„CAROL DAVILA” UNIVERSITY OF MEDICINE AND PHARMACY, BUCHAREST

DOCTORAL SCHOOL

MEDICINE

“ARTERIAL HYPERTENSION, GLYCEMIC PARAMETERS, AND THE EVOLUTION OF PATIENTS WITH COMPLICATED TYPE 2 DIABETES MELLITUS”

PHD THESIS SUMMARY

Doctoral advisor:

PROF. DR. ILIEŞIU ADRIANA MIHAELA

Doctoral student:

CHIVU CĂS. PÂRVU IRINA

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Introduction

There is a bidirectional influence between arterial hypertension (HTN) and diabetes mellitus (DM), involving common risk factors and target organ damage, while risk scores consider DM and HTN to be major factors [1,2]. The combination of HTN and DM is found in more than 70% of diabetics, and hypertensive diabetics have a cardiovascular (CV) risk up to 75% higher than those without DM [3]. DM prevalence is increasing and the recommendations from the American Diabetes Association (ADA) advocate for multifactorial control, with only 50% of patients reaching targets [4,5,6]. HTN is suboptimally controlled (40% of patients, 30.8% in Romania, in SEPHAR III - Study for the Evaluation of Prevalence of Hypertension and Cardiovascular Risk in Romania III) despite progress [7,8,9].

I have chosen a topic related to hypertensive patients with complicated DM because they represent a very high risk population in which the improvement of adverse event prediction models is necessary, beyond blood pressure (BP) and glycemic control. This issue is currently relevant, in the context of the obesity pandemic that will increase the number of patients with metabolic syndrome. The impact on healthcare costs is proportional to the number of complications and hospitalizations. BP shows spontaneous variations during the same day, between different days, from one month to another, and the independent prognostic significance of BP variability (BPV) has recently begun to be explored, without a threshold for increased risk [10]. Similarly, glycemic variability (GV) has more deleterious effects than sustained hyperglycemia, by activating oxidative stress [11]. The existing data leave into question: the degree to which BP fluctuations influence target organ damage and the evolution of diabetics, the complications, the optimal parameters for estimating BPV and control [10,12].

The research hypothesis derives from the idea that the evolution of hypertensives with complicated type 2 DM is influenced by BPV and control. The aim of the research is to study the impact of various forms of hypertension and BPV, in relation to glycemic parameters, on the evolution of diabetics, depending on complications, using classical approaches and alternative methods of data interpretation. Classical parameters provide an overview of the amplitude of fluctuations. The time series represented by the evolution of systolic, diastolic, mean BP and glycemia have a nonlinear dynamic, frequently leading to fractal objects. Tools are needed to assess the degree of complexity of curves, methods for analyzing nonlinear dynamics such as fractal geometry providing applications in biological systems. This approach is relatively new, and studies that have applied nonlinear dynamics models to biological systems have not evaluated in detail diabetic hypertensives with complications [13]. This thesis uses both types of parameters in parallel, global (classical) and alternative (fractal analysis), providing additional information, as well as a comparative approach.

The research includes 2 studies with complementary design. The first is a prospective observational cohort study, in outpatient hypertensives with complicated type 2 DM, with a follow-up for 16.5 months. Study 2 is retrospective and follows the evolution of a cohort of 156 diabetic and hypertensive hospitalized patients, in terms of CV respitalizations, treatment changes over 2 years, including all-cause mortality after 2 and 3 years.

I Current state of knowledge

1. Arterial hypertension

Chapter 1 is dedicated to the definition, pathophysiology, forms and profiles of HTN, and their reproducibility, as well as treatment targets and options, together with BPV and classic and alternative parameters for its estimation.

The definition of HTN depends on the method of assessment: office BP, ABPM (ambulatory blood pressure monitoring), and self-measured, in the Guidelines of the European Society of Cardiology (ESC) [1]. In diabetics, the relationship between BP and mortality is shaped like the letter "J", with increased mortality at the extremes [14]. The diagnosis must also include the additional risk and HTN-mediated target organ damage [1]. BP self-measurement appears to be a good predictor of CV events, and ABPM provides many recordings with better accuracy [1,15]. The higher incidence of CV events was demonstrated

in the non-dipper profile, and extreme dippers could have a higher risk of stroke [16]. White-coat (isolated office HTN) and masked (isolated ambulatory HTN) HTN exist, and the latter is associated with a risk of nephropathy in diabetics [17]. ABPM offers indices of variability (standard deviation (SD), coefficient of variation (CoV)), of arterial stiffness (AASI - ambulatory arterial stiffness index), reserved for research [1]. BPV refers to long-, medium-, and short-term variations independently associated with complications and CV events, especially in diabetics [10]. BPV assessment is performed by several parameters (SD, CoV - defined as SD/mean BP*100, average variability, day-night and night-day variation etc.). Optimal indices are under study, most studies use CoV of systolic BP/24h; a threshold of 10% is considered acceptable, other studies chose the 50th percentile [10,18]. CoV provides information about the amplitude of BP fluctuations, but not about the intrinsic structure of the dynamics [10,13]. ABPM measurements are a time series, and the fractal concept is applicable to processes generating irregular fluctuations in time; one can calculate the FD for ABPM curves [13,19]. Fractal geometry is still far from clinical medicine, but opens the possibility to explain physiological and pathological CV oscillations.

Dipping status, especially non-dipper, is difficult to reproduce, sleep quality being essential and ABPM should be repeated [20]. A recent trial on untreated young hypertensives compared AASI from 2 ABPMs, and the optimal reproducibility was for AASI/24h [21].

2. Diabetes mellitus

Chapter 2 encompasses the definition, diagnosis, glycemic parameters used to evaluate DM control, and treatment of type 2 DM, as well as the specifics of COVID-19 in diabetics.

DM represents a set of metabolic disorders that share hyperglycemia, with increased risk of CV and complications [22]. The main methods for evaluating glycemic control in addition to fasting glycemia are glycosylated hemoglobin (HbA1c), self-monitoring and continuous glucose monitoring (CGM) [22]. An additional parameter could be GV, the ADVANCE trial suggesting that glycemic fluctuations seem to be a better predictor of complications and CV risk [23]. DM complications, sometimes present at diagnosis, are the result of chronic hyperglycemia [22]. DM and HTN were found among comorbidities in patients with severe evolution of SARS-CoV-2 infection (severe acute respiratory syndrome coronavirus) in a

proportion of over 20% [24]. A pre-pandemic and during the pandemic analysis demonstrated a slight increase in self-measured BP in the pandemic [25].

3. The interrelation arterial hypertension - diabetes mellitus

The bidirectional causality between DM and hypertension is detailed in **Chapter 3** and has recently been tested in a study of 318,664 patients with a history of CV disease and type 2 DM, by Mendelian randomization on nucleotide polymorphisms, demonstrating that type 2 DM could cause HTN, the reverse being probably non-causal [26]. HTN and DM complicate each other, cardiopathy and nephropathy can coexist, without criteria to estimate the proportion in which HTN and DM participate. Masked HTN and non-dipper status are a common denominator in diabetics, who can also develop arterial hypotension, and intensive control has been addressed in many trials [1].

4. Arterial stiffness

Arterial stiffness, the subject of **Chapter 4**, a recognized predictor of CV morbidity and mortality, occurs before atherosclerotic involvement. It can also be estimated by the recently introduced index, AASI, automatically calculated on ABPM, more accessible than other methods [27].

II. Original research contributions

5. Work hypothesis and general objectives

The main objective of the doctoral thesis was the study of hypertensive and diabetic patients, in terms of evolution (complications, hospitalizations, BP and DM control, all-cause mortality) by means of BP parameters, including BPV by standard and alternative parameters, and glycemic parameters, for an individualized and more efficient management.

6. General research methodology

The doctoral thesis includes 2 research projects, a prospective one and a retrospective one. The prospective study refers to ambulatory hypertensive patients with complicated type 2 DM, and the retrospective one analyzed hospitalized diabetic hypertensives, regardless of the

presence of DM complications, in order to compare the impact of complications on the evolution, completing the first part, the 2 populations being disjoint.

Protection of human subjects. Both studies were carried out in accordance with the Declaration of Helsinki and were approved by the Ethics Committee.

Statistical considerations: quantitative variables are presented as mean±SD; comparisons have been made with ANOVA and non-parametric tests (Kruskal-Wallis). Categorical variables are reported as percentages, and comparisons have been made with chi-square or Fisher Exact tests. The null hypothesis was rejected when the p-value <0.05. Multivariate analysis was used to evaluate the relationships between end-points and covariate variables. Statistical programs used included Microsoft Excel (2013), Epi Info 7.2.2.2, MedCalc Version 19.5.2.

7. Study 1 – Blood pressure variability, glycemic parameters, and the evolution of patients with complicated type 2 diabetes mellitus

7.1. Introduction (research hypothesis and specific objectives)

The aim of this prospective observational cohort study is to analyze the impact of various forms of HTN and BPV, in relation to glycemic parameters, on the evolution of patients with complicated type 2 DM.

The objectives of study 1 are: 1) establishing the forms of HTN in patients with complicated type 2 DM, the role of BP evaluation methods: office, ABPM or at home, including BPV in the short, medium and long term; 2) evaluation of the impact of hypertension on the evolution (complications; quality of life, hospitalizations, mortality from any cause); quantification of hypoglycemic episodes; the impact of antidiabetic and antihypertensive treatment on the evolution; 3) studying the association between BPV in the short and long term and GV; 4) evaluation of the association between GV and complications; 5) investigation of alternative methods of estimating BPV and GV.

7.2. Patients and methods

Hypertensive patients with complicated DM type 2 who consecutively presented at the internal medicine office in the Outpatient Clinic of the "Prof. Dr. Th. Burghele" Clinical Hospital, who met the criteria (essentially, HTN and complicated type 2 DM, sinus rhythm,

excluding of recently decompensated diseases or pregnancy). 3 study visits have been carried out and the following data has been collected:

• **Data on inclusion** (after signing the informed consent, Annex A): demographics, complications, comorbidities, clinical parameters, EKG, echocardiography, ABPM/24 hours, ankle-brachial index (ABI), laboratory investigations, medication;

• **6-month visit data**: survival status, hospitalizations/new comorbidities, admissions to the intensive care unit (TICAR), treatment changes, clinical parameters, ABI, EKG, ABPM/24h, laboratory investigations, self-monitoring table data;

• **Telephone visit at one year** (on average at 16.5 months; in the context of the COVID-19 pandemic): vital status, hospitalizations, treatment changes, self-measured BP and glycemia.

7.3. Results

7.3.1. Descriptive data analysis

Figure 7.1 details the selection process; the 51 analyzed patients were divided into 2 subgroups according to BPV, versus the median 11% of CoV of systolic BP/24h: S1 (25 patients, 49.1%, low BPV, CoV < 11%) and S2 (26 patients, 50.9%, high BPV, CoV ≥ 11%). Figures 7.2 and 7.4 provide the distribution of age and comorbidities, and table 7.1 shows the characteristics at inclusion, the clinical parameters (mean BP=144.5/81.8 mmHg) and risk factors being similar between subgroups.

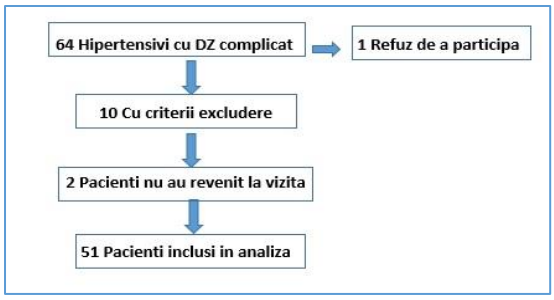


Figure 7.1. Patient selection.

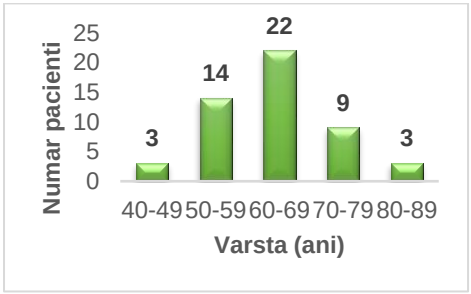


Figure 7.2. Patient age.

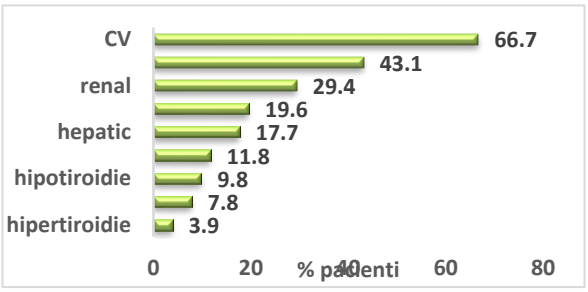


Figure 7.4. Comorbidities (similar in S1 - S2).

Table 7.1. Patient characteristics on inclusion (selection).

Parameter	Population value (n=51)	S1 value (n=25)	S2 value (n=26)	p-value
Male sex	22 (43.1%)	12 (48%)	10 (38.5%)	0.49
Age (years)	63.5 ± 9.3	62.8 ± 9.6	64.2 ± 9.2	0.58
Quality of life score	81.4 ± 8.5	80.4 ± 9.2	82.6 ± 3.4	0.88
DM duration (years)	8.74 ± 6.62	8.02 ± 5.77	9.44 ± 7.4	0.44

Figure 7.5 shows DM complications at the initial visit, similar between subgroups (respective p-values: 0.97, 0.68, 0.72, 0.24, 0.91, 0.95), on average 1.7 complications per patient, with no difference between subgroups (p=0.49) or by sex (p=0.55). Diabetic neuropathy was independently associated with creatininemia (p=0.048), and nephropathy – with nocturnal systolic BP (p=0.04).

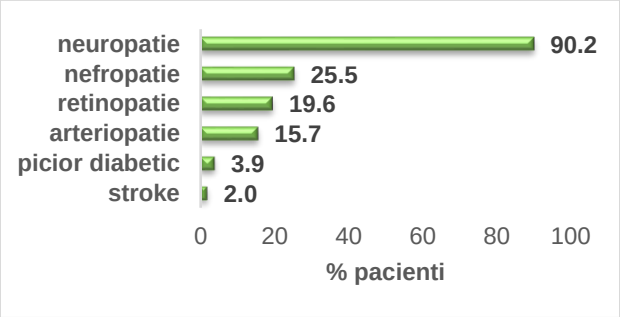


Figure 7.5. Prevalence of DM complications in the study lot, on inclusion.

EKG changes were dominated by ST-T changes (negative T waves, ST depression). At **transthoracic echocardiography**, the average LVEF was 59.1 ± 4.9 % (51% - 65%), preserved in all patients; 34 (66.7%) has LVH (p=0.04 between S1 and S2); 10 (19.6%) had valvular heart disease; 7 (13.7%) – wall motion abnormalities. 20 (39.2%) had normal diastolic function, and the rest, impaired relaxation. **Laboratory parameters**: significant differences between subgroups were recorded for HbA1c (p=0.03), LDL being in target at 36 (70%).

Figure 7.7 presents the classes of antihypertensive drugs on inclusion (on average, 2.9 ± 1 classes), and figure 7.8 illustrates the medication of the associated conditions. Antihypertensives were mainly administered in the morning (2.1 ± 0.9 classes), similarly in subgroups (p=0.64). FDC were used in 17 (33.3%) patients, ACEI + diuretic or ARB + CCB.

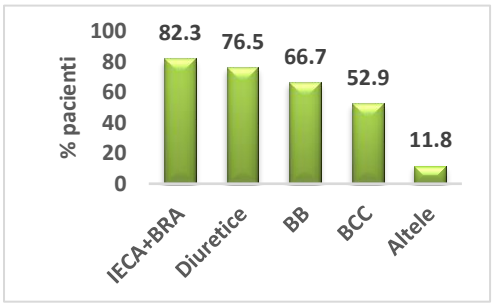


Figure 7.7. Antihypertensive treatment.

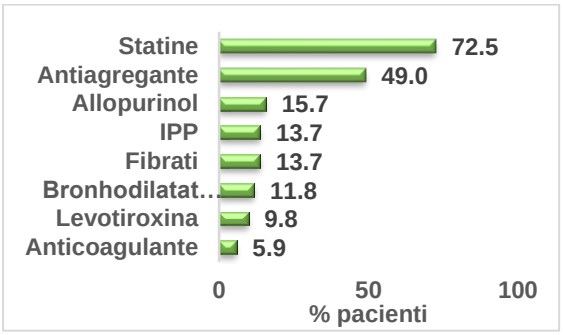
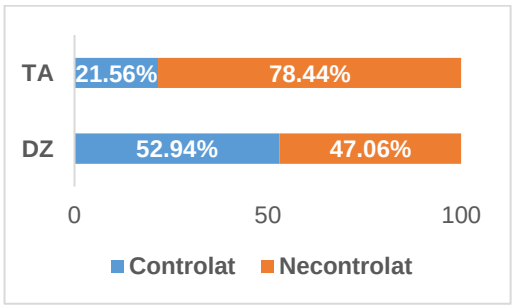


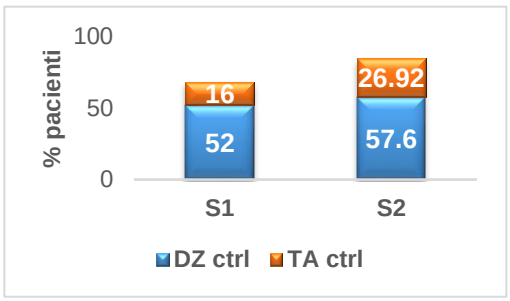
Figure 7.8. Treatment of comorbidities.

The **antidiabetic** therapeutic options were diet (100%), oral antidiabetics (82.4%) and insulin therapy (19.6%, only long-acting insulin), mostly combinations (1.9 ± 0.5 options).

DM control was defined according to the ADA, cumulatively by reaching the blood glucose and HbA1c target. On inclusion, 27 patients (52.94%) reached both targets, 30 (58.8%) having controlled blood glucose and 39 (76.5%) having HbA1c in target. **BP control** was achieved in 11 patients (21.6%), with office BP and mean BP at ABPM/24h in the established intervals. Office BP was within limits in 15 patients (29.4%), and the mean 24h-BP at ABPM - in 27 (52.9%). 17 (33.3%) patients had white coat HTN, and 4 (7.84%) had masked HTN. Figure 7.11 shows the situation of DM and TA control at the inclusion visit.



A



B

Figure 7.11. DM and BP control in the study lot (A) and sublots (B) on the first visit (p=0.36 for DM and p=0.34 for BP).

BP control was multivariately associated with renal dysfunction (p=0.03) and FD of nocturnal systolic BP (p=0.03), with a lower probability of control. Controlled DM was associated with the independent factors in figure 7.12: increased systolic office BP (p=0.047, OR=0.47), increased total cholesterol (p=0.02, OR=0.93), microalbuminuria (p=0.049, OR=0.007).

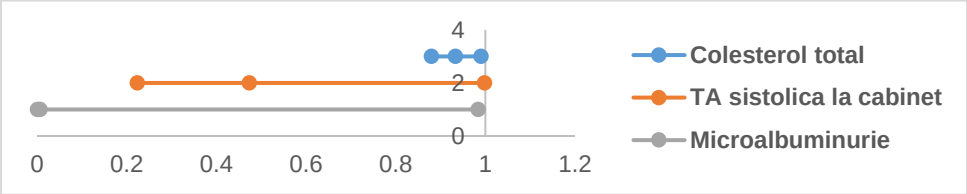


Figure 7.12. Predictors of lack of DM control (protection factors for controlled DM).

7.3.2. Evolution of patients with complicated DM

7.3.2.1. 6 months follow-up visit

Given the SARS-CoV2 pandemic and the patients' high risk, the visit was performed after 6.6 ± 1.4 months, on average. 9 patients (17.6%) underwent hospitalization, clinical and paraclinical parameters were similar, HbA1c being the only one significantly higher in S1 compared to S2 (7.1 ± 0.8 versus 6.3 ± 0.8, respectively, with p=0.002). Improvements were recorded, after treatment changes, for office BP (p=0.0001) and nocturnal dipping (p=0.048).

7.3.2.2. 16.5 months telephone visit

At the 16.5 month visit (delays in the context of COVID-19), the patients communicated the measurements from that morning: mean G 132.2 mg/dL, average BP 129.3/80.1 mmHg, no difference S1-S2 (p=0.84 and p=0.77 , respectively).

7.3.2.3. Evolution of glycemic parameters and diabetes control

DM control at 6 months was achieved in 26 patients (50.9%), similar to inclusion, without difference S1 - S2 (p=0.18), and 9 (17.6%) had treatment changes. Blood sugar was controlled in 24 (47%), and HbA1c in 37 patients (72.5%). The only influence on DM control at 6 months was the difference in blood sugar between visits (p=0.042, multivariate). At the telephone visit, 25 (52.1%) had blood glucose in the target range (132.2 mg/dL, similar between subgroups, p=0.84), controlled DM being associated with previously controlled DM (p=0.048).

7.3.2.4. Evolution of BP control

BP control at the 6-month visit was without difference S1 - S2 (p=0.92), after optimizing the treatment, reaching BP targets in 24 additional patients (47%). Parameters with difference depending on BP control are related to systolic and diastolic BP at ABPM and average systolic BP/7 days, and do not include treatment changes (p=0.28) or initially controlled BP (p=0.42). At the telephone visit, 70.8% had controlled BP (mean BP=129.3/80.1 mmHg, similar S1-S2, p=0.77). The Receiver Operating Characteristics (ROC) curve in figure 7.15 shows the good predictive value (area under the curve, AUC=0.795) of systolic BP/7 days for controlled BP

over 6 months. CoV of patients with controlled and uncontrolled BP at 6 months were comparable (p=0.67).

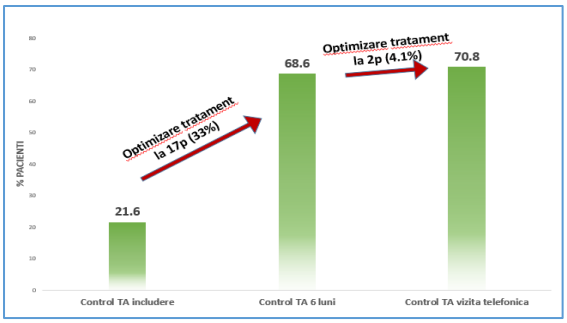


Figure 7.13. Evolution of BP control.

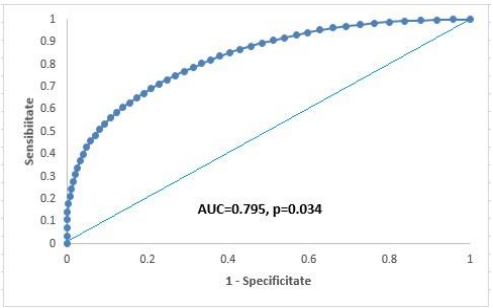


Figure 7.15. ROC curve for systolic BP over 7 days and BP control at 6 months.

7.3.2.5. Evolution of kidney function

Although mean creatininemia remained constant (1.08 vs 1.1 mg/dL, p=0.28), a deterioration of renal function was found in 14 (27.5%); thus, 15 (29.4%) had eGFR below 60 mL/min/1.73 m2. Worsening of renal function was independently associated with control HbA1c (p=0.02).

7.3.2.6. Arterial stiffness

There was a significant difference between AASI on inclusion and at 6 months (p=0.02), with therapy changes (33%). AASI was associated with nocturnal dipping on inclusion and at 6 months (p=0.03 and p=0.04, respectively). Between AASI at 6 months and IGB there was an anticorrelation (p=0.004, r2=0.15), illustrated in figure 7.16.

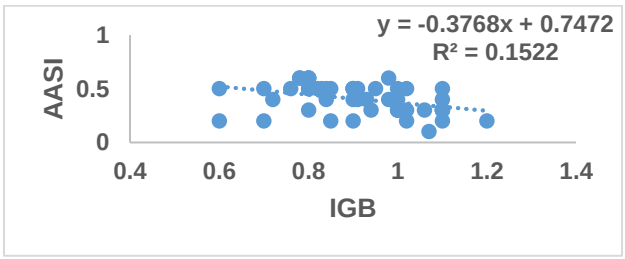


Figure 7.16. AASI – ABI correlation at the 6 months visit (p=0.0046).

7.3.2.7. Treatment changes. Chronotherapy

Declarative adherence was optimal, the antidiabetic treatment remained unchanged in the majority. Antihypertensive treatment underwent changes in 17 (33.3%) patients, with lower mean systolic BP/24h and diurnal systolic load in those with optimized therapy (121.3 mmHg vs 127.9 mmHg, p=0.01, respectively 21.2% vs 31.9%, p= 0.05). At the telephone visit, 2 patients (4.1%) applied the changes, without association with control (p=0.33). At the follow-

up visit, 18 (35.2%) were receiving FDC. The mean number of classes of antihypertensives was 2.9 ± 0.9, mainly in the morning (2 ± 0.9 classes), similar between subgroups (p=0.48).

7.3.2.8. Cardiovascular events. Hospitalizations

At the final telephone evaluation, 27 (52.9%) patients had had between 1 and 5 hospitalizations, on average 1.8. Of these, 15 had been for CV events (0.55/patient, p=0.41). Creatininemia was higher in hospitalized patients (1.3 vs 0.9 mg/dL, p=0.01).

7.3.2.9. All-cause mortality

1 year after inclusion, 2 patients died (3.9%), and after the final visit, the number of deceased patients was 3 (5.9%), all women and with an average age at death of 78.7 years.

7.3.3. Blood pressure variability – control, mortality

Short- and medium-term BPV and BPV thresholds were explored. Long-term BP and glycemic variations were detailed in subchapter 7.3.2.

7.3.3.1. Cut-off value to define increased blood pressure variability

76.5% (39 patients) were above the arbitrary threshold of 10%, and versus the average of 11.7%, 21 (41.2%) had increased BPV. Multivariate analysis demonstrated associations of both alternative thresholds for BPV with diurnal systolic BP CoV at inclusion (p=0.03 for the 10% threshold and 0.02 for the 11.7%) and its difference between visits (p=0.01 for 10% and 0.001 for 11.7%). There were no significant associations of thresholds with 7-day self-monitoring parameters or BP or DM control.

7.3.3.2. Short term blood pressure variability (over 24 hours)

24h-BPV was evaluated by ABPM, mean BP/24h was initially 129.9/72.8 mmHg, and after 6 months – 123.5/71.8 mmHg. Difference between subgroups was recorded for 24h systolic and diastolic BP CoV, day and night, at inclusion (p values<0.0001).

The day-night difference between ABPM parameters was significant at inclusion and at the 6-month visit for systolic BP (p=0.02 and 0.0002), diastolic BP (p=0.006 and 0) and CoV (p=0 at both visits). The comparative evolution of ABPM between inclusion and 6 months showed differences for systolic BP/24h (at inclusion 129.9mmHg, at 6 months 123.5mmHg, p=0.02).

The nocturnal dipping status based on the drop in systolic BP had the distribution on the subgroups in figure 7.18. The day-night variation of diastolic BP had a different distribution, with the coincidence of the profiles in only 23 patients (45.1%). Figure 7.19 provides an image

of this distribution, with the predominance of the non-dipper profile in both cases, with different weights (60% according to systolic BP and 37% according to diastolic BP). The profile matching between inclusion and the 6-month visit was 41.2% (figure 7.20).

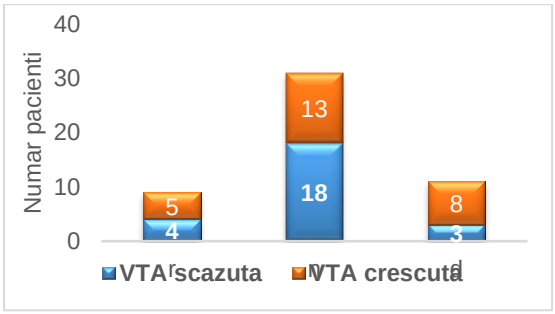


Figure 7.18. Profiles of systolic BP.

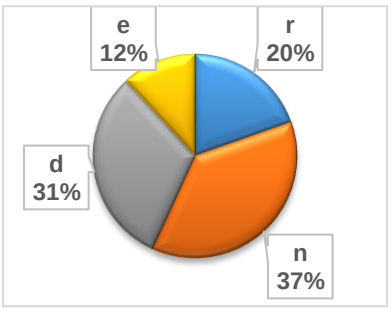


Figure 7.19. Profiles of diastolic BP.

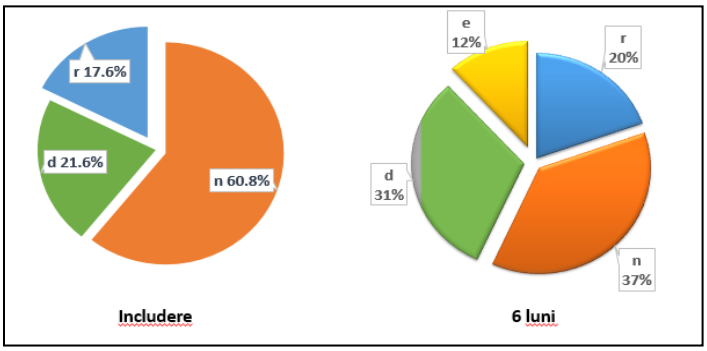


Figure 7.20. Evolution of the systolic BP nocturnal dipping profile between visits.

7.3.3.3. Medium-term blood pressure variability (from one day to the next)

The mean BP from self-monitoring at home over 7 days was 131.8/73.7, and the median CoV value for systolic BP over 7 days was 5.2%. The medium- and short-term BPV categories in relation to the corresponding medians coincided in 27 patients (52.9%).

BP in the 7 days following the initial visit was significantly lower than office BP on inclusion (144.5/81.8mmHg, p=0.00005 and r=0.4, for systolic BP) (figure 7.21).

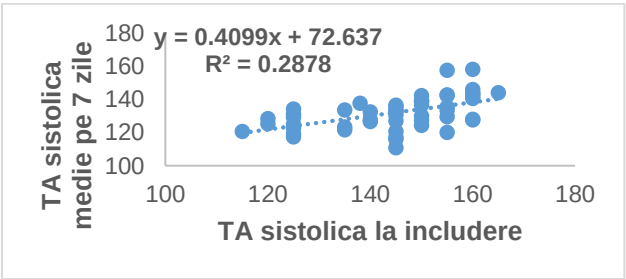


Figure 7.21. Correlation of systolic BP on inclusion and mean systolic BP over 7 days.

Among the parameters at inclusion, mean systolic BP/7 days was associated with: controlled BP (p=0.008), controlled DM (p=0.003), blood glucose (p=0.007), systolic BP/24h (p=0.002). Increased medium-term BPV was significantly associated at inclusion with systolic BP/24h (p=0.002), diurnal systolic load (p=0.03) and FD of diurnal systolic BP (p=0.01).

7.3.4. Medium-term glycemic variability

Day-to-day GV was assessed using the self-monitoring table for 7 days (Annex 2), by calculating global parameters and FD (subchapter 7.3.5). Mean blood glucose was 130.7mg/dL; the median CoV was 5.9%. Compared to the mean blood glucose at inclusion (140.1 mg/dL), from venous blood, the mean blood glucose from capillary blood/7 days was significantly lower (correlation figure 7.22), as it was when compared to the mean blood glucose at the 6-month visit (138.1mg/dL).

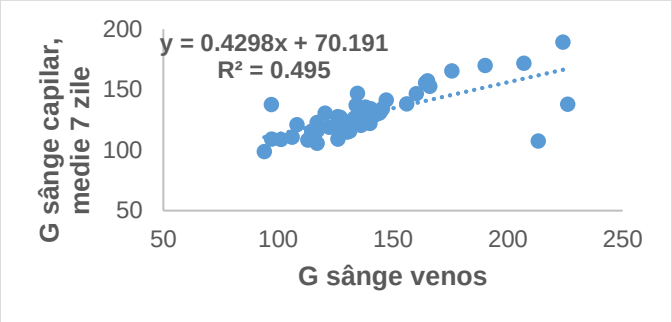


Figure 7.22. Correlation of venous blood glycemia on inclusion and mean capillary blood glycemia over 7 days (p=0.00001).

7.3.5. Fractal dimension, an alternate parameter to evaluate blood pressure and glycemic variability

FD were estimated for ABPM parameters, for the day and night measurement series, separately, in the context of different sampling intervals (table 7.15).

Table 7.15. Mean fractal dimensions of ABPM parameters, on inclusion. FD=fractal dimension, SBP=systolic BP, DBP=diastolic BP, MAP=mean arterial pressure, HR=heart rate, PP=pulse pressure, S=sublot.

ABPM parameter	Mean FD in the study lot	Mean FD in S1	Mean FD in S2	p-value
Diurnal SBP	1.2358 ± 0.03	1.2343 ± 0.03	1.2372 ± 0.03	0.76
Nocturnal SBP	1.1203 ± 0.02	1.124 ± 0.01	1.116 ± 0.02	0.24
Diurnal DBP	1.2426 ± 0.03	1.24 ± 0.03	1.244 ± 0.04	0.62

Nocturnal DBP	1.1136 ± 0.02	1.11 ± 0.02	1.117 ± 0.02	0.24
Diurnal MAP	1.254 ± 0.04	1.25 ± 0.04	1.2571 ± 0.04	0.6
Nocturnal MAP	1.1161 ± 0.02	1.1126 ± 0.02	1.1198 ± 0.02	0.24
Diurnal HR	1.226 ± 0.04	1.2255 ± 0.03	1.2265 ± 0.04	0.92
Nocturnal HR	1.1233 ± 0.02	1.1268 ± 0.02	1.1194 ± 0.03	0.29
Diurnal PP	1.2966 ± 0.05	1.2977 ± 0.03	1.2956 ± 0.06	0.47
Nocturnal PP	1.1235 ± 0.02	1.1259 ± 0.02	1.1209 ± 0.02	0.41

FD of diurnal systolic BP was significantly associated with office systolic BP (p=0.03), with systolic and diastolic BP in orthostatism (p=0.02 in both cases), with 24h, diurnal and nocturnal systolic BP at ABPM (p=0.01, 0.02 and 0.049, respectively), with diurnal systolic load at ABPM (p=0.02) and with BP controlled globally and in the office (p=0.02, 0.047 respectively). There were correlations with FD of all other parameters, except FD of nocturnal systolic BP and FD of nocturnal heart rate. FD of mean diurnal BP showed only one significant correlation, with eGFR by MDRD (p=0.002, r=0.38). There were no significant differences in FD between subgroups defined on the basis of different BPV thresholds (10%, 11% or 11.7%). FD is an acceptable predictor for BP control (figure 7.23).

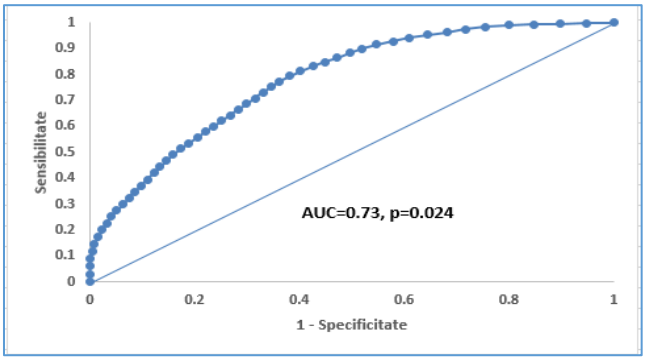


Figure 7.23. ROC curve and AUC of 0.73 for FD of systolic BP over 24h in identifying BP control categories, on inclusion.

Nocturnal decrease in FD. FD were significantly (p-value close to 0 in all cases) lower during the night. The average day-night difference for each parameter was: 9.34% for systolic BP, 10.38% for diastolic BP, 11% for MAP, 8.37% for heart rate and 13.35% for pulse pressure. Multiple significant associations were documented for controlled BP and antihypertensive medication classes. The nocturnal dipping of systolic BP and diastolic BP were associated with the nocturnal decrease in FD only for diastolic BP (p=0.03 and p=0.003, respectively) and for MAP (p=0.007 and p=0.003, respectively).

FD evolution. At the follow-up visit, FD remained significantly elevated during the day compared to the night, with near-zero p-values for all 5 parameters. There were no significant differences in mean FD at 6 months versus FD at inclusion for any parameter. FD of diurnal systolic BP at 6 months was significantly associated with improvement in quality of life (p=0.03) and BP controlled in the office at 6 months (p=0.049). There were no associations with long-term end-points or treatment changes.

FD at self-monitoring for 7 days. The mean values for FD at 7 days were without differences between subgroups, significantly lower than the corresponding diurnal ones at ABPM (FD mean of systolic BP/24h 1.2306 versus 1.1397 at 7 days, and diastolic BP/24h mean 1.2419 versus 1.1313 at 7 days, p-values close to 0 in both cases). There was no correlation between FD systolic BP on 7 days and ABPM (p=0.61).

7.3.6. Reproducibility of blood pressure profiles and blood pressure variability status

Reproducibility of nocturnal blood pressure profiles and overall 24-h BPV status was assessed by direct comparison of data from the inclusion and 6-month visits. The short-term and medium-term BPV status, relative to the respective CoV median, overlapped in 52.9%. The Pearson correlation coefficient between CoV of 24h systolic BP at the two visits with ABPM was 0.01 (p=0.43). Changes in antihypertensive treatment were not associated with reproducibility of dipping profile (p=0.79) or BPV according to any threshold (11%, 10% or 11.7% - p=0.16, 0.51 and 0.11, respectively).

7.3.6.1. Evolution of the nocturnal blood pressure profile

The reproducibility of the nocturnal dipping profile at the 6-month visit was 41.2% (21 patients maintained their initial profile), with no difference S1 - S2 (p=0.25). The most reproducible profile was non-dipper; the reproducibility of the nocturnal dipping profile was associated with the reproducibility of BPV through the median threshold (p=0.009), with blood glucose at 6 months (p=0.046, the average blood glucose in those with identical status being 148.7 mg/dL vs 130 mg/dL).

7.3.6.2. Blood pressure variability evolution

The reproducibility at the 6-month visit of the BPV status in relation to the median CoV systolic BP/24h was 49% (25 patients with identical status). Reproducibility according to the 10% threshold was 52.9% (27 patients), and according to the mean CoV was 45.1%; there were no differences between subgroups (p=0.48 and p=0.33, respectively). The only association was

between reproducibility of BPV by the median threshold and dipping status reproducibility (p=0.009), where 15 patients (60% of those with identical BPV status) kept their dipping status.

7.4. Discussion

The data from this prospective study provide a picture of the evolution of patients with complicated type 2 DM in terms of BPV and relative to glycemic parameters. Alternatives for assessing BPV and GV, and reproducibility of the BP profiles, are also explored.

7.4.1. Characteristics of the study population and sublots

The study population includes compensated outpatients, with type 2 DM and at least one complication, with BPV more pronounced than those without complications, to evaluate the evolution of a homogeneous group at high risk, from the point of view of BPV and of glycemic parameters [28]. Demographic parameters, risk factors and comorbidities were in trend in the literature and did not show differences between subgroups, but with a higher proportion of CV risk factors, being a selected population (Cardiology center) with metabolic syndrome [29,30]. The mean age of 63.5 ± 9.3 years is similar to that of the large hypertensive diabetic trials, ADVANCE (66 years) and ACCORD (62.2 years) [23,31]. Both subgroups had a female predominance, contrary to other analyses, but in Romania women are 52.3% in the urban environment [23,31,32]. The prevalence of non-CV diseases is comparable to that in the European registries, but in Romania prevention remains suboptimal, explaining the number of comorbidities by the lack of an early diagnosis [33,34]. Mean DM duration was 9 years, consistent with the inclusion criterion - complicated DM, as complications require an average of 6 years to develop [35]. Clinical data at inclusion show increased mean BP values (144.5/81.8 mmHg), close to ADVANCE (145/81 mmHg), but suboptimal adherence could explain the difference from the 136.6/78.3 mmHg in ALLHAT (adherent patients) [23, 36].

Among DM complications, neuropathy was present in 90% of patients, and nephropathy in 25%, although diabetic retinopathy is the most common microvascular complication - explained by the low rate of ophthalmological check-ups in Romanian diabetics [37,38]. Diabetic nephropathy showed independent association with mean nocturnal systolic BP in ABT, higher in those with nephropathy, confirming the link between renal damage and hypertension (nephropathy can be mixed). Cardiac involvement was documented in CV diseases in the present study, excluding patients with recent decompensations, explaining the prevalence below that of ADVANCE and A1chieve (27 – 30%) [23,39].

Patients with recent arrhythmias were excluded to increase ABPM accuracy. LVH was present at echocardiography in 2/3 of the patients, in the context of hypertensive heart disease in patients with poorly controlled BP and more prevalent in high BPV, probably also a consequence of the lack of control reflected by BPV. LVEF was normal in all patients, and diastolic dysfunction was confirmed in 60%, hypertensive diabetics having a known prevalence of diastolic dysfunction with preserved LVEF [40]. Laboratory data at inclusion showed that 70% of patients were within the LDL-cholesterol target, consistent with 72% on statins. The glycemic parameters, especially the average HbA1c of 6.8%, were consistent with the literature and in the ADA targets; in most large trials HbA1c was around 7% [4,23,30,31]. Patients with increased BPV and higher CV risk could be more compliant by being aware of this risk, with lower mean blood glucose. Microalbuminuria was present in 37.2%, more frequently than in primary care (23.3%), but the present patients have poorer control [41]. Uric acid, a marker of oxidative stress, averaged 6.1 mg/dL, higher than 5.4 mg/dL in SEPHAR III [42,43].

Antihypertensive treatment recommendations were followed, with each patient receiving approximately 3 classes of medication, mainly in the morning (2 classes) and in the evening (1 class), with no difference according to BPV (criterion not mentioned in the guide), similar to SEPHAR data [1, 7]. ACEI/ARB (82%), diuretics (77%) and BB (66%) were the most used classes of medication, possibly also through the lens of CV comorbidities, in accordance with other studies [1,44]. The use of FCD in one third of patients is an indicator of compliance with European level recommendations [1]. The therapy of comorbidities included antithrombotics, in more than half, and gastric protection was in the scheme in 13%, to prevent hemorrhagic complications. The antidiabetic treatment involved in 3/4 of the cases a combination of 2 options (diet plus ADO or plus insulin therapy), 16% had all 3 options. Long-acting insulin was part of the therapy for almost 20% of the group, the patients being chronic.

7.4.2. BP and DM control on inclusion

The definition of DM control in the present study was based on simultaneously meeting all ADA targets (glycemia, HbA1c), and for BP, office BP and at home (ABPM) were taken into account. Associations with partial control targets were also tested. For DM, a difference was found between controlled blood glucose (in 59% of patients) and HbA1c in the target range (in 76%), which would be explained by higher fasting glycemia, without postprandial peaks that could greatly influence the long-term average longer. The proportion of controlled DM (53%)

was similar to that of large trials, 50% in NHANES and 44.5% of non-compliant patients in ALLHAT [6,36]. The average blood glucose on inclusion was 140.1 mg/dL, and HbA1c – 6.8%, near recommended targets, with no difference between subgroups [4]. BP was controlled in 21.6% of patients at inclusion (concordant with the mean BP of 144.5/81.8 mmHg), far below other studies, most patients being referred by the general practitioner for uncontrolled BP. In SEPHAR III, BP control was achieved in 30.8% of the general population, and a meta-analysis of self-measured BP from 4 recent studies (2590 patients) demonstrated a control of 33.4% [7,8]. However, the degree of BP control was better when only office BP was considered (30%) and above literature results for ABPM (53%), one third being with white coat BP, an element that underlines ABPM in value monitoring.

Controlled DM presented univariate associations with controlled BP, a possible link being compliance. In multivariate analysis, systolic BP value, total cholesterol and microalbuminuria were associated with poorer DM control, confirming that all components of the metabolic syndrome should be controlled and that poor control predisposes to complications. DM control at inclusion (glycemia and HbA1c) was associated with mean 7-day glycemia. Poorly controlled BP at inclusion was associated with renal dysfunction, but also with FD of nocturnal systolic BP, suggesting a possible control parameter. An association with global indices of BPV was not documented, with complexity parameters providing additional information.

7.4.3. Evolution of hypertensive patients with complicated DM

Some of the follow-up visits were carried out later than the date established in the context of the COVID-19 restrictions, given the high-risk patients and lack of a vaccine at that time. BP markedly improved, associated with optimization of control under treatment changes. Although the quality of life score increased to 40%, the variations were too small to generate a significant difference. Laboratory data were similar at 6 months between subgroups and without differences at inclusion, except for microscopic hematuria (more frequent), possibly an independent risk factor for progression to end-stage renal disease [45]. HbA1c was similar at the 2 visits, but at 6 months its value in S2 was significantly lower; the mechanism of the correlation with BPV is not elucidated, but fluctuations in glycemic control could induce homeostasis imbalances, oxidative stress and sympathetic activation [46].

Glycemic parameters and DM control. Patients controlled on inclusion and those at 6 months had similar proportions, but the decrease in blood glucose between visits favored

control, in multivariate analysis. Average blood glucose/7 days (capillary blood) predicted better control, suggesting that self-monitoring could be a tool to maintain target parameters. ADA recommendations emphasize the importance of corroborating HbA1c with self-monitoring and CGM [4]. The average declarative glycemia from the telephone visit was similar to the 7-day average, and the proportion of control based on this value was slightly increased. HbA1c was not determined, in the context of the pandemic, patients avoided traveling to laboratories.

BP control was optimized after treatment adjustment, although treatment changes did not generate significant differences in control, with suboptimal adherence (declaratively, 33%) being the main factor [6]. BP control is related to systolic and diastolic BP for 24h, for 7 days, in turn correlated with systolic BP in the office, showing that the evaluation of the hypertensive diabetic and the control should take into account the values in the office, but also from the ABPM and self-measured, in addition to recommendations, as BPV is related to complications [1,47]. The question remains about the frequency of monitoring for hypertensive diabetics, both at home and periodic ABPM, in addition to office visits. The assessment of BP control at the telephone visit was made exclusively on the basis of the communicated BP, with a slight improvement. However, less than 5% of patients applied the recommended treatment changes at 6 months, the stated motivation being the fear of decompensation at a time when non-urgent admissions were restricted in Romania (COVID-19).

7.4.4. Blood pressure and glycemic variability: types, alternate parameters

A threshold CoV value to define increased BPV has not yet been established, 10% appears to provide good discrimination and is easy to use, some trials have used the mean CoV value of 11% or the 50th percentile [48,49,50]. In the present study, the median CoV of 11% was chosen to define the 2 subgroups of BPV, alternative thresholds also being tested. Being a small prospective study with few outcomes, the analyzed thresholds were not predictors for CV events or death. BP or DM control were not significantly related to elevated BPV defined by all thresholds, suggesting that although CoV is related to macroalbuminuria in diabetics and BPV has an impact on evolution, the cut-off for global BPV parameters is still a subject of research [49].

Short-term BPV involved the use of a dedicated ABPM device, standard, with measurements every 15 minutes during the day and 30 minutes during the night. For CoV of

24h and diurnal diastolic BP there were also significant differences between subgroups, so diastolic BP could also be used in the complex definition of BPV [10]. On both visits there were significant overnight decreases in systolic/diastolic BP and CoV. Nocturnal dipping of both systolic and diastolic BP, although initially similar between subgroups, was significantly reduced in S2 at 6 months, and significantly decreased between visits, linking increased BPV with increased CV risk, for which nocturnal dipping reduced is a predictor [28]. Mean/24h systolic BP decreased at 6 months, after treatment adjustments, in independent association with optimization of BP control. Significant correlations were demonstrated between pressure differences and nocturnal dipping between visits, suggesting that a complex analysis of evolution would be superior to simple office BP assessment from visit to visit.

Dipping profiles were evaluated by calculating the nocturnal decrease in systolic versus diastolic BP, and the proportions of the categories were different, more favorable for diastolic BP, although the predominance of non-dippers was confirmed in both [28]. It is possible to miss information by basing the calculation exclusively on systolic BP. Optimizing antihypertensive treatment led to an increase in control and the proportion of dippers.

BPV in the medium term. The patients completed the table on consecutive days following the inclusion visit, BP was measured with the same device verified at the office, so that the standardization of the collected data was ensured. Although relatively few values were recorded compared to ABPM, SD and CoV could be calculated: CoV was lower at 7 days as a result of fewer values, although CoV at ABPM was similar between visits. The mean BP was much reduced at longer assessments at home than in the office, confirming literature, but also the proportion of 33% of patients with white-coat hypertension in the group, and the 2 values were relatively well correlated [1]. The mean systolic BP was similar to that obtained during the day at inclusion ABPM (approximately 131.8 mmHg) and much higher than at 6 months ABPM (123.5 mmHg), considering the proximity to the first visit. The 7-day mean systolic BP was associated with controlled BP at both visits, but also with DM control parameters at inclusion, suggesting treatment compliance as a common link. On inclusion, increased BPV over 7 days was associated with systolic load at ABPM and diurnal signal complexity of systolic BP/24h, medium- and short-term BPV evolving in parallel, but the associations were no longer maintained at 6 months, more distant in time. In the absence of ABPM accessibility, self-monitoring at home could be superior to measurement at the office. The possible additional

value of BPV as a control parameter is also suggested by the guidelines, without specifying exactly which BPV and which parameters [1].

GV presented a median CoV of 5.9%, in trend with CoV values of systolic and diastolic BP in the medium term. There were no documented episodes of hypoglycemia during the 7 days, despite symptoms. There were no differences between the subgroups in glycemic parameters for 7 days (glucose, SD and CoV), and the fasting capillary blood glucose at home was much lower than that of venous blood, at both visits, being correlated. DM control was clearly associated with mean 7-day glycemia, but not SD and CoV, so GV was not confirmed as a control parameter.

Fractal data analysis. In an attempt to find new parameters for BPV evaluation, with additional information compared to global ones, FD was estimated for all time series recorded at ABPM and at 7-day self-monitoring, evaluating the degree of complexity of the resulting curves. FD estimation algorithms allow the use of limited time series such as those of ABPM and self-monitoring for 7 days [13]. The different measurement intervals during the day (every 15 minutes) compared to night (every 30 minutes) at ABPM required a differentiated calculation. In the future, this process could be automated or the ABPM software could include fractal analysis. This method has not yet been systematically applied to diabetic hypertensives, to our knowledge, except for the analysis of skin blood flow in HTN and diabetic retinopathy, and it could contribute to a better understanding of CV dynamics, but also to a more complex evaluation by methods fast.

FD was not associated with BPV values by CoV (all thresholds) for any of the parameters from ABPM, suggesting that fractal analysis is complementary to global parameters. FD values were much reduced compared to those obtained in normotensives in older studies, suggesting that reduced complexity could be associated with a system at risk of disease or already affected [51]. FD is associated with diurnal BP control, probably by CV mechanisms of diurnal BP self-regulation that global BPV parameters cannot capture. FD decreased significantly during the night for all parameters, at both visits, more substantially in those with controlled BP. At the 6-month visit, the FD of the studied parameters had similar properties to those at the first visit, uninfluenced by treatment changes, and a partial association with BP control was maintained. FD at 7 days was significantly lower, with no differences between sublots, but these time series included fewer measurements. Regarding DM control, no associations were obtained with FD

at 7 days, but the small number of determinations could have distorted the appearance of the curve, this analysis being able to benefit from CGM.

AASI decreased slightly but significantly between visits, although the interval was short, the correlation of AASI with nocturnal BP drop confirming data suggesting that nocturnal dipping may be a better predictor of arterial stiffness than AASI, especially in the elderly [52]. The expected negative correlation with IGB was almost as strong as in other studies, with a coefficient r=-0.37, stiffness being associated with atherosclerosis markers in diabetics as well [53]. AASI is automatically provided by ABPM software and could be used if a dedicated IGB device is not available.

7.4.5. Reproducibility

The reproducibility of short- and medium-term BPV is unclear, only long-term BPV being studied [54]. Due to changes in therapy, the state of the system was not the same, a test-retest correlation coefficient was not used, but a comparison of the coincidence of BPV categories. Reproducibility between baseline and 7-day BPV is suboptimal, 53% on consecutive days, although current recommendations encourage self-measurement of BP [1]. The best reproducibility was for the BPV threshold of 10% (52.9%), the widest threshold. The non-dipper status was the most reproducible in the present study, but the coincidence was just over 40%. The Spanish ABPM registry showed that in the comparative analysis of two consecutive 24h ABPM, 25% of patients had switched from dipper to non-dipper, but also vice versa, the dipping status being difficult to reproduce [55]. A solution would be BP self-monitoring for longer periods, the reproducibility of BP self-monitoring for 7 days being apparently superior to that of ABPM [56].

7.4.6. Study limits, research perspectives

The relatively small size of the study population represented a limit, the COVID-19 pandemic did not allow the follow-up of more very high-risk patients, the short follow-up period does not allow for the objective evaluation of CV events, of new complications. Estimation of FD by an optimized algorithm could bring new information about this alternative parameter of BPV. For the implementation of BPV as a control parameter, the optimal frequency of ABPM, the use of diastolic BP, and the threshold value remain under study. The observational nature limits the study of treatment impact, a randomized study would be ideal.

8. Study 2 – Evolution of diabetic hypertensive patients in clinical practice

8.1. Introduction (research hypothesis and specific objectives)

Retrospective observational cohort study aiming to analyze the evolution of hypertensive and diabetic patients in everyday practice, in relation to DM complications and the influence of antihypertensive therapy.

Objectives of study 2: 1) establishing the prevalence of DM, complicated and uncomplicated, in hypertensive patients; 2) evaluation of the association of DM complications with evolution (DM and BP control, changes in treatment, hospitalizations, all-cause mortality at 2 and 3 years); 3) studying the association between DM complications, clinical and paraclinical parameters, comorbidities; 4) the impact of antidiabetic and antihypertensive treatment on the evolution; 5) identification of possible predictors.

8.2. Patients and methods

The study lot included 156 consecutive patients, hospitalized at the Clinical Hospital "Prof. Dr Th. Burghele" between March - August 2017, with HTN and type 2 DM regardless of complications in the discharge diagnoses (excluding type 1 DM, readmissions), followed retrospectively for 2 years (hospitalizations, changes in treatment, control of DM and HTN and all-cause mortality). Demographic, clinical and paraclinical data were collected, and BP and glycemic parameters were noted on the next and last readmission. After 3 years, a vital status check was made on the platform of the National Health Insurance House.

8.3. Results

8.3.1. Descriptive data analysis

In the studied interval there were 1249 hospitalizations in Cardiology, of which 774 (61.2%) hypertensives, 254 (20.3%) diabetics, with 157 individual diabetic hypertensives (12.6%) (figure 8.1). The 156 included patients were divided into 2 groups, depending on the presence of DM complications, G1 (uncomplicated DM, 62 patients) and G2 (complicated DM, 94 patients) (figure 8.2).

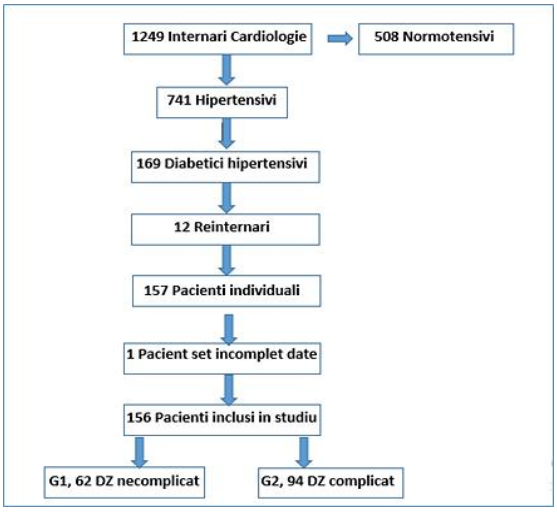


Figure 8.1. Patient selection. The 12 readmissions were in the studied interval.

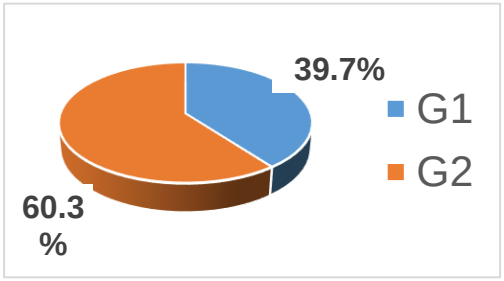


Figure 8.2. Study groups: G1 - uncomplicated DM, G2 - complicated DM.

8.3.1.1. Demographic data

Mean age was 66.7 ± 9.8 years, 59 (37.8%) patients were in the 60-69 years group, and 46.2% were men, with a similar distribution in the 2 groups (p=0.26).

8.3.1.2. Prevalence of risk factors and comorbidities

92 (58.9%) were obese at baseline, with no significant difference between groups (p=0.68). 40 (25.6%) patients were documented as smokers, similarly G1 - G2 (p=0.39). 110 patients (70.5%) had hypercholesterolemia under statin treatment, with LDL-cholesterol outside the target in 29%. DM duration was documented in 43 (27.6%), being 3.2 ± 2.1 years.

Comorbidities. On average, the patients had 3.6 ± 1.8 disease categories/patient. Associated diseases were grouped by categories, except for HTN and DM, and all patients had CV pathology from at least one subcategory (figures 8.6 and 8.7).

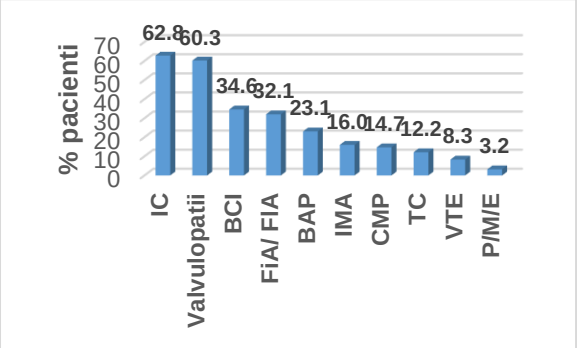


Figure 8.6. CV disease in the study lot.

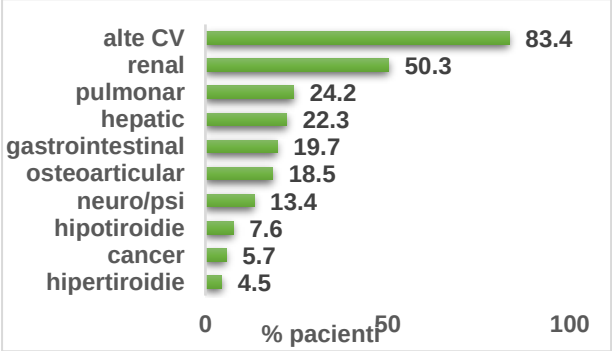


Figure 8.7. Comorbidities in the study lot.

During the 2 years of follow-up, 43 patients (27.4%) were admitted to TICAR, with an average of 0.5 admissions/patient, and the maximum number of TICAR admissions was 7.

8.3.1.3. Clinical parameters

The average length of hospital stay for the studied group was 5.6 ± 4.2 days. Mean BP at admission was 146.8/84.1 mmHg. The mean heart rate was 80.5 ± 20.1/min, and the O2 saturation was 95.3 ± 2.7 %.

8.3.1.4. Electrocardiographic parameters

Approximately 50.6% had sinus rhythm on EKG on admission, including sinus tachycardia, 32% had atrial fibrillation/flutter, with mean ventricular rate 80.1 ± 20.9/min. EKG changes were dominated by negative T waves (27.6%) and ST depression (21.8%).

8.3.1.5. Laboratory data

Laboratory investigations performed on the first admission generally had mean values within the normal range. 59 patients (37.8%) had eGFR <60 mL/min/1.73 m2, with mean eGFR 67.4 ± 21.3 mL/min/1.73 m2. Urinary changes at the first admission were dominated by leukocyturia (60.5%), hematuria (51.8%) and proteinuria (48.2%), 14.9% of patients having a positive urine culture. The distribution of HbA1c on relevant intervals for different degrees of control (targets of 6.5%, 7% and 8%) according to current recommendations is in figure 8.11.

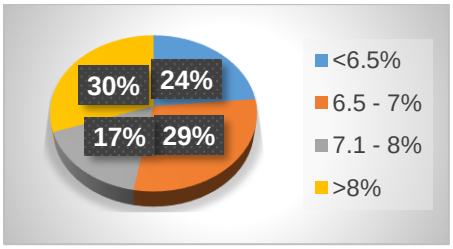


Figure 8.11. Glycated hemoglobin (HbA1c) in the study population.

8.3.1.6. Echocardiography

Echocardiography was performed in 125 (80.1%) patients, with standard parameters, but data on diastolic function were only specified in 119 (76.3%) (figure 8.13).

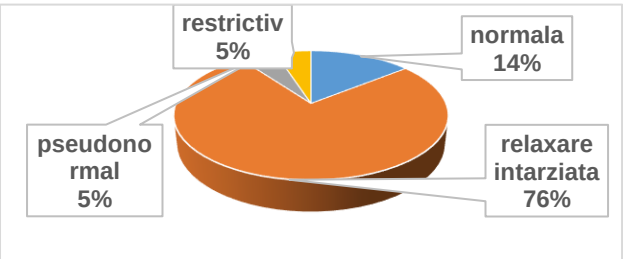


Figure 8.13. Diastolic function.

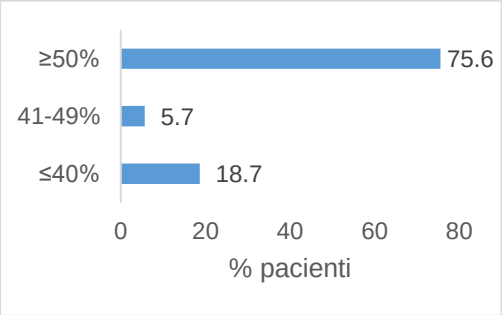


Figure 8.14. LVEF in the study lot.

LVEF was on average 51.9 ± 9.6% in the global study population (figure 8.14), other changes being valvular heart disease (60.3%), LVH (50%), and 56.7% of those with wall motion disorders (25% of the lot) had hypokinesia.

8.3.1.7. Antihypertensive treatment and therapy for comorbidities

Antihypertensive therapy was according to recommendations (3.4 ± 1.2 classes). Figure 8.16 shows the classes at first admission, and figure 8.17 illustrates the main drugs for associated conditions.

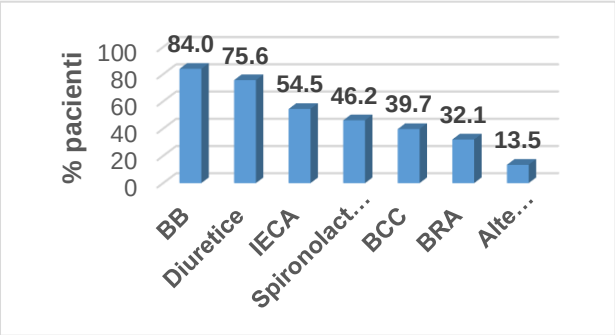


Figure 8.16. Antihypertensive treatment.

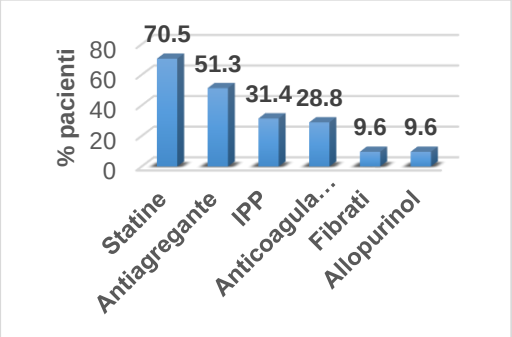


Figura 8.17. Treatment of comorbidities.

The number of antihypertensive drug classes showed a significant difference in means in the covariate analysis, in addition to BP on admission ($p<0.0001$): more classes in those with kidney disease ($p=0.002$), HVS ($p=0.0008$) and uncontrolled BP ($p=0.0007$). The number of antihypertensives prescribed at the first admission was significantly related to the systolic and diastolic BP values on the last admission ($p=0.02$ and 0.05, respectively), for hospitalized patients, as well as CFD at the last readmission ($p=0.02$). Antihypertensive chronotherapy was an important aspect, on average patients received 2 classes of antihypertensives in the morning, 0.2 at lunch and 1.6 in the evening, in the 151 patients (96.8%) who had them specified. 15 (9.6%) of the patients were treated with FDC at the first admission, with no significant

difference between G1 and G2 (p=0.61). CFD of 2 drugs were initially present in 12 patients, and triple - in only 3.

8.3.1.8. Diabetes therapy

The antidiabetic therapeutic options in the studied group included diet, oral antidiabetic drugs and insulin therapy, according to figure 8.20, with the majority of patients having combinations, so that the average number of therapeutic options was 1.66 (figure 8.21).

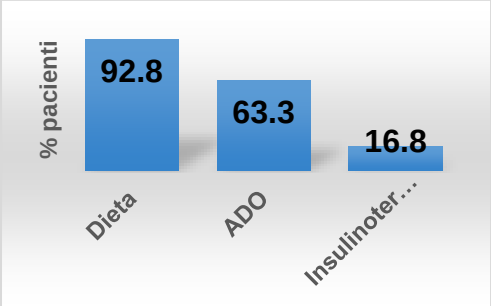


Figure 8.20. Diabetes therapy.

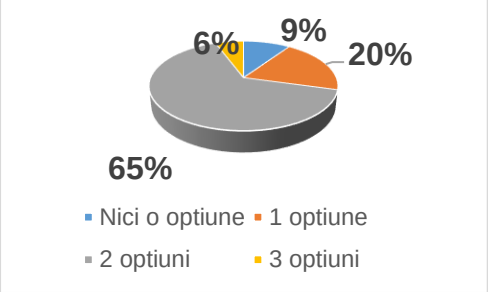
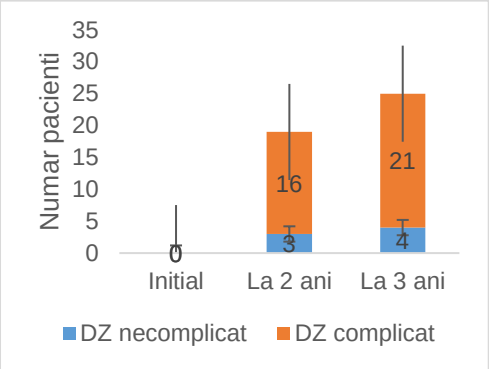


Figure 8.21. Treatment options in DM

The use of oral antidiabetics was associated with glycosuria (p=0.02), and insulin therapy - with controlled glycemia (p=0.02), heart failure (p=0.007), HbA1c (p=0.02).

8.3.1.9. All-cause mortality after 2 and 3 years

The proportion of patients who had died at the end of 2 years of follow-up was 12.2%, and after 3 years it reached 16% of the initial population. Figure 8.22 shows mortality in the study group at 2 years (19 deaths) and at 3 years (25 deaths), with a highly significant difference between G1 and G2 (p=0.006 at 2 years and p=0.001 at 3 years). In terms of dynamics, survival at 2 and 3 years after initial hospitalization illustrates the deepening of significant differences induced by the presence of DM complications, as in figure 8.23.



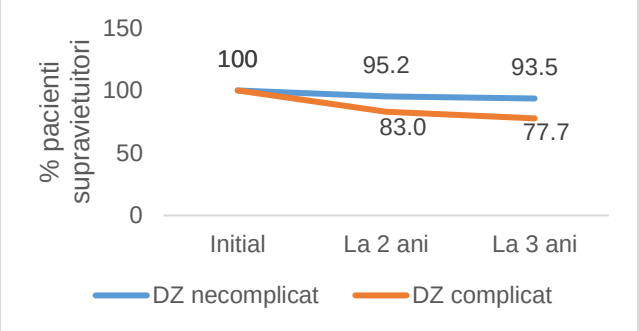
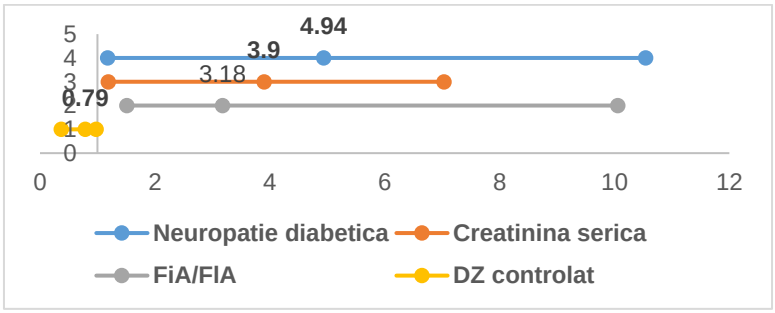
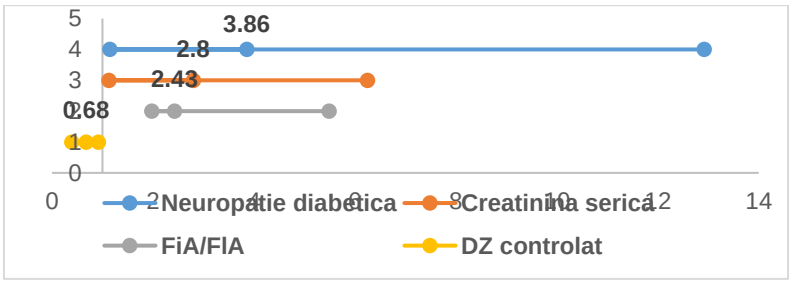


Figure 8.22. Mortality after 2 and 3 years.

Figure 8.23. Survival in G1 and G2.

Parameters significantly associated with all-cause mortality appear in figures 8.24 and 8.25 and do not include controlled BP (p-values 0.95 and 0.63, respectively, at 2 and 3 years). Creatininemia on first admission produced a strong association for 2- and 3-year mortality with excellent predictive value on the ROC curve (see figures 8.24, 8.25 and 8.26). At 2 years, mean creatinine was 1 ± 0.3 mg/dL vs 1.4 ± 0.7 mg/dL (p=0.048); at 3 years, similar values.





Parameter	p-value 2 years	OR 2 years	p-value 3 years	OR 3 years
Diabetic neuropathy	0.03	4.94	0.03	3.86
Serum creatinine	0.048	3.9	0.04	2.8
Atrial fibrillation/flutter	0.049	3.18	0.046	2.43
Controlled DM	0.03	0.79	0.04	0.68

Figures 8.24 şi 8.25. Forest diagrams and data table illustrating possible predictors of all-cause mortality after 2 and 3 years, in multivariate analysis.

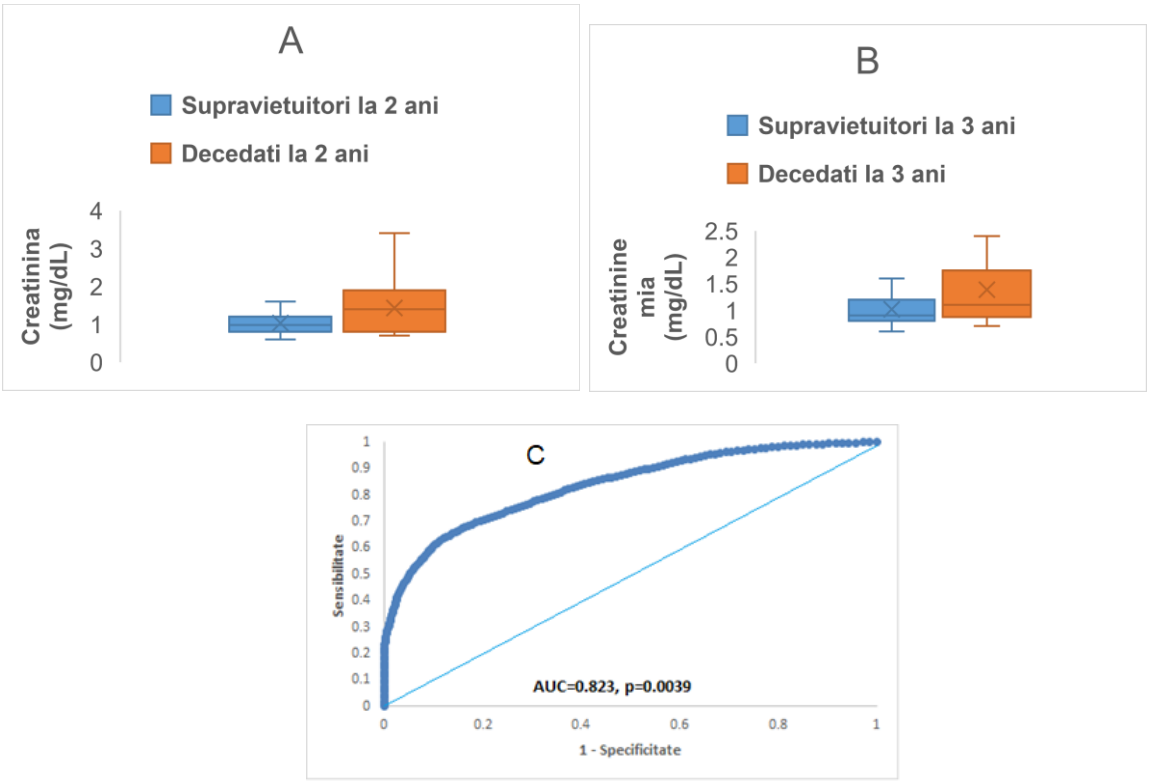


Figure 8.26. Association of initial creatinine and all-cause mortality within 2 (A) and 3 (B) years. ROC curve for creatinine and 3-year-mortality (C).

8.3.1.10. DM and HTN control

HTN and DM control on the first and last hospitalization was around 60% and 50%, respectively. There were 49 (31.4%) patients with HTN and DM controlled simultaneously at the first admission. Figure 8.27 and table 8.4 illustrate the control of HTN and DM on the first (90 patients, 57.7%, 77 patients, 49.3%, respectively), and at the last hospitalization (54 patients, 59.3%, 50 patients, 54.9%, respectively, of the 91 hospitalized patients).

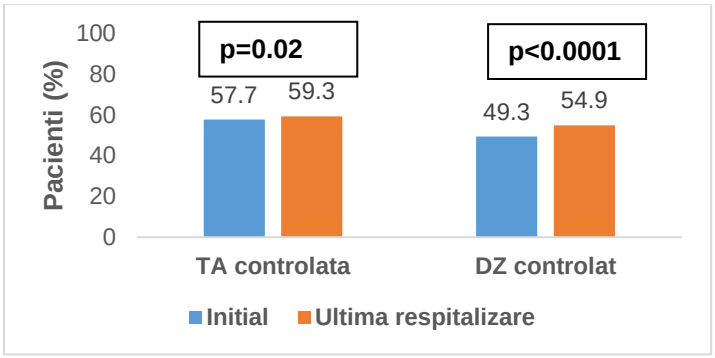


Figure 8.27. BP and DM control in the study lot initially and on the last admission.

Table 8.4. Mean BP and glycemic parameters on the first and last admission.

	Mean BP in population (mmHg)	**Mean BP in G1 (mmHg)**	**Mean BP in G2 (mmHg)**
Initially	146.8/84.1	145.7/84.2	147.5/84
Last readmission	142.5/83.2	140.9/82.7	144.6/83.9

Parameter	**Initially**	**Last readmission**
Mean glycemia in population (mg/dL) (mean ± SD)	156.6 ± 57.9	140.7 ± 44.9
Mean HbA1c in population (%) (mean ± SD)	7.51 ± 1.6	7.5 ± 1.9
Mean glycemia in G1 (mg/dL) (mean ± SD)	144.5 ± 43.9	140.9 ± 41
Mean HbA1c in G1 (%) (mean ± SD)	7.4 ± 1.7	7.5 ± 1.93
Mean glycemia in G2 (mg/dL) (mean ± SD)	164.5 ± 64.7	166.9 ± 68.7
Mean HbA1c in G2 (%) (mean ± SD)	7.6 ± 1.5	7.7 ± 1.5

Initially uncontrolled and controlled patients in terms of BP presented significant differences in certain parameters at first admission (table 8.5) [9].

Table 8.5. Parameters on the initial admission, as per controlled BP (selection).

Parameter	**Uncontrolled BP (N=66)**	**Controlled BP (N=90)**	**p-value**
Clinical characteristics			
Age (years)	64.2 ± 10.7	68.5 ± 8.7	**0.003**
Male sex (%)	33 (50%)	40 (44.4%)	0.55
Risk factors and cardiovascular diseases			
Obesity	47 (71.2%)	47 (52.2%)	**0.02**
Atrial fibrillation	14 (21.2%)	36 (40%)	**0.01**

The number of antihypertensive classes was significantly lower in those with BP in target (3.8 vs 3.2, p=0.0007), while controlled/uncontrolled diabetics had approximately the same number of therapeutic options (1.7 vs 1.6, p= 0.27). DM duration generated a borderline difference between the uncontrolled and the controlled (4.9 vs 1.9 years, p=0.07). Associations with baseline BP and DM control are detailed in Table 8.6.

Table 8.6. Associations of BP and DM control, in univariate and multivariate analysis (selection).

Controlled BP				
Parameter	**Univariate p-value**	**Multivariate p-value**	**OR**	**CI 95%**
Age	0.003	**0.048**	1.23	1.05 – 1.54

Number of drugs in the morning	0.004	**0.02**	0.19	0.05 - 0.76
Other antihypertensives	0.01	**0.02**	0.02	0.001 - 0.51
LV hypertrophy at echo	0.003	**0.005**	0.03	0.003 - 0.37
Controlled DM				
Parameter	**Univariate p-value**	**Multivariate p-value**	**OR**	**CI 95%**
Readmissions in 2 years	0.02	**0.02**	1.24	1.03 - 1.49
Insulin therapy	0.003	**0.01**	0.05	0.004 - 0.54

The significant difference between patients with initially uncontrolled and controlled BP was also maintained for hospitalized patients, the mean BP in those initially uncontrolled was 152.5/87.4 mmHg on the last admission, and 131.1/78.1 mmHg in those initially controlled (p=0.0005). Regarding BP and DM control at the last readmission, the logistic regression will be detailed in subchapter 8.3.3.

8.3.2. Diabetes mellitus complications – study groups

The two groups, the control group (G1, uncomplicated DM, 62 patients) and the group with complicated DM (G2, 94 patients) showed significant differences in clinical, paraclinical, treatment parameters and evolution (mortality - subchapter 8.3.1.9) (table 8.7). TICAR admissions and their number in the 2 years were associated with complicated DM (p=0.003 for both), with 0.2 in G1 and 0.7 in G2. Those with complications were relatively older (65.5 ± 10.6 years in G1 vs 67.6 ± 9.2 years in G2, p=0.17).

Table 8.7. Comorbidities and risk factors according to DM complications (selection).

Parameter	**G1 (N=62)**	**G2 (N=94)**	**OR**	**CI 95%**	**p-value**
Dyslipidemia	34 (54.8%)	76 (82.6%)	2.27	1.03 - 4.006	**0.04**
Other CV diseases	46 (74.2%)	85 (90.4%)	3.28	1.34 – 8.01	**0.007**
Atrial fibrillation/flutter	16 (25.8%)	34 (36.2%)	2.12	1.04 - 4.33	**0.04**
Myocardial infarction	4 (6.5%)	21 (22.3%)	3.21	1.45 – 6.5	**0.008**
Heart failure	30 (48.4%)	68 (72.3%)	2.21	1.14 - 4.33	**0.02**
Kidney disease	23 (37.1%)	56 (59.6%)	2.49	1.29 - 4.83	**0.006**
Liver disease	20 (32.3%)	15 (16%)	0.39	0.18 - 0.85	**0.02**
Osteoarticular disease	5 (8.1%)	17 (18.1%)	2.92	1.26 - 6.71	**0.01**

BP on the first admission in the 2 groups was 145.7/84.2mmHg and 147.5/84mmHg, respectively, and HR was 79.4/min and 91.3/min, respectively, with no intergroup difference.

Figure 8.28 shows DM complications in G2, initially. 32 patients (20.5%) had a history of major macrovascular damage (heart attack and/or stroke), and major microvascular damage was present in 68 patients (43.5%).

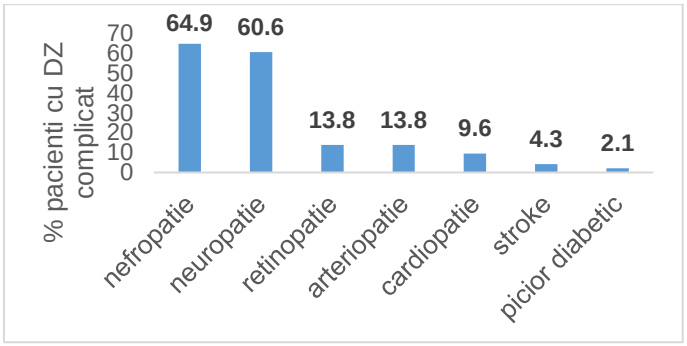


Figure 8.28. Prevalence of DM complications in G2.

DM duration was strongly associated with the presence of complications (p-value < 0.0001), 1.2 years on average in G1 and 6.1 years on average for G2. Diabetic nephropathy, the most common in the study, showed significant associations in a multivariate model with heart failure (p=0.01, OR=3.37), ACEI (p=0.006, OR=0.28) and TICAR hospitalizations (p=0.02, OR =3.14). DM duration in patients with nephropathy was higher (9.4 versus 1.6 years, p=0.002).

As for antihypertensive treatment, figure 8.29 shows the proportion of patients who had each class of antihypertensives, in the 2 groups.

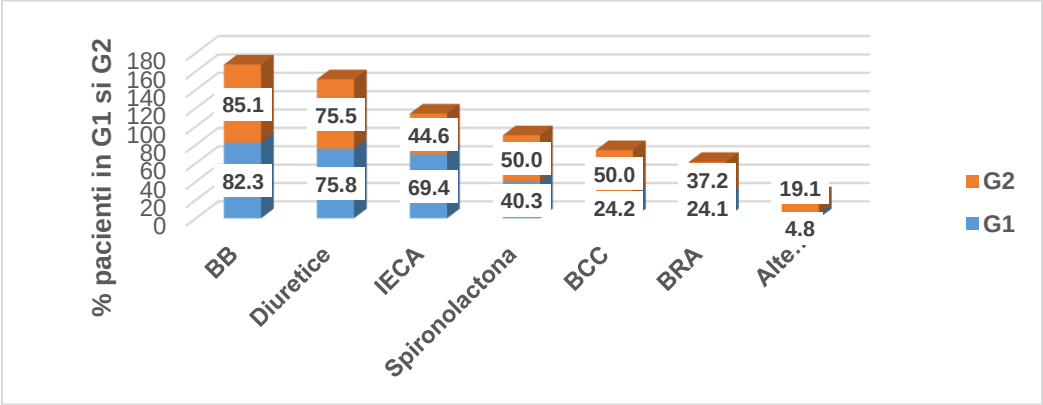


Figure 8.29. Antihypertensive drugs in the 2 study groups.

Chronotherapy. The number of antihypertensive classes was different between groups: 2.2 vs 1.9 (p=0.05) in the morning, 0.1 vs 0.3 (p=0.02) at noon, 1.6 in both groups in the evening (p=0.08). An association was found between the number of antihypertensive classes at first

admission and complications (p=0.03, 3.2 in G1 versus 3.6 in G2), especially nephropathy (p=0.01, 3.3 in those without and 3.7 in those with nephropathy) (Figure 8.30). The number of complications correlated with the number of antihypertensive classes (p=0.02, r=0.189).

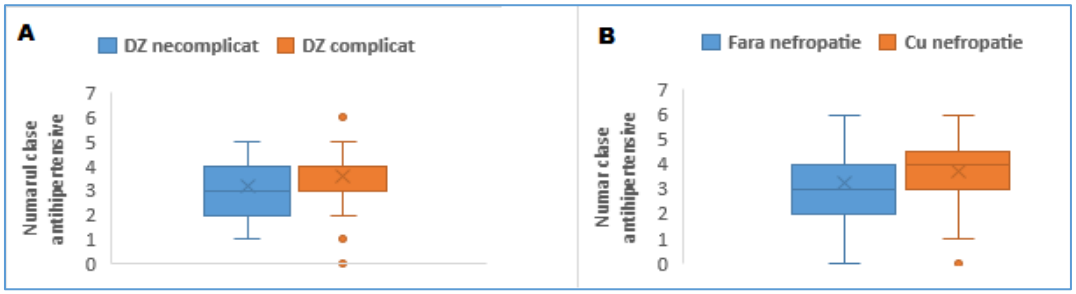


Figure 8.30. Relation between the number of antihypertensive classes and DM complications (A), especially diabetic nephropathy (B).

Laboratory data in relation to DM complications only showed differences for creatininemia (p=0.02), eRFG (p=0.006) and total cholesterol (p=0.01). The probability of LDL values being in the therapeutic target was approximately 3 times higher in patients with complicated DM (p=0.008, OR 3.15, CI 95% 1.31 - 6.87). EKG and echocardiographic parameters showed no differences between the 2 groups, except for LVEF (p=0.04) and diastolic function (p=0.02). Diastolic function was specified in 38 patients in G1 and in 81 in G2, the predominant being impaired relaxation (89.5% in G1 and 69% in G2). LVEF, documented in 123 patients, averaged 54.5% in G1 and 50.7% in G2, with low LVEF in 5 (21.7%) patients in G1 and 18 (78.3%) patients in G2.

8.3.3. Rehospitalizations. Particularities of rehospitalized patients, treatment evolution

Of the 156 included patients, 91 (58.3%) were rehospitalized in the Cardiology department during the following 2 years, 37 (59.7%) from G1 and 54 from G2 (57.4%), p=0.78. Of these, 29 (31.9%) had TICAR admissions, on average 0.7/patient, with no significant association between TICAR admissions and ward admissions (p=0.13). In the whole group, patients had 1.5 readmissions/2 years, and in G1 there were 1.43, similar to 1.66 in G2 (p=0.57). The main causes of hospitalization were heart failure decompensations (57 patients, 62.6%), atrial fibrillation (29, 31.8%), and acute or chronic coronary syndromes (21, 23.1%). The number of readmissions was associated with age at first hospitalization (p=0.048) and female gender (p=0.048), and the number of days of hospitalization was correlated with initial age (p=0.04,

r=0.344, figure 8.33). TICAR admissions and their number were associated with DM complications (p=0.007 and p=0.008, respectively).

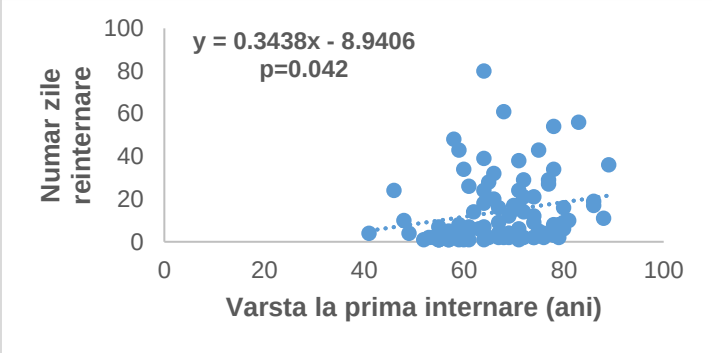


Figure 8.33. Correlation of the number of readmissions and age on first admission.

The first readmission occurred after approximately 7.4 ± 5.1 months, mean BP was 142.5/83.2 mmHg, mean glycemia 156.6 ± 60.2 mg/dL, and mean HbA1c 7.6 ± 1.7%. The last hospitalization in the 2 years of follow-up occurred after approximately 16.2 months, mean BP was 142.5/83.2mmHg, mean glycemia 140.7 ± 44.9 mg/dL, and mean HbA1c 7.5 ± 1.9%. The interval after which the first hospitalization occurred correlated with ST-T depression on EKG (p=0.03), valvulopathies (p=0.045), and initially controlled diastolic BP (p=0.008).

Out of the patients with rehospitalizations, 11 died at 2 years, and 13 deaths were recorded at 3 years (p=0.99 and 0.36, respectively). In readmitted patients, mortality at 2 and 3 years showed similar associations, including diabetic nephropathy (p=0.006 and 0.0004, respectively) and number of DM complications (p<0.0001 for both).

Evolution of renal function. On the last readmission, creatinine averaged 1.3 ± 0.7 mg/dL. On the first admission, eRGF <60 mL/min/1.73m^2 was present in 59 (37.8%) of the patients. On the last readmission, of the 91 hospitalized, 72 (79.1%) had renal dysfunction according to this threshold, and in 30 (32.9%) an increase in creatinine was documented. In logistic regression, deterioration of renal function was associated with retinopathy (p=0.03, OR 7.73).

Rehospitalizations were associated with the number of antihypertensive classes that patients received at first admission (on average, 3.6 classes in those subsequently hospitalized, compared to only 3.1 classes in those without readmissions, p=0.03). The number of days of hospitalization was correlated with the number of classes of antihypertensives on the first admission, with p=0.007, and R^2=0.04. On readmission, 5 patients (5.5%) received FDC of

antihypertensives in addition to those already on FDC, although changes of antihypertensive treatment occurred in 29 (31.8%) of the patients who were rehospitalized (figure 8.35). Changes in DM treatment could not be quantified, as medication and doses were not systematically specified in discharge summaries.

DM and BP control at the last admission showed independent associations in the subpopulation of patients with readmissions (table 8.12). The association between previously controlled DM and controlled DM on the last visit was strong and expected (p-value close to 0). DM complications did not have a significant link with DM controlled at the last readmission (p=0.3). Controlled BP at the last readmission was significantly influenced by systolic BP (p=0.01, 152.3 mmHg in those without control vs 139.8 mmHg), and diastolic BP at the first hospitalization (0.02, 87.6 mmHg in those without control vs 80.8 mmHg), plus an association with BP controlled at baseline (p=0.01, OR=1.67).

Table 8.12. Factors influencing BP and DM control on the last rehospitalization in the readmitted patients' subpopulation (multivariate model).

Parameter	**OR**	**CI 95%**	**p-value**
Controlled BP on last admission			
Controlled BP on first admission	1.67	1.09 – 2.48	**0.02**
LV hypertrophy at echo	0.15	0.02 – 0.87	**0.03**
Wall motion abnormality at echo	0.18	0.03 – 0.95	**0.04**
Microalbuminuria	0.2	0.04 – 0.84	**0.03**
Controlled DM on last admission			
Controlled DM on first admission	4.54	1.29 – 12.2	**0.004**
Q wave	0.03	0.002 – 0.46	**0.01**
Inverted T waves	7.11	1.01 – 50.04	**0.048**

8.4. Discussion

This study analyzes the therapeutic control and evolution of hypertensive diabetics admitted to the Cardiology department, in daily practice, in relation to DM complications and antihypertensive therapy. Study 1, prospective and focused on BPV and glycemic parameters in outpatients with complicated DM, is complementary, covering other aspects of the evolution.

8.4.1. Characteristics of the study population

In the current study, HTN was among the diagnoses in approximately 61% of Cardiology admissions, confirming data from university hospitals, where 69.6% had HTN, and according to SEPHAR III Romania has a high prevalence of HTN [7,57]. In the present real-life cohort, diabetics represented 20% of hypertensives, close to the results of a study on 503 patients of a metropolitan hospital (17.3%) [58]. The mean age was 66.7±9.8 years, similar to ADVANCE (66 years) and ACCORD (62.2 years) [23,31]. The present research documented a female predominance of 53.85%, in agreement with the country data from Romania, but different from the large-scale trials [32,23,31]. Obesity in the group of hospitalized patients, 58.9%, exceeds the literature prevalence - up to 45.8% in the Center for Disease Control data for diabetics from 2020 [29]. Dyslipidemia was prevalent, and most were receiving statin treatment, the LDL-cholesterol targets in force being reached at 71%, without lipid-lowering combinations at that time. The age of DM was documented at 27.6%, demonstrating that DM is still perceived as a qualitative FR, although numerous studies link the duration of evolution to complications [59]. The mean disease duration obtained, of 3.24 years, is shorter than in ADVANCE (7.7 years), but in some patients the diagnosis is late [23]. The duration of hospitalization for the entire batch (5.5 days) was below that of the European CV disease statistics for Romania (7.3 days in 2018) [60]. More than a quarter of the patients were hospitalized in TICAR, with an average of 0.5/patient, the hospitalized patients being with serious CV pathology and multiple comorbidities. Non-CV diseases were dominated by renal pathology, each patient having at least one category of comorbidities, on average 3.6 categories. The prevalence was similar to that of the European registries of CV diseases and included as frequent diagnoses entities mentioned by the main prevalence statistics of recent years, in the ALLHAT trial the history of myocardial infarction was around 20% [36,61,62]. The main reasons for hospitalization are consistent with the discharge diagnoses, dominated by heart failure, anginal symptoms and arrhythmias, and combinations.

One third had systolic BP values under 139 mmHg, similar to ADVANCE (145/81 mmHg), and 46% had diastolic BP below 90 mmHg, with an average of 146.8/84.1 mmHg, consistent with an average age of approximately 66.7 years, elderly patients showing a tendency to isolated systolic hypertension [23]. The 16,878 adherent patients in ALLHAT had a mean BP of 136.6/78.3 mmHg, suggesting that adherence is probably also important in the present study

[36]. EKG confirmed atrial fibrillation in approximately 30%, acute or chronic ischemic changes predominated, along with various conduction and rhythm disorders (causes of heart failure decompensation and similar to the ischemic pathology in the diagnoses). More than 3 quarters had echocardiographic data, the mean LVEF being 52%, with 75% of patients with preserved LVEF explained by the known prevalence of preserved LVEF in diabetics [40]. 76% of patients had diastolic dysfunction of the delayed relaxation type, half had LVH, confirming literature trends [40]. The glycemic parameters, especially the mean HbA1c of 7.5% in the present study, were comparable to the literature - around the target value of 7% in the vast majority of large-scale trials, but the present values could be slightly above the target as these are decompensated patients [4,23,30,31]. The lipid profile was, on average, with an LDL-cholesterol of 99 mg/dL, well above the limit of 70 or even 55 mg/dL recommended by the guidelines, closer to the target than that of ACCORD (105 mg/dL) [31]. Microalbuminuria was rarely measured, but proteinuria was present in 48.2%, significantly more than in primary care studies (23.3%) [41].

Antihypertensive treatment was along the recommended line [1]. The links between the classes of antihypertensives and other diseases, such as heart failure, ischemic heart disease, liver diseases, are also observed by logistic regression. Complicated DM has been associated with treatment with BB, CCB, and other antihypertensives. Patients received on average more than 3 classes of medication, explained by the status of multiple comorbidities and advanced disease, similar to SEPHAR III [7]. The number of medication classes was significantly increased, especially in those with kidney disease, hypertensive heart disease, but also controlled BP. The data obtained are different from the results of a study on patients from primary care, with compensated patients, where 58% received ACEI, 41% BB, 24% CCB, and 12% ARB [44]. FDCs were used in less than 10%, but the first admission in 2017 predates the 2018 guideline, where the FDC recommendation is firm [1]. Comorbidities therapy included antithrombotics in almost 3 quarters, corresponding to ischemic heart disease and arrhythmias with possible thromboembolic complications, fibrates, allopurinol in small proportion, gastric protection in one third of the participants, to prevent possible hemorrhagic complications in elderly patients, with renal comorbidities and hepatic. The patients with atrial fibrillation in the group had a CHA_2DS_2-VASc score of at least 2 because they were both hypertensive and diabetic, so they fell under the anticoagulation recommendation [63].

Diabetes treatment was in almost 2/3 of the cases represented by the use of a combination of 2 options (diet and ADO or diet and insulin therapy), 6% had 3 treatment options, but 15 patients (9%) with newly diagnosed DM were not yet treated. Patients with glycemic values controlled under oral antidiabetics and those with heart failure had less frequent insulin therapy, and those with glycosuria - a higher probability.

8.4.2. Arterial hypertension and diabetes mellitus control

The present cohort is in line with the trends mentioned for DM and HTN control on a national and European level, in the United States of America or Australia. Simultaneous control at first admission was in 31.4% of patients: DM was controlled in 50% of patients at first admission, confirming known data, such as 50% in NHANES and 44.5% of nonadherent patients in the ALLHAT trial [6,36]. The mean blood glucose on the first admission was 156.6 mg/dL, and HbA1c – 7.51%, above the recommended targets [4]. A meta-analysis of self-monitored BP from 4 studies on a total of 2590 patients showed a 33.4% BP control, in a Chinese registry the level was 40%, and in Romania the control was 30.8% [7,8,41]. HTN was controlled in 57.3% of patients at the first hospitalization, being patients with cardiac pathology, monitored more frequently. The mean BP on the initial admission was 146.8/84.1 mmHg, above the suggested limit, but more optimistic than in a study at a metropolitan hospital, where only 33.4% were in the target, but the patients were older [1,58]. Patients with initially controlled BP were significantly older, obese and with more comorbidities, confirming data on better monitored frail patients [64]. An important parameter for control estimation is adhesion, generally declarative, being the main factor contributing to suboptimal control [6].

The predictors of BP control were: the number of antihypertensive drugs administered in the morning, the combination of other classes of antihypertensives and the presence of hypertensive heart disease. A study dedicated to the identification of predictors of lack of BP control in hypertensive diabetics confirmed that they include isolated systolic BP at inclusion, uncontrolled BP at inclusion, use of oral hypoglycemic agents versus diet or insulin therapy, use of more than 3 classes of antihypertensives [44]. The predictors of BP controlled at the last readmission, results from the present research, are BP at inclusion, BP controlled at the first hospitalization, microalbuminuria and HVS. The predictors of initially controlled DM, confirmed by multivariate analysis, are insulin therapy (protective factor) and readmissions, proving that the frequency of re-evaluations leads to better control, but those with insulin have

decompensations that could disturb the glycemic balance. Later controlled DM was clearly associated with initially controlled DM.

8.4.3. Diabetes mellitus complications' impact on patients' evolution (rehospitalizations, treatment changes, all-cause mortality)

More than 60% of the included hypertensive diabetics had DM complications on the first admission, which marked differences in terms of evolution. The MENTOR study documented that 76.7% of type 2 diabetics in Romania have at least one DM complication [38]. DM duration of evolution was very strongly associated with complications, reinforcing the idea that DM is more than a qualitative risk, with a negative impact on prognosis.

Diabetic nephropathy and neuropathy were prevalent, in almost 2/3 of G2, although retinopathy seems to be the most frequent microvascular complication, possibly underestimated in Romania [37]. Diabetic nephropathy can precede the diagnosis of DM by years, so the duration of DM is an important association, confirmed by the present study ($p=0.002$) [37,59]. The patients in the present study were diabetic, hypertensive and with more serious pathologies, the risk of renal dysfunction being all the greater. And the diabetic retinopathy-nephropathy association is emphasized in the ADA standard, along with HTN, dyslipidemia and chronic hyperglycemia [59]. Diabetic neuropathy is confirmed by the ADA in 30-50% of diabetics, the percentage being around 60 in the present study, possibly in relation to a later diagnosis [ADA 11 2020]. Macrovascular complications were in approximately 14% of patients, less than 5% of patients had a stroke, and diabetic foot was present in 2%. These complications are sometimes noted separately from DM, which explains the lower proportion than in large trials (27–30%) [23,39]. Microvascular complications occurred in 53.5% of the over 66,000 type 2 diabetics in the multinational A1chieve trial, but in the present study the percentages are higher, similar to Russia, explained by the authors through late diagnosis and lifestyle [39]. Between the 2 study groups there were significant differences in CV, renal and liver diseases, confirming that complicated DM is a strong risk factor, especially in hypertensives [1]. The lipid profile was more controlled in diabetics with complications, explainable within a stricter control of risk factors. They had a significantly lower LVEF, and diastolic dysfunction of the delayed relaxation type dominated the picture in both groups, but in G2 there were also patients with more severe dysfunction. The relationship between nephropathy and glycemia, renal function and lipid profile is expected, being a cause of end-

stage chronic kidney disease [29,37]. Diabetics with nephropathy had more admissions in TICAR, highlighting the increased risk of adverse outcome. The association with insulin therapy and ACEI treatment is explained by the need for an intensive treatment to optimize glycemic control and an antiproteinuric therapy with a proven renoprotective effect [1].

Rehospitalizations. Almost 60% were hospitalized in the Cardiology department, without the possibility of checking possible hospitalizations in other cardiology services. A study that analyzed 123,235 Medicare diabetics found that the 5-year risk of readmissions in those over 65 was around 56.2% in the poor adherence cohort [65]. Patients at risk (ischemic changes, valvulopathies, alcohol consumption) had more frequent readmissions, and those with controlled BP parameters returned to the hospital faster than the others, suggesting that more frequent visits are the premise of better control. The main causes and significant associations of readmissions were major CV diseases, but age on first admission and female gender were also significantly different between those with and without readmissions. Romania ranks 7th in the European Union for hospitalizations for CV diseases, with almost 3,000/100,000 inhabitants, so the current statistics fall within this trend [66]. DM complications had a measurable impact: significantly more TICAR admissions in 2 years, increasing CV risk. Diabetic retinopathy has been associated with an increased risk of worsening renal dysfunction.

Antihypertensive treatment and treatment changes in the two study groups. The presence of DM complications was strongly associated with the use of ACEI (p=0.002), being the known renoprotective effect and on cardiac remodeling, with CCB (p=0.001), a class proven to improve BPV, of rilmenidine (in renal damage) [67]. There was a clear association between the presence of complications and the number of classes of antihypertensive medication, higher in those with complicated DM, but also with the number of complications, especially nephropathy. The number of antihypertensive classes was higher in the patients who returned to the hospital, and the chronotherapy was significantly different in the subgroup of those hospitalized, who received more drugs in the morning.

Antihypertensive treatment changes affected 31.8% of readmitted patients, by adding, replacing or eliminating one or more classes, and in 3 patients ACEI was replaced with ARB in the context of cough. There was inertia in changing antihypertensive treatment, as the proportion of controlled BP was around 50% at readmission and only about a third of patients received different treatment recommendations, including dose adjustment required in 2 patients

with arterial hypotension. This inertia was also manifested in the use of FDC, with only 5% receiving them upon hospitalization, despite the recommendations of the 2018 guideline and the objective of improving adherence [1]. Diabetes treatment was not systematically described as preparations and/or doses, so it did not allow for changes to be evaluated.

All-cause mortality. In this study, the causes of death could not be explored because there was no database, but only the Integrated Information System of the National Health Insurance House, publicly accessible on the platform http://siui.casan.ro:82/ Insure/, where the vital status can be ascertained, not the cause of possible death. A CV cause (AMI, arrhythmia) could only be confirmed for 3 deaths out of the 19, as they occurred in the hospital.

Mortality at 2 years of 12% and 16% at 3 years, with the significant difference in favor of G2 at both evaluations, demonstrates that this population at risk is influenced by the presence of DM complications, with the differences increasing from one year to another, the only factor of protection documented in this study being the DM control. The predictors identified for mortality at 2 and 3 years were mainly related to DM complications, especially nephropathy and renal damage (creatininemia), but also to markers of severe CV diseases (atrial fibrillation, heart failure, ischemic EKG changes, ultrasound, TICAR admissions), atrial fibrillation being the only one confirmed by logistic regression as an independent predictor. In very recent studies, diet and insulin therapy were not predictors of evolution either, but poor glycemic control (Hba1c > 8%) was clearly associated with the composite endpoint of CV death [68]. Intensive BP control led to a 32% decrease in DM-related deaths in previous research [37]. Among the paraclinical parameters, creatininemia at the first admission showed a very good predictive value for all-cause mortality in the ROC analysis. Among patients with rehospitalizations, mortality was not significantly different compared to those without rehospitalizations, the factors with which significant associations were registered were similar to those of the entire lot. The main cause of death of type 2 diabetic patients are CV diseases and macrovascular complications, but all complications are independent predictors of mortality, as shown by a large analysis of 3711 patients from the ETRDS (Early Treatment Diabetic Retinopathy Study), among whom diabetics type 2 had a mortality of 25% at 5 years, mostly caused by acute coronary events (56%) [69].

8.4.4. Study limits and perspectives for future research

This retrospective study accesses data already recorded in the hospital's IT system, assuming partial data. The population size was relatively small, due to the medium level number of beds in the hospital. The bias of including patients hospitalized in Cardiology means a selection of more severe patients. The lack of a complete picture of subsequent admissions is caused by the lack of a national system. Assessment of HTN and DM control was based on data measured on admissions. A large prospective study, possibly with ABPM, would allow a more accurate assessment of control and evolution, according to BP profiles.

9. Conclusions and original contributions

Both research studies target hypertensive diabetics, a common combination, but capture different aspects of their evolution

9.1. Final conclusions

Study 2, retrospective

Study 2, Objective 1:

-DM is frequently associated with HTN, both diagnoses being common (20% and 60%, respectively) in hospitalized patients and many hypertensive diabetics have complications (60%).

-Real life differs from the selected lot

Study 2, Objective 2:

-DM nephropathy is independently associated with the severity of CV damage and with a more severe evolution (admissions to the intensive care unit for CV diseases).

-In real life, control is achieved in 40% of hypertensives and 50% of diabetics, and those with both diseases controlled are less than a third of the studied population.

-The control of risk factors (obesity, dyslipidemia) in the studied population was suboptimal, but comparable to literature data.

-Rehospitalizations are common in hypertensive diabetics (60%), and patients with complicated DM had significantly more admissions into the intensive care unit for CV disease in 2 years, suggesting an increased CV risk.

-Mortality is significantly increased in patients with complicated DM, and the difference versus those without complications increases over time.

Study 2, Objective 3:

-Duration of DM evolution is strongly associated with complications, therefore DM is more than a qualitative risk factor, although still perceived as such, duration being rarely mentioned in medical documents.

-Diabetic nephropathy and neuropathy were the most prevalent, in almost 2/3, although retinopathy is possibly underestimated in Romania.

Study 2, Objective 4:

-The frequency of re-evaluations and the use of several classes of medication increase the degree of BP and DM control.

Study 2, Objective 5:

-Many classes of antihypertensives are needed to achieve control, yet physicians show inertia, preferring dose increases over CFDs or new drugs, even though adherence could be optimized.

-Creatinine on the first admission had a very good predictive value for all-cause mortality.

Study 1, prospective

Study 1, Objective 1:

- Various forms of HTN are also common in patients under treatment, especially white-coat HTN: over 33% of patients had white-coat HTN, and almost 8% had masked HTN.

-Dipping profiles evaluated by nocturnal decrease of systolic versus diastolic BP were markedly different, more favorable for diastolic BP, although the predominance of non-dippers was confirmed in both cases.

-The reproducibility of BP and BPV profiles is suboptimal, especially in conditions of variation in the therapeutic scheme and suboptimal adherence. Non-dipper status and the widest threshold of 10% for defining BPV were the most reproducible.

-Hypertensive diabetic outpatients see the doctor mainly for the lack of BP and DM control, but compliance with treatment changes is suboptimal (33%).

Study 1, Objective 2:

-DM and HTN control is suboptimal, consistent with literature data.

-DM control at inclusion, reflected by venous blood glucose and HbA1c, was significantly associated with the 7-day mean blood glucose, self-determined from capillary blood, so that all glycemic parameters were in agreement in the short, medium and long term.

-Mean systolic BP/7 days is associated with controlled DM, these patients probably being more adherent to all recommendations.

-HTN control optimized by treatment changes increases dippers' proportion and improves BPV.

- Echographically documented left ventricular hypertrophy, a marker of hypertensive heart disease, is associated with increased BPV, a possible consequence of suboptimal control reflected by BPV.

-The most prevalent complications of DM in the study population were diabetic neuropathy and nephropathy, closely related to disease duration.

-DM complications were independently associated with renal function and mean 24-hour systolic BP, and had similar prevalence in low/high BPV subgroups.

-Risk factors: one third of the patients were smokers and more than half were obese, but 70% had LDL-cholesterol values within the recommended target at that time.

-More than a quarter of the patients presented small deteriorations of renal function in a 6-month interval, correlated with the parameters of mean diastolic BP at ABPM and HbA1c.

-Quality of life: although it improved in over 40% of patients, the variations were too small in absolute value to lead to a significant difference.

-Events such as hospitalizations and mortality were in low numbers in the context of the relatively short follow-up period, adapted to the conditions of the COVID-19 pandemic.

-The AASI-ABI inverse correlation reinforces the idea that stiffness is associated with markers of atherosclerosis in diabetics, and the correlation of AASI with the nocturnal BP drop suggests that nocturnal dipping could be an estimator of arterial stiffness.

Study 1, Objective 3:

-Increased BPV is related to reduced nocturnal dipping, a risk factor for CV events and DM retinopathy, therefore increased BPV is associated with increased CV risk.

-BPV could represent parameter of control, along with office BP, BP values at ABPM, and self-measured BP. The optimal frequency of BPV determinations, the use of systolic or diastolic BP, and the threshold remain under discussion. For hypertensive diabetics, complex BP analysis may be superior to simple office BP assessment from visit to visit.

-On inclusion, medium- and short-term BPV evolved in parallel. In the absence of an ABPM device, self-monitoring at home could serve as an assessment of control better than office measurement.

-Although with similar DM control between subgroups (estimated by blood glucose and HbA1c), those with increased BPV had much lower HbA1c, patients aware of their higher CV risk, with the help of the physician, being more compliant.

-Most patients had at least 2 antidiabetic treatment options.

-Global GV parameters at 7 days were not associated with DM control, only the mean blood glucose for 7 days showed an association with controlled DM.

Study 1, Objective 4:

-Medium-term GV estimated by classic or alternative parameters did not show associations with DM control, antidiabetic treatment or complications, the series of values being limited, but CGM in a future study could improve this analysis.

Study 1, Objective 5:

-FD was not associated with BPV by CoV for any of the ABPM parameters, suggesting that the information obtained by fractal analysis is complementary to that provided by global parameters.

-FD values were much reduced compared to those of normotensives in other studies, a reduced complexity may be associated with a system at risk of disease or already affected by it.

-FD values showed a significant nocturnal decrease on both visits, the more substantial reduction being associated with BP control.

-FD provides additional information to global BPV and GV parameters including definition of increased BPV and BP control (excellent predictive value). These nonlinear dynamics methods have so far not been used systematically in diabetic hypertensives and could optimize the understanding of CV dynamics, leading to a more complex individualized assessment by rapid methods.

9.2. Original contributions

The innovative contribution of the thesis is supported by the global vision of the evolution of hypertensive diabetics, using 2 studies that complement each other. Remarkable aspects of outpatients versus hospitalized patients have been identified, and the impact of DM complications and increased BPV in the short, medium and long term was analyzed.

The originality is provided by the study of the optimal parameters for estimating BPV, by comparative evaluation of the information derived from both the classical, global parameters (SD, CoV), and from the alternative parameters, the fractal analysis. This type of analysis has not been systematically performed in previous studies in diabetic hypertensives in relation to DM complications.

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List of scientific papers published as a result of doctoral research

Articles published in indexed journals:

1. Ilieşiu AM, Cordoş I, **Pârvu I (corresponding author)**, Verde I, Liteanu AS, Hodorogea AS, Rădăvoi GD. Antihypertensive drugs and blood pressure variability. Farmacia. 2021;Vol. 69(2):200-207. **doi:10.31925/farmacia.2021.2.2.** ISI, impact factor=1.433. ISSN 0014-8237.**https://farmaciajournal.com/wp-content/uploads/art-02-Iliesiu_Parvu_Radavoi_200-207.pfd**

2. **Pârvu I**, Verde I, Nicolae C, Ilieșiu A. Blood pressure control in hypertensive patients with type 2 diabetes mellitus. Internal Medicine. 2021;18(2):49-59. CNCSIS B+. ISSN 1220-5818. **Link: https://sciendo.com/pfd/10.2478/inmed-2021-0156.**

Papers presented at scientific events organized by national and international professional associations:

1. Blood pressure profile and variability in hypertensive diabetics/ Profilul şi variabilitatea tensiunii arteriale la pacienţii diabetici şi hipertensivi. Irina Pârvu, Ion Relu Ondin Zaharia, Andreea Simona Hodorogea, Ana Ciobanu, Adriana Mihaela Ilieşiu. Congresul Naţional de Medicina Internă, Online. 2021, 03 iunie, Canal 3. Internal medicine - Volum rezumate - Congresul Naţional de Medicină Internă - www.srmi.ro, 117-118.

2. Antihypertensive therapy in patients with diabetes and hypertension in clinical practice/ Terapia antihipertensivă la bolnavii diabetici și hipertensivi în practica clinică /

Antihypertensive therapy in diabetic and hypertensive patients in clinical practice (57). **I. Pârvu**, C. Nicolae, A.S. Liteanu, A.S. Hodorogea, I.T. Nanea, A.M. Ilieșiu. Congresul Naţional de Cardiologie, Bucureşti, România, Virtual Meting. Lucrari rapid comentate/Rapid fire abstracts. Revista Româna de Cardiologie. 2020;Vol 30, Supliment 2020:81-82.

3. Blood pressure and diabetes control – data from clinica practice/ Controlul hipertensiunii arteriale si diabetului zaharat – date din practica clinica. Irina Pârvu, Ioana Verde, Adriana Ilieşiu. Simpozion "Zilele Spitalului Prof. Dr. Th. Burghele", 2020, Bucureşti, România.

4. Blood pressure profile in diabetes mellitus – diagnostic aspects with a therapeutic impact/ Profilul tensional în diabetul zaharat – aspecte diagnostice cu impact terapeutic. **Irina Pârvu.** Simpozion "Zilele Spitalului Prof. Dr. Th. Burghele", Bucureşti, 2019, România.

5. Dyslipidemia in diabetes mellitus – from guidelines' recommendations to current practice/ Dislipidemia în diabetul zaharat - de la recomandările ghidurilor la practica curentă. Irina Pârvu. Conferinta in cadrul mesei rotunde "Bolile cardiovasculare la bolnavul cu diabet zaharat – între cardiolog şi diabetolog". Congresul National de Medicină Internă, 2019, Calimăneşti-Căciulata, România.

6. Cardiovascular risk in the diabetic patient with HTN/ Riscul cardiovascular la bolnavul diabetic care asociaza HTA. Irina Pârvu; Simpozion "Zilele Spitalului Prof. Dr. Th. Burghele", 2018, Bucureşti, România.