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ORIGINAL RESEARCH ARTICLE

Impact of AIFA Note 100 on innovative antidiabetic prescribing eligibility in two Italian local health authorities: drug utilization and patient characteristics

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ABSTRACT

Introduction: Type 2 diabetes mellitus (T2DM) is a common chronic disease with management, associated with cardiovascular and renal comorbidities. In January 2022, AIFA Note 100 extended prescribing authority for innovative antidiabetic drugs (SGLT-2 inhibitors, GLP-1 receptor agonists, and DPP-4 inhibitors) to General Practitioners, influencing treatment patterns and management of high-risk patients.

Methods: A retrospective observational analysis used administrative data from two Local Health Authorities in Italy, comparing three cohorts: Pre-COVID (2018), COVID (2020-2021), and Post-Note 100 (February 1, 2022 to January 31, 2023). Adults (≥18 years) with at least one prescription of non-insulin glucose-lowering drugs (ATC A10B) were included. Profiles were described, focusing on acarbose, DPP-4 inhibitors, metformin, pioglitazone, SGLT-2 inhibitors, GLP-1 receptor agonists, and sulfonylureas. Clinical characteristics included comorbidities, heart failure, hypertension, and chronic kidney disease. Healthcare costs (pharmaceuticals, outpatient specialist care, and hospitalizations) were analyzed.

Results: Over 140,000 subjects were included. In the Post–Note 100 phase, GLP-1 receptor agonists and SGLT-2 inhibitors increased among new users (GLP-1 receptor agonists: 1.2% to 9.3%; SGLT-2 inhibitors: 2.6% to 14.1%) and among prevalent users, with a reduction in sulfonylureas and a decline in metformin monotherapy. Among patients with ≥2 comorbidities, SGLT-2 inhibitors became the most prescribed class. Use rose in heart failure, while both GLP-1 receptor agonists and SGLT-2 inhibitors increased in chronic kidney disease.

Conclusions: Expansion of prescribing eligibility introduced by AIFA Note 100 led to a shift toward innovative therapies, aligning prescribing with guidelines, particularly in comorbid patients. Real-world data highlight the impact and support the evaluation of long-term outcomes.

Keywords: Diabetes mellitus, type 2, Drug prescription, Glucagon-like peptide-1 receptor agonists, Health policy, Sodium-glucose transporter 2 inhibitors

Introduction

Type 2 diabetes mellitus (T2DM) represents one of the major public health challenges globally and in Italy. In Italy, according to the most recent national data, diabetes affects approximately 6.2% of the population, corresponding to nearly 4 million individuals, with type 2 diabetes accounting for about 90% of cases. (1). T2DM is associated with a high risk of cardiovascular, renal, and cerebrovascular complications, leading to significant morbidity, mortality, and healthcare costs for the Italian National Health Service (NHS). (1).

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In recent years, the therapeutic landscape of T2DM has expanded with the introduction of new drug classes: sodium–glucose cotransporter 2 inhibitors (SGLT-2 inhibitors) and glucagon-like peptide-1 receptor agonists (GLP-1 RAs). Beyond their glucose-lowering efficacy, these agents have demonstrated clinically meaningful extra glycemic benefits, such as reductions in major cardiovascular events, renal protection, decreased all-cause mortality, and, in some cases, a favorable impact on body weight (2-4). The consolidation of this evidence has led major international (ADA/EASD) and national (SID–AMD) guidelines to recommend their early and preferential use in patients at high cardiovascular risk or with established chronic kidney disease (5-7).

Among these regulatory tools, AIFA Note 100 represents a particularly relevant case. Unlike many other AIFA Notes, which primarily define reimbursement criteria, AIFA Note 100 introduced a structural change in prescribing pathways by extending prescribing authority for selected antidiabetic

drugs from specialists to General Practitioners (GPs). This change has implications not only for access to treatment but also for prescribing behavior, appropriateness, and healthcare system organization. In addition, the drug classes involved—SGLT-2 inhibitors, GLP-1 receptor agonists, and DPP-4 inhibitors—are associated with higher acquisition costs compared with traditional therapies, raising important challenges for the sustainability of the NHS.

Until 2022, the prescription of SGLT-2 inhibitors, GLP-1 receptor agonists, and DPP-4 inhibitors was restricted to diabetes and endocrinology specialists. While ensuring appropriate use, this limitation may have reduced timely initiation in primary care and contributed to variability in access across healthcare settings.

The publication of AIFA Note 100 in the Italian Official Gazette No. 19 of January 25, 2022 (8), represented a major turning point, extending prescribing authority for SGLT-2 inhibitors, GLP-1 receptor agonists, and DPP-4 inhibitors to General Practitioners (GPs). The aim of this measure was to promote more timely, homogeneous, and widespread access to innovative therapies, in line with scientific recommendations and with the equity principles of the NHS.

Early monitoring analyses conducted by AIFA showed an immediate and substantial increase in the use of innovative antidiabetic drugs. In the first nine months following the introduction of AIFA Note 100, consumption of innovative antidiabetic therapies increased by 35%, with a 30% rise in expenditure and a particularly marked growth in SGLT-2 inhibitors (+56%) (9). The report updated 18 months confirmed this trend, showing an overall 54% increase in consumption and a more than 150% rise in SGLT-2 inhibitors prescribed as monotherapy (10). These findings suggest a rapid uptake of the revised prescribing criteria introduced by AIFA Note 100 in primary care and an ongoing transformation of prescribing patterns.

The broader access to innovative therapies resulting from the revision of prescribing eligibility criteria introduced by AIFA Note 100 raises new questions about real-world drug use, therapeutic appropriateness, management of complex patients, and healthcare costs. In this context, analyses based on local administrative healthcare data can help describe changes in prescribing patterns and their clinical and organizational implications. In this context, the present study analyzes the real-world data from two Italian Local Health Authorities to describe changes in T2DM drug utilization, treatment patterns in relation to comorbidities, and the impact of AIFA Note 100 on the consumption and costs of antidiabetic therapies.

Methods

This is a retrospective observational study using real-world data, with the aim of describing the evolution of treatment patterns in T2DM following the introduction of the revised prescribing criteria defined by AIFA Note 100. This regulatory measure, issued in 2022, extended prescribing authority for SGLT-2 inhibitors, GLP-1 receptor agonists, and DPP-4 inhibitors to GPs, through a revision of prescribing eligibility criteria, with potential implications for prescribing practices in primary care.

The analysis used linked administrative healthcare databases from two Italian Local Health Authorities, including population registry, exemptions, hospital discharge records, outpatient drug dispensing, and specialist services, with anonymized identifiers to ensure data protection compliance. The analysis was conducted using data from two Italian Local Health Authorities: ATS Bergamo (Lombardy Region), serving approximately 1.1 million inhabitants, and Azienda Sanitaria Universitaria Giuliano Isontina (ASUGI), serving approximately 370,000 inhabitants. These settings represent large and medium-sized healthcare organizations within the Italian National Health Service, allowing for the evaluation of prescribing patterns across different population contexts. Although both LHAs are located in Northern Italy, the findings may not be fully representative of the entire NHS, given the known regional variability in healthcare organization and prescribing practices. The study was submitted for approval to the competent Territorial Ethics Committee of the Local Health Authority acting as study coordinator, in accordance with current regulatory requirements, and was registered in the AIFA Observational Studies Register.

Study cohorts and selection criteria

The study population was divided into three cohorts, defined to represent different regulatory and epidemiological contexts:

- Pre-COVID cohort: January 1 – December 31, 2018
- COVID cohort: March 1, 2020 – February 28, 2021
- Post–Note 100 cohort: February 1, 2022 – January 31, 2023

The selection of the three time periods was driven by both regulatory and epidemiological considerations. The Post–Note 100 cohort was defined to capture the first 12 months following the revision of prescribing criteria introduced by AIFA Note 100 (January 25, 2022), based on data availability.

The pre–Note 100 period was further divided into two distinct cohorts (Pre-COVID and COVID) to account for the potential impact of the COVID-19 pandemic, which significantly affected healthcare access and delivery starting from February 2020. This approach allows a more appropriate comparison between the Pre-COVID cohort—less influenced by healthcare disruptions—and the Post–Note 100 cohort, in order to better interpret changes associated with the regulatory modification.

The use of three separate cohorts, therefore, enables the distinction between secular trends, pandemic-related effects, and changes potentially associated with the revision of prescribing criteria.

Individuals aged ≥18 years who, during the reference period of each cohort, had received at least one prescription for “other blood glucose–lowering drugs, excluding insulins” (ATC A10B) were included. Patients who were removed from the population registry for reasons other than death during the observation period were excluded. For each patient, the index date was defined as the date of the first prescription of a glucose-lowering drug within the inclusion period.

The study design is graphically summarized in Figure 1.

Description of the therapeutic profile

At index date, ongoing treatment was characterized by classifying therapies as monotherapy or combinations of multiple pharmacological classes, also accounting for the possible concomitant use of insulin. The therapeutic classes analyzed included metformin (ATC: A10BA02), sulfonylureas (ATC: A10BB), pioglitazone (ATC: A10BG03), acarbose (ATC: A10BF01), DPP-4 inhibitors (ATC: A10BH), GLP-1 receptor agonists (ATC: A10BJ), SGLT-2 inhibitors (ATC: A10BK), and insulin (ATC: A10A). In addition, for each patient, the following were distinguished:

- initiation of a new therapy, defined as the absence of prescriptions for glucose-lowering drugs (ATC A10) in the 12 months prior;
- continuation of an ongoing treatment.

This distinction allowed for a specific assessment of the impact of AIFA Note 100 on new treatment initiations.

Identification of comorbidities

Clinical characteristics were described by analyzing a 365-day characterization period prior to the index date. Three comorbidities relevant to the management of T2DM were considered based on their established clinical relevance in the management of T2DM and its cardio-renal complications: (5,11)

- heart failure,
- arterial hypertension,
- chronic kidney disease.

Comorbidities were identified using hospital diagnoses (ICD-9-CM codes), exemption codes, outpatient specialist services, and, where appropriate, recurrent use of cardiovascular or antihypertensive medications. This approach allowed the study population to be stratified according to the presence and number of comorbidities (0,1,2, or 3). Detailed algorithms for the identification of comorbidities (including ICD-9-CM codes, exemption codes, and procedure codes) are reported in the Supplementary Material.

Data analysis

The analysis was performed using a descriptive approach, with variables reported as absolute frequencies and percentages. Results were stratified by temporal cohort, therapeutic profile, type of treatment (newly treated vs. previously treated patients), and presence, number, and type of comorbidities. In addition, trends in the use of different therapeutic classes were analyzed in newly treated patients compared with those already on treatment, with particular focus on changes observed following the introduction of the revised prescribing criteria defined by AIFA Note 100. No direct clinical outcomes, hospitalizations, or cardiovascular events were evaluated. Data processing was performed on a PostgreSQL database (version 17.4) using SQL queries; additional analyses for the development of summary tables and figures were conducted using Microsoft® Excel® for Microsoft 365 MSO (Version 2510, Build 16.0.19328.20244), 64-bit. Healthcare costs were calculated from the perspective of the Italian National Health Service and estimated over a 12-month period following the index date for each patient. Costs included pharmaceutical expenditures (antidiabetic and other drugs), outpatient specialist services, and hospitalizations, based on reimbursement tariffs available in administrative databases. Costs were calculated at the individual patient level and aggregated according to the treatment profile at index date, without attribution to individual drug

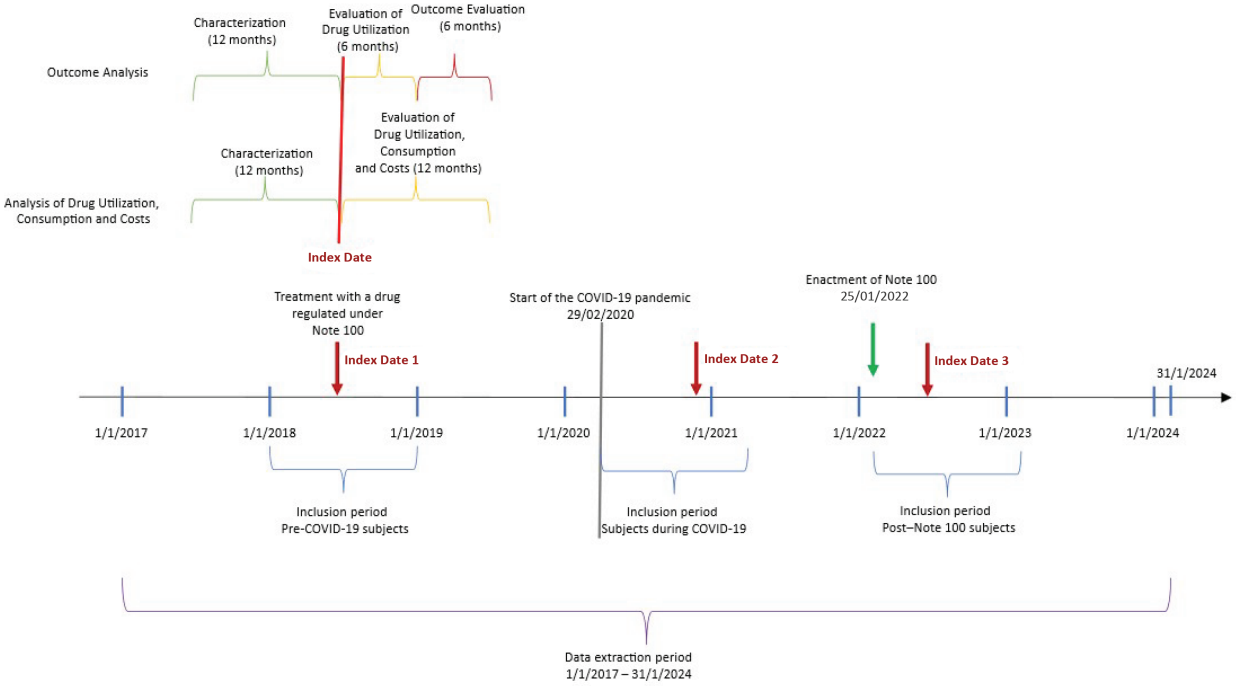

FIGURE 1 - Study design.

classes. Treatment exposure was not updated over time; therefore, costs were attributed based on the therapeutic regimen at the index date. Consequently, cost estimates reflect the overall healthcare resource utilization associated with each treatment group rather than the isolated cost of specific therapies.

Results

The analysis included three temporal cohorts—Pre-COVID (2018), COVID (2020-2021), and Post–Note 100 (2022-2023)—comprising 60,559, 61,472, and 66,788 individuals, respectively. The cohorts were not mutually exclusive, as the same individual could be included in more than one cohort. Demographic characteristics were comparable across periods, with a consistently higher prevalence of males (ranging from 56.8% to 57.2%) and a mean age between 68 and 72 years. The distribution of comorbidities highlights the clinical complexity of the study population: the absence of comorbidities was observed in approximately one quarter of patients (from 27.1% to 25.3%), while hypertension was the most prevalent condition (from 73.8% to 75.2%), consistent with the advanced mean age of the included patients Heart failure was the second most common comorbidity, increasing from 1.4% in the Pre-COVID cohort to 1.9% in the Post–Note 100 cohort, while chronic kidney disease prevalence remained stable at 0.7% across all cohorts (Table 1).

The distribution of patients according to multimorbidity status is reported in Supplementary Table S1. Across cohorts, most patients had one comorbidity, while the proportion of patients with two or three comorbidities remained limited but slightly increased in the Post–Note 100 cohort.

Across the three cohorts, treatment patterns at the index date show a consistent predominance of metformin monotherapy, which remains stable at approximately 64% from the Pre-COVID through the Post–Note 100 period. In contrast, reliance on sulfonylurea-based regimens declines over time. Sulfonylurea monotherapy decreases from 15.2% in the Pre-COVID cohort to 9.2% in the Post–Note 100 cohort, and the combination of metformin with a sulfonylurea shows a parallel reduction, falling from 7.3% to 4.7%. These shifts are accompanied by gradual or more pronounced uptake of newer glucose-lowering agents. It should be noted that the interpretation of temporal changes in prescribing patterns should also consider differences in the availability and market penetration of glucose-lowering drug classes across the study periods, particularly for SGLT-2 inhibitors and GLP-1 receptor agonists, which became more widely used in clinical practice over time. DPP-4 inhibitor monotherapy increases modestly, from 2.9% in the first cohort to 3.5% in the last, whereas both GLP-1 receptor agonists and SGLT-2 inhibitors demonstrate marked growth when used as monotherapy: each class accounts for 1.3% in the Pre-COVID cohort and rises to 5.1% and 4.5%, respectively, in the Post–Note 100 cohort. Additionally, in the Post–Note 100 period, 2.2% of patients received a GLP-1 receptor agonist in combination with metformin, bringing the overall proportion of GLP-1–based therapy to an estimated 7.3%. Regimens with a prevalence below 0.5% are grouped under "Other" (Fig. 1S, Fig. 2).

Figure 2 shows trends in the use of DPP-4 inhibitors, GLP-1 receptor agonists, and SGLT-2 inhibitors across the three cohorts. Over the three cohorts, use of DPP-4 inhibitors declines, SGLT-2 inhibitor use shows a moderate upward trend, and GLP-1 receptor agonist use increases.

The analysis of new treatment initiations (Fig. 3) shows an even more pronounced change following the revised prescribing criteria introduced by AIFA Note 100. In the Post–Note 100 cohort, initiation of therapy with GLP-1 receptor agonists reached 9.3% (compared with 1.2% in the Pre-COVID cohort), while SGLT-2 inhibitors showed the most substantial growth, with a marked increase compared with previous periods. In parallel, the use of sulfonylureas as initial therapy declines sharply; metformin remains the most frequently initiated treatment, although it shows a slight decrease. (Fig. 3)

Among patients already on treatment (Fig. 4), the use of SGLT-2 inhibitors doubles from the Pre-COVID to the Post–Note 100 period (from 1.6% to 3.3%), while GLP-1 receptor agonists increase fourfold (from 1.8% to 7.7%); conversely, the use of sulfonylureas decreases substantially.

To formally assess these differences, comparisons between the Pre-COVID and Post–Note 100 cohorts were performed using chi-square tests. The analyses showed differences in the use of the investigated therapeutic classes between the Pre-COVID and Post–Note 100 periods. Figures 3 and 4 report the percentage distribution of drug use among newly treated and previously treated patients, respectively.

Differences between the two periods were assessed using the chi-square test. Among newly treated patients, the use

TABLE 1 - Demographic and clinical characteristics of T2DM patients across the three cohorts

	Pre-Covid19		Covid19		PostNote100	
	mean	**SD**	**mean**	**SD**	**mean**	**SD**
Age	70.1	12.0	70.4	12.0	70.5	12.1
	Number of subjects	%	Number of subjects	%	Number of subjects	%
Males	34,367	56.8%	34,734	56.5%	38,181	57.2%
No comorbidities	16,403	27.10%	15,514	25.20%	16,878	25.30%
Chronic kidney disease (CKD)	445	0.70%	425	0.70%	479	0.70%
Hypertension	44,116	73.80%	45,918	74.60%	49,834	75.20%
Heart failure	823	1.40%	733	1.20%	1,261	1.90%

of DPP-4 inhibitors increased from 2.5% (95% CI: 2.2-2.9) to 3.5% (95% CI: 3.2-3.9; p < 0.001). A more pronounced increase was observed for SGLT-2 inhibitors (from 2.6% [95% CI: 2.3-3.0] to 14.1% [95% CI: 13.4-14.9]; p < 0.001) and GLP-1 receptor agonists (from 1.2% [95% CI: 0.9-1.4] to 9.3% [95% CI: 8.7-9.9]; p < 0.001). Conversely, a significant reduction in the use of metformin was observed, decreasing from 73.4% (95% CI: 72.4-74.5) to 63.8% (95% CI: 62.8-64.8; p < 0.001), while no significant differences were found for pioglitazone.

Similar trends were observed among previously treated patients. The use of DPP-4 inhibitors increased from 3.6% (95% CI: 3.4-3.8) to 4.1% (95% CI: 3.9-4.3; p < 0.001), SGLT-2 inhibitors from 1.6% (95% CI: 1.5-1.7) to 3.0% (95% CI: 2.9-3.2; p < 0.001), and GLP-1 receptor agonists from 1.7% (95% CI: 1.6-1.9) to 7.1% (95% CI: 6.9-7.4; p < 0.001). In contrast, no statistically significant differences were observed for metformin and pioglitazone in this group.

Stratification by comorbidity status revealed variations in therapeutic patterns. Among subjects without comorbidities (restricted to those treated with acarbose, DPP-4 inhibitors, metformin, pioglitazone, SGLT-2 inhibitors, GLP-1 receptor agonists, or sulfonylureas), metformin- and sulfonylurea-based

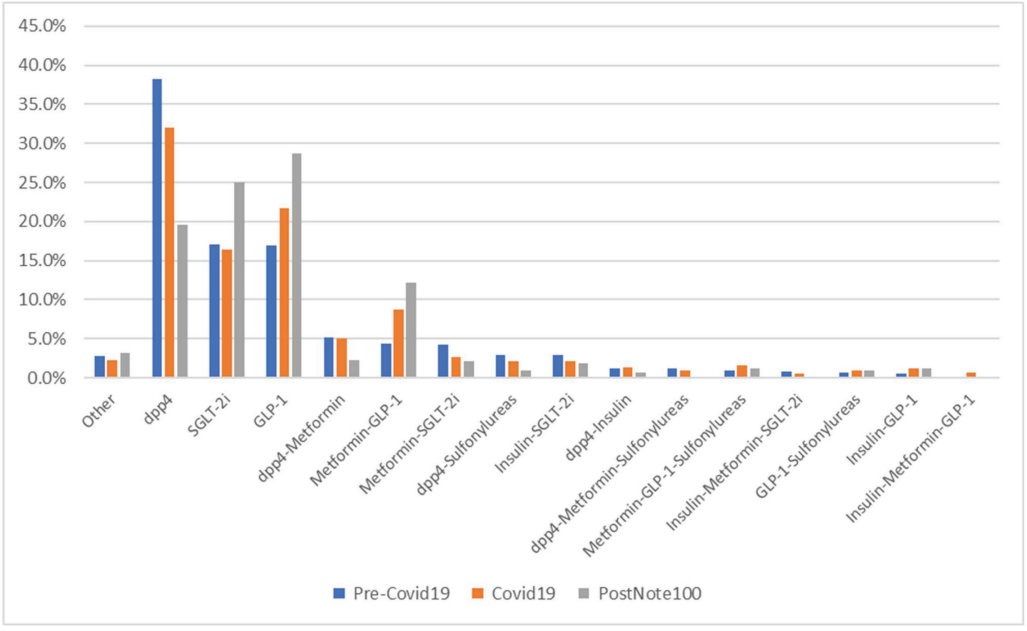

FIGURE 2 - Distribution limited to subjects treated with SGLT-2 inhibitors, DPP-4 inhibitors, or GLP-1 receptor agonists, either as monotherapy or in combination with other glucose-lowering agents.

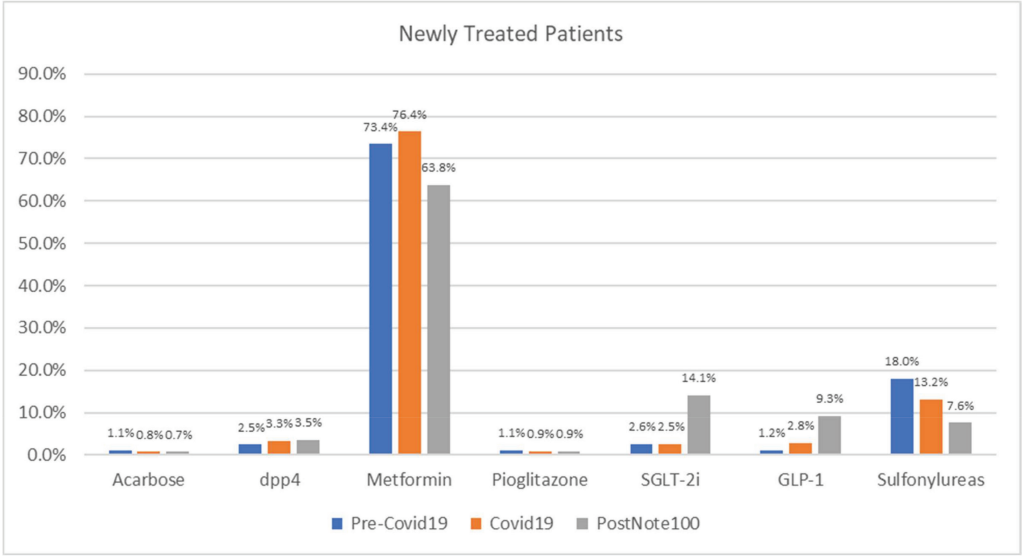

FIGURE 3 - Percentage distribution of newly treated patients according to glucose-lowering drug class.

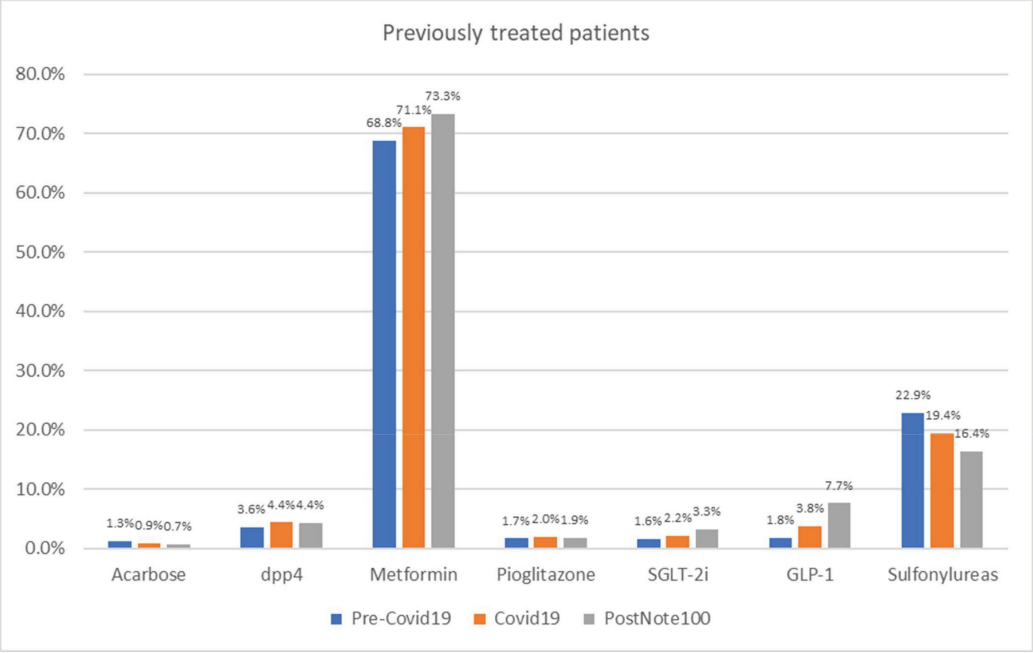

FIGURE 4 - Percentage distribution of patients already on treatment according to glucose-lowering drug class.

regimens remain the most common. However, in the Post–Note 100 cohort, the use of DPP-4 inhibitors, GLP-1 receptor agonists, and SGLT-2 inhibitors increases (Table 2s).

Among patients with one comorbidity, a more pronounced decline in the use of sulfonylureas is observed, alongside a progressive uptake of innovative drug classes. In subjects with two comorbidities, SGLT-2 inhibitors become the most frequently prescribed class in the Post–Note 100 cohort, surpassing metformin, while GLP-1 receptor agonists and DPP-4 inhibitors show substantial increases. In patients with three comorbidities, a simplification of therapeutic profiles emerges, with SGLT-2 inhibitors becoming the most commonly used class, followed by DPP-4 inhibitors.

Analyses by individual comorbidity confirm a growing orientation toward innovative therapies. In patients with heart failure, a marked increase in the use of SGLT-2 inhibitors is observed, which became the most frequently used treatment in the Post–Note 100 cohort. Among subjects with chronic kidney disease, although DPP-4 inhibitors remain widely used, the use of GLP-1 receptor agonists and SGLT-2 inhibitors has also increased. Finally, in hypertensive patients, a progressive shift from sulfonylureas toward innovative therapeutic classes was observed.

Across cohorts, costs vary substantially. In the Post–Note 100 cohort, GLP-1 receptor agonist and SGLT-2 inhibitor regimens carry higher drug costs, but, in more complex patients, these are often offset by lower hospitalization and outpatient expenditures. Stratification by comorbidity shows that the mean annual per-patient costs rise with clinical complexity (Tables 3s-5s; Figs 2-4s). Among patients without comorbidities, overall costs are low: metformin averages about €180-290 per year, SGLT-2 inhibitors €800-1,000, and GLP-1 receptor agonists €1,800-2,300, with hospitalization costs generally below €1,000–1,300. In heart failure, costs are markedly higher, with substantial hospital utilization; sulfonylurea regimens have non–diabetes-related hospitalization costs around €3,065-3,603, while SGLT-2 drug costs decline across cohorts, but hospitalization costs reach €6,392 in Post–Note 100. In chronic kidney disease, overall costs are highest; outpatient specialist costs are particularly elevated with DPP-4 monotherapy (€20,201-€29,543), whereas GLP-1 receptor agonist and SGLT-2 inhibitor regimens show drug costs around €2,000-2,300 without corresponding increases in hospitalization. In hypertension, which affects ~74-75% of patients, costs are intermediate: metformin drug costs rise from €212 to €369 across cohorts, SGLT-2 inhibitor costs decline from €1,314 to €796, GLP-1 receptor agonists range from €1,822 to €2,254, and hospitalization costs remain below €1,500 (Table 2).

Due to the multidimensional structure of cost components (pharmaceutical, outpatient, and hospitalization costs) and stratification by treatment profiles, Table 2 presents a detailed breakdown to allow comprehensive interpretation of resource utilization patterns across cohorts.

Treatment patterns shifted from Pre-COVID to Post–Note 100 toward broader use of SGLT-2 inhibitors and GLP-1 receptor agonists, with declines in sulfonylureas and metformin monotherapy. These changes were most pronounced in comorbid patients, with SGLT-2 inhibitors predominating in heart failure and multimorbidity, and GLP-1 receptor agonists rising across profiles. Although drug costs increased, non–disease-related hospitalization costs tended to fall in more complex patients, indicating alignment with guidelines and higher–value prescribing under AIFA Note 100.

TABLE 2 - Description of mean costs for healthcare services provided to subjects without comorbidities

	Comorbidities: None																		
	Pre-Covid19							Covid19							Post Note100						
	No of subjects	Antidiabetic drugs	Other Drugs	Outpatient services (diabetes-related)	Outpatient services (non–diabetes-related)	Hospitalizations (diabetes-related)	Hospitalizations (non–diabetes-related)	No of subjects	Antidiabetic drug	Other Drugs	Outpatient services (diabetes-related)	Outpatient services (non–diabetes-related)	Hospitalizations (diabetes-related)	Hospitalizations (non–diabetes-related)	No of subjects	Antidiabetic drug	Other Drugs	Outpatient services (diabetes-related)	Outpatient services (non–diabetes-related)	Hospitalizations (diabetes-related)	Hospitalizations (non–diabetes-related)
Other	243	386.13	767.28	60.83	881.34	46.55	1,060.22	214	422.42	359.46	0.53	593.87	98.72	604.09	199	498.28	475.65	0.60	1,217.03	–	953.35
Sulfonylureas_assoc	33	663.76	474.76	79.96	841.08	174.64	1,135.52	31	875.57	296.00	–	1,025.35	–	1,141.57	35	578.73	359.62	1.38	750.81	–	336.23
GLP-1_assoc	3	1,711.50	73.00	68.50	91.50	–	–	NA	1,307.00	60.00	2.50	633.50	–	–	11	2,271.13	247.25	0.63	604.25	–	3,868.63
GLP-1_assoc-Sulfonylureas_assoc	NA	2,060.25	600.75	117.25	411.75	–	–	11	1,802.25	1,246.88	–	280.50	–	–	19	1,546.36	223.79	0.71	441.14	–	–
SGLT-2 inhibitors_assoc	NA	1,190.75	663.50	84.50	561.50	–	–								NA	2,974.50	201.00	–	1,080.50	–	–
SGLT-2 inhibitors_assoc-Sulfonylureas_assoc	NA	636.00	574.00	116.50	304.50	–	–	NA	962.00	268.25	–	441.50	–	–	NA	1,203.75	536.75	1.25	807.75	–	–
SGLT-2 inhibitors_assoc-GLP-1_assoc	NA	2,343.00	178.00	94.00	1,871.00	–	–	NA	2,394.00	683.00	–	369.00	–	6,476.00	15	1,698.55	336.27	0.45	697.36	–	135.27
Metformine_assoc	105	471.58	277.19	72.46	532.87	31.65	670.05	104	519.05	224.92	1.86	464.51	–	455.17	82	681.02	208.68	0.89	375.27	–	447.52
Metformine_assoc-Sulfonylureas_assoc	1,304	272.82	627.99	62.60	863.00	68.92	857.75	1,139	312.60	496.94	0.45	759.00	51.93	638.06	906	521.26	381.53	0.55	637.76	50.70	879.66
Metformine_assoc-GLP-1_assoc	57	1,912.44	228.88	80.28	494.28	–	974.40	151	2,000.18	298.34	0.71	415.37	–	166.78	362	2,134.79	368.74	0.71	859.78	90.85	651.68
Metformine_assoc-GLP-1_assoc-Sulfonylureas_assoc	16	1,920.42	367.33	65.33	573.42	–	–	33	1,923.76	711.92	0.20	758.92	–	932.84	40	2,413.13	1,098.47	–	1,223.30	–	625.97
Metformine_assoc-SGLT-2 inhibitors_assoc	68	978.55	416.14	79.25	617.16	–	817.73	50	829.32	154.47	0.29	630.58	–	326.74	70	987.04	368.45	1.17	652.36	26.75	923.25
Metformine_assoc-SGLT-2 inhibitors_assoc-Sulfonylureas_assoc	NA	1,284.50	110.75	60.00	639.00	–	–	NA	732.00	24.33	–	404.67	–	–	NA	697.00	26.00	1.67	323.33	–	921.00
Metformine_assoc-SGLT-2 inhibitors_assoc-GLP-1_assoc	NA	2,334.00	376.00	105.00	8,391.00	–	5,851.00								11	2,807.88	155.63	–	1,195.00	–	–

(Continued)

TABLE 2 - *(Continued)*

	Comorbidities: None																				
	Pre-Covid19							Covid19							Post Note100						
	No of subjects	Antidiabetic drugs	Other Drugs	Outpatient services (diabetes-related)	Outpatient services (non–diabetes-related)	Hospitalizations (diabetes-related)	Hospitalizations (non–diabetes-related)	No of subjects	Antidiabetic drug	Other Drugs	Outpatient services (diabetes-related)	Outpatient services (non–diabetes-related)	Hospitalizations (diabetes-related)	Hospitalizations (non–diabetes-related)	No of subjects	Antidiabetic drug	Other Drugs	Outpatient services (diabetes-related)	Outpatient services (non–diabetes-related)	Hospitalizations (diabetes-related)	Hospitalizations (non–diabetes-related)
DPP4_assoc	NA	866.00	73.00	81.00	90.00	–	–	NA	971.50	881.00	1.00	738.50	–	–	8	1,241.17	118.17	0.83	570.67	–	1,248.17
DPP4_assoc-Sulfonylureas_assoc	23	769.53	655.24	89.35	988.59	–	1,236.12	17	870.08	378.23	–	1,064.31	–	994.69	17	736.38	324.38	–	832.92	–	2,330.54
DPP4_assoc-Metformine_assoc	72	742.56	399.46	80.74	700.07	3.28	103.22	81	634.69	224.05	1.64	560.23	–	–	77	652.86	541.67	1.03	836.24	31.83	365.21
DPP4_assoc-Metformine_assoc-Sulfonylureas_assoc	16	788.67	246.75	92.83	763.58	–	557.17	15	756.64	318.36	–	1,285.91	–	314.55	9	1,046.00	366.43	1.43	400.14	–	1,074.00
DPP4_assoc-Metformine_assoc-SGLT-2 inhibitors_assoc-GLP-1_assoc	NA	3,087.00	21,071.00	69.00	1,887.00	–	–														
Sulfonylureas_only	1,838	273.80	913.36	61.30	975.75	85.31	1,118.09	1,417	303.72	755.94	0.71	763.26	38.27	1,065.91	1,214	442.18	708.14	0.63	919.70	43.97	1,305.41
GLP-1_only	157	1,883.65	466.74	83.39	899.52	21.82	407.80	311	1,778.75	326.27	1.04	763.88	0.86	792.88	683	2,141.20	422.35	0.59	930.31	10.08	813.14
SGLT-2 inhibitors_only	175	973.80	239.45	75.58	748.47	–	313.02	226	786.62	293.79	0.91	804.41	19.11	535.12	296	878.69	829.62	0.61	969.47	95.60	2,425.76
Metformine_only	10,323	180.65	659.70	60.47	827.96	43.08	776.44	9,913	200.76	597.01	0.61	751.96	31.82	748.47	11,072	283.67	608.47	0.62	811.98	40.13	839.62
DPP4_only	234	696.66	834.07	85.24	1,215.31	1.36	843.23	312	616.85	731.85	0.98	907.83	59.04	760.47	348	671.57	1,071.57	0.64	1,141.71	8.11	2,019.62
DPP4_assoc-GLP-1_assoc								NA	1,269.00	529.00	–	141.00	–	8,704.00							
DPP4_assoc-SGLT-2 inhibitors_assoc								NA	701.50	6.00	–	392.50	–	–	NA	1,144.33	135.67	–	582.33	–	–
DPP4_assoc-Metformine_assoc-SGLT-2 inhibitors_assoc															NA	386.00	19.50	–	603.00	–	–

(Note: in accordance with WP29 Opinion 05/2024 on anonymization techniques, also referenced by the EDPB (European Data Protection Board), the principle of k-anonymity was applied; therefore, group sizes with fewer than 6 subjects are not reported.)

Discussion

Across three cohorts in two Northern Italian Local Health Authorities (LHAs), patients were older, predominantly male, and frequently affected by hypertension, with a slightly increasing prevalence of heart failure over time. Prescribing patterns observed in the Post–Note 100 period appear to align with ADA/EASD (5) and KDIGO (11) recommendations: the use of metformin and sulfonylureas declined, DPP-4 inhibitors increased modestly, and GLP-1 receptor agonists and SGLT-2 inhibitors showed a marked increase, particularly among patients at high cardio-renal risk. Analyses stratified by multimorbidity indicate that SGLT-2 inhibitors became the most frequently prescribed class in patients with two comorbidities and, together with DPP-4 inhibitors, in those with three comorbidities, while sulfonylureas and pioglitazone progressively decreased. These findings are consistent with Italian real-world evidence. Previous analyses have documented an increasing use of SGLT-2 inhibitors and GLP-1 receptor agonists, alongside a progressive reduction in the use of older glucose-lowering agents. (12) Similarly, AIFA monitoring reports on AIFA Note 100 (9,10) have shown a substantial increase in the uptake of innovative antidiabetic therapies following the extension of prescribing authority to general practitioners, with particularly marked growth in SGLT-2 inhibitors. In this context, our results support and extend existing national evidence by providing detailed insights into prescribing patterns according to comorbidity burden and treatment status (newly treated vs. previously treated patients). An additional aspect deserving attention is the increased use of innovative therapies among newly treated patients observed in the Post–Note 100 cohort. While metformin remains the most frequently initiated therapy, the growing uptake of GLP-1 receptor agonists and SGLT-2 inhibitors may reflect a shift toward earlier use of guideline-recommended agents in selected high-risk patients. However, this trend may also raise questions regarding alignment with traditional stepwise treatment approaches. The reduction in metformin use among newly treated patients may raise concerns regarding potential inappropriate prescribing. However, stratified analyses indicate that the increase in the use of innovative therapies was more pronounced among patients with a higher burden of comorbidities. This suggests that these therapies are preferentially prescribed in clinically complex patients, where they are more likely to be indicated according to current guidelines, rather than reflecting inappropriate use.

This finding should therefore be interpreted with caution, as administrative data do not allow full assessment of clinical appropriateness, including potential contraindications or intolerance to metformin. From an economic perspective, mean annual costs increased during the COVID and Post–Note 100 periods and were highest among patients with ≥2 comorbidities, reflecting greater clinical complexity. Although pharmaceutical costs were higher for GLP-1 receptor agonists and SGLT-2 inhibitors compared with traditional therapies, total healthcare costs per patient did not appear to be systematically higher in high-risk profiles. This finding suggests a potential balance between increased drug expenditure and reductions in other cost components, particularly hospitalizations and outpatient specialist services. This observation is consistent with clinical evidence showing that SGLT-2 inhibitors and GLP-1 receptor agonists reduce cardio-renal events (2-4), which may translate into lower healthcare resource utilization and costs, as suggested by real-world analyses (12).

From a policy perspective, these findings have relevant implications for the Italian National Health Service. The observed increase in the use of SGLT-2 inhibitors and GLP-1 receptor agonists following revised prescribing criteria introduced by AIFA Note 100 suggests that extending prescribing authority to General Practitioners may improve access to guideline-recommended therapies, particularly in patients at high cardio-renal risk. This may contribute to reducing variability in access and promoting a more homogeneous implementation of therapeutic recommendations across care settings. At the same time, the broader use of high-cost therapies requires careful monitoring to ensure prescribing appropriateness and long-term sustainability of healthcare expenditure. In this context, real-world analyses such as the present study can support policymakers in evaluating the impact of regulatory interventions on both clinical practice and resource allocation.

This study has several limitations. First, it relies on administrative data, where the identification of comorbidities is based on diagnostic codes, exemption records, and healthcare utilization, potentially leading to under-ascertainment. This is particularly relevant for chronic kidney disease (CKD), for which the observed prevalence in our cohorts (approximately 0.7%) is substantially lower than estimates reported in the literature, where CKD affects approximately 20-40% of patients with T2DM. (11,13) This discrepancy likely reflects the absence of laboratory data, such as estimated glomerular filtration rate (eGFR), and suggests that only more advanced or clinically recognized CKD cases are captured in our data. A similar, although less pronounced, limitation may also apply to heart failure. Second, the study was primarily designed as a descriptive analysis. However, additional inferential analyses were conducted to compare the Pre-COVID and Post–Note 100 cohorts, and statistically significant differences were identified for the main therapeutic classes. Nevertheless, no formal causal inference analyses were performed, and the findings should therefore be interpreted with caution. In addition, the study was conducted in two Local Health Authorities in Northern Italy and may not fully reflect national prescribing patterns. Regional heterogeneity in healthcare organization, access to therapies, and prescribing behavior across Italy may limit the generalizability of these findings. Finally, the study cohorts were not mutually exclusive, as the same individuals could be included in more than one period. While this reflects real-world population dynamics, it may introduce complexity in the interpretation of temporal trends, as part of the observed increase in innovative therapies in the Post–Note 100 cohort may be attributable to treatment persistence rather than new prescribing alone. However, analyses conducted in newly treated patients—who are not influenced by prior treatment exposures—show consistent and marked increases in the initiation of GLP-1 receptor agonists and SGLT-2 inhibitors, supporting the interpretation of

a genuine shift in prescribing patterns following the revised prescribing criteria introduced by AIFA Note 100. Overall, in this study setting, the revised prescribing criteria introduced by AIFA Note 100 appear to have contributed to a shift toward therapies more closely aligned with current guidelines, particularly among patients with greater cardio-renal risk, without a clear proportional increase in total healthcare costs in this study setting among the most clinically complex patients.

Conclusion

This real-world study, conducted in two Northern Italian Local Health Authorities, shows that the introduction of AIFA Note 100 was associated with substantial changes in prescribing patterns for non-insulin glucose-lowering drugs. In particular, a progressive reduction in the use of metformin monotherapy, sulfonylureas, and pioglitazone was observed, alongside a marked increase in the use of GLP-1 receptor agonists and SGLT-2 inhibitors, especially among patients with greater cardio-renal risk. The observed prescribing patterns are consistent with current international and national recommendations (5,6,11) supporting a shift toward more appropriate and targeted therapeutic strategies in complex patients. From a healthcare system perspective, although the uptake of innovative therapies was associated with higher pharmaceutical costs, overall healthcare expenditure did not increase proportionally in higher-risk patients, suggesting a potential rebalancing of costs across care components. Overall, in this study setting, AIFA Note 100 appears to have facilitated the adoption of more guideline-aligned therapies in routine clinical practice. Further studies, including analyses in other regional settings and with longer follow-up, are needed to better assess its impact on clinical outcomes and long-term healthcare sustainability.

Disclosures

Conflict of interest: The authors report no conflicts of interest.

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Authors' contributions: All authors contributed to the study conception and design, data acquisition, analysis and interpretation, drafting and critical revision of the manuscript, approved the final version, and agreed to be accountable for all aspects of the work.

Data Availability Statement: The data supporting the findings of this study are not publicly available due to privacy and legal restrictions. The authors processed the data on behalf of the Local Health Authorities (data controllers) and are therefore not authorized to share them.

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