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Adherence to guideline recommended medical therapies in type 2 diabetic patients with chronic critical limb ischemia

Elisabetta Iacopi[*], *Alberto Coppelli*, *Nicola Riitano*, *Lorenza Abbruzzese*, *Letizia Pieruzzi*, *Chiara Goretti*, *Alberto Piaggesi*

Diabetic Foot Section, Pisa University Hospital, Pisa, Italy

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ABSTRACT

Aim: The aim of this study was to evaluate the adherence to guideline recommended medical therapies in type 2 diabetic patients with chronic critical limb ischemia (CCLI).

Methods: We retrospectively analyzed the data of 1315 admissions performed in our Department, focusing on diabetic foot patients (842–64%) of which 603 consecutive type 2 diabetic patients with CCLI (M/F(%): 73/27; age: 70.3 ± 10.4 yrs; diabetes duration: 17.3 ± 13.7 yrs; BMI: 27.7 ± 5.3 Kg/m^2; HbA1c 7.8 ± 1.8%) referred to a third-level Center from 2011 to 2015. We focused on medical therapy of diabetes, dyslipidemia, hypertension, peripheral vascular disease and smoke habits.

Results: In total, at admission, 66.6% of patients had HbA1c levels higher than recommended; 65.9% of patients were on statins; 81.4% on anti-hypertensive treatment and 72.4% on antiplatelet drugs. Concerning smoke habits, 27% of patients were no-smokers; 41% former smokers and 32% active smokers. Among all patients, only 24% were prescribed all five guideline recommended therapies while 32% reached four out of five of these. As for patients treated with anti-hypertensive drugs, we observed higher levels of systolic pressure (138.0 ± 29.5 vs 107.7 ± 36.6 $p < 0.02$) while no differences were observed in diastolic pressure levels.

Conclusions: In conclusion, when it comes to diabetic patients with a severe limb and life threatening clinical condition, we noticed a lower-than-expected application of international guideline-recommended medical therapies. In fact, only one out of four patients was following all the recommended therapies. Nevertheless, these patients did not reach the standard targets requested to prevent cardiovascular disease.

1. Introduction

The International Diabetes Federation (IDF) estimated that the number of patients who present a diabetic foot ulcer (DFU) each year ranges from 9.1 to 26.1 million [1]. This is a chronic pathology with a multi-factorial pathogenesis, in which Peripheral arterial disease (PAD) represents the leading cause of non–injury-related amputations and disabilities in

* Corresponding author at: Via Paradisa 2, 56126 Pisa, Italy.
E-mail address: elisabettaiacopi@gmail.com (E. Iacopi).
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diabetic patients. Its presence confers a 3 to 6-fold increase in risk of cardiovascular mortality and major cardiovascular events [2] (see Table 1).

Prevalence of PAD and its more severe stage, critical limb ischemia (CLI), is twofold in diabetic patients than in general population, and leads to a further increase in cardiovascular risk [3].

Despite that endovascular or surgical revascularization procedures represent the most important component of therapy for CLI, medical therapy still plays a central role in the way this condition is handled. As a matter of fact, lifestyle changes and control of risk factor increase the short and long-term patency of angioplasties and by-passes and shortens therefore the ulcers' healing time, resulting in a reduction of the recurrences rate [4].

As indicated by the most important international guidelines, patients with PAD should undergo to a structured program of management and treatment, and this becomes even more important in diabetics [5]. Despite this, these patients are less likely to be treated according to the guidelines than other patients suffering from cardiovascular diseases [6].

To control cardiovascular risk factors in DM, the American Diabetes association (ADA) guidelines, recommend a multifactorial aggressive strategy [7]. This should include optimization of glycaemic control as a mainstay: it has been reported that every 1% increase in glycosylated hemoglobin is associated with a 25% increase in the risk of PAD's complications [8]. The American Diabetes Association strongly recommends to reach and to maintain the value of 6.5% (48 mmol/mol) in type 2 patients with no severe complication unless this can be obtained without increasing the risk of hypoglycemia. In type 1 diabetics or in patients with high level of comorbidity, the recommended target value increases to 7% (53 mmol/mol) [9].

All guidelines focused on the use of antiplatelet therapies, although, despite some controversial issues, their use in primary prevention is today quite uniquely refuted [10]. Instead patients with history of cardiovascular events, stroke or PAD are considered at high risk and should be treated with acetylsalicylic acid [11]. Alternatively, in patients that does not tolerate acetylsalicylic acid, clopidogrel should be used [12]. After a cardiac ischemic event or a revascularization procedure, a double antiplatelet therapy combining acetylsalicylic acid with clopidogrel - or with P2Y12 inhibitors - should be implemented for at least one year [13].

Anti-hypertensive treatment should be always considered in diabetic patients after domiciliary monitoring of blood pressure and exclusion of secondary causes [14]. In diabetic patient without cardiovascular risk factors or chronic severe complications the suggested value is 140 mmHg for systolic pressure and 90 mmHg for diastolic pressure. This level fell down until 130/80 in patients with cardiovascular event or equivalent conditions, such as PAD, or micro-vascular complication, such as chronic kidney disease [15].

Regarding lipid lowering drugs, cardiologic and diabetes scientific societies agree on identifying LDL cholesterol as the primary parameter to be monitored [16]. The ADA says that in primary prevention, applicable in patient with neither cardiovascular previous events nor ischemic equivalent conditions, such as PAD, the optimal target LDL level is below 100 mg/dl, while in patients with cardiovascular pathologies like PAD, the threshold should fall to 70 mg/dl [17].

Eventually, all diabetic patients should be informed regarding the importance of smoke abstinence in order to reduce cardiovascular risk and optimize foot ulcers' outcomes [18]. Counseling, replacement nicotine therapy or other drugs could be prescribed to achieve this target [19].

Despite the guidelines, which clearly set the indications for an adequate management of risk factors in these extremely complex patients, the frequency of recurrences is very high, possibly related to their sub-optimal application [20].

2. Subjects, materials and methods

2.1. *Aim of the study*

The aim of the study was to evaluate the actual implementation of the therapeutic recommendations of ADA for high risk patients with CCLI (Tab. 1), attending a third-level centre.

2.2. *Patients and methods*

We retrospectively searched the databases of our Department for all the patients admitted in our Department between January 2011 and December 2015 for critical limb ischemia, and reviewed their medical records. All the patients, before admission, were followed by General Practitioners inside a program of proactive screening and management of peripheral vascular disease structured and financed by the Tuscany Regional Health Authority [21]. We collected data regarding clinical history, focusing both on diabetes, its chronic complications, and on comorbidities. We mainly looked into clinical history or ultrasound assessment data regarding ischemic heart disease or heart failure, cerebro-vascular or carotid arteries disease, clinical history information about presence of hypertension or the need for hemodialysis, and clinical history or lab exams to prove the presence of hypercholes-

Table 1 – Target and level of recommendation [9].

Risk factor	Target	Strenght of recommendation	Quality of evidence
Glycaemic control	<7%	1	A
Antiplatelet therapy	Yes	1	A
Hypertension therapy	130/80 mmHg	3	C
Statins	LDL < 70 mg/dl	2	A
Smoking cessation	To stop	1	C

terolemia and chronic kidney disease. We collected furthermore data regarding medical therapies taken by the patient before admission and severity of chronic diabetes complications. All the clinical and laboratory assay results performed during admission (where not otherwise defined, all the parameters were assessed by common laboratory kit assays), were derived by patients' folders, including details such as body weight, systolic and diastolic blood pressure, fasting plasma glucose, glycohemoglobin (A1c), fasting total cholesterol and triglycerides, HDL cholesterol, LDL cholesterol (by the Friedewald equation), serum creatinine, creatinine clearance (by the Cockroft-Gault formula) [22]. Also, we searched for foot surgical procedures and peripheral revascularizations performed during admission. Based on the information taken from the patients' folders, the Charlson comorbity index [23] of each patient was calculated to grade the severity of comorbidities.

As per standard protocol of our hospital, patients at admission had provided formal consent to the introduction of their data in a database and to their non-nominal use in an aggregate form. The protocol of the study was submitted to our local Ethical Committee and received its approval.

2.3. Outcome

We evaluated the adherence of the therapies at admission to the recommendations of International Guidelines in patients admitted and treated for critical limb ischemia. In particular we searched for use of antihypertensive, lipid lowering and antiplatelet drugs, for smoking abstinence and for good glycol-metabolic control.

Secondarily, we analyzed the level of pressure or lipid control in patients treated with anti-hypertensive and lipid lowering drugs and compared to people who didn't receive similar treatments.

We then compared the patients which were following the ADA guidelines to the other ones, to test the clinical efficacy of the recommendations.

2.4. Statistical analysis

Quantitative variables are expressed as mean, median, and standard deviation and qualitative variables as frequencies and percentages. Data were compared with Chi-square and Fisher's exact test for the categorical data and with Student t-test for the continuous variables. The statistical analysis was performed with the SAS software (SAS Institute, Cary, NC). A p value of less than 0.05 was considered statistically significant.

3. Results

We retrospectively searched among 1315 admissions performed in our Department from January 2011 until December 2015. Out of them, 842 (64.0%) were related to diabetic foot diagnosis, while the other 473 (36.0%) were associated to other diabetes-related problem or metabolic diseases. Among diabetic foot patients, 603 (71.6%) were affected by critical limb ischemia, while the others (239–28.4%) presented a non-critical limb ischemia according to ADA parameters [24]. In Fig. 1 is reported the consort diagram of the study population. For all other evaluations, as yet reported, we focused on patients admitted for critical limb ischemia, while the others served as a control group.

3.1. Clinical characteristics of the population

As detailed in table 2, patients were predominantly male (73%), affected from type 2 diabetes (93%), with a long history of diabetes, and overweight. Three out of four of all patients smoked at admission or had previously smoked. Analysing the comorbidities we observed a high prevalence and distribution of diabetic macroangiopathy: cardiopathy (49.3%), cerebrovascular disease (32%) and carotid artery disease (43.2%). A high prevalence of both hypertension (81.4%) and dyslipidaemia (65.9%) was observed as well.

Analysing the prevalence of chronic diabetic complications, patients suffered from retinopathy in 73.2% of cases and from neuropathy in 47.8% of cases. Also renal function was frequently affected: 58.8% of patients presented diabetic nephropathy, typically micro or macroalbuminuria, 36.2% presented renal failure and eventually 13.2% of patients was regularly submitted to haemodialysis.

The severity of patients' clinical state is witnessed by Charlson comorbidity score index which was 6.8 ± 2.2. All details are reported below in Table 2.

Ischemic patients were significantly older, had a longer duration of DM, a higher prevalence of chronic complications than the controls, and their comorbidities, expressed with Charlson index, were more important.

According to the procedures performed during admission, 94.8% of patients underwent to a lower limb revascularization procedure: 96.6% of them was a percutaneous revascularization, endovascular or subintimal, while 3.4% of revascularization was surgical. Furthermore 78.5% of patients required a foot surgical procedure. 31 patients did not undergo to revascularization procedures despite the indication: 18 for severe comorbidities or because bedridden, 7 for not technical feasibility and 6 for patient's consent retirement.

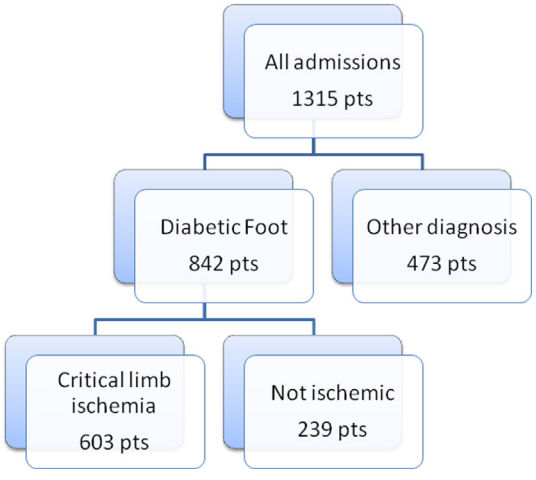

Fig. 1 – Consort diagram of the study population.

Table 2 – Clinical characteristics, comorbidities and chronic complications of the population.

Clinical characteristics and comorbidities	All patients	Ischemic patients	Controls	p
Patients (n)	842	603	239	–
Male/Female (%/%)	72/28	73/27	71/29	–
Mean age (yrs)	68.3 ± 11.2	70.3 ± 10.4	66.3 ± 12.2	<0.02
Type of diabetes (1/2%)	9/91	7/93	14/86	ns
Duration of diabetes (yrs)	15.1 ± 11.2	17.3 ± 13.7	11.5 ± 10.5	<0.05
Smoke habits (yes/no/former-%)	34/27/39	32/27/41	45/25/30	ns
Systolic blood pressure (mmHg)	127 ± 35	130 ± 35	123 ± 35	ns
Diastolic blood pressure (mmHg)	77 ± 12	75 ± 12	81 ± 13	ns
BMI (Kg/m^2)	27.9 ± 6.1	27.7 ± 5.3	28.7 ± 7.1	ns
HbA1c (%; mmol/mol)	8.0 ± 1.9/62 ± 17	7.8 ± 1.8/62 ± 16	8.5 ± 2.3/63 ± 19	ns
Total colesterol (mg/dl)	134 ± 45	134 ± 45	135 ± 45	ns
HDL colesterol (mg/dl)	60 ± 41	56 ± 44	67 ± 39	ns
LDL colesterol (mg/dl)	74 ± 35	74 ± 35	75 ± 36	ns
Tryglicerides (mg/dl)	211 ± 154	205 ± 136	223 ± 183	ns
Creatininemia (mg/dl)	1.6 ± 1.5	1.6 ± 1.5	1.4 ± 1.4	ns
eGFR (ml/min)	54.2 ± 24.2	47.2 ± 22.9	61.3 ± 26.3	ns
Ischemic heart disease (%)	42.2	49.3	24.4	<0.05
Cerebrovascular disease (%)	27.7	32.0	16.9	<0.05
Carotid artery disease (%)	37.4	43.2	22.6	<0.05
Hypertension (%)	76.2	81.4	63.2	<0.02
Dyslipidemia (%)	62.1	65.9	52.4	ns
Diabetic retinopathy (%)	69.9	73.2	61.6	<0.05
Laser treated (%)	35.5	40.2	23.6	<0.02
Diabetic neuropathy (%)	48.9	47.8	51.8	ns
Charcot disease (%)	7.7	5.6	12.9	<0.02
Diabetic nefropathy (%)	61.2	58.8	67.3	ns
Renal failure (%)	34.7	36.2	30.9	ns
Hemodyalisis (%)	11.8	13.2	8.2	<0.05
Charlson index score	6.4 ± 2.0	6.8 ± 2.2	5.2 ± 1.9	<0.05

3.2. *Medical therapies*

Eventually we focused on therapy followed by patients at admission, as detailed in table 3.

Regarding the antidiabetic therapies, more than 60% of patients were on insulin, associated in 44.2% of patients with oral treatment; 24.9% of patients took metformin, 8.4% of patients oral incretin treatment and 3.9% incretin therapy subcutaneously. Eventually 3.4% of patients took Sulphonylureas and 0.4% of patients other oral hypoglycaemic agents (OHAs).

Analysing treatment other than OHAs, we observed that only 65.9% of patients took lipid lowering drugs, all statins. As for anti-hypertensive treatments, 81.4% of patients took antihypertensive drugs, as reported in table 3. In 36.7% of cases patients took only one type of treatment, 43.2% of patients took two different therapies, 14.4% took three different treatments and 5.7% of patients were treated with four different classes of antihypertensive therapies (Fig. 2).

Antiplatelet therapy, was prescribed overall in 72.4% of all patients, 53.4% of patients took only cardio aspirin, 6.9% of patients only Clopidogrel and 11.9% of patients took both classes of therapies. Eventually 0.2% of patients took Ticlopidine. Furthermore 4.9% of patients were treated with other antiplatelet drugs or anticoagulant.

When compared to controls, ischemic patients showed a higher prevalence of lipid-lowering, anti-hypertensive and antiplatelet treatments.

3.3. *Adherence to guidelines*

We then analysed overall adherence to recommended guidelines: use of antihypertensive drugs, of lipid lowering therapy, of antiplatelet drugs, smoking status and optimal glycometabolic control. First of all, we observed that only 33.4% of all patients reached a level of glycosilated haemoglobin below 7%. As detailed below in Fig. 3, only 32% of patients followed all therapies and smoke abstinence and this percentage reduced to 24% when adding an optimal glycometabolic control to selection criteria.

We also analysed the differences in glycaemic, lipid and pressure control among patients treated and not treated according to the guidelines.

Regarding lipid control, as reported below in Table 4, there was no differences in lipid metabolism among patients treated and not treated with hypolipidemic therapy.

Also, when analysing blood pressure control, we found that, despite the treatment, while diastolic blood pressure was not different among the two groups of patients, systolic blood pressure was higher in treated patients ($p < 0.02$), as reported in Table 4.

We tried to correlate the number of anti-hypertensive drugs classes taken with the systolic blood pressure control. As reported below in Fig. 4, we observed a significant increase in percentage of well-controlled patients increasing the number of anti-hypertensive drugs taken (37.6% in patient taking one drug, 40.0% with two drugs, 75.0% with three drugs and

Table 3 – Medical therapy of general population.

Medical therapy	Ischemic patients	Controls	p
Antidiabetic drugs			
Insulin (%)	21.8	19.8	ns
Mixed (oral and insulin) (%)	44.2	38.9	ns
Metformin (%)	24.9	33.8	ns
Oral incretins (%)	8.4	8.8	ns
Subcutaneous incretins (%)	3.9	4.8	ns
Sulphonylureas (%)	3.4	1.2	ns
Glitazones or other oral (%)	0.4	0.5	ns
Other treatments			
Lipid lowering drugs (%)	65.9	52.3	<0.05
Antihypertensive therapy (%)	81.4	65.6	<0.05
Ace inhibitors (%)	37.3	36.9	ns
Sartans (%)	24.6	25.1	ns
Calcium blockers (%)	36.6	35.9	ns
Diuretics (%)	38.6	44.8	ns
Beta blockers (%)	20.2	21.8	ns
Alpha litics (%)	2.2	4.0	ns
Antiplatelet-anticoagulant (%)	72.4	56.2	<0.02
ASA (%)	53.4	55.9	ns
Clopidogrel (%)	6.9	4.0	ns
Asa and Clopidogrel (%)	11.9	9.2	ns
Ticlopidine (%)	0.2	0.4	ns
Other or anticoagulant (%)	4.9	4.1	ns

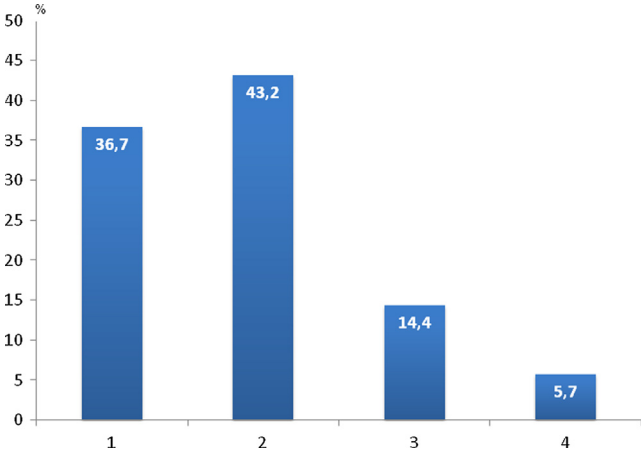

Fig. 2 – Number of antihypertensive treatment taken by the patients.

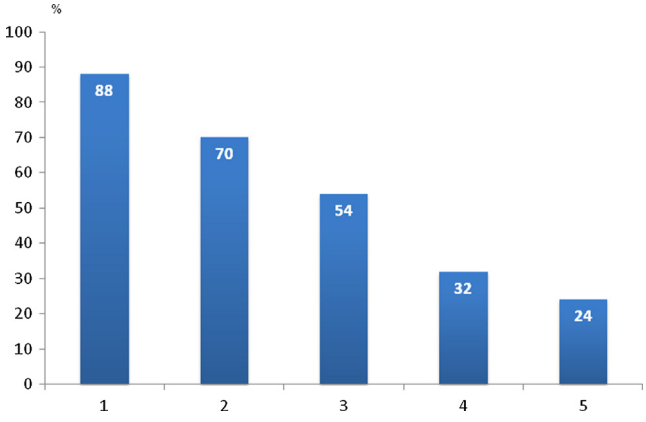

Fig. 3 – Number of guidelines adhered.

71.9% with four drugs – $p < 0.01$ one vs three and four and two vs three and four).

4. Discussion

In our study we analyzed an highly selected group of patients admitted in a specialized center during 4 consecutive years to detect if cardiovascular prevention was actually implemented in this high-risk patients. This could be considered a "proxy" of the real possibility to prevent recurrences or cardiovascular events in these patients.

The picture we faithfully painted traces the published evidence: the typical patient suffering from CLI and foot ulcer is a male, affected by type 2 diabetes, overweight or obese and with a high prevalence of comorbidities and micro and macro-vascular chronic diabetes complications. The arterial disease is multidistrict in most patients, interesting coronary and cervical arteries as well as peripheral ones. When compared to DM patients admitted for problems others than CLI, patients proved to be more co-morbid and complicated, older and with a long duration of DM.

In recent years attention has been posed on the real nature of diabetic foot syndrome: it characterized itself as a relapsing-remitting chronic disease [25]. As such, its long term evolution is strictly related not only to a prompt and aggressive management of acute episodes but also to the adequate medical management during remissions [26]. In this phases in fact, when the acute ulcer is resolved, the patient feels better and his/her attention to the recommended target

Table 4 – Lipid and pressure control in patients treated or not treated with adequate drugs.

Parameter	Treated	Not treated	p
Total cholesterol (mg/dl)	138.8 ± 42.2	138.2 ± 42.5	ns
LDL cholesterol (mg/dl)	75.0 ± 35.4	76.6 ± 28.7	ns
HDL cholesterol (mg/dl)	54.8 ± 17.8	56.2 ± 18.9	ns
Tryglicerides (mg/dl)	204.9 ± 135.6	205.8 ± 137.8	ns
Systolic blood pressure (mmHg)	138.0 ± 29.5	107.7 ± 36.6	<0.02
Diastolic blood pressure (mmHg)	73.0 ± 27.4	76.9 ± 29.0	ns

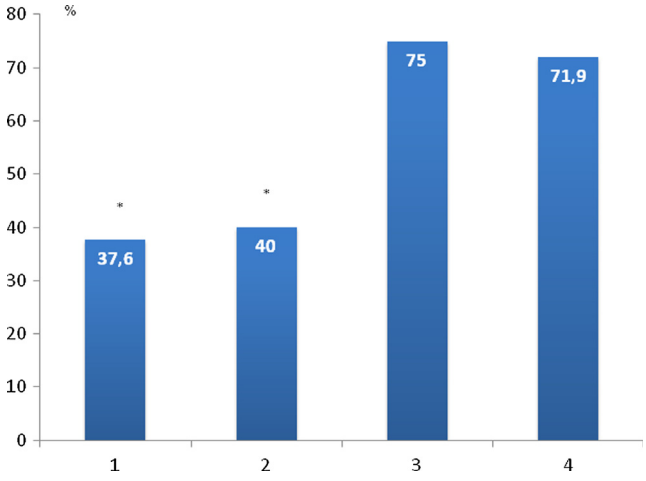

Fig. 4 – Rates of well controlled patients according to number of antihypertensive drugs. (*p < 0.01 Number one vs three and four and Number two vs three and four).

and lifestyle adherence gradually falls [27]. While such an attitude can be justifiable in the patient, it should be absolutely contrasted by physicians.

CLI represents in diabetic patients not only the most important direct cause of non-healing ulcers and lower limb amputation but also a marker of increased cardio-vascular risk, both for death and for myocardial infarction or stroke [28]. Eventually, diabetic patients who had suffered from an ulcer, and had reached complete healing, in presence of PAD presents an increased recurrences risk [29]. For all these reasons, patients with diabetes and CLI, first and after the revascularization procedures should receive an aggressive cardiovascular risk management [30] to reduce recurrences and especially to reduce cardiovascular events and mortality [31].

Despite this, among this high-risk cohort, only 33.4% of patients reached the recommended target for diabetes control. This parameter is particularly important considering that it has been reported that each 1% increase in glycosylated hemoglobin is associated with a 25% increase in the risk of PAD and with a strong increase of its severity [32]. This is even more impressive in consideration of the anti-diabetic treatment prescribed to patients: only 60% of them used insulin therapy despite the indications and the poor glycemic control; new therapeutic strategies, as incretins, were used by slightly more than 10% of patients, and only one out of four of all patients was prescribed metformin, an important drug also in terms of cardiovascular protection. This phenomenon, known as therapeutic inertia, consists in delaying treatment intensification despite suboptimal glycemic control [33]. This is even less justified considering that in the last few years we have witnessed a significant increase of antihyperglycemic drugs classes, safer and more effective [34]. Therapeutic inertia is responsible of the continue rise of the proportion of diabetics who fail to achieve glycemic goals; it prolongs the duration of patients' hyperglycemia increasing the risk of diabetes-associated complications and reducing therefore life expectancy [35].

Since in our study we had no way to distinguish if the therapies were not prescribed by the physician or not assumed by the patient, we cannot exclude a component of patients' poor compliance. Nevertheless, since all these patients were followed regularly by their GPs for a chronic condition, we would expect a better control on the application of therapy compared with what we found.

This difference represents an important issue in diabetic patients. Diabetes, as all chronic disease, is often managed by GPs or other domiciliary specialists. In these contexts, despite the awareness of severity of the disease and of its possible complication, a delay in introduction or intensification of medical management is usually observed, a behaviour responsible of a worse outcomes and increased health costs [36].

Therapeutic inertia is even less justifiable in case of CLI: in this case patients should be considered and treated as if they had had an acute coronary ischemic episode. Once the patient have been revascularized, patency is strictly associated to reduction in platelet activation and coagulation cascade, justifying therefore the need for a combined antiplatelet therapy [37]. In our population we observed the use of antiplatelet therapy in 72% of patients and this proportion, despite too small, represent the guideline most adhered in our population. The most alarming data is that only slightly more than 11% of patients were prescribed a double antiplatelet therapy after PTA. At the moment of our study, inhibitors of P2Y12 were at beginning of their activity and were only very rarely used in CLI while their initial spread were limited to patients with coronary artery disease [38].

In our population 81.4% of patients took anti-hypertensive medications, with no significant apparent effect on systolic blood pressure which was higher than in controls. Also in blood pressure control therapeutic inertia plays a crucial role [39]: about 37% of patients, despite the poor goal achievement, was prescribed only one hypotensive drug. This is important when we consider that the number of patients with blood

pressure values at target increases with the number of antihypertensive drugs used.

Blood pressure control is mandatory in diabetic patients with CLI to control the impact of CLI on cardiovascular risk [40]. In diabetic patients hypertension is often resistant to pharmacotherapy, while drug-related side effects are more frequent in diabetic patients than in non diabetic hypertensive patients [41].

Despite the well known protective effect of statins both in primary and in secondary prevention [42], in our cohort of patients only 65.9% is prescribed hypolipemic drugs.

The findings about the smoke habits are quite dramatic: 63% of patients smoked at admission or had previously smoked and, among these, 32% were active smoker. The importance of smoking abstinence is important in diabetic patients affected by CLI not only for prevention of cardiovascular events and for improvement of lower limb outcome [43] but also because of its worsening impact on diabetes control, also as secondhand smoking [44].

Eventually we went to analyze overall the guidelines management and observed that only one out of four patient followed all recommended guidelines including optimal glycemic control.

Our study represents the first comprehensive approach to all recommended guidelines in diabetic patients suffering from critical limb ischemia and the first overall analysis of adherence to these guidelines and of impact of this target on therapeutic goals. It clearly creates an image of real life management and underlines, also in terms of medical management, the importance of an early referral of patients to high expertise centers. The late referral to third level centers has in fact demonstrated in recent few years its role in worsening the outcomes and reducing the chance of limb salvage in diabetic patients [45].

Despite that the association among statins or antiplatelet assumption and outcomes in patients with limb ischemia who underwent to vascular procedures it has been previously reported in the Literature [46], focusing particularly on ischemic heart disease [47], this is in our knowledge the first analysis which compares the adherence to all recommended medical therapies in diabetic patients suffering from CLI.

We are aware of the limitations of our study, the most important being the fact that this is a single center study and the heterogeneity of patients prescribed to patients admitted could be due to the referral role of our center which attracts patients from all parts of the country and abroad. Also the retrospective analysis does not allow to reach conclusions on the possible clinical consequences of poor systemic treatment.

5. Conclusion

Our data confirm the poor adherence of diabetic patients to the recommended preventative therapies. This condition would require a re-orienting educational training of physicians who have to deal with a progressive chronic disease, as diabetes, with the aim of preventing its complications like the diabetic foot. The underestimation of the importance of prevention and of the treatment of risk factors, spread among general practictioners and also diabetologists, explains the therapeutic inertia which characterizes the inadequacy of management of many chronic disease, in particular diabetes and cardiovascular disease, often associated.

On the other side even when completely applied, guidelines do not necessarily associate with an optimal metabolic or pressure control. This “weakness” of the medical therapy in contrasting the symptoms of the disease is most likely related to the progression of the pathology and speaks of the need for more frequent controls and more aggressive therapeutic strategies.

In the end, our data support the necessity of a complete re-evaluation of our strategies for risk prevention in very high-risk diabetic foot patient.

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Author contributions: A.P., A.C. and E.I. conceived of and designed the study, acquired and analyzed data, wrote and reviewed the manuscript. N.R. and C.G. acquired and reviewed data and reviewed the manuscript. L.A. and L.P. reviewed the manuscript. A.P. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2019.107898.

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