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PATTERNS OF USE OF INSULIN THERAPY, CLINICAL CHARACTERISTICS, AND LEVEL OF METABOLIC CONTROL IN PEOPLE WITH TYPE 2 DIABETES

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Patterns of use of insulin therapy, clinical characteristics, and level of metabolic control in people with type 2 diabetes

IDELSON-GNOCCHI

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Index

Rationale

Despite therapeutic advances, a relevant proportion of subjects with type 2 diabetes (T2DM) does not reach the desired therapeutic targets, especially among patients treated with insulin alone or in combination with oral glucose-lowering agents.

In the previous editions of the AMD Annals, the average levels of HbA1c were 8.1 ± 1.7% among subjects treated with multiple injections of insulin, and 8.4 ± 1.6% among those on insulin therapy in association with oral glucose-lowering agents. Furthermore, one patient in four had HbA1c values above 9.0% despite insulin therapy.

The AMD Annals initiative also documented a substantial therapeutic inertia both in initiating insulin therapy and in intensifying treatment. In fact, at the time of the first basal insulin prescription the average HbA1c levels were 8.9 ± 1.6%, but about half of the subjects already had HbA1c values> 8.0% two years before the introduction of the therapy with insulin. Furthermore, 2 years after the initiation of insulin therapy, almost 50% of patients continued to have HbA1c values> 8.0%.

The purpose of this analysis is to describe the current prevalence of use of insulin therapy in T2DM patients, their socio-demographic and clinical characteristics, and what is the profile of the quality of care indicators in these patients.

Objectives

- To evaluate the proportion of patients with T2DM on insulin therapy and their level of metabolic control;
- To describe the epidemiological characteristics and associated complications in relation to the type of insulin scheme.

Materials and methods

This monograph of the AMD Annals is based on the data used in the 2018 Annals Report, which include patients seen in 2016 and, for data on insulin doses and insulin treatment schemes, on the data of the Full Data Circle database, which includes patients active in the year 2015 (https://aemmedi.it/annali-amd/).

Centers selection

To participate in the initiative, the centers had to be equipped with information systems (computerized medical records) capable of guaranteeing, in addition to the normal management of patients in charge, the standardized extraction of the information required by the AMD Data File. The latter provides all the information needed for the description of the socio-demographic and clinical characteristics considered.

Patients selection

This analysis concerns patients with T2DM "active" in the index year, i.e. all patients with at least one prescription of diabetes drugs and at least one of the following parameters: weight and / or arterial pressure. Compared to previous editions, the criterion of active patient has been adapted to the changes in clinical practice; in fact, the registration of laboratory values on metabolic control in the electronic medical records does not necessarily imply, in many situations, the execution of a specialist visit, due to the automatic transfer of laboratory data on medical records. For this reason, having at least one HbA1c measurement in the index year was no longer considered to define active patients. The new criterion was agreed with diabetologists to capture the number of patients who actually performed at least one visit to the clinic.

Description of the variables used

Data analyzed include socio-demographic characteristics (age, sex), and clinical parameters (duration of diabetes, average values of BMI, HbA1c, arterial pressure, lipid profile, albuminuria, glomerular filtration rate). If not reported on the medical records, LDL values were calculated using the Friedwald formula. LDL cholesterol was calculated only if total cholesterol, HDL cholesterol, and triglycerides values were measured on the same date, and if the triglycerides values did not exceed 400 mg/dl.

The glomerular filtrate (eGFR) was calculated with the CKD-Epi formula.

Glucose-lowering drugs were classified through ATC codes, while cardiovascular events were classified through ICD9-CM codes.

The denominator of the analyses consists of patients with at least one detection of the parameters of interest during the index year. If the same patient had made multiple measurements of a parameter during the index year, the most recent value was evaluated.

Statistical analysis

The following list of indicators was used to describe the characteristics of people with T2DM treated with insulin, the level of metabolic control, and the kind of insulin treatment:

- Distribution of the study population by HbA1c classes (<=7.0%, 7.0-8.0%, >8.0%)
- Mean age
- Distribution by gender
- Prevalence of current smokers
- Mean duration of diabetes (years)
- Mean levels of HbA1c
- Mean levels of body mass index
- Mean levels of blood pressure
- Mean levels of blood lipid parameters
- Prevalence of major macrovascular complications (myocardial infarction, stroke, chronic heart failure, angina)
- Prevalence of major microvascular complications (diabetic retinopathy, diabetic nephropathy, chronic kidney disease)
- Type of basal insulin
- Type of short-acting insulin
- Average doses of insulin
- Distribution by classes of insulin doses (<50, 50-80, >80 UI)
- Distribution by classes of insulin doses (<50, 50-80, >80 UI) in people with established cardiovascular disease

Information on insulin doses was derived from the Full Data Circle database.
The following patient subgroups have been considered:

1. Patients treated with insulin (± other glucose-lowering agents) vs. patients treated with glucose-lowering agents other than insulin. These data were derived from the AMD Annals database.
2. Patients stratified by insulin scheme (data derived from the Full Data Circle):

- Basal insulin only
- Basal insulin + 1 injection of fast-acting insulin
- Basal insulin + 2 injections of fast-acting insulin
- Basal insulin + 3 injections of fast-acting insulin
- No basal insulin, 3 injections of fast-acting insulin

Classification of complications

The following table shows the definition used for the stratification of the population based on the presence of cardiovascular complications.

Table: Classification of complications based on the ICD-9-CM coding system

Complication:	ICD-9CM
Myocardial infarction	Da 410 a 410.92 412
Stroke	430 431 432 432.0 432.1 432.9 433.11 433.21 433.31 433.81 433.91 434.01 434.11 434.91 436
Chronic heart failure	428 428.0 428.1 428.9 402.01 402.11 402.91 404.01 404.11 404.91
Angina	413 413.0 413.1 413.9 411.1
Diabetic retinopathy	361.01 361.02 14.24 369.x
Chronic kidney disease	585

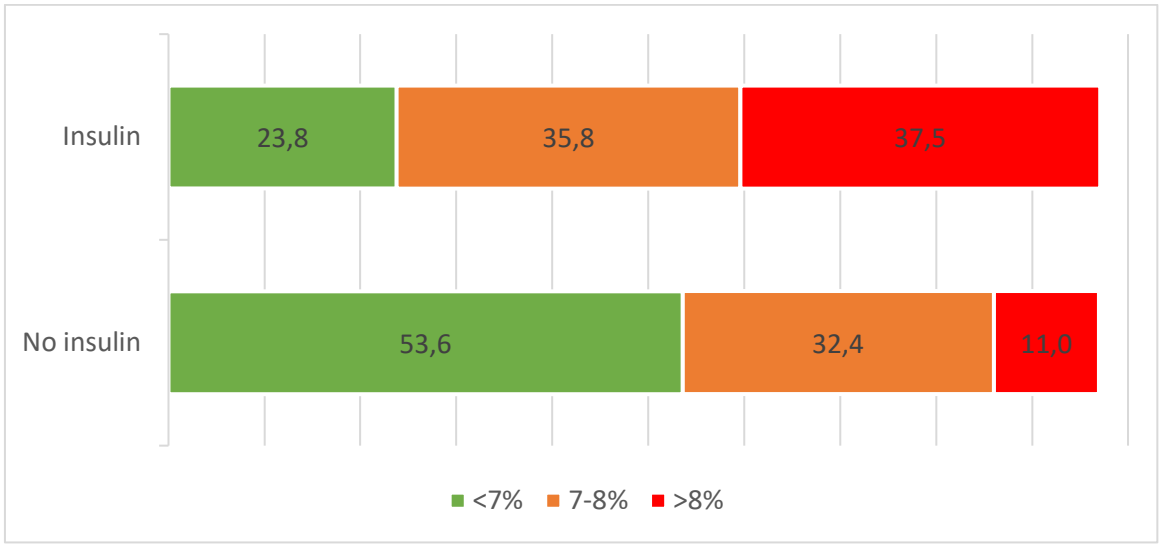
Diabetic nephropathy was defined as presence of albuminuria or eGFR <60 ml/min*1,73 m^2.

Results

1. People treated with insulin (± other glucose lowering drugs) vs. people treated with glucose lowering drugs other than insulin

Overall, 140,716 patients treated with insulin and 261,984 patients treated with other glucose-lowering drugs were evaluated. Insulin-treated patients thus represented 34.9% of all T2DM treated patients in the AMD Annals database.

Patient distribution according to HbA1 classes



The graph shows the difficulty in achieving adequate metabolic control among subjects in insulin treatment, over a third of which has HbA1c values> 8.0%. Among the subjects not treated with insulin, one in two is at target, while the others would require therapeutic intensification, considering however that HbA1c values between 7% and 8% could be appropriate for elderly/frail patients.

This indicator stratified by region is shown in Appendix.

Socio-demographic and clinical characteristics

Patients treated with insulin

	Overall	HbA1c classes		
Characteristics		<7%	7-8%	>8%
N	140716	33493	50345	52823
Age (years)	70.1±11.2	70.6±11.1	71.1±10.4	68.7±11.7
Males (%)	55.3	60.3	55.3	51.9
Smokers (%)	17.4	17.3	16.4	18.3
Duration of diabetes (years)	16.6±10.4	15.8±10.8	17.6±10.3	16.2±10.1
HbA1c (%)	7.9±1.4	6.4±0.5	7.5±0.3	9.3±1.3
Body mass index (kg/m2)	30.0±5.7	29.2±5.5	29.7±5.5	30.8±6.0
Systolic blood pressure (mmHg)	136.2±19.0	134.8±18.9	136.6±18.9	137.0±19.1
Diastolic blood pressure (mmHg)	75.9±9.8	75.0±9.7	75.7±9.6	76.7±9.8
Total cholesterol (mg/dl)	168.8±40.9	162.8±39.3	166.1±38.6	175.0±43.1
HDL cholesterol (mg/dl)	47.7±13.9	48.1±14.3	48.3±13.9	46.8±13.6
LDL cholesterol(mg/dl)	92.9±33.6	89.9±32.6	91.2±32.1	96.4±35.2
Triglycerides (mg/dl)	147.0±102.4	129.2±78.3	137.9±83.2	166.8±125.5

Data are mean±standard deviation or percentage

The table shows that subjects on insulin therapy with HbA1c> 8.0% tend to be younger, with a higher prevalence of women and with a higher BMI. Even blood pressure and lipid values tend to be higher, outlining an overall profile of higher risk of micro and macrovascular complications.

Patients treated with glucose-lowering drugs other than insulin

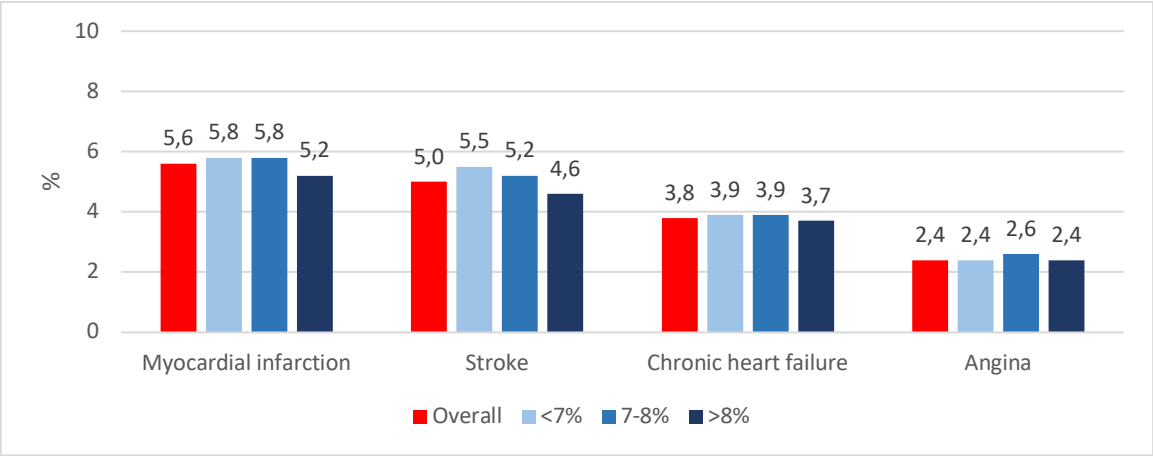
	Overall	HbA1c classes		
Variabile		<7%	7-8%	>8%
N	261984	140302	84929	28875
Age (years)	67.9±10.9	67.7±10.6	68.7±10.7	66.6±12.4
Males (%)	57.4	58.4	56.0	56.9
Smokers (%)	17.1	17.0	16.5	19.3
Duration of diabetes (years)	9.8±7.9	9.1±7.6	11.0±8.1	10.4±8.5
HbA1c (%)	7.0±1.0	6.3±0.4	7.4±0.3	9.0±1.1
Body mass index (kg/m2)	29.4±5.3	29.3±5.3	29.4±5.3	30.1±5.7
Systolic blood pressure (mmHg)	135.5±17.9	134.8±17.6	136.2±18.0	137.1±18.8
Diastolic blood pressure (mmHg)	77.5±9.4	77.2±9.4	77.5±9.4	78.6±9.9
Total cholesterol (mg/dl)	172.7±37.9	171.0±36.7	172.8±37.7	180.7±42.7
HDL cholesterol (mg/dl)	49.5±13.0	50.2±13.2	49.1±12.8	47.2±12.6
LDL cholesterol(mg/dl)	96.4±32.4	95.4±31.6	96.0±32.2	101.7±36.2
Triglycerides (mg/dl)	139.3±84.1	130.9±71.5	143.2±85.0	168.5±120.8

Data are mean±standard deviation or percentage

The same trends are also evident among subjects not treated with insulin, indicating that HbA1c values >8.0% represent a more general marker of risk.

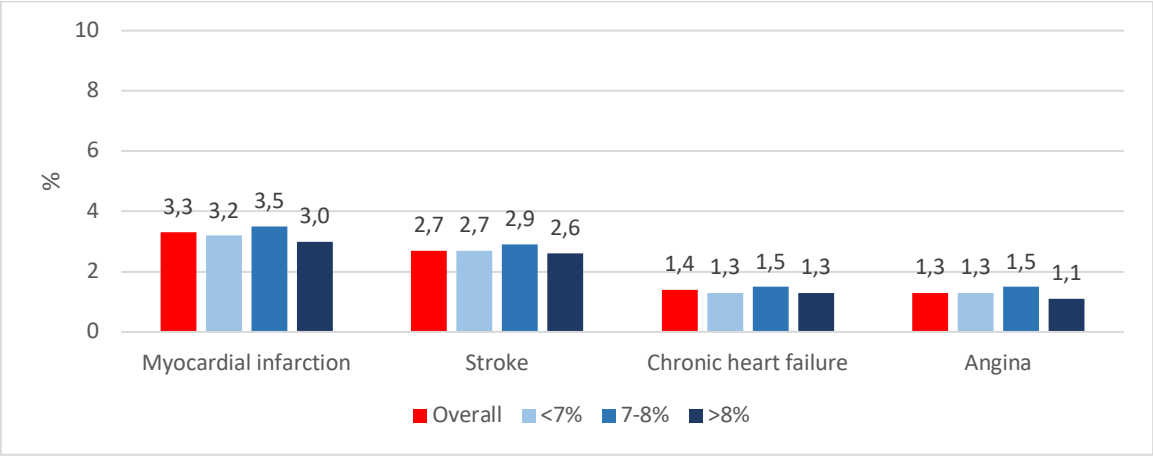
Prevalence of macrovascular complications

Patients treated with insulin



The prevalence of cardiovascular complications among subjects on insulin therapy does not appear to vary significantly with respect to HbA1c levels.

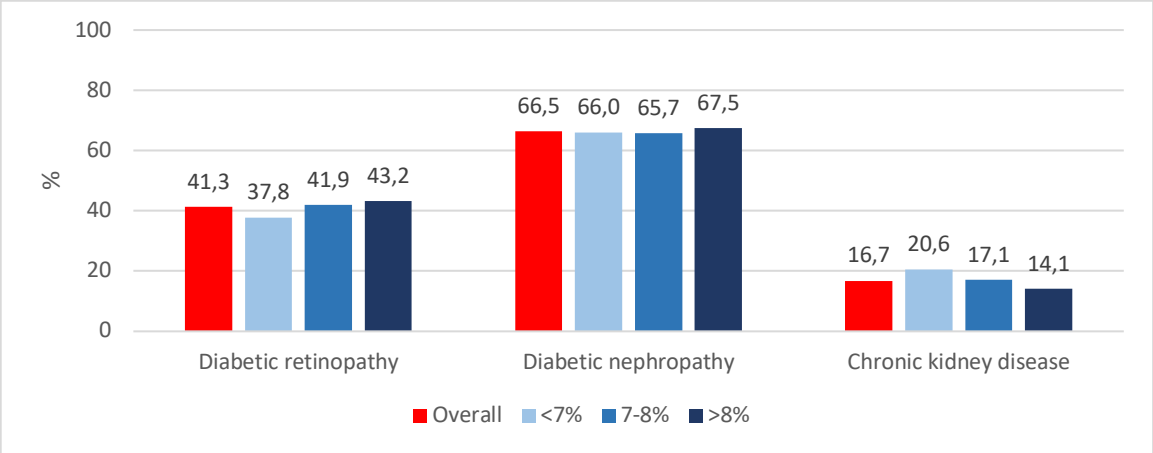
Patients treated with glucose-lowering drugs other than insulin



Similarly, among the subjects not treated with insulin the prevalence of cardiovascular complications does not seem to vary in relation to HbA1c levels. All the cardiovascular complications examined have a higher prevalence among subjects on insulin therapy.

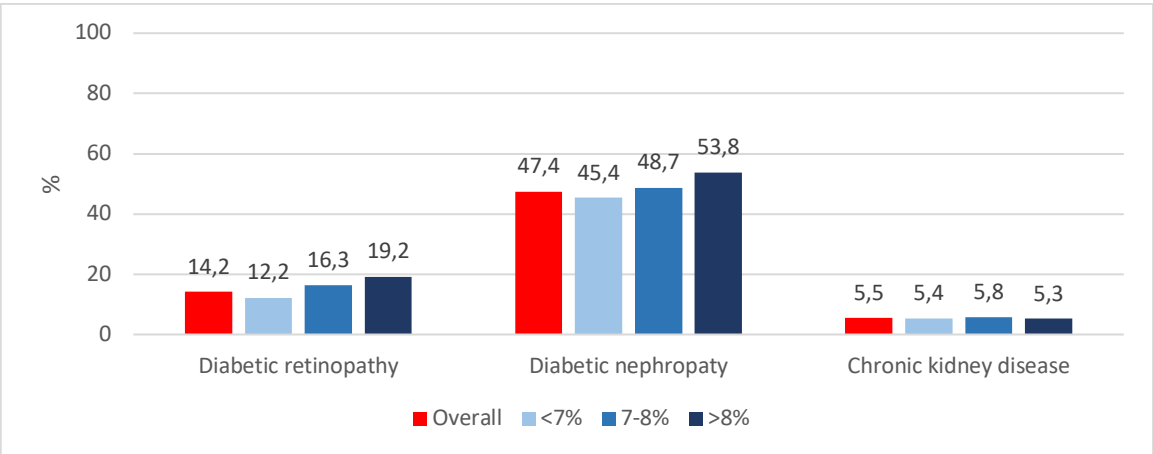
Prevalence of microvascular complications

Patients treated with insulin



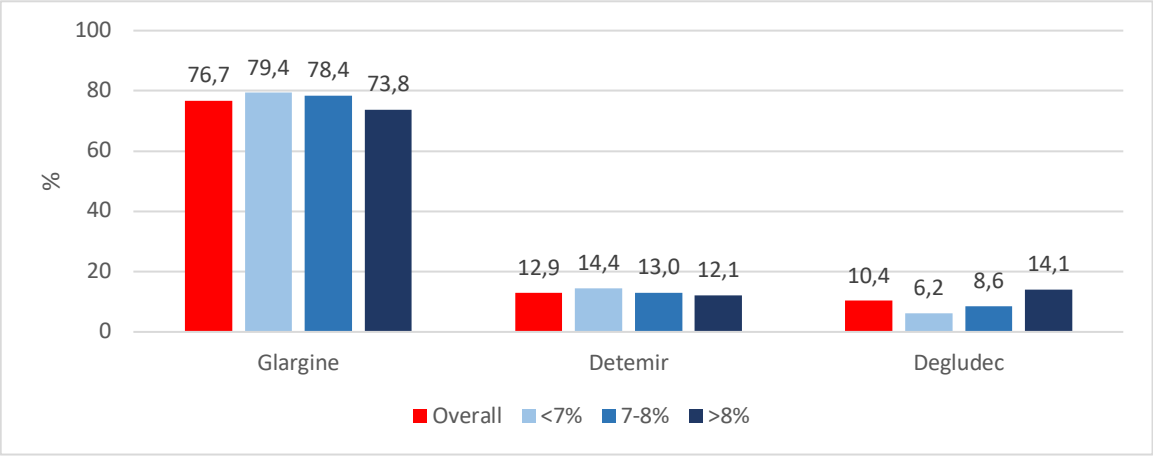
Among the microvascular complications, the prevalence of retinopathy and diabetic nephropathy grows with increasing levels of HbA1c, although the trends are not particularly marked. For renal failure, however, there is a reverse trend, with a higher prevalence among subjects in good metabolic control. However, the cross-sectional nature of the analysis does not allow to draw any causal inference.

Patients treated with glucose-lowering drugs other than insulin



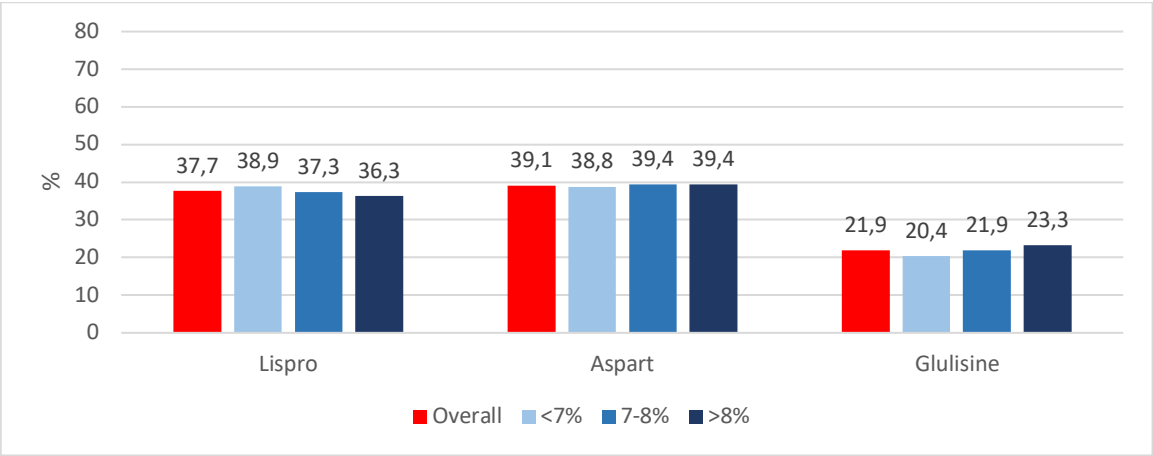
Among subjects not treated with insulin, the prevalence of microvascular complications is markedly lower, and the increasing trend with increasing HbA1c values is present both for diabetic retinopathy and for nephropathy, but not for renal failure.

Type of basal insulin



Among basal insulins, insulin Glargine is the most used in all the HbA1c subgroups. The use of insulin Degludec tends to increase with increasing levels of HbA1c.

Type of fast-acting insulin



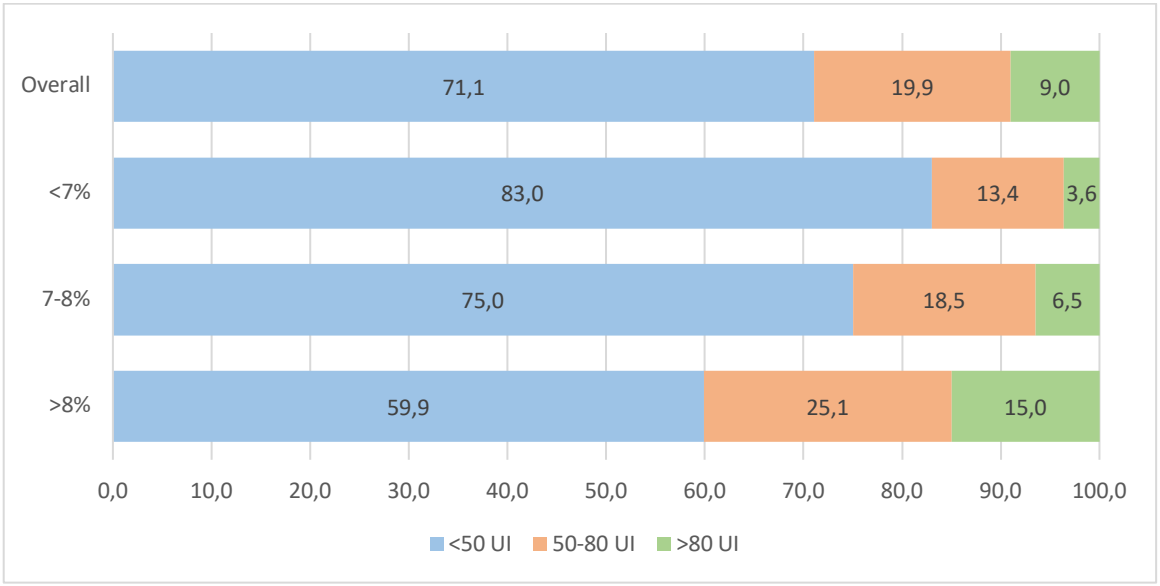
As for the fast-acting insulins, Lispro and Aspart are used in similar percentages, and without substantial differences based on the levels of HbA1c. Conversely, the use of Glulisine tends to increase with increasing levels of HbA1c. The percentages do not add up to 100%, as there are small percentages of subjects treated with human insulin (1-2%).

Doses of insulin

Population	Total UI /day Median (5°-95° percentile)	UI/kg/day Median (5°-95° percentile)
Overall	31 (8-96)	0.4 (0.1-1.1)
HbA1c<7%	24 (6-74)	0.3 (0.1-0.9)
7%<HbA1c<8%	30 (8-86)	0.4 (0.1-1.0)
HbA1c >8%	40 (8-110)	0.5 (0.1-1.2)

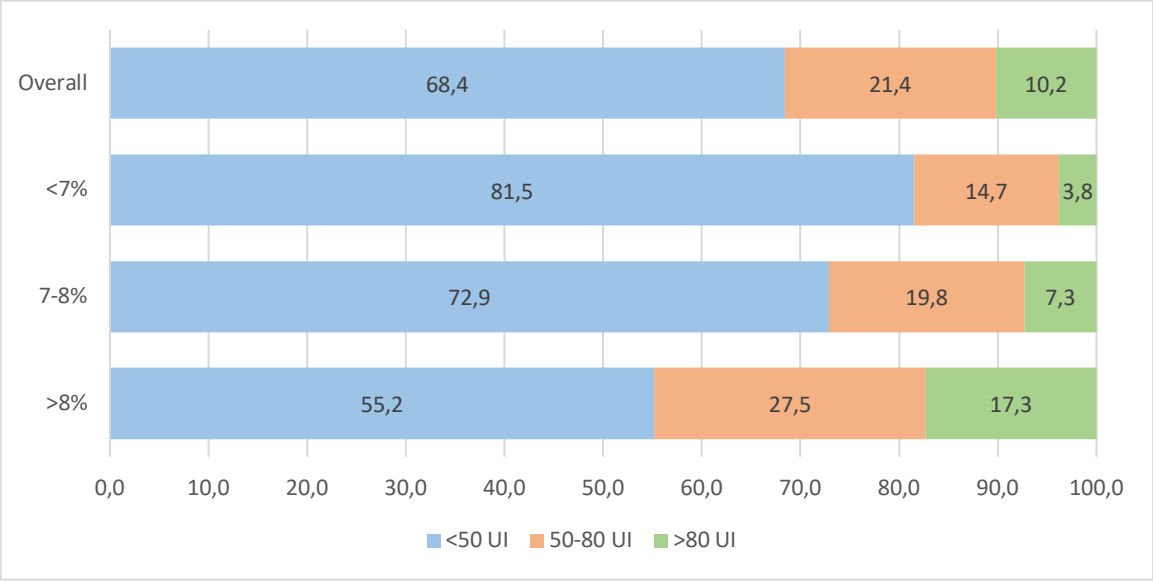
Overall, the total insulin dose increases with increasing HbA1c levels, with marked variability, as shown by the width of the ranges.

Distribution by insulin dose



The total insulin dose exceeds 80 IU in a minority of patients in good metabolic control, while the percentage grows to 15% among patients with HbA1c> 8.0%. It should be noted that among the subjects with inadequate metabolic control, around 60% are treated with less than 50 IU of insulin.

Distribution by insulin dose among patients with established cardiovascular disease



A similar picture emerges analyzing the subjects with established cardiovascular disease, although the percentage of subjects treated with 50 IU or more is higher in all HbA1c groups.

Discussion

Overall, 34,9% of the population with DM2 actively followed in 2016 (reference year for the 2018 Annals) (1) was treated with insulin, in various schemes and dosages, as documented in the Full Data Circle - FDC- database relative to patients seen in 2015 (2). The FDC population represented around 10% of the population treated with insulin in 2016, and it will be analyzed in the comments to the 2nd chapter of the results.

The "inertia" with which insulin treatment is started was already emphasized in the previous editions of the Annals. In fact, the average HbA1c levels at the time of the first insulin prescription was equal to 8.9 ± 1.6%, with half of the subjects already presenting HbA1c values >8.0% two years before insulin initiation. Moreover, even after 2 years from the beginning of insulin therapy, almost 50% of patients still maintained HbA1c levels> 8.0%, documenting the difficulty in adhering to the recommendations of Italian Guidelines (3).

Data relative to the present analysis offer a more optimistic picture, with the percentage of patients on insulin treatment with HbA1c > 8% dropped to 37.5%. However, the percentage of patients in poor metabolic control still remains three times higher as compared to the case history of patients not treated with insulin (11%). These data thus confirm that insulin treatment represents a "marker" of greater care complexity. In other words, it is patients who have a persistently poor metabolic control that are prescribed insulin therapy. In patients on insulin treatment, the association between HbA1c> 8% and younger age, higher prevalence of the female gender, higher BMI and worse control of the lipid profile outlines an overall picture of higher risk of micro and macrovascular complications in this population, needing insulin treatment due to the difficulty in reaching the desired targets of good metabolic control. It will be interesting to reassess this situation in the light of the new AMD Annals Campaign, relative to patients seen in the year 2018. In fact, it will be possible to assess whether the use of the "new" classes of non-insulin drugs (SGLT2i and GLP1 receptor agonists) has increased, with a plausible concomitant reduction in the proportion of insulin-treated patients. It will be also possible to assess the percentage of subjects "on target" from a metabolic point of view, without the use of insulin.

The analysis of socio-demographic and clinical characteristics documents that patients showing a greater difficulty in reaching the desired target are younger (average age of 68.7 vs. 70.6 years for insulin-treated patients with HbAc1 >8.0% and <=8.0%, respectively; average age of 66.6 vs. 67.7 years for non-insulin-treated patients with HbAc1 >8.0% and <=8.0%, respectively). Furthermore, the prevalence of women was higher among patients with HbA1c levels over 8.0% (5).

The population treated with insulin is older (average age: 70.1 vs. 67.9 years), with a significantly longer duration of illness (16.6 vs. 9.8 years of diabetes), documenting the increasing difficulty in maintaining optimal glycemic targets as the duration of diabetes increases (1).

In both groups, the body mass index lies in the area of marked overweight or obesity (average BMI of 30 vs. 29.4 in patients treated and not treated with insulin, respectively), with a slightly worse picture in insulin treated patients and in particular in those with worse metabolic control. The concomitance of younger age, higher BMI and worse metabolic control suggests the presence of a cluster of patients that shows greater difficulty or resistance to following a healthy lifestyle (diet and physical activity). In the absence of these cornerstones of diabetes therapy, it is inevitable that a more intensive pharmacological treatment is required.

Among subjects treated with insulin, the proportion of those with poor metabolic control (HbA1c> 8%) is higher among female patients. The prevalence of female gender increases from 39.7% among patients treated with insulin and HbA1c <7.0% to 48.1% among those with HbA1c levels >8.0%, while among patients not treated with insulin the prevalence increases from 41.6% to 43.1%. These findings are in line with the gender analysis carried out on the data of the 2011 AMD Annals (4) and published in Diabetes Care in 2013 (3), and confirmed by the gender analysis of the 2016 data (6).

The other parameters that identify a higher cardiovascular risk (worse lipid profile and smoking) are also more frequently reported in patients with HbA1c> 8%. The marked increase in triglycerides in this class of patients supports the hypothesis that there are greater difficulties in following adequate lifestyles among patients with poor metabolic control; however, with the same HbA1c levels, the worst values are found in patients not treated with insulin, perhaps indicating greater attention by diabetologists to the overall risk profile in more complex patients, such as insulin-treated ones.

As for macrovascular complications, the first observation concerns the likely "under-reporting" of previous myocardial infarction: the overall percentage of 5.6% in insulin-treated patients, which drops to 3.3% in those who do not receive insulin therapy, is significantly lower than expected both from previous population studies and from FDC data (9.3%).

In contrast, the percentage of subjects with stroke in insulin-treated patients is similar to that described in the FDC (5.6% vs. 4.6%), while the lower frequency of cerebro-vascular events is confirmed in patients not on insulin therapy (2.7%), which, in any case, are younger and have a significantly lower duration of diabetes.

In both treatment groups, low percentages of patients have a history of heart failure or angina, although the prevalence increases among insulin-treated subjects, particularly with regard to heart failure (3.8% vs. 1.4%). These findings suggest a problem of under-reporting of these complications; it is also possible that patients with heart problems tend to reduce the visits to the diabetes center to intensify those to the cardiologist.

The frequency of complications does not seem to be related to the worsening of metabolic control; indeed, the lowest rates of macrovascular complications are found in patients with HbA1c> 8%. This result cannot be easily interpreted due to the cross-sectional nature of the analysis; however, it is plausible that diabetologists intensify treatment particularly in patients who have had a major cardiovascular event; it is also possible that patients with more severe overall conditions, including worse metabolic control, may also be those less likely to survive.

Also the percentage of patients with microvascular complications is markedly higher in insulin-treated patients compared to patients not treated with insulin; in this case, however, the frequency of complications (retinopathy and nephropathy) increases, as can be expected, with the worsening of metabolic control, confirming the close causal link between metabolic control and microangiopathy, regardless of the kind of therapy.

Renal failure is by far the least represented among microvascular complications, both in insulin-treated (16.7% of cases vs. 66.5% of patients with nephropathy) and in patients not on insulin therapy (5.5 % vs. 47.4%). A possible explanation for this low rate could be sought in the likely prevailing nephrological follow-up of patients with advanced renal complications, who enter the treatment pathways for chronic kidney disease. Similar to macrovascular complications, in patients treated with insulin, the prevalence of renal failure decreases with the worsening of metabolic

control (from 20.6% in patients with HbA1c <7.0% to 14.1% among those with HbA1c <8.0%), probably for the same reasons discussed above. This trend, on the other hand, cannot be detected in subjects not on insulin treatment.

Regarding the use of different types of insulin, both basal and rapid analogues, no significant variations in the distribution are observed based on metabolic control, except for degludec and glulisine, which seem to be used more frequently with the worsening of metabolic control.

Insulin glargine was by far the most common basal analogue prescribed by Italian diabetologists in 2016 (in over 76% of cases), while among the fast-acting analogues, lispro and aspart were used in similar proportions of patients.

As it can be reasonably understood, the average daily dosage, in patients on insulin therapy, tends to increase with the worsening of metabolic control (probably in an attempt to make the treatment more effective, "forcing" insulin resistance with larger amounts). Although the variability of the dosages, within the groups with the same metabolic control, is very high, the median use expressed in IU/Kg/day remains fairly low, ranging from 0.3 for values of HbA1c <7% to 0.5 IU/kg for values of HbA1c > 8%. High daily insulin doses (over 80 IU / day) are used with an almost fivefold higher frequency, passing from the group of patients with HbA1c <7% to those with HbA1c> 8%.

However, about 60% of subjects in poor metabolic control receive insulin therapy with doses lower than 50 IU/day: this could be interpreted as an index of "inertia" in titrating insulin doses to obtain a more adequate metabolic control.

This impression does not change if we analyze the cases of subjects with a previous cardiovascular event: in this case as well, over 55% of patients receive less than 50 IU/day of insulin, despite HbA1c levels> 8%. It is therefore possible that there is a tendency to be poorly "aggressive", once the insulin treatment has been initiated, in subsequent variations of the dosages, which should lead to the desired metabolic goals.

The high prevalence of elderly or frail subjects may partly justify this "caution" in intensifying the treatment, aimed at obtaining less stringent metabolic targets, but at the same time more "protective" with respect to the risk of hypoglycemia.

In summary, the population with DM2 on insulin treatment is the most complex, with a worse cardiovascular risk profile, a greater prevalence of macrovascular complications and with a higher burden of microvascular complications (retinopathy and nephropathy). In this population, the group with the worst metabolic control, despite insulin therapy, shows a clustering of all the risk factors, such as smoking and out-target values of BMI, blood pressure, total cholesterol, LDL cholesterol, and triglycerides, suggesting a possible greater difficulty/resistance to adopt an adequate lifestyle, including a constant adherence to a healthy diet and continuous physical activity. The greater prevalence of women in this group of patients confirms the data on the worst cardiovascular risk profile of women, as already highlighted in the dedicated publications of the AMD Annals (5,7).

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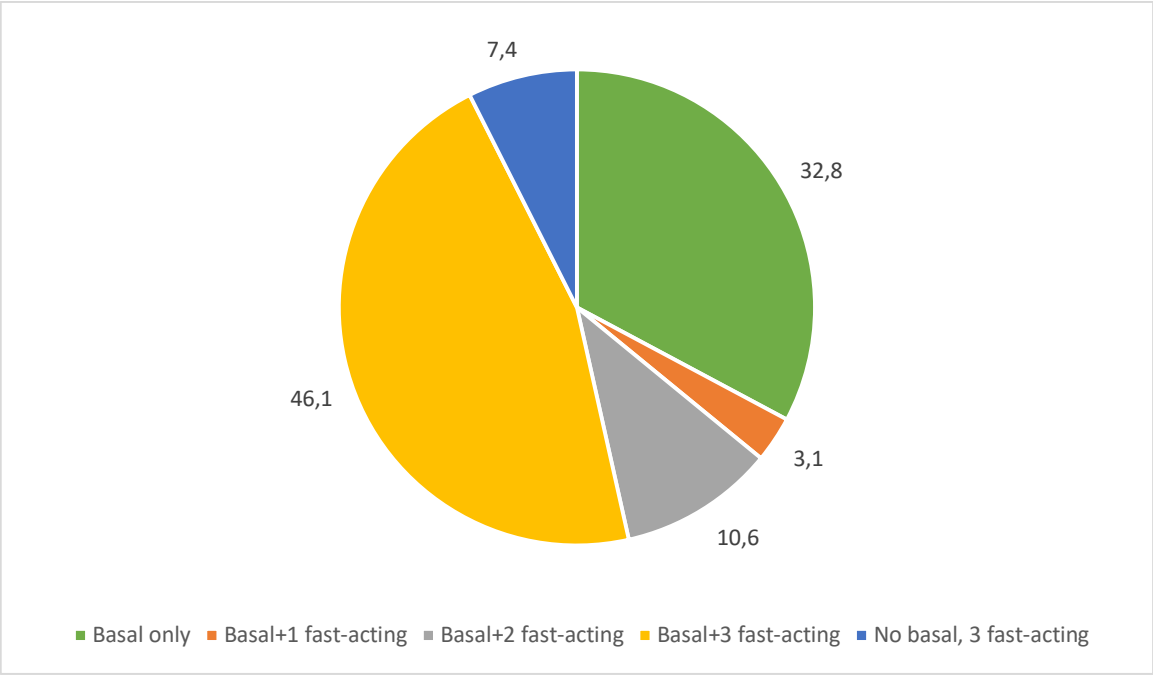
Authors: Valeria Manicardi, Alberto Rocca

2. Insulin schemes

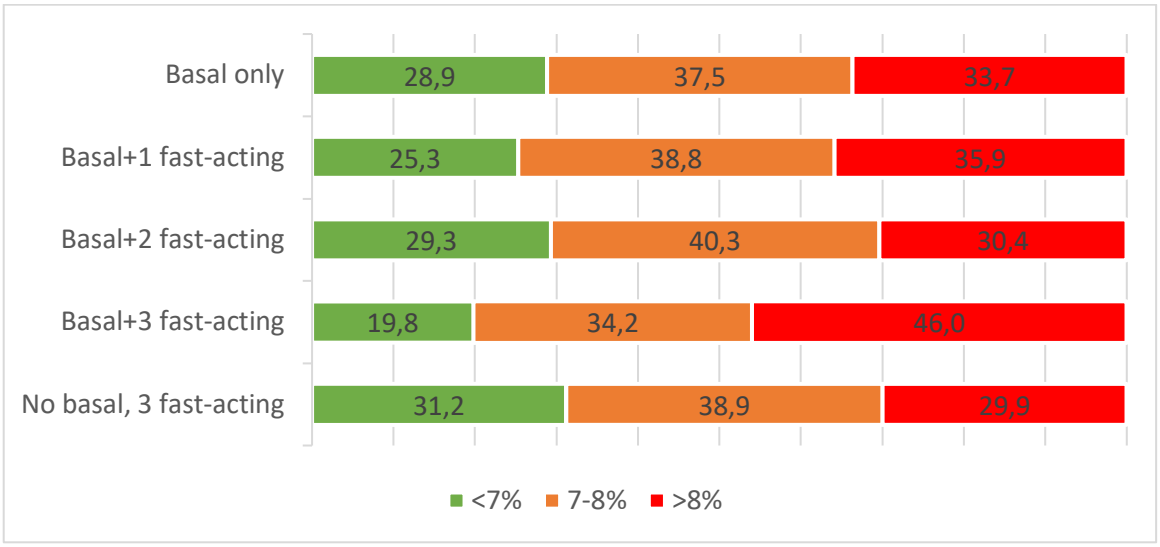
The T2DM population treated with insulin (± other glucose-lowering agents other than insulin) was stratified according to the type of insulin scheme used. The information on the scheme was available in the Full Data Circle database for a total of 13.494 subjects.

Distribution of the study population according to the insulin scheme



The most frequently used schemes (with or without other glucose-lowering agents) are the basal-bolus (basal + 3 fast-acting; 46.1%) and basal insulin alone (32.8%).

Distribution of insulin schemes according to HbA1c classes



In the different schemes, about one-quarter to one-third of patients reached HbA1c levels <7.0%, while significant proportions, ranging between 29.9% and 46.0%, showed inadequate metabolic control despite insulin treatment. The picture is particularly unfavorable for patients on basal-bolus therapy (basal + 3 fast-acting).

Socio-demographic and clinical characteristics by insulin scheme

Patients treated with basal insulin (± glucose-lowering agents other than insulin)

	Overall	HbA1c classes		
Characteristics		<7%	7-8%	>8%
N	4493	1275	1654	1486
Age (years)	68.6±11.6	68.0±11.9	69.9±10.7	67.6±12.0
Males (%)	56.8	61.0	56.3	53.7
Smokers (%)	19.2	19.8	17.6	20.3
Duration of diabetes (years)	13.9±9.0	12.3±9.5	15.1±8.9	14.0±8.4
HbA1c (%)	7.7±1.4	6.3±0.5	7.5±0.3	9.2±1.2
Body mass index (kg/m2)	29.7±5.6	29.1±5.5	29.4±5.3	30.5±5.8
Systolic blood pressure (mmHg)	134.2±17.1	133.0±17.4	134.7±16.7	135.0±17.0
Diastolic blood pressure (mmHg)	76.8±9.3	76.3±9.3	76.5±9.2	77.6±9.4
Total cholesterol (mg/dl)	167.9±40.1	164.5±40.6	165.9±37.3	173.3±42.5
HDL cholesterol (mg/dl)	47.5±13.5	47.6±13.7	48.6±13.8	46.1±12.8
LDL cholesterol(mg/dl)	93.9±33.1	92.5±33.6	92.5±31.9	96.9±34.0
Triglycerides (mg/dl)	142.8±95.0	131.2±90.1	135.8±87.6	161.2±104.4

Data are mean±standard deviation or percentage

Among the subjects treated with basal insulin, one third had HbA1c values> 8.0%, with mean HbA1c values of 9.2%. This group is characterized by the younger age, a higher prevalence of women, a higher BMI and a worse blood pressure and lipid profile.

Patients treated with basal insulin + 1 injection of fast-acting insulin

	Overall	HbA1c classes		
Characteristics		<7%	7-8%	>8%
N	427	105	161	149
Age (years)	71.3±10.5	70.7±10.5	71.6±9.8	71.5±11.5
Males (%)	52.7	52.4	55.9	49.0
Smokers (%)	16.4	16.5	15.3	14.6
Duration of diabetes (years)	17.7±10.7	15.4±10.9	17.7±10.3	19.1±10.7
HbA1c (%)	7.8±1.2	6.4±0.4	7.5±0.3	9.1±1.0
Body mass index (kg/m2)	29.0±5.5	28.0±5.1	29.1±5.0	29.5±6.2
Systolic blood pressure (mmHg)	134.7±16.4	135.1±16.5	135.5±16.6	133.9±16.1
Diastolic blood pressure (mmHg)	75.8±10.1	76.1±10.8	75.9±9.2	75.4±10.8
Total cholesterol (mg/dl)	163.4±37.7	167.8±37.6	159.8±37.5	164.0±38.2
HDL cholesterol (mg/dl)	48.9±14.3	51.3±15.0	48.7±14.3	47.3±13.8
LDL cholesterol(mg/dl)	90.2±31.3	95.2±31.6	87.0±31.3	90.4±31.1
Triglycerides (mg/dl)	127.3±62.7	114.9±46.9	128.1±65.7	133.8±67.8

Data are mean±standard deviation or percentage

Patients treated with a basal-plus scheme are older and have a longer duration of illness. Even in this group, over one third of the patients has HbA1c values above 8.0%, with an average HbA1c of 9.1%. Individuals with unsatisfactory metabolic control are more often female and have a higher BMI.

Patients treated with basal insulin + 2 injections of fast-acting insulin

	Overall	HbA1c classes		
Characteristics		<7%	7-8%	>8%
N	1448	415	570	430
Age (years)	71.1±11.2	72.8±10.2	71.4±10.5	69.1±12.4
Males (%)	51.7	56.6	51.1	47.7
Smokers (%)	17.4	14.1	17.6	20.2
Duration of diabetes (years)	18.1±10.3	17.0±10.4	19.1±10.2	17.7±10.2
HbA1c (%)	7.7±1.3	6.4±0.4	7.5±0.3	9.1±1.1
Body mass index (kg/m2)	29.2±5.7	28.8±5.4	29.0±5.6	29.7±6.0
Systolic blood pressure (mmHg)	133.5±16.3	132.5±15.0	133.5±17.5	134.9±15.9
Diastolic blood pressure (mmHg)	75.2±8.8	74.7±8.3	75.1±9.0	75.9±8.8
Total cholesterol (mg/dl)	166.6±38.6	162.3±38.8	166.3±37.4	171.7±39.3
HDL cholesterol (mg/dl)	51.3±15.1	50.1±14.9	52.6±15.6	50.5±14.4
LDL cholesterol(mg/dl)	91.2±31.7	89.6±32.9	90.4±31.7	94.1±30.4
Triglycerides (mg/dl)	130.2±79.3	125.8±63.0	124.4±79.5	143.1±91.7

Data are mean±standard deviation or percentage

Patients treated with a basal insulin injection and two injections of fast-acting insulin have characteristics similar to those treated with the basal-plus scheme. In this case, however, as HbA1c levels increase, age decreases, the prevalence of women and smokers increases, and blood pressure and lipid profile worsen.

Patients treated with basal insulin + 3 injections of fast-acting insulin

	Overall	HbA1c classes		
Characteristics		<7%	7-8%	>8%
N	6308	1215	2093	2817
Age (years)	70.1±10.9	71.4±10.9	71.4±10.2	68.6±11.2
Males (%)	55.9	60.5	55.9	54.1
Smokers (%)	17.6	16.2	16.1	19.6
Duration of diabetes (years)	17.6±10.1	17.0±10.8	18.5±10.0	17.2±9.7
HbA1c (%)	8.2±1.5	6.4±0.5	7.5±0.3	9.4±1.3
Body mass index (kg/m2)	31.4±5.9	30.5±5.8	31.2±5.7	32.0±6.1
Systolic blood pressure (mmHg)	134.5±17.0	132.3±17.8	134.4±16.3	135.6±17.1
Diastolic blood pressure (mmHg)	76.0±9.4	74.6±9.5	75.5±8.8	77.0±9.7
Total cholesterol (mg/dl)	165.5±40.7	159.5±37.5	162.3±39.8	170.2±41.5
HDL cholesterol (mg/dl)	46.3±13.9	46.6±13.9	46.4±13.9	46.1±13.9
LDL cholesterol(mg/dl)	91.2±33.4	87.8±31.0	89.3±32.8	94.1±34.2
Triglycerides (mg/dl)	154.7±109.6	134.1±71.0	143.0±82.0	171.4±132.9

Data are mean±standard deviation or percentage

Patients on basal-bolus insulin therapy represent the group with the greatest problems of metabolic control, as documented by the high prevalence (46%) of subjects with HbA1c> 8.0%. The latter have an average HbA1c of 9.4%, a younger age, a higher female prevalence, a markedly higher BMI and worse blood pressure and lipid values.

Patients treated with 3 injections of fast-acting insulin and no basal insulin

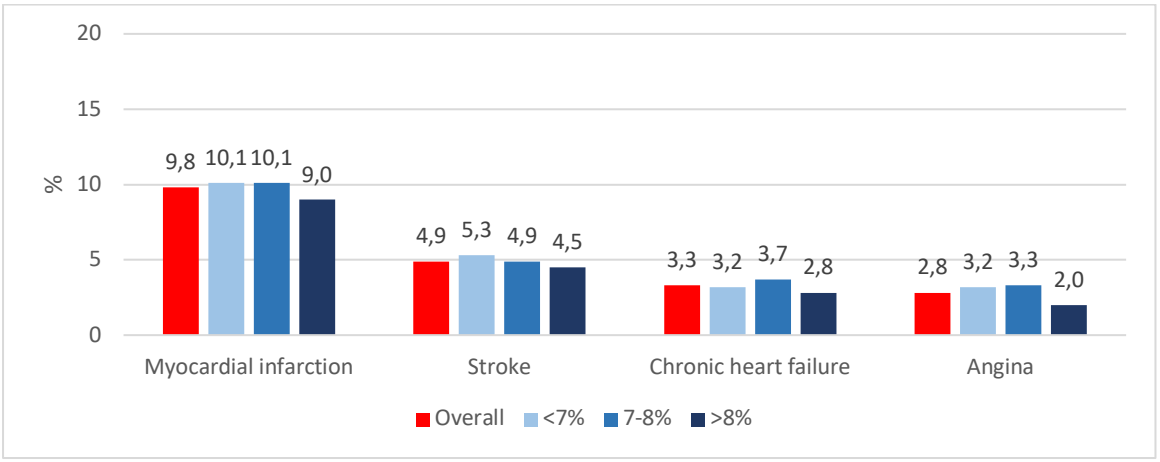
	Overall	HbA1c classes		
Variabile		<7%	7-8%	>8%
N	1019	303	378	291
Age (years)	72.4±11.1	72.9±11.4	73.4±10.4	70.0±11.3
Males (%)	55.2	55.1	53.7	56.4
Smokers (%)	13.7	15.1	12.6	14.3
Duration of diabetes (years)	16.2±10.6	15.5±10.6	17.0±10.7	16.1±10.4
HbA1c (%)	7.6±1.4	6.3±0.5	7.5±0.3	9.3±1.3
Body mass index (kg/m2)	30.1±6.1	28.9±5.7	30.4±6.0	31.4±6.0
Systolic blood pressure (mmHg)	132.1±15.1	130.9±15.7	132.5±15.2	133.3±14.3
Diastolic blood pressure (mmHg)	74.8±8.2	73.3±8.7	75.2±8.2	75.6±7.7
Total cholesterol (mg/dl)	168.5±42.0	165.2±42.7	166.9±38.3	173.6±45.2
HDL cholesterol (mg/dl)	48.7±14.9	49.6±15.7	49.0±14.4	47.4±14.4
LDL cholesterol(mg/dl)	92.0±33.7	91.0±33.3	91.5±32.2	93.5±35.9
Triglycerides (mg/dl)	145.6±90.6	127.0±61.0	142.2±75.6	170.0±123.4

Data are mean±standard deviation or percentage

Patients on insulin treatment with fast-acting insulin alone represent a small group, of fairly advanced age. Even in this case, subjects with poor metabolic control have a higher BMI and less favorable blood pressure and lipid values.

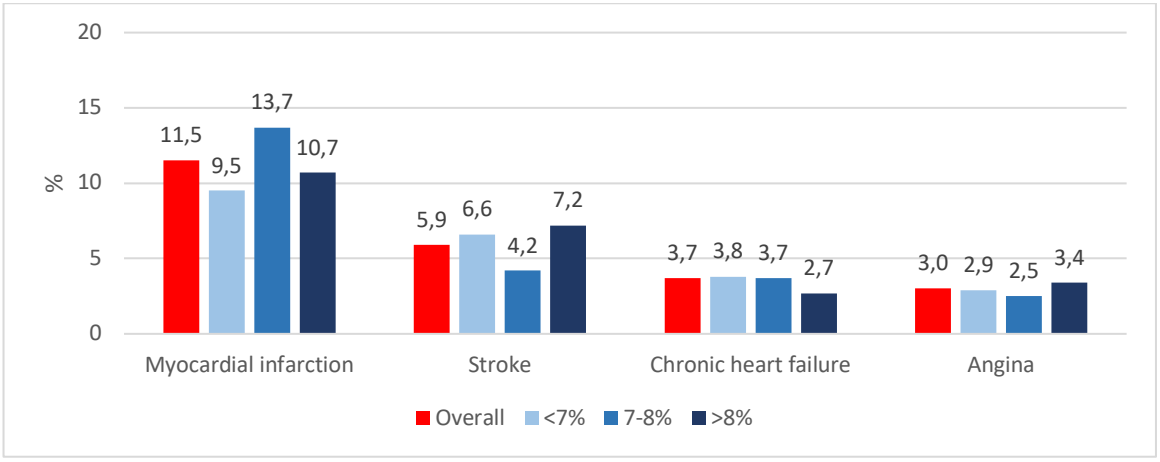
Prevalence of macrovascular complications according to insulin scheme

Patients treated with basal insulin (± glucose-lowering agents other than insulin)



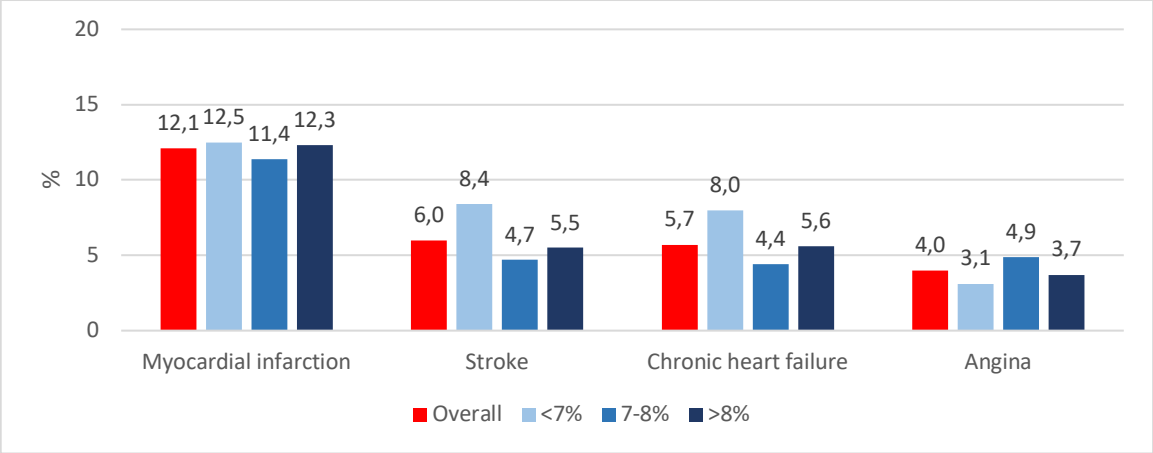
Among subjects treated with basal insulin alone, the prevalence of cardiovascular complications is high, especially with regard to myocardial infarction, without a clear trend of association with HbA1c values. In general, the prevalence of different complications is lower in the subgroup with HbA1c > 8.0%, probably indicating greater attention to metabolic control in subjects with macrovascular complications.

Patients treated with basal insulin + 1 injection of fast-acting insulin



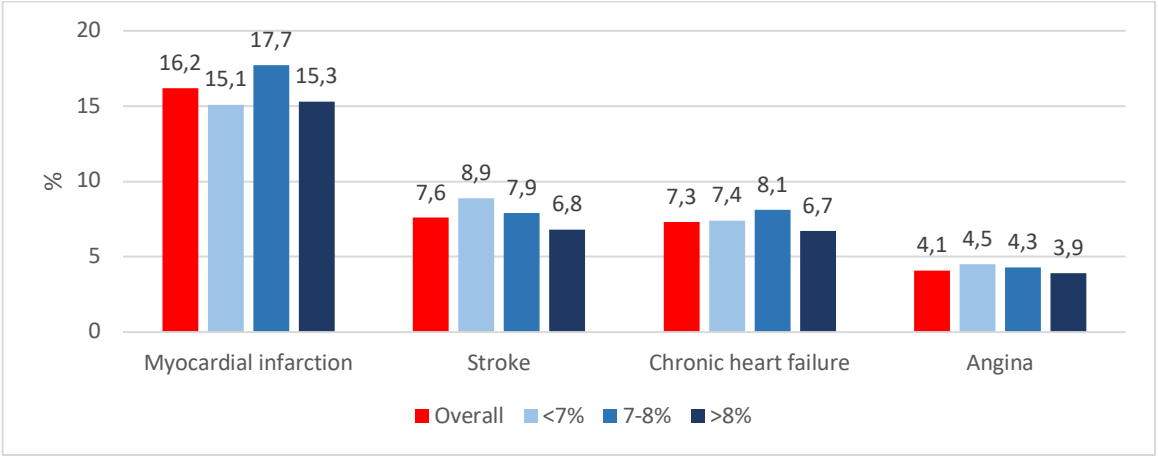
For patients in basal-plus insulin therapy, the same considerations made in the previous paragraph apply. However, there is a higher prevalence of previous stroke among subjects with poor metabolic control.

Patients treated with basal insulin + 2 injections of fast-acting insulin



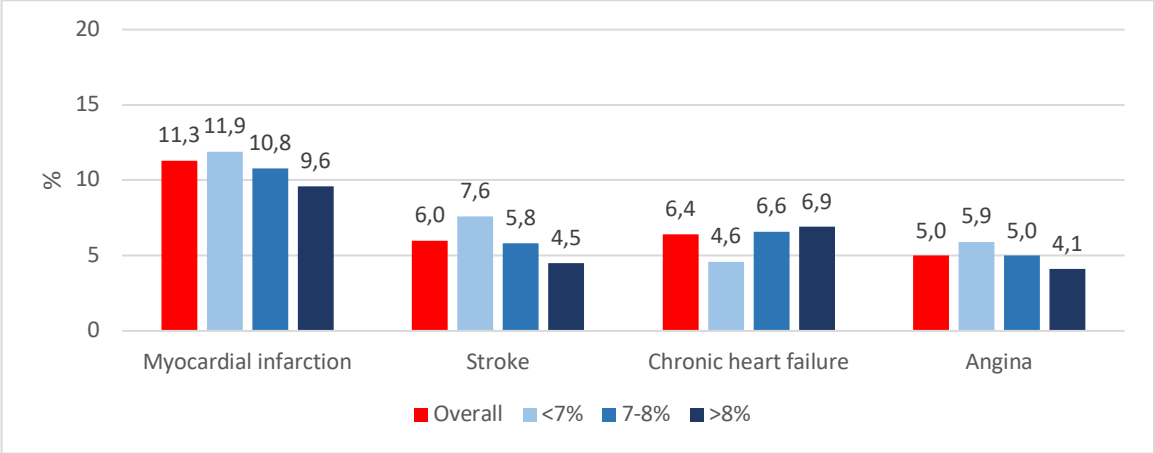
Also for this subgroup the prevalence of complications tends to be greater in the subgroup with better metabolic control, probably indicating greater attention to subjects with complications.

Patients treated with basal insulin + 3 injections of fast-acting insulin



The subgroup of patients on basal insulin+ 2 injections of fast-acting insulin is characterized by the highest prevalence of cardio vascular complications, with a slightly lower prevalence in the subgroup with HbA1c > 8.0%.

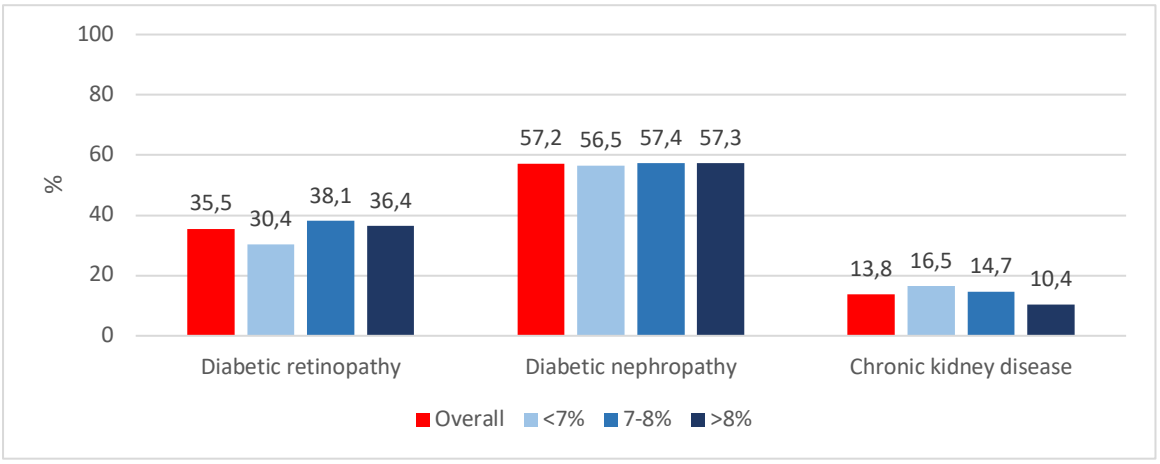
Patients treated with 3 injections of fast-acting insulin and no basal insulin



The same considerations made for the previous subgroup apply also to these patients.

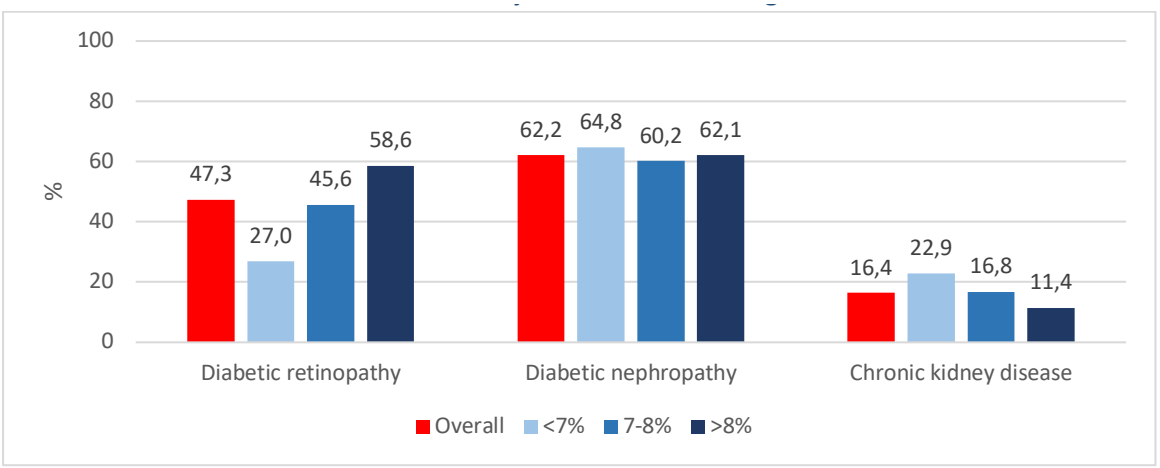
Prevalence of microvascular complications according to insulin scheme

Patients treated with basal insulin (± glucose-lowering agents other than insulin)



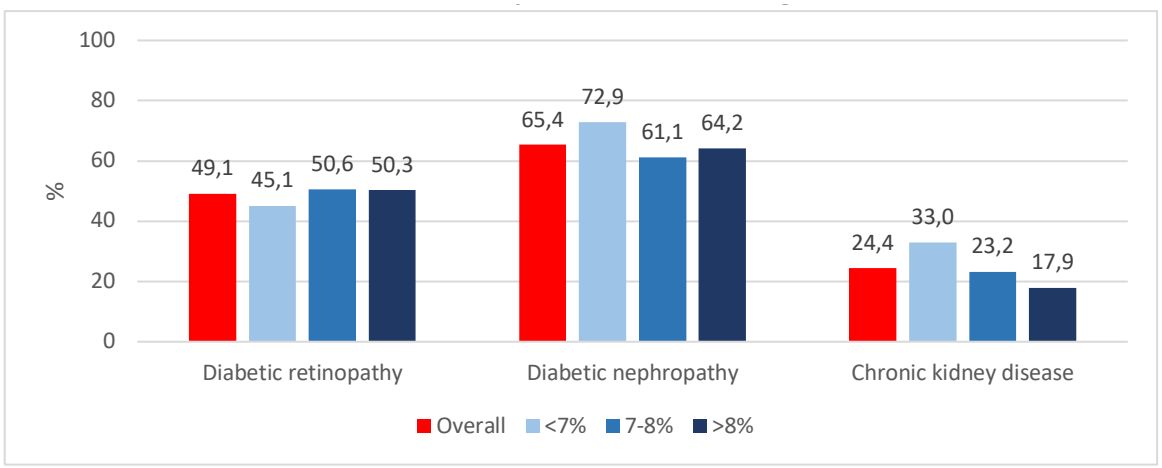
A high prevalence of microvascular complications is found in patients treated with basal insulin alone. While the prevalence of retinopathy and nephropathy is slightly lower among subjects in good metabolic control, the prevalence of chronic kidney disease is higher.

Patients treated with basal insulin + 1 injection of fast-acting insulin

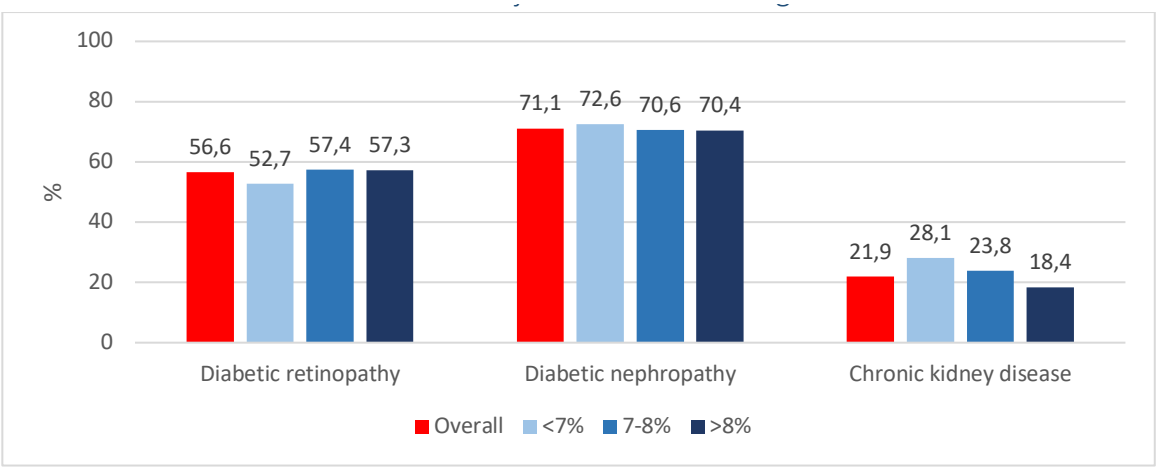


Among subjects on basal-plus insulin therapy, the prevalence of retinopathy markedly increases with increasing levels of HbA1c, while no differences emerge with regard to diabetic nephropathy. The prevalence of renal failure decreases with increasing levels of HbA1c.

Patients treated with basal insulin + 2 injections of fast-acting insulin

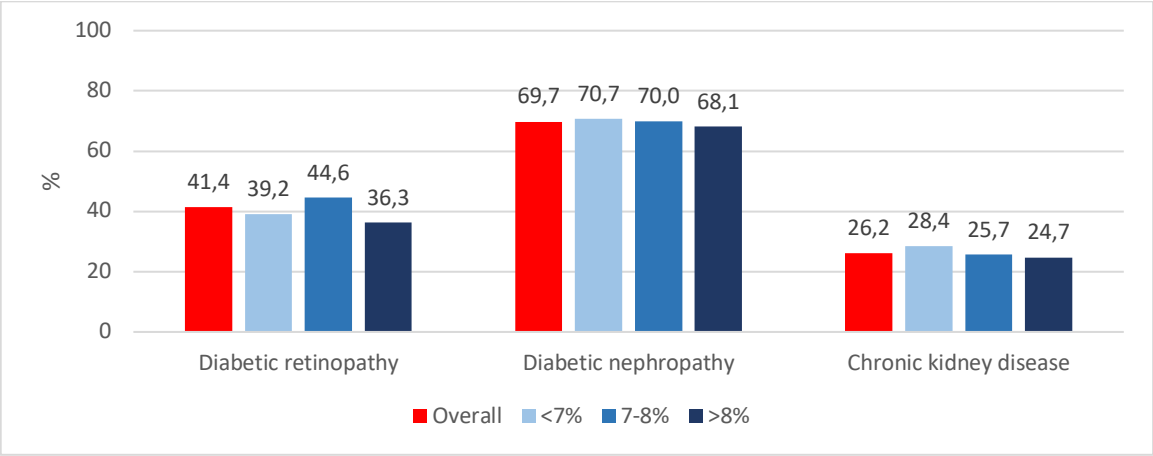


Patients treated with basal insulin + 3 injections of fast-acting insulin



Patients treated with basal insulin and two or more injections of fast-acting insulin show a particularly high prevalence of microvascular complications. The highest prevalence of chronic kidney disease among subjects in good metabolic control is confirmed, indicating greater attention to patients with reduced glomerular filtration rate.

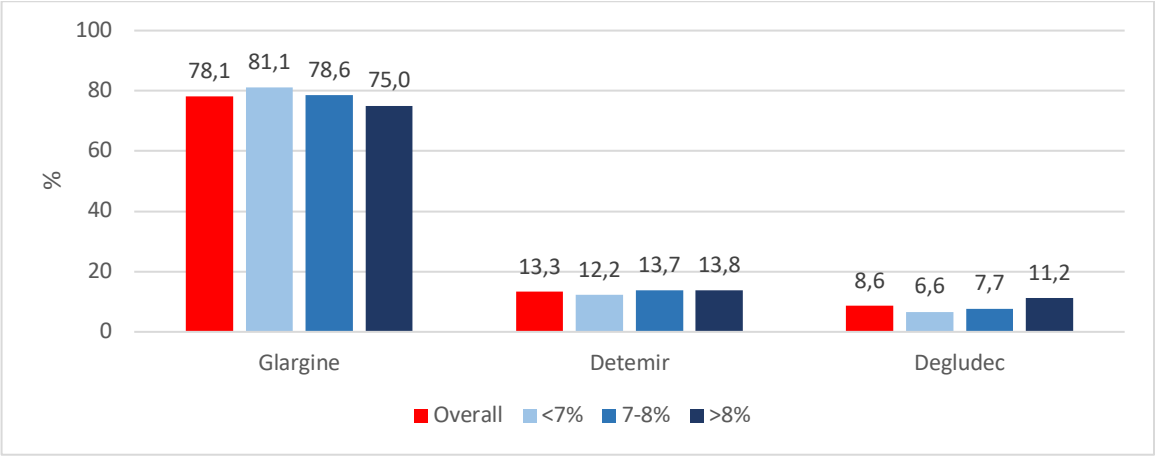
Patients treated with 3 injections of fast-acting insulin and no basal insulin



Even among patients treated with fast-acting insulin alone, the prevalence of microvascular complications is high, with no clear trend in relation to HbA1c levels.

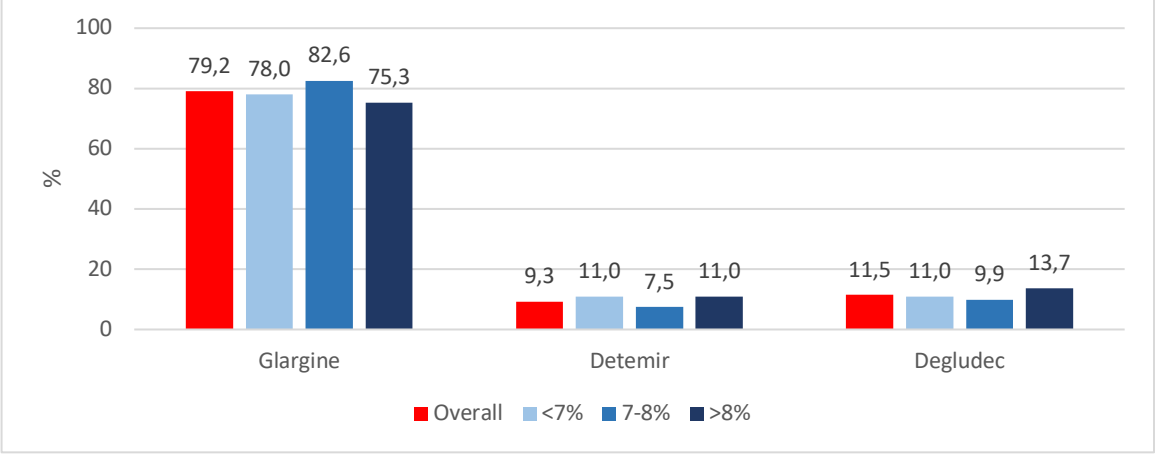
Type of basal insulin in relation to insulin scheme

Patients treated with basal insulin (± glucose-lowering agents other than insulin)



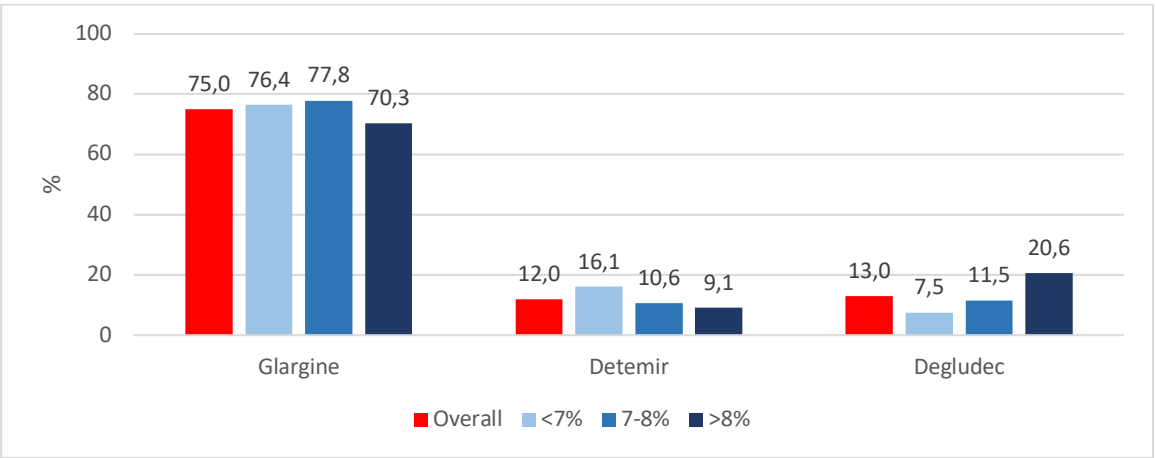
Among patients on basal insulin alone, insulin Glargine is the most commonly used in all HbA1c subgroups. The use of insulin Degludec grows with increasing HbA1c values.

Patients treated with basal insulin + 1 injection of fast-acting insulin



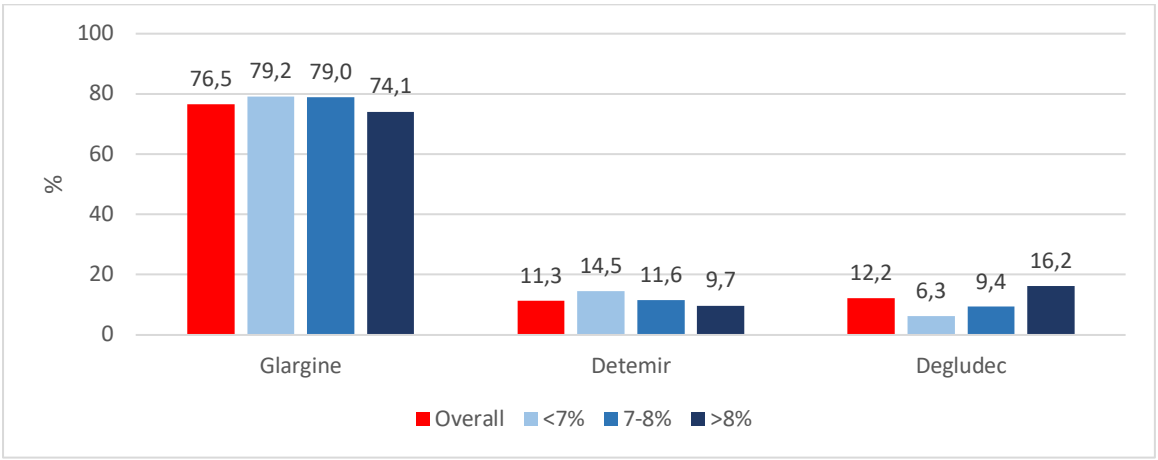
Even among patients treated with a basal-plus scheme, insulin Glargine is by far the most widely used, being prescribed to over three-quarters of the sample. The utilization rates of insulin Detemir and Degludec are similar and do not appear to be influenced by HbA1c levels.

Patients treated with basal insulin + 2 injections of fast-acting insulin



Even in this subgroup, insulin Glargine is used in three quarters of the sample. The frequency of use of insulin Degludec increases with increasing values of HbA1c, while for insulin Detemir there is an opposite trend.

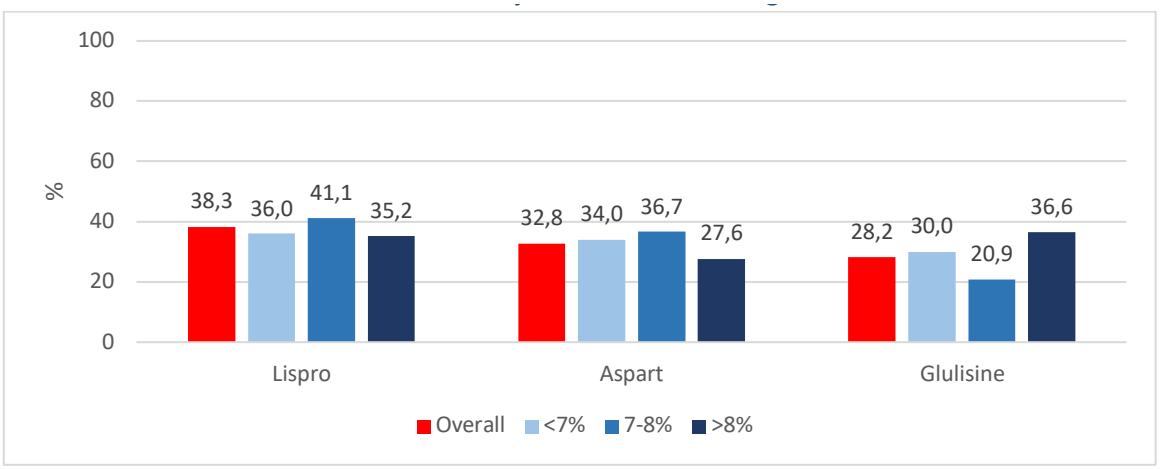
Patients treated with basal insulin + 3 injections of fast-acting insulin



Similar considerations apply to this subgroup.

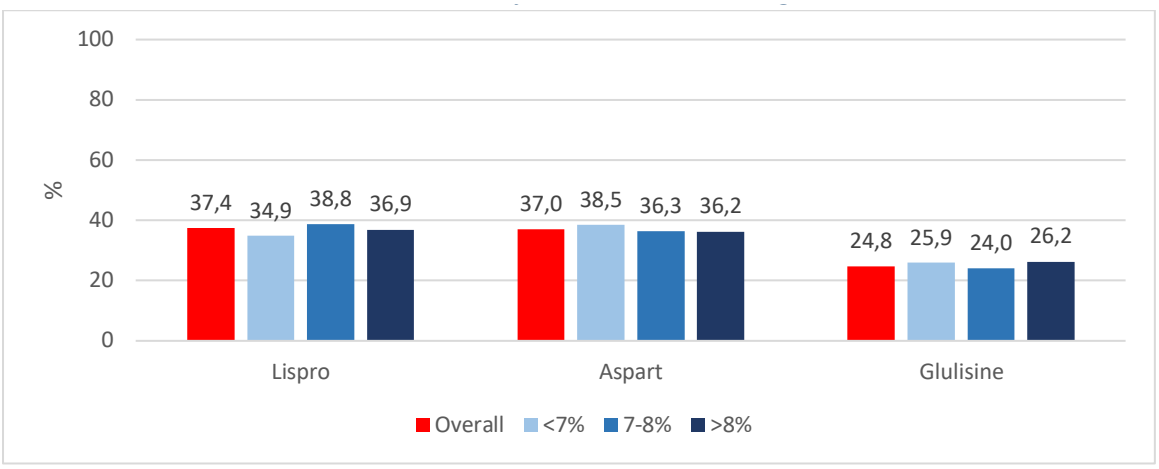
Type of fast-acting insulin in relation to insulin scheme

Patients treated with basal insulin + 1 injection of fast-acting insulin

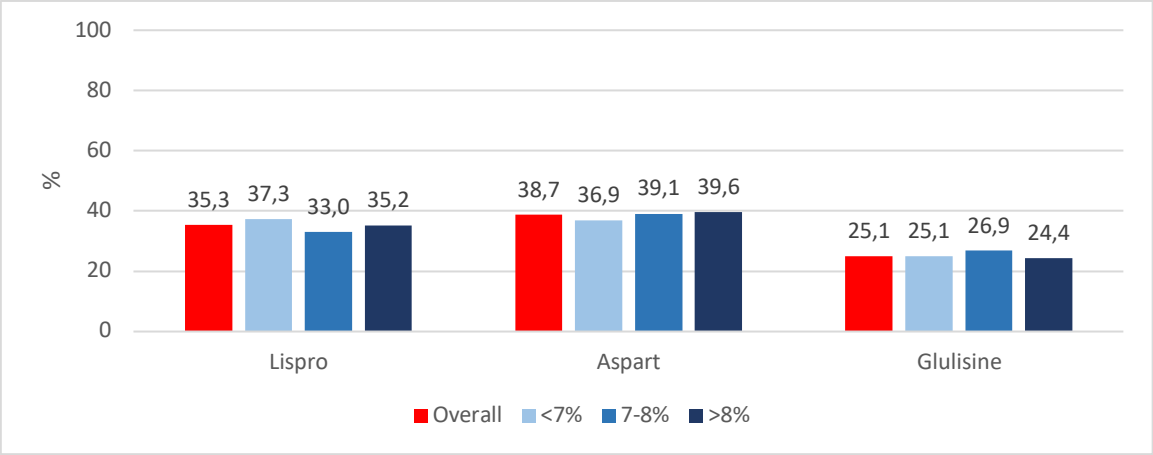


Among patients treated with a basal-plus regimen, the use of different types of fast-acting insulin is similar, resulting slightly higher for Lispro. Among subjects with HbA1c> 8.0% the use of Glulisine is more frequent.

Patients treated with basal insulin + 2 injections of fast-acting insulin

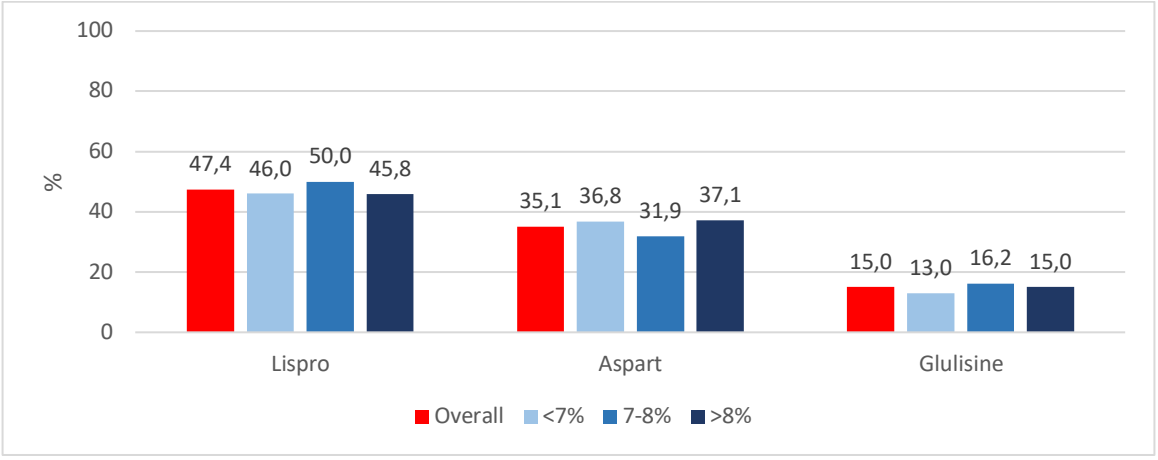


Patients treated with basal insulin + 3 injections of fast-acting insulin



Among patients treated with two or more rapid injections in combination with basal insulin, more than 30% are treated with Lispro or Aspart, and a quarter with insulin Glulisine. There are no substantial differences in relation to the level of metabolic control.

Patients treated with 3 injections of fast-acting insulin and no basal insulin



Among patients treated only with multiple injections of fast-acting insulin, the use of Lispro prevails, followed by Aspart. The percentages of use are similar in the different HbA1c ranges.

Insulin doses (total UI/day)

Insulin scheme	Overall	HbA1c<7%	7%<=HbA1c<=8%	HbA1c >8%
Basal only	12 (6-32)	10 (5-26)	12 (6-30)	14 (6-36)
Basal + 1 injection of fast-acting	22 (10-49)	19 (10-40)	22 (10-44)	24 (10-63)
Basal + 2 injections of fast-acting	29 (15-66)	27 (14-60)	29 (16-62)	33 (17-79)
Basal + 3 injections of fast-acting	53 (26-112)	44 (23-90)	50 (26-103)	60 (28-124)
3 injections of fast-acting, no basal	26 (12-59)	22 (12-50)	24 (12-52)	30 (15-70)

Data expressed as median and 5th -95th percentile.

The median insulin doses are quite low, both for patients on basal insulin alone and in those on multiple injections, especially considering the average BMI which is high in all subgroups. For all insulin schemes, the median doses increase with increasing HbA1c values and with the increase in the number of daily insulin doses.

Doses of insulin per Kg of body weight (UI/Kg/day)

Insulin scheme	Overall	HbA1c<7%	7%<=HbA1c<=8%	HbA1c >8%
Basal only	0.2 (0.1-0.4)	0.1 (0.1-0.3)	0.2 (0.1-0.4)	0.2 (0.1-0.4)
Basal + 1 injection of fast-acting	0.3 (0.1-0.6)	0.3 (0.1-0.5)	0.3 (0.2-0.6)	0.3 (0.2-0.7)
Basal + 2 injections of fast-acting	0.4 (0.2-0.8)	0.4 (0.2-0.7)	0.4 (0.2-0.8)	0.4 (0.2-0.9)
Basal + 3 injections of fast-acting	0.6 (0.3-1.3)	0.5 (0.3-1.1)	0.6 (0.3-1.2)	0.7 (0.4-1.4)
3 injections of fast-acting, no basal	0.3 (0.2-0.7)	0.3 (0.2-0.6)	0.3 (0.2-0.7)	0.4 (0.2-0.8)

Data expressed as median and 5th -95th percentile.

The median daily doses of insulin per Kg are quite low for all insulin therapy schemes. The doses slightly increase, and only for some schemes, with increasing HbA1c levels, while they increase with the number of daily administrations of insulin.

Doses of basal insulin (total UI/day)

Insulin scheme	Overall	HbA1c<7%	7%<=HbA1c<=8%	HbA1c >8%
Basal only	12 (6-32)	10 (5-26)	12 (6-30)	14 (6-36)
Basal + 1 injection of fast-acting	14 (6-36)	12 (6-30)	14 (6-32)	16 (5-44)
Basal + 2 injections of fast-acting	14 (6-38)	12 (5-34)	14 (6-34)	16 (6-44)
Basal + 3 injections of fast-acting	20 (8-45)	16 (6-38)	20 (8-44)	24 (10-48)
3 injections of fast-acting, no basal	-	-	-	-

Data expressed as median and 5th -95th percentile.

The median basal insulin doses are quite low, both for patients on basal therapy alone and in those treated with multiple injections. For all insulin therapy schemes, the doses increase with increasing values of HbA1c and increasing number of daily insulin administrations.

Doses of basal insulin per Kg of body weight (UI/Kg/day)

Insulin scheme	Overall	HbA1c<7%	7%<=HbA1c<=8%	HbA1c >8%
Basal only	0.2 (0.1-0.4)	0.1 (0.1-0.3)	0.2 (0.1-0.4)	0.2 (0.1-0.4)
Basal + 1 injection of fast-acting	0.2 (0.1-0.4)	0.2 (0.1-0.4)	0.2 (0.1-0.4)	0.2 (0.1-0.5)
Basal + 2 injections of fast-acting	0.2 (0.1-0.5)	0.2 (0.1-0.4)	0.2 (0.1-0.5)	0.2 (0.1-0.5)
Basal + 3 injections of fast-acting	0.2 (0.1-0.5)	0.2 (0.1-0.4)	0.2 (0.1-0.5)	0.3 (0.1-0.5)
3 injections of fast-acting, no basal	-	-	-	-

Data expressed as median and 5th -95th percentile.

The median doses of basal insulin per Kg of body weight are quite low for all insulin therapy schemes. Doses appear to be little influenced by HbA1c levels and number of insulin injections.

Doses of short-acting insulin (total UI/day)

Insulin scheme	Overall	HbA1c<7%	7%<=HbA1c<=8%	HbA1c >8%
Basal only	-	-	-	-
Basal + 1 injection of fast-acting	6 (4-16)	6 (4-14)	6 (4-16)	8 (4-18)
Basal + 2 injections of fast-acting	15 (8-35)	14 (8-30)	14 (8-31)	16 (8-40)
Basal + 3 injections of fast-acting	32 (15-72)	26 (14-59)	30 (16-66)	36 (16-18)
3 injections of fast-acting, no basal	26 (12-59)	22 (12-50)	24 (12-52)	30 (15-70)

Data expressed as median and 5th -95th percentile.

The median doses of short-acting insulin increase with increasing levels of HbA1c and increasing number of daily insulin doses.

Doses of short-acting insulin per Kg of body weight (UI/Kg/day)

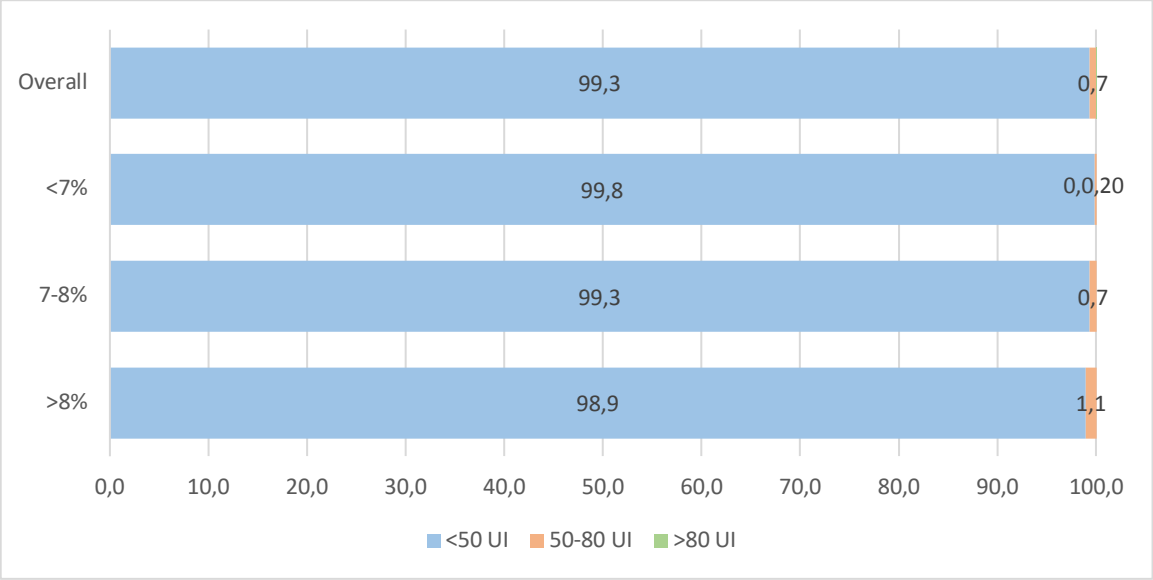
Insulin scheme	Overall	HbA1c<7%	7%<=HbA1c<=8%	HbA1c >8%
Basal only	-	-	-	-
Basal + 1 injection of fast-acting	0.1 (0.1-0.2)	0.1 (0.1-0.2)	0.1 (0.1-0.2)	0.1 (0.1-0.2)
Basal + 2 injections of fast-acting	0.2 (0.1-0.4)	0.2 (0.1-0.4)	0.2 (0.1-0.4)	0.2 (0.1-0.5)
Basal + 3 injections of fast-acting	0.4 (0.2-0.8)	0.3 (0.2-0.7)	0.4 (0.2-0.7)	0.4 (0.2-0.9)
3 injections of fast-acting, no basal	0.3 (0.2-0.7)	0.3 (0.2-0.6)	0.3 (0.2-0.7)	0.4 (0.2-0.8)

Data expressed as median and 5th -95th percentile.

The median doses of short-acting insulin per Kg of body weight increase with the number of daily insulin injections, while they do not seem to be influenced by the levels of HbA1c.

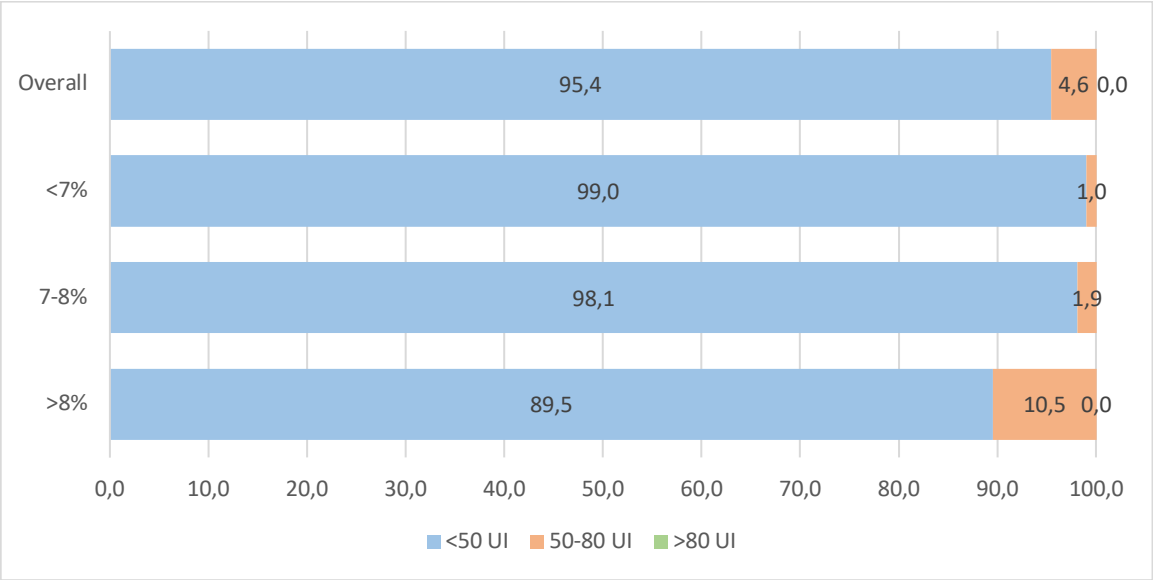
Distribution of insulin dose classes according to HbA1c classes

Patients treated with basal insulin (± glucose-lowering agents other than insulin)



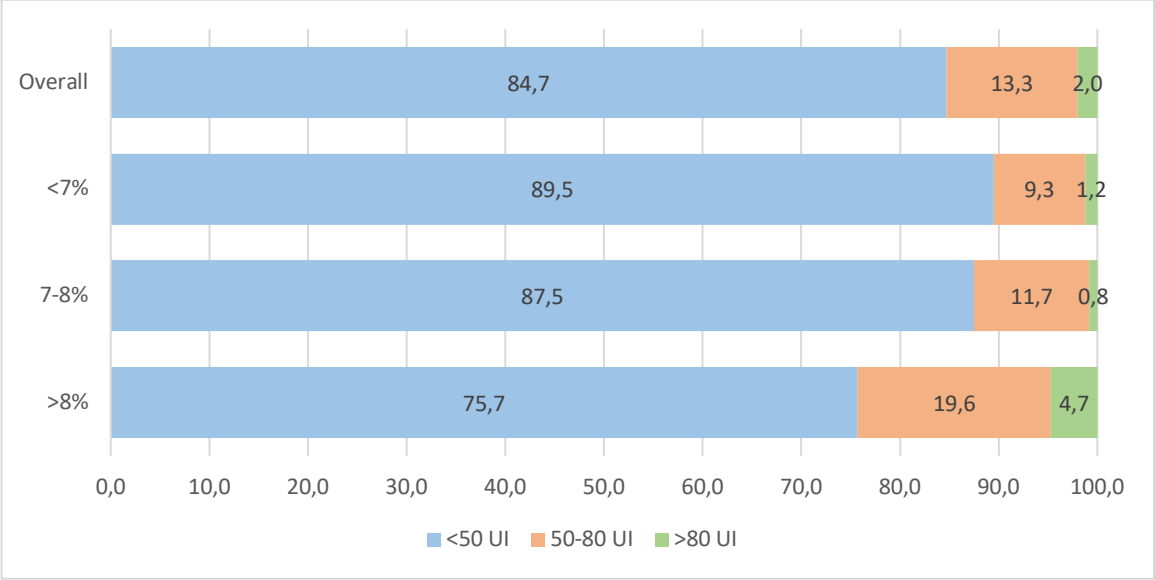
Among patients treated with basal insulin alone, the vast majority is treated with less than 50 IU, regardless of the level of HbA1c.

Patients treated with basal insulin + 1 injection of fast-acting insulin



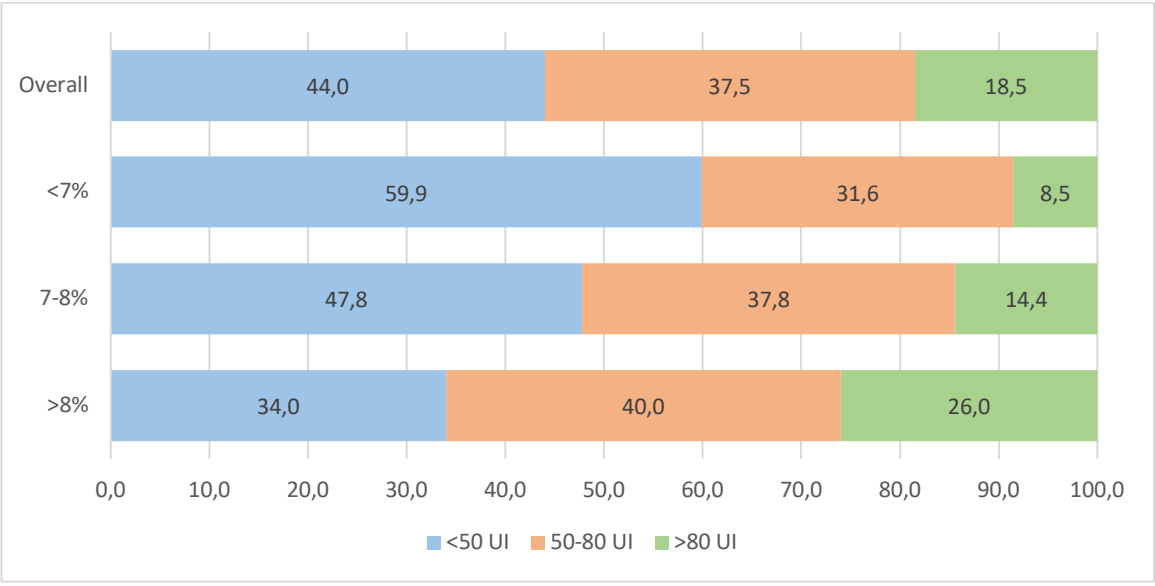
Nearly all patients on basal-plus therapy are being treated with less than 50 IU insulin. In the subgroup of patients with HbA1c > 8.0%, 10.5% of subjects receive between 50 and 80 IU, while higher dosages are not registered.

Patients treated with basal insulin + 2 injections of fast-acting insulin



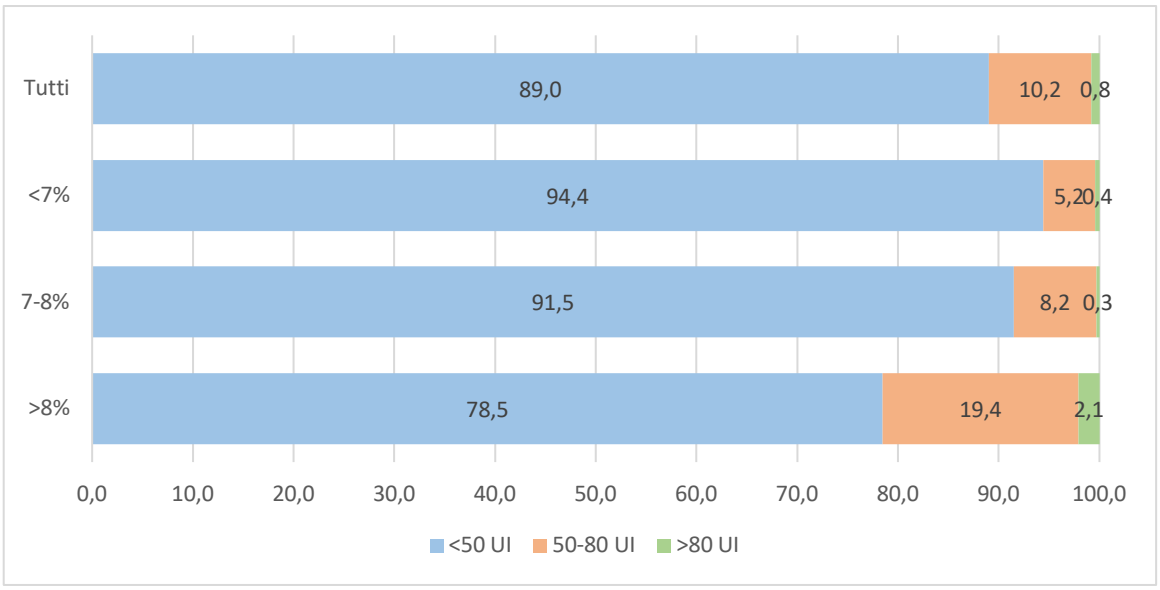
Among patients on basal insulin + 3 injections of fast-acting insulin, the majority are treated with less than 50 IU insulin. The proportion of patients treated with 50-80 IU grows from 9.3% among those who have a HbA1c level <7.0% to 19.6% among those with HbA1c> 8.0%. The percentage of subjects who receive more than 80 IU remains very low.

Patients treated with basal insulin + 3 injections of fast-acting insulin



Multiple daily injections insulin therapy is associated with the use of higher insulin doses. In particular, among subjects with HbA1c> 8.0% one third receives less than 50 IU, 40% receive 50-80 IU and a quarter is treated with over 80 IU.

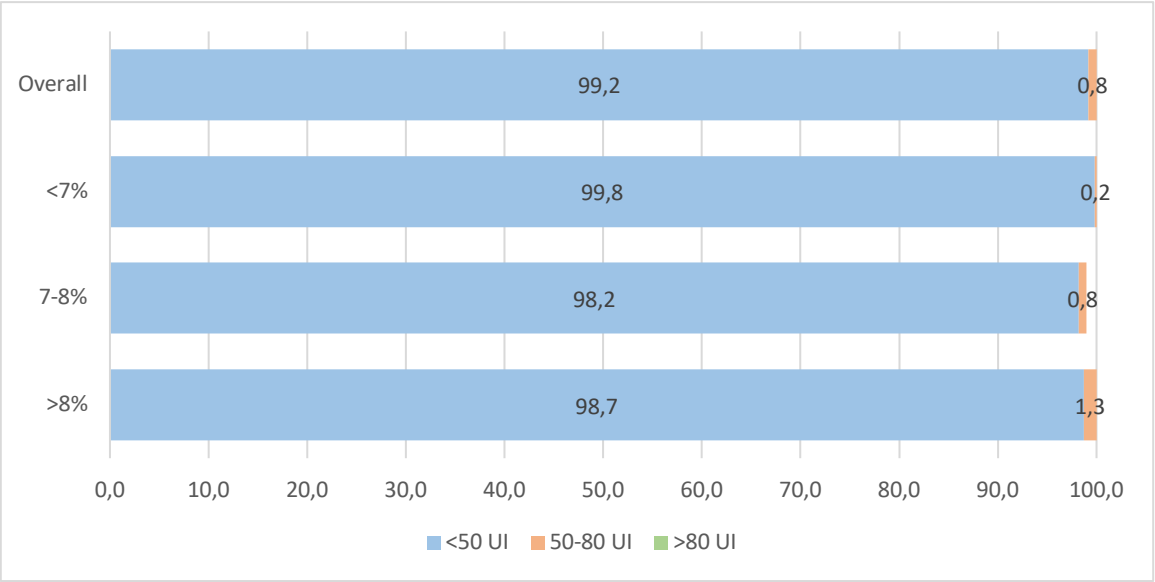
Patients treated with 3 injections of fast-acting insulin and no basal insulin



Among patients treated only with multiple injections of fast-acting insulin, the doses used are generally low. The percentage of subjects treated with 50 IU or more increases with increasing HbA1c values, while remaining modest.

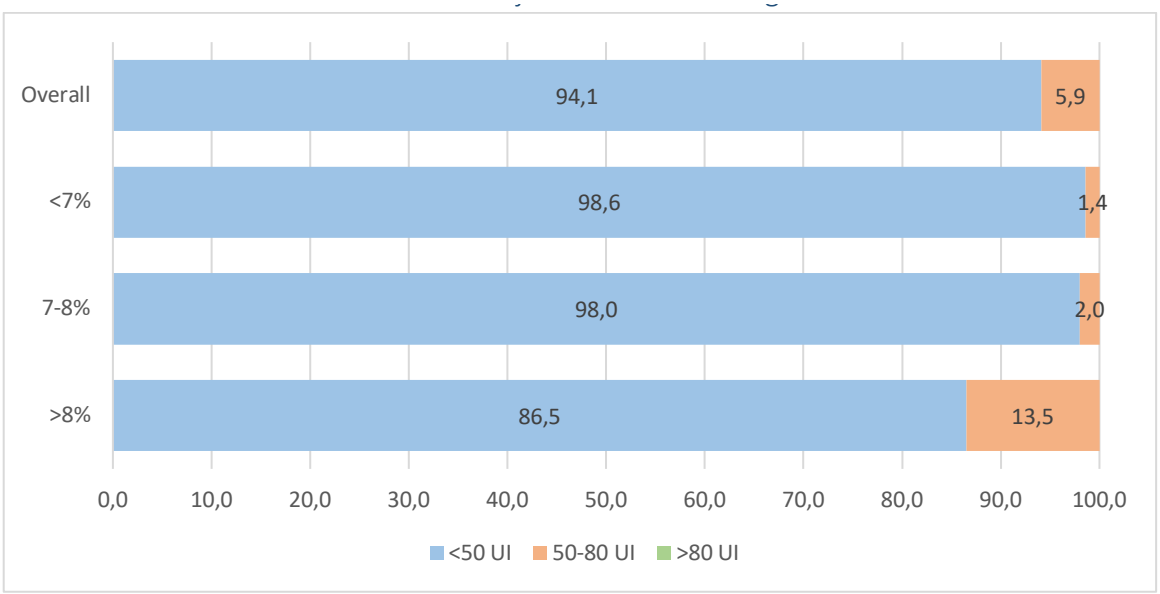
Distribution of insulin dose classes according to HbA1c classes in patients with established cardiovascular disease

Patients treated with basal insulin (± glucose-lowering agents other than insulin)



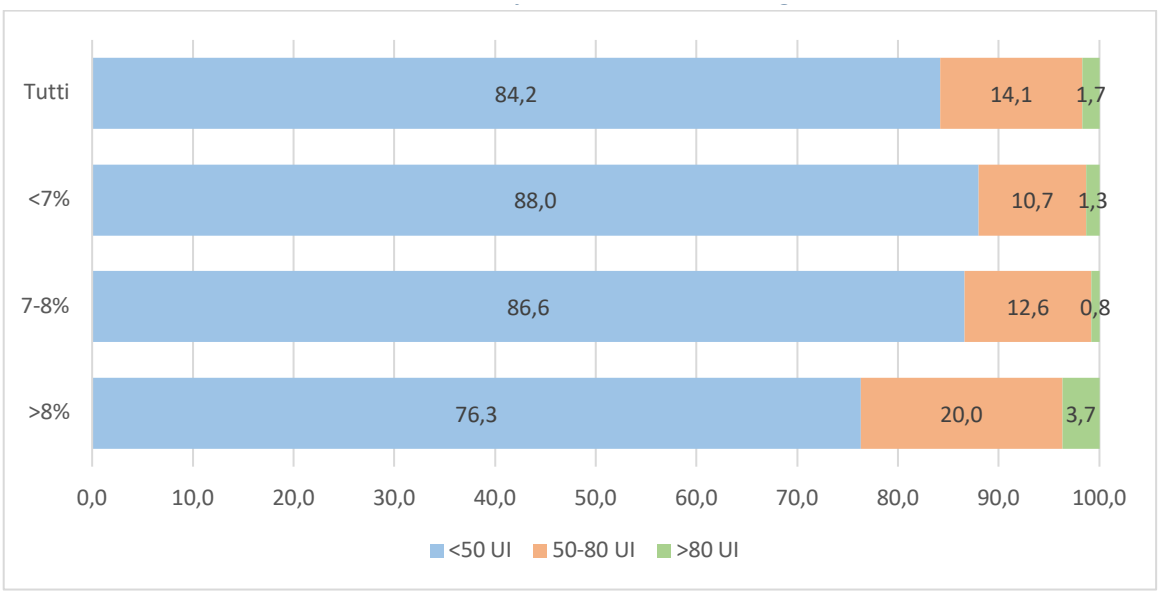
Among patients with established cardiovascular disease on therapy with basal insulin alone, almost all of them receive less than 50 IU, regardless of the level of metabolic control.

Patients treated with basal insulin + 1 injection of fast-acting insulin



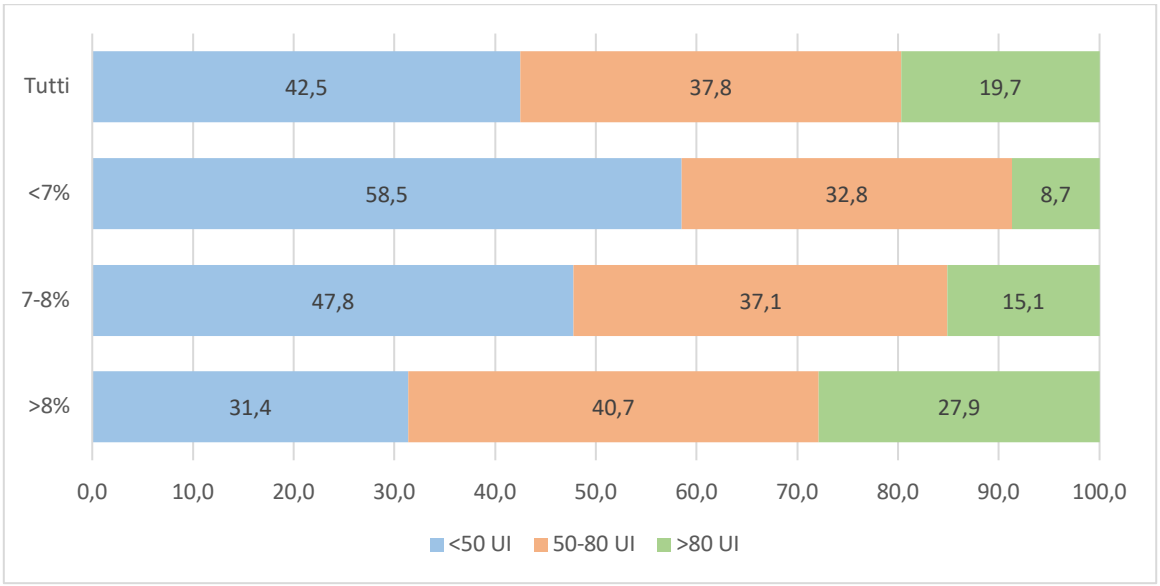
Among subjects with established cardiovascular disease treated with the basal-plus scheme, almost all of them receive less than 50 IU; among subjects with inadequate metabolic control, 13.5% receive between 50 and 80 IU of insulin.

Patients treated with basal insulin + 2 injections of fast-acting insulin



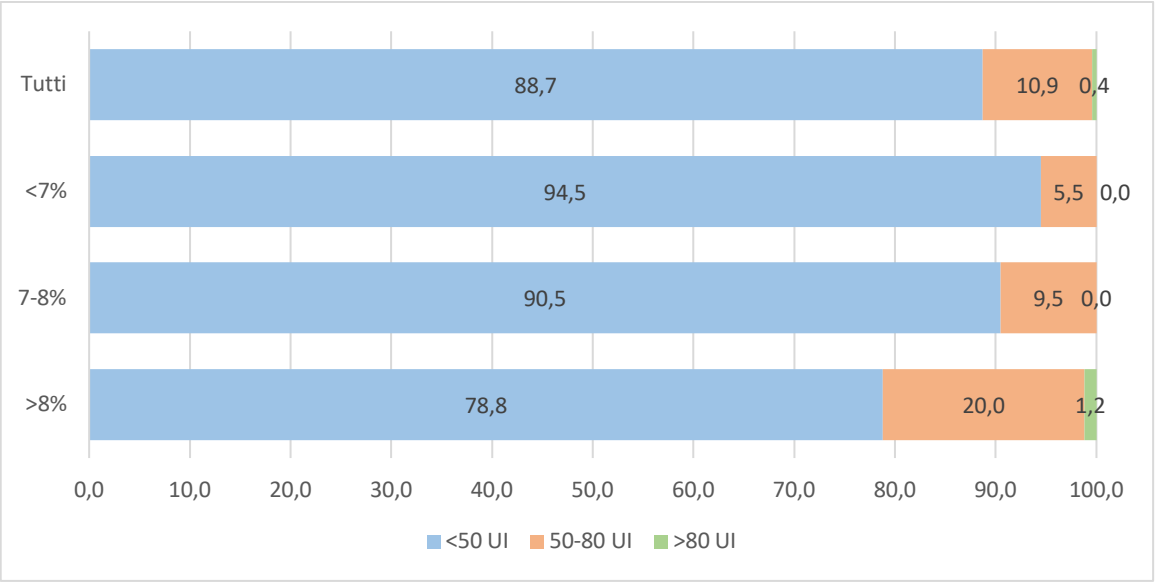
Among patients with previous major cardiovascular events in basal and two fast-acting insulin administrations, the majority receives less than 50 IU; as the levels of HbA1c increase, the proportion of subjects receiving between 50 and 80 IU of insulin increases, to reach 20% among subjects with HbA1c> 8%.

Patients treated with basal insulin + 3 injections of fast-acting insulin



Among the subjects with established cardiovascular disease treated with multiple insulin injections, the percentage of those receiving less than 50 IU is halved, passing from HbA1c values <7.0% to values> 8.0%. The proportion of subjects receiving between 50 and 80 IU or more than 80 IU of insulin increases in parallel.

Patients treated with 3 injections of fast-acting insulin and no basal insulin



In this subgroup, the vast majority of patients receives less than 50 IU; the percentage of subjects treated with 50-80 IU insulin increases with the increase in HbA1c values.

Number of visits per year according to insulin scheme and metabolic control levels

Insulin scheme	Overall	HbA1c<7%	7%<=HbA1c<=8%	HbA1c >8%
Basal only	2.9±1.8	2.9±2.1	2.8±1.6	2.9±1.7
Basal + 1 injection of fast-acting	3.1±2.1	3.0±2.3	2.9±2.0	3.3±2.2
Basal + 2 injections of fast-acting	2.8±2.0	2.5±1.6	2.8±2.0	3.2±2.2
Basal + 3 injections of fast-acting	2.7±1.7	2.5±1.7	2.6±1.5	2.9±1.7
3 injections of fast-acting, no basal	2.5±1.7	2.4±1.8	2.5±1.4	2.7±1.7

For all insulin schemes, the average number of visits in a year increases with increasing HbA1c values, with the only exception of patients on basal insulin alone. The highest frequency of visits is found in patients treated with a basal-plus scheme and poor metabolic control, while the lowest frequencies are found among subjects with HbA1c <7.0%.

Discussion

In a subgroup of patients with insulin-treated type 2 diabetes (approximately 13,500 subjects, followed in the Full Data Circle Centers) an analysis was performed on the level of metabolic control, the socio-demographic and clinical characteristics, the prevalence of macrovascular and microvascular complications and the type of insulin used and dosages, stratifying the population according to the insulin scheme adopted: only basal insulin, basal plus scheme with one or two injections of short-acting insulin, basal bolus scheme or treatment with rapid insulin alone.

Subjects on basal insulin alone represented 32.8% of the insulin-treated population. They were younger than those treated with more intensive insulin patterns and had a shorter duration of diabetes; these data are justified by the frequent prescription of basal insulin as the initial insulin treatment, as also indicated by the international guidelines and the Italian AMD-SID standards of care (1).

The most widely used insulin scheme is basal bolus, present in 46.1% of patients. Patients on basal-bolus are older than those treated with basal insulin alone (average age 70.1 vs. 68.6 years), with longer disease duration (17.6 vs. 13.9 years), higher BMI (31.4 vs 29.7 Kg/m^2) and with a higher average HbA1c value (8.2% vs. 7.7%).

The basal plus scheme (basal insulin + 1 rapid insulin administration) is used in a minority of patients (3.1%), while in 10.6% of the subjects rapid insulin is administered twice a day, in addition to basal insulin. These two schemes are used in subjects older than those in basal bolus (71.3 and 71.1 vs. 70.1 years) and with a lower BMI, probably reflecting the will of the diabetologist to be less aggressive, with the use of a lower number of rapid insulin administrations, in older subjects. The use of two injections of fast-acting insulin combined with basal insulin in a fairly high percentage of subjects, significantly higher than the basal- plus scheme, reflects both the need to intensify therapy compared to the single administration of rapid insulin, and the presence of particular eating habits such as skipping the breakfast or having a very light dinner that is low in carbohydrates, making a complete basal bolus scheme not necessary.

Administration of rapid insulin alone (three injections), without basal insulin, is used in 7.4% of patients with a more advanced average age than the other groups (72.4 years) and a better level of metabolic control.

Despite the start of insulin therapy, the achievement of glycemic goals continues to be extremely difficult, even with the adoption of more complex insulin schemes. Among patients on basal insulin therapy alone, less than 30% are on target with a HbA1c <7%, while 33.7% of the patients have poor metabolic control (HbA1c >8%), with an average HbA1c of 9.2%. The situation is even worse in subjects treated with more complex insulin schemes. In the basal bolus group, just under 20% of the patients have an HbA1c <7% and as many as 46% of subjects have a HbA1c over 8%, with an average value of 9.4%. These findings reflect the use of the basal bolus scheme in more difficult and complex patients (as also indicated by the higher prevalence of micro and macrovascular complications in these subjects). On the other hand, poor metabolic control in patients on basal bolus scheme can be also due to a reduced adherence to insulin therapy, because the complexity of performing four daily injections (with their negative impact on daily life habits) can lead to an incorrect execution of the injections or to an inappropriate self-reduction of the total daily injections. At the same time, in type 2 diabetes therapeutic intensification based on the adoption of the basal bolus scheme should be accompanied by structured therapeutic educational sessions for patient and his

relatives (and/or caregivers) to identify in advance special needs and easily respond to emergency situations that may arise. In future analyses, it will be interesting to evaluate other therapeutic intensification strategies, such as the association of a GLP-1 receptor agonist or an SGLT-2 inhibitor with basal insulin.

Within each insulin scheme subgroup, a stratification of patients was performed according to their HbA1c value: <7%, between 7 and 8% and >8%. Subjects with poor metabolic control (HbA1c> 8%) were younger, with higher BMI, a less favorable lipid and pressure profile, a greater prevalence of smokers and women as compared to the population with HbA1c at target.

The poor metabolic control is therefore associated with a greater difficulty in achieving the other goals of care: body weight, lipids, blood pressure and smoking. In this subgroup of patients at high cardiovascular risk, it would be useful to start other therapeutic strategies with drugs able to exert cardioprotective effects. The figure relative to the female gender, more represented in the subgroup of patients with worse metabolic control, is in line with the greater difficulty in achieving the goals of treatment and the worst cardio-vascular risk profile that emerges in women, as also shown in the AMD Annals Monograph 2011 (2) as well as in the study published in Diabetes Care in 2013.

The prevalence of macrovascular and microvascular complications was very high in the population treated with insulin, as compared to the general population with diabetes, and increased with the complexity of the insulin scheme used. In particular, the prevalence of myocardial infarction was 9.8% in subjects with basal insulin alone, 11.5% in those on basal plus, and 16.2% in those on basal bolus compared to 4% in the general diabetes population as it emerges from the 2018 Annals (3). An increasing trend is also present for the prevalence of stroke (from 4.9 to 7.6%), heart failure (from 3.3 to 7.3%) and to a lesser extent for angina (from 2.8 to 4.1%). A similar trend was also documented for microvascular complications: the prevalence of retinopathy was 35.5% in the population treated with basal insulin, 47.3% in patients on basal plus and 56.6% in the subjects on basal bolus, as compared to 22.8% in the general diabetes population. The prevalence of nephropathy also markedly increases with the complexity of insulin treatment from 57.2% to 71.1% while chronic renal failure raises from 13.8% to 21.9%. This reflects the greater use of insulin therapy, especially with intensive schemes, in complicated subjects, both at the microvascular and macrovascular level. Chronic renal failure is more frequent in the subgroup treated with rapid insulin alone (26.2%), probably due to a greater need to correct postprandial peaks in these patients who are also older.

The presence of complications was evaluated in the different insulin schemes subgroups also as a function of the HbA1c value. The prevalence of macrovascular complications was lower in patients with poor metabolic control, suggesting a greater attention in patients with previous cardio-cerebrovascular events or with heart failure. With regard to microvascular complications, retinopathy was more frequent in subjects with HbA1c> 8%, while for nephropathy this trend was less evident. As for patients with chronic renal failure, an opposite trend was documented: the prevalence was in fact lower in subjects with poor metabolic control, suggesting even in this case a greater attention of the diabetologists to reach the therapeutic targets in patients with chronic kidney disease and with reduction of the glomerular filtration rate.

Data show that glargine is the most commonly basal insulin used in all HbA1c subgroups and for all the therapeutic schemes (basal, basal plus and basal bolus). The use of degludec grows with increasing HbA1c values in the scheme with basal insulin alone. In the basal plus scheme, the rates of use of detemir and degludec are similar and do not appear to be influenced by HbA1c levels.

Finally, in patients treated with the basal bolus scheme the frequency of use of degludec is greater among subjects with HbA1c> 8.0%, while for detemir there is an opposite trend. As for fast-acting insulin analogues, the use of different types of prandial insulin analogues is similar both in patients treated with a basal-plus regimen and in patients treated with the basal bolus regimen, lispro being always the most frequently used. Among the subjects with HbA1c> 8.0% treated with the basal plus regimen, the use of glulisine is more frequent than in the other therapeutic schemes.

With regard to basal insulins, it should be remembered that due to the time horizon of the present monograph, the insulin glargine considered is exclusively insulin glargine U100. The choice of basal insulin was certainly influenced by pharmacoeconomic considerations and regulatory constraints (presence of the therapeutic plan for insulin degludec). Moreover, some clinical considerations can also be made. First, the nightly increase in blood glucose attributable to a transient increase in hepatic glucose production in the absence of compensatory insulin secretion is a frequent occurrence in patients with type 2 diabetes and is responsible for hyperglycemia upon awakening. Fasting hyperglycemia is therefore an early disease target, and oral glucose-lowering agents are not always able to correct this metabolic abnormality, with consequent indication for early use of the evening basal insulin to limit this phenomenon (4-6). The duration of action of insulin glargine U100 is adequate to counteract the dawn phenomenon without the need to use a longer-acting insulin such as insulin degludec. Second, the glycemic variability, highlighted as a phenomenon characterizing type 2 diabetes in Monnier's studies, could be more adequately controlled with insulin degludec (7). It can be hypothesized that at the time of data collection the use of technologies to reveal this phenomenon (such as flash or continuous monitoring of blood glucose levels) was low in type 2 diabetes. On the other hand, some of the new oral drugs for the treatment of diabetes have been shown to be able to favorably influence this parameter, probably reducing the need for insulin degludec (8,9). However, the low use of insulin degludec remains difficult to explain in consideration of the reduction in the risk of hypoglycemia as compared to glargine U100 (10,11). It can be hypothesized that the advantage in terms of reduction in the risk of hypoglycemia in the transition from NPH to glargine U 100 was considered sufficient, and that among patients treated with degludec are those with the greatest risk of hypoglycemia. Data from the literature indicate a greater efficacy of degludec in optimizing HbA1c levels as compared to detemir and NPH, while the data with respect to glargine U 100 are less homogeneous (12,13). In this regard, however, it should be noted that the data analyzed refer to 2016 and that insulin degludec has become available in Italy since 2015, so the differences could be, at least in part, linked to this aspect. The more frequent use of degludec in patients with poor metabolic control in the basal bolus alone or basal bolus schemes is accompanied by a downward trend in the use of detemir, thus suggesting a prevalent shift from this insulin. This phenomenon is not present for the basal plus scheme; this could be attributable to the fact that this type of therapeutic scheme is used in the presence of controlled fasting blood glucose and therefore a variation in the basal insulin is not necessary.

With regards to the fast-acting analogs, the technical note published by AMD, SID and SIEDP in 2017 stated that "there is no scientific evidence showing significant differences in terms of the mechanism of action, efficacy, tolerability and safety between insulins glulisine, lispro and aspart, although individual drugs may diversify for additional therapeutic indications. Instead, there are differences between the insulins mentioned in terms of administration modalities and therapeutic indications in subgroups of patients or specific pathological conditions". The slight difference in the prescription of lispro and aspart could be related to the mode of administration. The unavai-

lability of insulin aspart in vial for injection with a syringe could guide the choice towards insulin lispro for a range of elderly patients or those with cognitive problems in which the change of the device could be problematic. Glulisine could simply be penalized by being the most recently introduced insulin analogue on the market. Increased use of the latter insulin in poorly controlled patients on basal plus therapy may be associated with the slight difference in pharmacokinetics. In the aforementioned document it is emphasized that "from the point of view of pharmacokinetics and pharmacodynamics there is some evidence according to which insulin glulisine is characterized, with respect to lispro and aspart, by a slightly more rapid onset, with a reduction of the post-prandial glycemic peak, hyperglycaemic peak time, and overall blood glucose range in the first 30-60 minutes after administration (14). This effect seems more evident among obese subjects (BMI 30-40 Kg/m^2) but has not been proven, through studies designed ad hoc, if it translates into a demonstrable clinical benefit. The basal plus scheme prescription is generally motivated by the need to correct the postprandial peak in the main meal, and may favor the choice of an insulin with potentially faster action. It should be noted, however, that the size of this subgroup is rather low and therefore the percentage differences observed could be related to the play of chance, rather than to a specific therapeutic choice.

In conclusion, although it cannot be excluded that organizational / administrative problems and even therapeutic inertia may affect the choice and maintenance of the type of insulin, the data reported may be supported by specific clinical explanations.

Data show that the median insulin doses are quite low, both for patients on basal therapy alone, and in those on multiple-injection therapy, especially considering the average BMI which is high in all subgroups. This observation also applies if we consider the median pro-kg doses of insulin that are between 0.1 and 0.4 IU/kg/day in all groups, with the exception of the basal-bolus group that uses the highest insulin doses (0.5-0.7 IU/kg/day). As expected, for all insulin therapy schemes, the median doses increase with the worsening of glycemic control and with the increase in the number of daily insulin injections, up to 60 IU/day among subjects treated with a basal-bolus scheme that have HbA1c values> 8%. The average insulin doses are in line with those shown in the AMD Annals monograph 2017 (15) and significantly lower than those reported in the literature (16).

For all the insulin therapy schemes, the majority of patients is treated with less than 50 IU of insulin (percentage ranging between 84.7% and 99.3% of subjects). The only exception is represented by the group on basal-bolus in which the percentage of patients in therapy with 50-80 IU considerably increases to 37.5% and that in therapy with more than 80 IU raises to 18.5%. In general, in all groups the percentage of subjects treated with more than 50 IU increases with increasing HbA1c values, although remaining modest.

The distribution by dose of insulin in subjects with previous cardiovascular events shows a similar trend, with most patients being treated with less than 50 IU of insulin (percentage ranging between 84.2% and 99.2% of subjects). Among patients with previous major cardiovascular events treated with multiple daily injections of insulin, the share of those receiving between 50 and 80 IU (37.8%) or more than 80 IU insulin (19.7%) is increasing. The percentage of subjects treated with more than 50 IU increases with increasing HbA1c values and this is particularly evident in the basal-bolus treatment group in which those who receive less than 50 IU halve passing by HbA1c values <7.0% at values> 8.0%. No significant difference in insulin doses was found when comparing the total population with patients with previous cardiovascular event.

Finally, the analysis of the number of visits per year according to the insulin scheme and the level of metabolic control shows, as expected, that the average number of visits in a year increases with

the increase in HbA1c values, with the only exception of patients on basal therapy alone where the average number of visits remains stable and around 2.8-2.9 visits/year. Unexpectedly, the highest frequency of visits is not found in patients with a more complex insulin scheme but in those treated with a basal-plus scheme and with poor metabolic control (3.3 visits/year). This could be linked to the need, in this group, to intensify insulin treatment moving from a basal-only scheme to one with the addition of one injection of a rapid analogue, and therefore to the need for these subjects to be viewed more frequently. On average, the entire population considered is seen in a diabetes center every 3.8-4.8 months. In general, the number of visits in a year is in line with the indications of the Italian Standards for the Treatment of Diabetes Mellitus (1), which recommend that the evaluation of HbA1c should be carried out no less than 2 times per year in every patient with diabetes and 4 times a year in patients with poor or unstable metabolic control or in those who have had their therapy changed. These data are similar to those shown in the AMD Annals 2017 monograph, based on the Full Data Circle (15), in which the average number of visits per year in subjects on insulin treatment was 2.6-2.8, and those documented in the AMD Annals 2018 monograph, which showed an average of 2.5 visits / year in subjects treated with insulin (3).

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Conclusions

From the data relative to the 2018 AMD Annals edition, it emerges that 34.9% of people with DM2 are on insulin treatment with different patterns, from basal insulin alone, to basal plus, to basal bolus. This population is older and with a longer disease duration compared with DM2 patients not treated with insulin, with a higher prevalence of both micro- and macrovascular complications, which increases as the level of metabolic control worsens.

Among patients on insulin treatment, those in poorest metabolic control (HbA1c >8.0%) are also younger, with a higher BMI, a less favorable lipid profile and blood pressure, a higher prevalence of smokers and a higher percentage of women as compared to the population at target. This clinical profile identifies a subpopulation of patients who have a higher cardiovascular risk, due to a greater difficulty in reaching the targets of all cardiovascular risk factors (body weight, HbA1c, blood pressure, lipids and smoking).

It is possible that this subpopulation shows greater difficulty in, or resistance to adopting appropriate lifestyles and in which an intensification of the pharmacological treatment is therefore necessary. The higher prevalence of women in this subpopulation is consistent with the worst cardiovascular risk profile described in the monograph on gender differences in DM2 in the 2012 AMD Annals edition, also confirmed in the 2018 AMD Annals edition.

The analysis of insulin patterns and doses, derived from the data collection of the 2017 Full Data Circle, confirms that the population treated with more complex patterns (basal bolus) and higher insulin doses (> 50 UI/day) includes above all the patients with worse metabolic control (HbA1c> 8%), who are younger, with higher BMI, worse lipid profile, higher blood pressure and with a higher prevalence of women.

Despite insulin treatment, a high percentage of this population is still unable to reach the desired HbA1c targets, therefore the therapy proves in fact ineffective.

It is to be hoped that the new AMD Annals data collection in 2019 will testimony a decrease in the use of insulin in patients with DM2 and a significant increase in the use of new classes of glucose-lowering drugs, such as GLP1-RA and SLT2i, which are able to reduce body weight, optimize metabolic control and significantly improve cardiovascular risk factors, reducing cardiovascular events and mortality.

Valeria Manicardi

Appendix

Distribution of patients by HbA1c classes and region

Patients treated with insulin

	N	<7.0%	7.0-8.0%	>8.0%
Abruzzo	6171	22.2	39.0	38.8
Calabria	2892	28.8	36.4	34.8
Campania	3634	33.4	30.9	35.6
Emilia Romagna	18604	22.3	35.6	42.0
Friuli Venezia Giulia	3319	21.9	42.3	35.8
Lazio	13366	27.6	37.0	35.5
Liguria	2690	29.7	34.0	36.3
Lombardia	15026	23.6	36.8	39.6
Marche	8899	21.3	38.3	40.4
Molise	1328	26.5	39.2	34.3
Piemonte	22405	25.7	36.9	37.3
Puglia	185	17.0	34.1	48.9
Sardegna	6269	33.6	34.8	31.6
Sicilia	1738	23.3	34.3	42.4
Toscana	6302	23.2	37.4	39.4
Trentino Alto Adige	4178	21.2	35.9	42.8
Umbria	5026	26.4	39.1	34.5
Veneto	18684	21.2	37.2	41.6

Patients treated with glucose-lowering drugs other than insulin

	N	<7.0%	7.0-8.0%	>8.0%
Abruzzo	12516	51.1	38.1	10.8
Calabria	6242	60.3	29.0	10.7
Campania	9593	63.1	24.7	12.2
Emilia Romagna	24094	50.7	34.9	14.4
Friuli Venezia Giulia	5663	57.9	34.8	7.3
Lazio	34535	63.3	28.1	8.6
Liguria	5951	57.0	29.6	13.4
Lombardia	29539	53.1	35.5	11.4
Marche	17859	49.8	36.7	13.5
Molise	1973	68.6	27.5	4.0
Piemonte	37697	53.7	34.8	11.6
Puglia	265	50.0	34.6	15.4
Sardegna	12269	64.6	27.7	7.7
Sicilia	2967	55.9	31.7	12.3
Toscana	12213	55.6	33.6	10.8
Trentino Alto Adige	8118	58.1	31.0	10.9
Umbria	6995	48.3	39.7	12.0
Veneto	33495	50.8	36.3	12.8