevated body count and elevated albumin/creatinine ratio (table 2). Furthermore, the pattern no-dipper was significantly associated with increased antihy- pertensive drugs in single morning dose. These results indi- cate the strong association between the absence of adequate decrease in BP during sleep (no-dipper pattern) and dia- betes, the presence of kidney disease, aging and central obe- sity.

**Table 2:** Logistic regression model of the circadian profile (dipper/non-dipper) of ambulatory BP in hypertensive patients

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Variable** | **Coefficient** | **Standard Error** | **p-value** | **Odds Ratio** | **95% Confidence Interval** |
| Estimated Glomerular Filtration Rate | 0.012 | 0.001 | <0.011 | 1.012 | (1.010-1.015) |
| Age | -0.015 | 0.002 | <0.011 | 0.945 | (0.981-0.988) |
| Diabetes | -0.352 | 0.052 | <0.011 | 0.703 | (0.635-0.778) |
| HDL Cholesterol | 0.009 | 0.001 | <0.001 | 1.009 | (1.006-1.012) |
| Tobacco Use | 0.322 | 0.062 | <0.001 | 1.381 | (1.223-1.559) |
| Triglycerides | 0.007 | 0.003 | 0.007 | 1.008 | (1.002-1.013) |
| Body Mass Index | -0.012 | 0.005 | 0.007 | 0.988 | (0.979-0.997) |
| Albumin/Creatinine Ratio | -0.002 | 0.001 | 0.006 | 0.998 | (0.997-0.999) |
| Constant | -0.125 | 0.217 | 0.564 | - | - |

The Odds Ratios with their 95% Confidence Intervals for the depth of nocturnal systolic blood pressure dip as the dependent variable (0 - non-dipper, 1 - dipper) are provided below. These are adjusted for each ml/min/1.73m² increase in estimated glomerular filtration rate, each year of age, each mg/dL increase in HDL cholesterol, each 10 mg/dL increase in triglycerides, each kg/m² increase in body mass index, and each 10 mg/gCR increase in albumin/creatinine ratio. Diabetes is defined as 0 - no, 1 - yes. Smoking status is defined as 0 - no, 1 - yes. Glu- cose level is estimated using the CKD-EPI equation. The variables in the model are listed in order of importance, obtained through forward stepwise logistic regression variable selection.

## Effects of the Time of intake of Antihypertensive Drugs

Chronotherapy applied to drugs improves the diag- nosis and treatments of diseases by administering drugs ac- cording to the biorhythms that dictate the functioning of the human organism, since with this technique (called chronotherapy) we manage to optimize the effectiveness provided by each medication, thus how to advance in the prevention, diagnosis and treatment of pathologies, being able to improve cardiovascular results and reduce this risk.

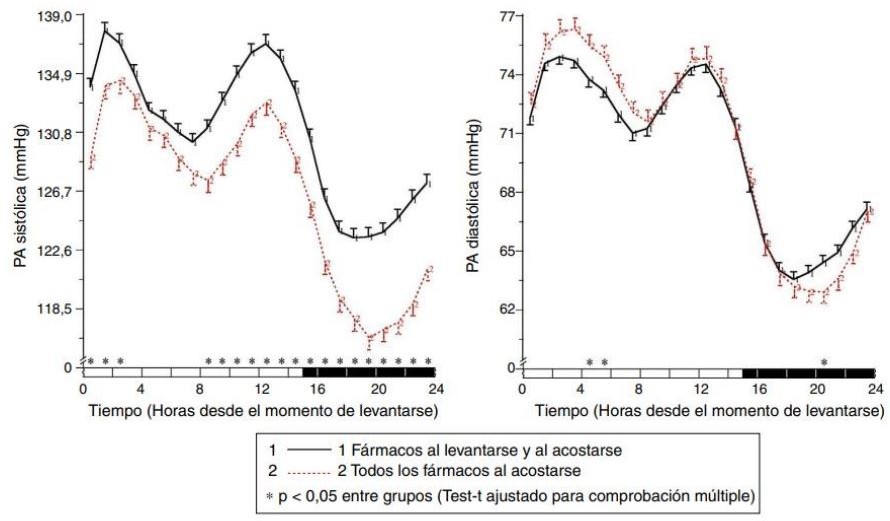
In general, hypertensive subjects, including pa- tients with diabetes, ingest all your antihypertensive medica- tion in the morning. However, it has been documented that diverse circadian rhythms in physiological and biochemical functions and processes can significantly affect pharmacoki- netics (release processes, absorption, distribution, metabol- ization and elimination) and pharmacodynamics (effects pharmacological) of antihypertensive drugs. Therefore, cir- cadian timing or the timing of drug administration over 24 hours can modify the pharmacokinetics or the therapeutic and adverse effects of drugs [20-22].

Descriptive studies [23,24] and a good number of randomized clinical trials with antihypertensive drugs have documented relevant differences in their effectiveness for re- duce BP, duration of action, safety profile and effects on pat- tern circadian BP that depend on the time of day of its ad- ministration (chronotherapy) [20-22]. For example, the monotherapy intake of ACEI or ARA-II at at bedtime, rather than upon rising, reduces BP more during sleep. Sleep without loss of efficiency during active hours, which leads to an increase significant depth towards a more dipper profile. These results, furthermore, are independent of the terminal half-life of the drug (usually calculated only at from studies in which patients were treated in the morning) and appear to be rather related to the activation of the ren- in-angiotensin-aldosterone system (RAAS) during the se- cond half of the sleep period [25].

Moyá et al. [26] investigated the influence of the time of day (in relation to the cycle of rest/wake of each sub- ject) of antihypertensive treatment on the circadian profile and the degree of control of ambulatory BP, as well as on clinical parameters and analytical tests of interest, in hyper- tensive patients with diabetes, the results of the study, in

First, that patients with diabetes who ingested the full dose of ≥1 antihypertensive drugs at bedtime, compared with those taking all night medication upon waking up, had a lower prevalence of metabolic syndrome and chronic kid- ney disease (49 vs. 54%; p = 0.023); they had the quotient al- bumin/creatinine, glucose, total cholesterol and LDL-choles- terol significantly minor (p < 0.001); and had an estimated glomerular filtration rate and HDL-cholesterol significantly higher (p < 0.001). Intake of ≥1 antihypertensive drugs in full dose at bedtime was associated with a mean resting BP significantly less than treatment with all medication upon rising (p <0.001). The depth was significantly lower and the prevalence of the non-dipper pattern higher with all medica-

tion upon rising (68.6%) than with ≥1 drug upon waking. going to bed (55.8%; p < 0.001), and was reduced even more in patients taking all medication at bedtime (49.7%; p < 0.001), because this last group was characterized by having the lowest resting mean SBP (figure 3). The prevalence of riser pattern was much higher (23.6%) in patients taking all medication upon getting up than in those who took either any (20.0%), or all drugs at the same time. go to bed (12.2%; p < 0.001). This last group presented the highest rate of pa- tients with Well-controlled ambulatory BP (p < 0.001), which was achieved with a smaller number of antihyperten- sive drugs (P < 0.001) compared with those treated at get up [26].



**Figure 3:** Circadian Pattern of Systolic Blood Pressure (left) and Diastolic Blood Pressure (right) in hypertensive patients with diabetes evalu- ated through 48-hour ambulatory blood pressure monitoring (ABPM) and classified based on their antihypertensive treatment scheme: medi- cation intake both upon waking up and before going to bed (solid line) or intake of all medication at bedtime (dashed line). The shaded bar on the horizontal axis of the graphs indicates the average nighttime rest period of the patients

## Influence of Chronotherapy on Cardiovascular risk in Patients with and without Diabetes

It has been discovered that asthma, allergic rhini- tis, cancer, arthritis, heart attacks, etc. To cite some exam- ples, they have a greater incidence at certain times of the day; heart attacks myocardial acute events are more fre- quent in the morning; otherwise, allergic rhinitis it is more frequent at night. Thus, the treatment must also follow a rec-

ommendation or application scheme adhered to a schedule based on the individual characteristics of the patient.

Most ABPM studies carried out to date have many limitations, including the use of arbitrary fixed bands of clock hours to define wake/rest (or erroneously day/night), which results in the calculation of values which do not repre- sent the true BP activity/rest means for each individual; and most of the published results are derived from studies based

on a single ABPM record for each patient at the time of in- clusion, under the apparent erroneous assumption that the ambulatory BP profile remains unchanged during the years of follow-up despite the effects of treatment antihyperten- sive, aging and the development of damage to target organs or concomitant diseases [5,6,27].

In this sense, the Ambulatory Monitoring for Pre- diction of CV Events study (MAPEC) was designed to prospectively investigate the comparative prognostic value of various parameters derived from ABPM and study whether the intake of the dose. Complete with at least one antihypertensive drug at bedtime works best control of BP and reduction of CV risk than conventional therapy based on administer all medication in the morning upon rising [5,11,27,28,29]. In this study Prospectively, 3,344 subjects participated, of which 2,610 were hypertensive patients. Ac- cording to ABPM criteria [30,31]. At the time of inclusion and then annually (or with more frequently if it was neces- sary to adjust antihypertensive treatment based on ABPM results) during a median of 5.6 years of follow-up, BP and physical activity (wrist actigraphy) were monitored simulta- neously for 48h to in order to determine in a precise and in- dividualized way the averages of activity and rest of the PA. The results of the MAPEC study, the first in which partici- pants were periodically evaluated using ABPM, indicate, first of all, that the average rest, but not activity, SBP is the most significant predictor of CV events in a survival model adjusted for the significant variables of sex, age, diabetes, anemia and chronic kidney disease (for every 1-DT of eleva- tion, hazard ratio [HR] 1.63; 95% CI [1.44-1.85]; p < 0.001 for the rest mean; 0.94 [0.81-1.08]; p = 0.348 for the average activity). The assessment of the possible joint contribution of several parameters derived from ABPM as predictors of CV risk revealed that the best fitted model includes only the mean of resting SBP (HR = 1.23; 95% CI [1.16-1.32]; p < 0.001) and the depth of SBP (HR = 0.98; 95% CI [0.97-0.99];

p = 0.019). Furthermore, when the average of SBP rest was adjusted for both mean SBP activity and BP clinical, only the first significantly predicted the increased risk of CV events, both in the general population [5,27] and specifical- ly in patients with diabetes [8]. Which More importantly, analysis of changes in ambulatory BP over the years of Fol- low-up revealed a 17% decrease in CV risk for every 5 mmHg of reduction in mean resting SBP, independent of

changes in BP clinical or in the average activity calculated from ABPM [5,6,27]. These results, Taken together, they in- dicate that resting mean BP could be a new target therapeu- tics for reducing CV risk that requires, obviously, the evalua- tion accuracy of patients using ABPM [31].

The MAPEC study thus constitutes the first prospective trial of the impact of Antihypertensive chronotherapy on CV risk. In this study, patients ran- domized to take medication at bedtime were characterized by having in their last evaluation with ABPM, after 5.6 years of follow-up, lower mean rest of BP, greater depth, lower prevalence of the non-dipper pattern and greater prevalence of controlled ambulatory BP than patients taking the entire medication when getting up [29]. Patients treated at bed- time had an HR of Total CV events significantly lower than patients treated upon rising (0.39; 95% CI [0.29-0.51]; p < 0.001). The difference between groups was also significant for the total of major events, that is, the sum of CV death, heart attack, myocardium and ischemic and hemorrhagic stroke (0.33; 95% CI [0.19-0.55]; p < 0.001). These The re- sults were validated in high CV risk subgroups and further characterized due to a high prevalence of nocturnal hyper- tension, including patients with diabetes [32], resistant hy- pertension [28] and chronic kidney disease [33].

# Conclusions

The prevalence of subclinical BP alterations, detect- ed by ABPM, is elevated in patients with diabetes and are as- sociated with the presence of other risk factors. Vascular risk such as metabolic control, BMI and more atherogenic lipid profile. The non-dipper pattern and nocturnal BP aver- ages are determinants in the risk of micro and macrovascu- lar complications of diabetes and although there are no rec- ommendations of the main scientific societies for the use of ABPM specific in patients with diabetes, if there is strong evidence that, in patients hypertensive diabetics, the use of antihypertensive drugs before going to bed probably favors BP control and reduces macrovascular events.

The ABPM studies published to date reviewed here agree on document the high prevalence of an altered circadian BP pattern in patients with diabetes. Most impor- tantly, the prevalence of the riser pattern, associated with

the highest CV risk among all possible BP patterns, it is more than double in patients with diabetes than without it. Patients with diabetes also have a significant elevation of am- bulatory PP over 24 hours, reflecting greater arterial stiff- ness and may thus be an added cause of the documented higher CV risk in them [34]. One of the determining charac- teristics of the BP profile in diabetes is the high average BP during nighttime rest hours, in turn causing a high preva- lence of nocturnal hypertension and, as a consequence, er- rors in diagnosis of hypertension when it is based exclusive- ly on the clinical measurement of BP or even in home self-

-measurements (AMPA). These results, taken together, largely explain the higher CV risk of patients with diabetes and justify the need to use ABPM as an essential diagnostic tool for hypertension in patients with diabetes, both for the correct assessment of their CV risk to establish the most ap- propriate therapeutic scheme for the control of high noctur- nal BP and ambulatory PP, which could in turn result in a significant reduction in CV events, as has already been de- monstrated [32].

The goal of antihypertensive treatment is to re- duce BP with the aim of preventing damage to target organs and reduce the risk of CV events. The beneficial effects asso- ciated with BP reduction are consistent and, to some extent, independent of the medication used.

The therapeutic strategy of a single morning dose, still common, does not take into account that the correla- tion between BP level and CV risk is much greater for ABPM than for clinical measures of PA [5,35]; than the mean resting BP, but not the mean activity or 24 h nor clini- cal BP, is an independent prognostic marker CV [5,6,8,27,28] risk and that the effectiveness in reducing the level (mainly of the resting average) and improve the circa- dian pattern of BP towards a more dipper profile of a good number of antihypertensive drugs from 6 different families and their combinations depends markedly on the time of in- take in relation to the cycle of activity and rest of the patient [20-22]. In the specific field of diabetes, the results of the study by Moyá et al. [26] document a significantly lower CV risk markers and a better metabolic profile in patients with diabetes treated at bedtime compared to those taking all medication when getting up; The results also document a lower average rest period of the BP and reduced prevalence

of the no-dipper/riser pattern of high CV risk in patients with diabetes treated at bedtime. These results indicate that bedtime treatment, together with ABPM assessment to establish the correct diagnosis of hypertension and avoid possible nocturnal hypotension associated with treatment, should be the preferred therapeutic regimen in patients with diabetes [26]. On the other hand, the results of the MAPEC study [5,11,27,28,29,32,33], indicate that reducing the average of the period of BP rest and increase the depth towards a more dipper profile (two new therapeutic objec- tives that require evaluation of patients with ABPM) signifi- cantly reduce CV morbidity and mortality and intake of the full dose of at least one antihypertensive, preferably all, at bedtime reduces significantly the risk of CV events in both the general hypertensive population [29] as specifically in patients with diabetes [32]. In this sense, it is notable that al- ready in 2012, the American Diabetes Association recog- nized the clinical relevance of antihypertensive chronothera- py by recommending that hypertensive patients with dia- betes. They should be treated with ≥1 drug at bedtime [36]. This recommendation implies in fact that bedtime treat- ment should be the therapeutic regimen of choice in all pa- tient with diabetes newly diagnosed with hypertension. The blocking of RAAS receptors achieved through the ingestion of the ACEI or ARA II at the time of lying down is superior to any other treatment regimen in reducing the risks of CVD, diabetes and CKD [37]. Diabetes is associated with greater BP variability than non-diabetics along with worse damage to vascular and renal function [38]. This same rec- ommendation, complemented with the indication to use ABPM as a new gold standard for diagnosis of hypertension and individualized assessment of CV risk, has recently been extended to other groups, including elderly subjects and pa- tients with chronic kidney disease, previous CV event and resistant hypertension or secondary [31].

# Practical Ideas

Patients with diabetes present a significant elevation of ambulatory PP throughout 24 hours, which reflects greater arterial stiffness and may thus be a cause added to the documented increased CV risk, in them the prevalence of the riser pattern, associated with the highest CV risk among all possible BP patterns, it is more twice as much as in

patients without diabetes.

One of the determining characteristics of the BP profile in diabetes is the high average BP during the hours of night rest, in turn causing a high prevalence of nocturnal hypertension and, as a consequence, errors in diagnosis of hypertension when it is based exclusively on clinical measurement of the BP or even by AMPA.

Antihypertensive treatment at bedtime should be the therapeutic regimen of choice in all patients with diabetes newly diagnosed with

hypertension. He blockade of RAAS receptors achieved by ingestion of the ACEI or ARA II at bedtime is superior to any other treatment regimen for reduce the risks of CVD, diabetes and CKD.

In diabetics, ABPM should be included in routine clinical care, as method to confirm the diagnosis of hypertension, to determine the nyctameral pattern of BP these patients and assess the response to treatment by facilitating chronotherapy, non-optimal control or to see the degree of control in 24 hours.

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