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Real World Evidence in Italy in Patients with Cardio-Renal-Metabolic sindrome (CRM)

Retrospective Observational Study from an Italian Administrative Database

Report 23/11/2023

BACKGROUND
OBJECTIVES CRM

PRELIMINARY REPORT:

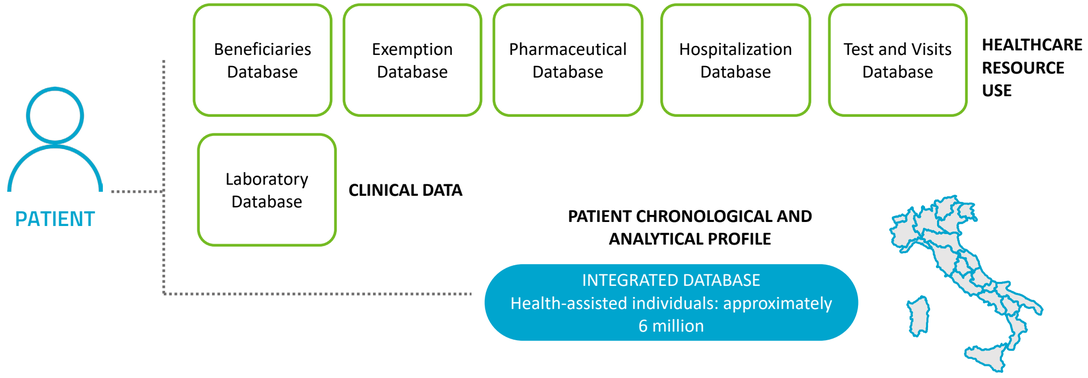
- To analyze the **DEMOGRAPHIC AND CLINICAL CHARACTERISTICS** of patients with HF, T2D, CKD and AMI*.

Note: **OTHER COHORT** - Also patients with AMI will be identify BUT only for characteristics evaluation.

FINAL REPORT:

- To evaluate the **KEY OUTCOMES** in patients with HF, T2D, CKD.
- To describe **HEALTH CARE RESOURCE USE AND ESTIMATE DIRECT COSTS** for Italian National Health Service (INHS) (derived from health care resource utilization in term of drug treatments, diagnostic tests, specialist visits and hospital admissions) among patients with HF, T2D, CKD.

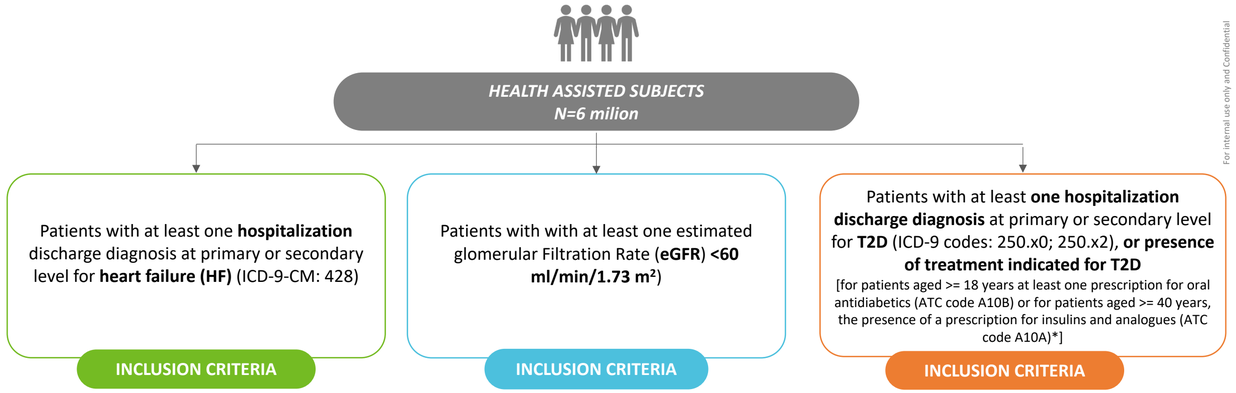
DATASOURCE
ADMINISTRATIVE DATABASE



TIME PERIODS OF ANALYSIS

- **DATA AVAILABILITY:** from January 2010 (some LHUs) – up to March 2023 at the latest.
- **INCLUSION PERIOD:** from January 2018 - December 2019.
- **INDEX DATE:** the date of the first match to the inclusion criteria.
- **CHARACTERIZATION PERIOD:** all available period, at least 12 months before index date (all patients had at least 1 year of data availability period before index date).
- **FOLLOW UP PERIOD:** all available period after index date (all patients had at least 1 year of data availability period after index date).

METHODS – STUDY DESIGN
STUDY POPULATION – INCLUSION AND ESCLUSION CRITERIA



EXCLUSION CRITERIA: Patients under 18 years AND/OR Patients with no continuous inclusion during the study period AND/OR Patients who died at index date. *For T2D patients aged >= 40 years included by the presence of a prescription for insulins and analogues (ATC code A10A)] patients affected by T1D will be excluded (ICD-9 codes: 250.x1; 250.x3, during all available study period).

NOTE: OTHER COHORT - Also patients with AMI (identified by the presence of at least one hospitalization discharge diagnosis at primary or secondary level for AMI – ICD-9-CM Code: 410) BUT only for characteristics evaluation.

RESULTS – HF CHARACTERISTICS
BASELINE CHARACTERISTICS OF HF PATIENTS

HF

DEMOGRAPHIC CHARACTERISTICS AND COMORBIDITY PROFILE	Pts with HF N=41,795
Age at index date, mean (SD)	79.1 (11.2)
18-39 years, n (%)	214 (0.5)
40-59 years, n (%)	2,478 (5.9)
60-79 years, n (%)	15,267 (36.5)
≥80 years, n (%)	23,836 (57.0)
Male (n, %)	21,114 (50.5)
Treated with sglt2-i, n (%)	189 (0.5)
HF index – in primary diagnosis	20,849 (49.9)
Follow-up (years), mean (SD)	2.5 (1.6)
Comorbidity profile	
Diabetes, n (%)	14,559 (34.8)
CKD, n (%)	21,149 (50.6)
CV disease, n (%)	19,688 (47.1)
Hypertension, n (%)	37,921 (90.7)
AMI, n (%)	2,900 (6.9)
Diabetic retinopathy, n (%)	154 (0.4)
COPD, n (%)	14,942 (35.8)
OSA and CSA, n (%)	335 (0.8)
Atrial fibrillation, n (%)	8,925 (21.4)
Hyperlipidemia, n (%)	18,158 (43.4)
Thyroid disease, n (%)	6,099 (14.6)
Depression, n (%)	7,841 (18.8)
Osteoarthritis and Osteoporosis, n (%)	2,179 (5.2)

COMORBIDITY PROFILE, LABORATORY TESTS	Pts with HF N=41,795
Laboratory measurements	
Triglycerides (mg/dL), mean (SD)	108.9 (59.5)
Total cholesterol (mg/dL), mean (SD)	145.5 (42.2)
Glycated hemoglobin (mmol/mol), mean (SD)	50.6 (17.7)
Creatinine (mg/dL), mean (SD)	1.4 (1.0)
eGFR (ml/min/1.73 m2), mean (SD)	62.1 (37.0)
Patients with Proteinuria, n (%)	234 (0.6)

Note The total number of urine albumin tests over 3 months was 1,367. Of which 318 tests (23.3%) indicated proteinuria. Considering the only patients wit at least one urine albumin tests over 3 months N= 1,010 the percentage of patients with proteinuria was 23% (N=234).

STARTING FROM THE SAMPLE POPULATION OF **6 MILLION OF HEALTH-ASSISTED INDIVIDUALS**, **41,795 PATIENTS WITH HF HAVE BEEN IDENTIFIED** DURING INCLUSION PERIOD.

IN LINE WITH PUBLISHED EVIDENCES[1-2], THE MAIN COMORBIDITIES FOUND WERE:

HYPERTENSION (91%)
CKD (51%)
CV DISEASE (47%)
HYPERLIPIDEMIA (43%)
COPD (36%)
DIABETES (35%)

METHODOLOGIC NOTE: For identification codes of comorbidity, see **HERE**

References:
1. Metra M, et al. Cardiovascular and noncardiovascular comorbidities in patients with chronic heart failure. Journal of Cardiovascular Medicine 12.2 (2011): 76-84.
2. Damman K, et al. Renal impairment, worsening renal function, and outcome in patients with heart failure: an updated meta-analysis. Eur Heart J 35: 455–469, 2014.

RESULTS – HF CHARACTERISTICS

HF

LIST OF THE MOST FREQUENT DRUGS AND HOSPITALIZATIONS DURING 12 MONTH CHARACTERIZATION PERIOD AMONG HF PATIENTS

THE MOST FREQUENTLY DRUGS PRESCRIBED AND THE MOST FREQUENT HOSPITALIZATIONS IDENTIFIED DURING 12 MONTHS BEFORE THE INDEX DATE ARE SHOWN IN THE TABLES BELOW.

		Pts with HF N=41,795
ATC code	**Drugs**	
B01	Antithrombotic agents	31,592 (75.6)
A02	Drugs for acid related disorders	29,514 (70.6)
J01	Antibacterials for systemic use	28,910 (69.2)
C09	Agents acting on the renin-angiotensin system	27,553 (65.9)
C03	Diuretics	26,774 (64.1)
C07	Beta blocking agents	23,684 (56.7)
C10	Lipid modifying agents	17,920 (42.9)
R03	Drugs for obstructive airway diseases	14,936 (35.7)
M01	Antiinflammatory and antirheumatic products	14,193 (34.0)
C01	Cardiac therapy	13,187 (31.6)

	Pts with HF N=41,795
DESCRIPTION (MDC Classification)	
Circulatory System	6,369 (15.2)
Respiratory System	3,627 (8.7)
Musculoskeletal System And Connective Tissue	1,508 (3.6)
Nervous System	1,385 (3.3)
Kidney And Urinary Tract	1,307 (3.1)
Digestive System	1,302 (3.1)
Hepatobiliary System And Pancreas	529 (1.3)
Skin, Subcutaneous Tissue And Breast	484 (1.2)
Infectious and Parasitic DDs	465 (1.1)
Blood and Blood Forming Organs and Immunological Disorders	446 (1.1)

RESULTS - HF OUTCOMES

HF

OUTCOMES: OVERALL HOSPITALIZATION (ANY CAUSES AND CARDIOVASCULAR) – MORTALITY

The findings from this review are generally consistent with findings of outcomes of published studies. [1-3]

➢ **ALL CAUSE HOSPITALIZATIONS AND HF HOSPITALIZATION**

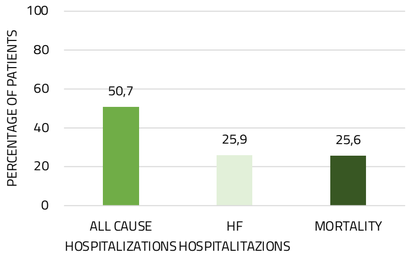
In line with previous studies, after the first 12 months of the index HF hospitalization, around half of patients experienced at least one all-cause rehospitalization and around 26% of patients had at least one HF rehospitalization.[1,2]

➢ **MORTALITY**

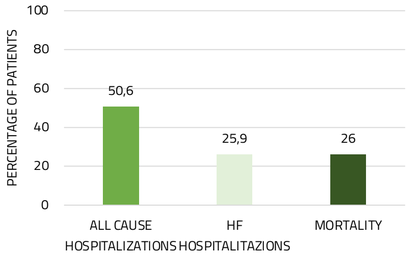
Despite advancements in HF treatment, the 1-year mortality rate remains high at approximately 30%, increasing to approximately 40% at 5 years.[3] In this analysis, data highlighted that the percentage of patients who died during the first 12 months of follow-up was about 26%.

References

1. *Leszek P, et al. Burden of hospitalizations in newly diagnosed heart failure patients in Poland: real world population based study in years 2013-2019. ESC Heart Fail. 2022 Jun;9(3):1553-1563.*
2. *2. Degli Esposti L, et al. Heart failure in the Veneto region of Italy: analysis of therapeutic pathways and the utilization of healthcare resources. Expert Rev Pharmacoecon Outcomes Res. 2020 Oct;20(5):499-505. doi: 10.1080/14737167.2020.1718494. Epub 2020 Jan 23. PMID: 31971025.*
3. *3. Khera RP, Pandey A, Ayers, C R, et al. Contemporary epidemiology of heart failure in fee-for-service medicare beneficiaries across healthcare settings. Circ Heart Fail. 2017;10(11):e004402.*



NOTES: Pts with HF N=41,795. The index-date was excluded from the analysis.



NOTES: Pts with HF not treated with GLP1i and SGLT2i in the period preceding and in the 12 months following the index date. N=40,669.
The index-date was excluded from the analysis.

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RESULTS- HF HEALTHCARE RESOURCE CONSUMPTIONS AND COSTS

HF HEALTHCARE RESOURCE CONSUMPTIONS AND COSTS

HF

AVERAGE ANNUAL HEALTHCARE RESOURCE CONSUMPTION PER PATIENT WITH HF, DURING FIRST YEAR OF FOLLOW-UP
(DEATHS EXCLUDED, N=31,103)

	Pts with HF N=31,103
Number of drug prescriptions, mean (SD)	25.7 (14.9)
Number of hospitalizations, mean (SD)	0.8 (1.2)
Number of outpatient specialist services, mean (SD)	8.6 (12.9)

- Published studies reported that the **hospitalizations are the largest component of direct medical costs for HF, with estimates ranging from 49% to 73% of total costs.**
- In this analysis, approximately 62% of the average total cost is related to hospitalizations.

References: Osenenko, et al. Burden of hospitalization for heart failure in the United States: a systematic literature review. Journal of Managed Care & Specialty Pharmacy 2022 28:2, 157-167.
Dovizio M. Analisi Del Burden Clinico Ed Economico Dei Pazienti Con Diagnosi Di Scompenso Cardiaco: Analsi Retrospettiva Su Dati Di Real-world In Italia. 2 Congresso GIRF 2023 ISPOR Italy - Rome Chapter

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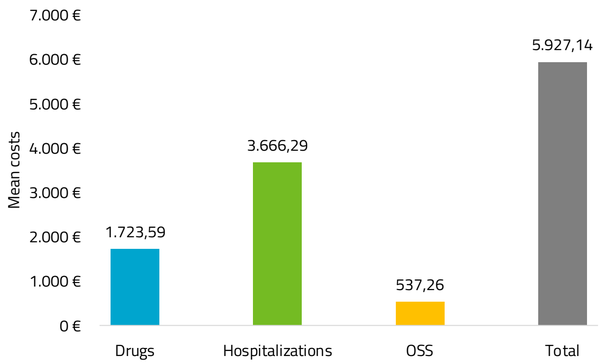
AVERAGE ANNUAL COST PER PATIENT WITH HF, DURING FIRST YEAR OF FOLLOW-UP
(DEATHS AND OUTLIERS EXCLUDED, N=30,638)



Note. The index-date was excluded from the analysis.

RESULTS - CKD CHARACTERISTICS
BASELINE CHARACTERISTICS OF CKD PATIENTS

CKD

DEMOGRAPHIC CHARACTERISTICS AND COMORBIDITY PROFILE

	Pts with CKD N=217,658
Age at index date, mean (SD)	76.9 (12.0)
18-39 years, n (%)	1,870 (0.9%)
40-59 years, n (%)	17,490 (8.0%)
60-79 years, n (%)	93,345 (42.9%)
≥80 years, n (%)	104,953 (48.2%)
Male (n, %)	94,106 (43.2)
Treated with sglt2-i, n (%)	861 (0.4)
Follow-up (years), mean (SD)	3.0 (1.5)
Comorbidity profile	
Diabetes, n (%)	63,333 (29.1)
Heart failure, n(%)	20,574 (9.5)
CV disease, n (%)	57,674 (26.5)
Hypertension, n (%)	185,106 (85.0)
AMI, n (%)	7,294 (3.4)
Diabetic retinopathy, n (%)	462 (0.2)
Hyperlipidemia, n(%)	85,134 (39.1)

COMORBIDITY PROFILE, LABORATORY TESTS

	Pts with CKD N=217,658
Laboratory measurements	
Triglycerides (mg/dL), mean (SD)	132.4 (79.7)
Total cholesterol (mg/dL), mean (SD)	175.6 (44.9)
Glycated hemoglobin (mmol/mol), mean (SD)	51.1 (14.7)
Creatinine (mg/dL), mean (SD)	1.5 (1.1)
eGFR (ml/min/1.73 m2), mean (SD)	46.4 (12.4)
Patients with Proteinuria, n (%)	2,367 (1.1)

Note The total number of urine albumin tests over 3 months was 20,229. Of which 3,145 tests (15.5%) indicated proteinuria. Considering the only patients wit at least one urine albumin tests over 3 months N= 14,892 the percentage of patients with proteinuria was 19% (N=2,367).

STARTING FROM THE SAMPLE POPULATION OF **6 MILLION OF HEALTH-ASSISTED INDIVIDUALS,217,658 PATIENTS WITH CKD HAVE BEEN IDENTIFIED** DURING INCLUSION PERIOD.

IN LINE WITH PUBLISHED EVIDENCES[1-2], THE MAIN COMORBIDITIES FOUND WERE:
HYPERTENSION (85%)
HYPERLIPIDEMIA (39%)
DIABETES (29%)
CV DISEASE (27%)

IN LITERATURE, **INCIDENCE OF HF** IN CKD IS REPORTED AROUND 17-21%[3]. IN OUR ANALYSIS CHARACTERISTICS AT BASELINE WERE REPORTED BUT WHEN LOOKING AT ALL FOLLOW-UP, PROPORTION OF PATIENTS WITH HF WAS FOUND TO BE 20.4%.

METHODOLOGIC NOTE: For identification codes of comorbidity, see **HERE**

References:
*[1]MacRae C, et al. Comorbidity in chronic kidney disease: a large cross-sectional study of prevalence in Scottish primary care. Br J Gen Pract. 2021 Feb 25;71(704):e243-e249. [2]Fraser et al. The burden of comorbidity in people with chronic kidney disease stage 3: a cohort study. BMC Nephrol 16, 193 (2015). [3]Cozzolino m et al. nephron, 2018 140:39–47. de nicola l et al. clin j am soc nephrol, 2011, 6:2421–2428;**House AA et al. Kidney International (2019) 95, 1304–1317*

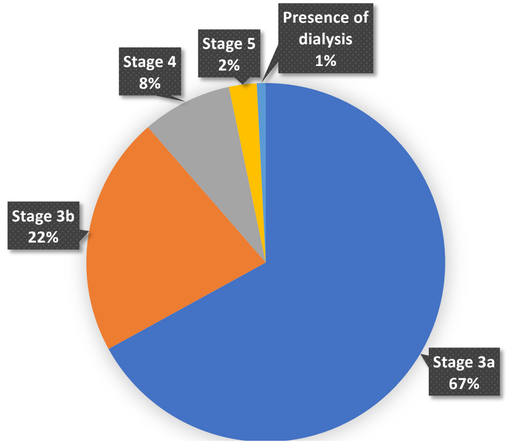
RESULTS - CKD CHARACTERISTICS
STAGE OF CKD PATIENTS

CKD

THE FIGURE AND TABLE BELOW SHOWS THE DETAILS RELATING TO THE STAGE FOR THE CKD PATIENTS INCLUDED (N=217,658).

	Stage, n (%)	Follow-up (years), mean (SD)
Pts with CKD N=217,658		
Stage 3a	145,860 (67.0)	3.2 (1.3)
Stage 3b	46,977 (21.6)	2.9 (1.6)
Stage 4	17,729 (8.1)	2.4 (1.7)
Stage 5	5,423 (2.5)	2.4 (1.8)
Presence of dialysis	1,669 (0.8)	3.3 (1.7)

FREQUENCY OF CKD PATIENT IN EACH STAGE



RESULTS – CKD CHARACTERISTICS

CKD

LIST OF THE MOST FREQUENT DRUGS AND HOSPITALIZATIONS DURING 12 MONTH CHARACTERIZATION PERIOD AMONG CKD PATIENTS

THE MOST FREQUENTLY DRUGS PRESCRIBED AND THE MOST FREQUENT HOSPITALIZATIONS IDENTIFIED DURING 12 MONTHS BEFORE THE INDEX DATE ARE SHOWN IN THE TABLES BELOW.

		Pts with CKD N=217,658
ATC Code	**Drugs**	
C09	Agents acting on the renin-angiotensin system	145,185 (66.7)
A02	Drugs for acid related disorders	135,823 (62.4)
J01	Antibacterials for systemic use	132,851 (61.0)
B01	Antithrombotic agents	129,509 (59.5)
C07	Beta blocking agents	91,475 (42.0)
C03	Diuretics	89,378 (41.1)
C10	Lipid modifying agents	87,145 (40.0)
M01	Antiinflammatory and antirheumatic products	75,291 (34.6)
A11	Vitamins	68,689 (31.6)
A10	Drugs used in diabetes	57,218 (26.3)

	Pts with CKD N=217,658
DESCRIPTION (MDC Classification)	
Circulatory System	13,257 (6.1)
Respiratory System	6,211 (2.9)
Kidney And Urinary Tract	5,927 (2.7)
Musculoskeletal System And Connective Tissue	5,593 (2.6)
Digestive System	4,714 (2.2)
Nervous System	4,378 (2.0)
Myeloproliferative DDs (Poorly Differentiated Neoplasms)	2,750 (1.3)
Hepatobiliary System And Pancreas	2,552 (1.2)
Skin, Subcutaneous Tissue And Breast	1,969 (0.9)
Eye	1,828 (0.8)

RESULTS - CKD OUTCOMES

CKD

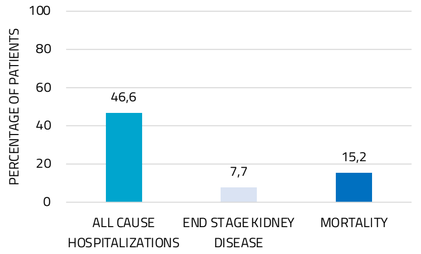
OUTCOMES: ALL CAUSE HOSPITALIZATION, MORTALITY AND END-STAGE KIDNEY DISEASE

The findings from this analysis are generally consistent with findings of outcomes of published studies. [1-2] Health care utilization in term of hospitalization among adult CKD patients is high. Previous studies have also reported that older age, female sex, concomitant cardiovascular disease, reduced eGFR, and diabetes may predict hospitalization in patients with CKD.

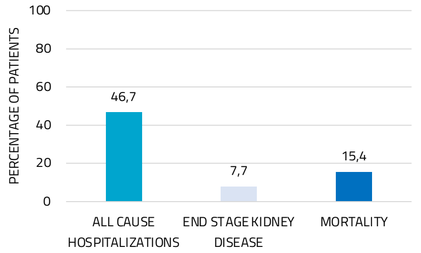
- **ALL CAUSE HOSPITALIZATIONS**
  During the first 12 months follow-up, 47% of patients had at least one all-cause rehospitalization.

- **MORTALITY**
  During the first 12 months follow-up, the 1-year mortality rate remains high at approximately 15%.

- **END-STAGE KIDNEY DISEASE**
  During the first 12 months follow-up, 7.7 % of patients had a EGFR change ≥ 40% from baseline value.



NOTES: Pts with CKD N=217,658. The index-date was excluded from the analysis.



NOTES: Pts with CKD not treated with GLP1i and SGLT2i in the period preceding and in the 12 months following the index date. N=213,500.The index-date was excluded from the analysis.

References

1. *Schrauben SJ, Chen HY, Lin E, Jepson C, Yang W, Scialla JJ, Fischer MJ, Lash JP, Fink JC, Hamm LL, Kanthety R, Rahman M, Feldman HI, Anderson AH; CRIC Study Investigators. Hospitalizations among adults with chronic kidney disease in the United States: A cohort study. PLoS Med. 2020 Dec 11;17(12):e1003470.*
2. *S. Khan et al. Health care utilization among patients with chronic kidney disease. Kidney International. Volume 62, Issue 1, July 2002, Pages 229-236*

RESULTS- CKD HEALTHCARE RESOURCE CONSUMPTIONS AND COSTS

CKD HEALTHCARE RESOURCE CONSUMPTIONS AND COSTS

CKD

AVERAGE ANNUAL HEALTHCARE RESOURCE CONSUMPTION PER PATIENT WITH CKD, DURING FIRST YEAR OF FOLLOW-UP
(DEATHS EXCLUDED, N=184,604)

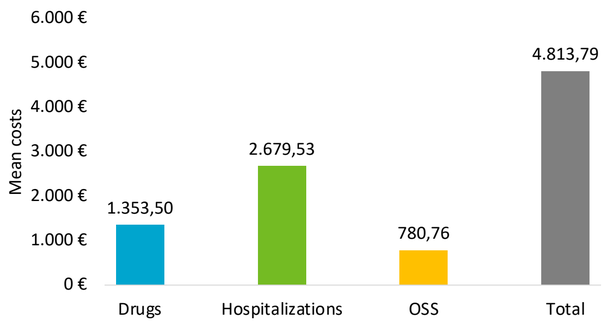
	Pts with CKD N=184,604
Number of drug prescriptions, mean (SD)	20.4 (13.1)
Number of hospitalizations, mean (SD)	0.7 (1.1)
Number of outpatient specialist services, mean (SD)	8.3 (13.6)

- Published studies reported that the **Hospitalizations account for a large fraction of the cost of care in CKD population, particularly due to cardiovascular disease and CKD.**[1]
- In this analysis, approximately 56% of the average total cost is related to hospitalizations.

References

1. *Escobar C, Palacios B, Aranda U, Capel M, Sicras A, Sicras A, Hormigo A, Alcázar R, Manito N, Botana M. Costs and healthcare utilisation of patients with chronic kidney disease in Spain. BMC Health Serv Res. 2021 Jun 1;21(1):536.*

AVERAGE ANNUAL COST PER PATIENT WITH CKD, DURING FIRST YEAR OF FOLLOW-UP
(DEATHS AND OUTLIERS EXCLUDED, N=183,569)



Note. The index-date was excluded from the analysis.

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RESULTS - T2D CHARACTERISTICS
BASELINE CHARACTERISTICS OF T2D PATIENTS

T2D

DEMOGRAPHIC CHARACTERISTICS AND COMORBIDITY PROFILE	Pts with T2D N=412,296
Age at index date, mean (SD)	69.1 (12.9)
18-39 years, n (%)	8,549 (2.1)
40-59 years, n (%)	80,310 (19.5)
60-79 years, n (%)	232,008 (56.3)
≥80 years, n (%)	91,429 (22.2)
Male (n, %)	215,410 (52.2)
Treated with sglt2-i, n (%)	7,457 (1.8)
Follow-up (years), mean (SD)	4.0 (1.2)
Comorbidity profile	
CKD, n (%)	65,418 (15.9)
Heart failure, n(%)	18,576 (4.5)
CV disease, n (%)	70,637 (17.1)
Hypertension, n (%)	320,924 (77.8)
AMI, n (%)	11,051 (2.7)
Diabetic retinopathy, n (%)	1,654 (0.4)
Anemia, n (%)	29,605 (7.2)
Hyperlipidemia, n(%)	205,356 (49.8)

METHODOLOGIC NOTE: For identification codes of comorbidity, see **HERE**

COMORBIDITY PROFILE, LABORATORY TESTS	Pts with T2D N=412,296
Laboratory measurements	
Triglycerides (mg/dL), mean (SD)	148.7 (106.0)
Total cholesterol (mg/dL), mean (SD)	171.9 (45.1)
Glycated hemoglobin (mmol/mol), mean (SD)	58.3 (18.0)
Creatinine (mg/dL), mean (SD)	1.1 (0.9)
eGFR (ml/min/1.73 m2), mean (SD)	77.4 (39.0)
Patients with Proteinuria, n (%)	1,567 (0.4)

Note The total number of urine albumin tests over 3 months was 21,851. Of which 2,120 tests (9.7%) indicated proteinuria. Considering the only patients wit at least one urine albumin tests over 3 months N= 15,876 the percentage of patients with proteinuria was 9.8% (N=1,567).

STARTING FROM THE SAMPLE POPULATION OF **6 MILLION OF HEALTH-ASSISTED INDIVIDUALS,217,658 PATIENTS WITH CKD HAVE BEEN IDENTIFIED** DURING INCLUSION PERIOD.

IN LINE WITH PUBLISHED EVIDENCES[1], THE MAIN COMORBIDITIES FOUND WERE:
HYPERTENSION (78%)
HYPERLIPIDEMIA (50%)
CV DISEASE (17%)
CKD (16%)

References:
[1]Nowakowska M, et al. The comorbidity burden of type 2 diabetes mellitus: patterns, clusters and predictions from a large English primary care cohort. BMC Med. 2019 Jul 25;17(1):145. doi: 10.1186/s12916-019-1373-y. Erratum in: BMC Med. 2020 Jan 25;18(1):22.

RESULTS - T2D CHARACTERISTICS

LIST OF THE MOST FREQUENT DRUGS AND HOSPITALIZATIONS DURING 12 MONTH CHARACTERIZATION PERIOD AMONG T2D PATIENTS

T2D

THE MOST FREQUENTLY DRUGS PRESCRIBED AND THE MOST FREQUENT HOSPITALIZATIONS IDENTIFIED DURING 12 MONTHS BEFORE THE INDEX DATE ARE SHOWN IN THE TABLES BELOW.

		Pts with T2D N=412,296
ATC code	**Drugs**	
A10	Drugs used in diabetes	325,486 (78.9)
C09	Agents acting on the renin-angiotensin system	264,644 (64.2)
J01	Antibacterials for systemic use	243,508 (59.1)
A02	Drugs for acid related disorders	222,489 (54.0)
C10	Lipid modifying agents	214,743 (52.1)
B01	Antithrombotic agents	208,430 (50.6)
M01	Antiinflammatory and antirheumatic products	158,726 (38.5)
C07	Beta blocking agents	151,538 (36.8)
C03	Diuretics	101,055 (24.5)
C08	Calcium channel blockers	91,589 (22.2)

	Pts with T2D N=412,296
DESCRIPTION (MDC Classification)	
Circulatory System	16,273 (3.9)
Musculoskeletal System And Connective Tissue	8,950 (2.2)
Respiratory System	6,840 (1.7)
Nervous System	6,619 (1.6)
Digestive System	5,802 (1.4)
Kidney And Urinary Tract	5,077 (1.2)
Eye	3,640 (0.9)
Hepatobiliary System And Pancreas	3,605 (0.9)
Endocrine, Nutritional And Metabolic System	2,859 (0.7)
Skin, Subcutaneous Tissue And Breast	2,763 (0.7)

RESULTS - T2D OUTCOMES

T2D

OUTCOMES: ALL CAUSE HOSPITALIZATION, HF HOSPITALIZATION, MORTALITY AND END-STAGE KIDNEY DISEASE

Although direct comparisons with the same analysis populations are not available in the literature, the findings from this analysis are generally consistent with findings of outcomes of published studies. [1-3] Analyzes relating to outcomes in patients with T2D are frequently stratified according to the presence of comorbidities and particular treatment or clinical settings. Our analysis cohort of patients with diabetes can therefore be defined as heterogeneous.

- **ALL CAUSE HOSPITALIZATIONS**

During the first 12 months follow-up, 17% of patients had at least one all-cause rehospitalization.

- **HF HOSPITALIZATIONS**

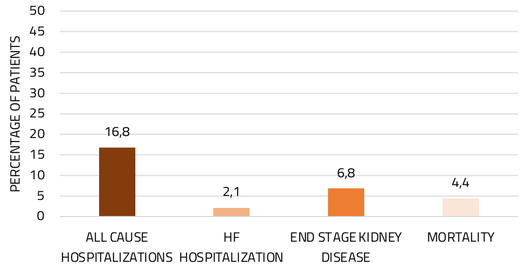
During the first 12 months follow-up, 2.1% of patients had at least one all-cause rehospitalization.

- **MORTALITY**

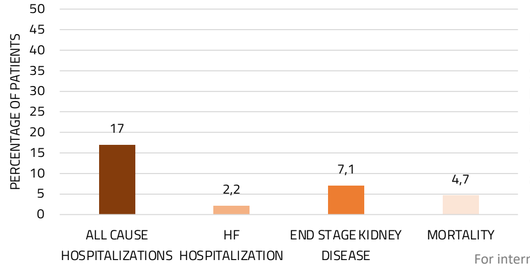
During the first 12 months follow-up, 4.4% died.

- **END-STAGE KIDNEY DISEASE**

During the first 12 months follow-up, 6.8% of patients had a EGFR change ≥ 40% from baseline value.



NOTES: Pts with T2D N= 412,296. The index-date was excluded from the analysis.



NOTES: Pts with T2D not treated with GLP1i and SGLT2i in the period preceding and in the 12 months following the index date. N= 378,141.The index-date was excluded from the analysis.

References:

1. *AbuHammad, G.A.R., Naser, A.Y. & Hassouneh, L.K.M. Diabetes mellitus-related hospital admissions and prescriptions of antidiabetic agents in England and Wales: an ecological study. BMC Endocr Disord 23, 102 (2023).*
2. *Palazzuoli A, Iacoviello M. Diabetes leading to heart failure and heart failure leading to diabetes: epidemiological and clinical evidence. Heart Fail Rev. 2023 May;28(3):585-596.*
3. *Silvia A. G. de Vries MD. Use of hospital care among Dutch diabetes patients. Diabetes Obes Metab.2023;25:2268–2278*

RESULTS- T2D HEALTHCARE RESOURCE CONSUMPTIONS AND COSTS

T2D HEALTHCARE RESOURCE CONSUMPTIONS AND COSTS

T2D

AVERAGE ANNUAL HEALTHCARE RESOURCE CONSUMPTION PER PATIENT WITH T2D, DURING FIRST YEAR OF FOLLOW-UP (DEATHS EXCLUDED, N=394,230)

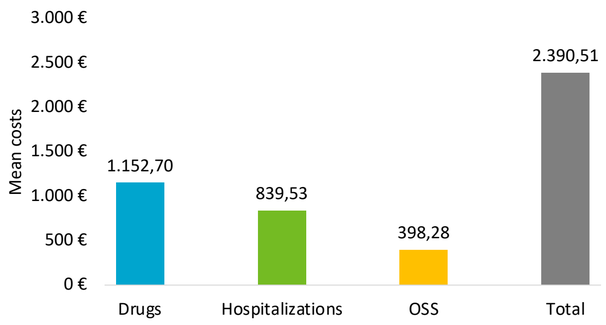
	Pts with T2D N=394,230
Number of drug prescriptions, mean (SD)	19.3 (11.9)
Number of hospitalizations, mean (SD)	0.2 (0.7)
Number of outpatient specialist services, mean (SD)	5.8 (7.5)

- Published studies reported that the **treatment and hospitalizations account for a large fraction of the cost of care in T2D population.** [1,2]
- In this analysis, approximately 35% and 48 of the average total cost are related to hospitalizations and treatments, respectively .

References:
1. American Diabetes Association: The Cost of Diabetes. Available athttps://diabetes.org/about-us/statistics/cost-diabetes. Last update: 13/11/2023.
2. Silvia A. G. de Vries MD. Use of hospital care among Dutch diabetes patients. Diabetes Obes Metab.2023;25:2268–2278

AVERAGE ANNUAL COST PER PATIENT WITH T2D, DURING FIRST YEAR OF FOLLOW-UP

(DEATHS AND OUTLIERS EXCLUDED, N=393,485)



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Note. The index-date was excluded from the analysis.

RESULTS - T2D OUTCOMES

OUTCOMES: STRATIFICATION AMONG PATIENTS TREATED OR NOT WITH SGLT-2 INIBITORS

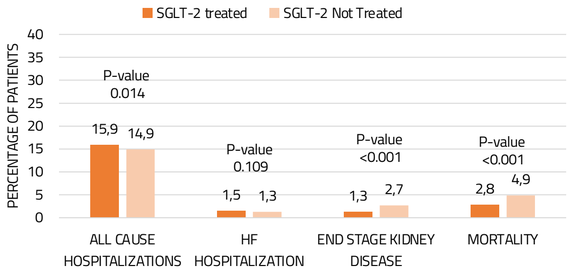
T2D

To create a balanced characteristics distribution between patients treated or not with SGLT-2 agents, a propensity score matching (PSM) method was applied. The propensity score was estimated using a logistic regression model, considering the following confounding variables: age, sex, comorbidity profile (as presence of: CKD, HF, CV disease, hypertension, AMI, diabetic reinopathy, anemia, hyperlipidemia. A 1:1 matching algorithm was applied. After PSM, The outcomes analysis was performed. Outcomes were evalutated during the first 12 months of follow-up after the identification of T2D . The presence of treatment was assessed both in the period before the identification of diabetes in the dataset and in the 12 months following the index date.

BASELINE CHARACTERISTICS OF PATIENTS TREATED WITH SGLT2 OR NOT POST PSM

	PTS WITH T2D TREATED WITH SGLT2-I N=15,919	PTS WITH T2D UNTREATED WITH SGLT2-I N=15,919	P-value
AGE AT INDEX DATE, MEAN (SD)	63.2 (10.1)	63.0 (12.8)	0.233
MALE (N, %)	8,922 (56.0)	8,945 (56.2)	0.795
COMORBIDITY PROFILE			
CKD, N (%)	1,679 (10.5)	1,642 (10.3)	0.498
HEART FAILURE, N(%)	636 (4.0)	610 (3.8)	0.452
CV DISEASE, N (%)	2,906 (18.3)	2,845 (17.9)	0.374
HYPERTENSION, N (%)	12,303 (77.3)	12,287 (77.2)	0.831
AMI, N (%)	707 (4.4)	672 (4.2)	0.335
DIABETIC RETINOPATHY, N (%)	133 (0.8)	92 (0.6)	0.006
ANEMIA, N (%)	725 (4.6)	662 (4.2)	0.084
HYPERLIPIDEMIA, N(%)	9,248 (58.1)	9,270 (58.2)	0.803

OUTCOMES ANALYSIS AMONG PATIENTS TREATED WITH SGLT2 OR NOT POST PSM



NOTE: The index-date was excluded from the analysis.

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RESULTS - AMI CHARACTERISTICS
BASELINE CHARACTERISTICS OF AMI PATIENTS

AMI

DEMOGRAPHIC CHARACTERISTICS AND COMORBIDITY PROFILE	Pts with AMI N=15,808
Age at index date, mean (SD)	69.3 (13.2)
18-39 years, n (%)	159 (1.0)
40-59 years, n (%)	3,814 (24.1)
60-79 years, n (%)	7,764 (49.1)
≥80 years, n (%)	4,071 (25.8)
Male (n, %)	10,630 (67.2)
Follow-up (years), mean (SD)	3.2 (1.3)
Comorbidity profile	
Diabetes, n (%)	4,682 (29.6)
Heart failure, n(%)	1,120 (7.1)
CKD, n(%)	4,610 (29.2)
OtherCV disease, n (%)	4,175 (26.4)
Hypertension, n (%)	11,269 (71.3)
Diabetic retinopathy, n (%)	44 (0.3)
Hyperlipidemia, n(%)	6,524 (41.3)

METHODOLOGIC NOTE: For identification codes of comorbidity, see **HERE**

COMORBIDITY PROFILE, LABORATORY TESTS	Pts with AMI N=15,808
Laboratory measurements	
Triglycerides (mg/dL), mean (SD)	131.1 (83.2)
Total cholesterol (mg/dL), mean (SD)	169.7 (46.2)
Glycated hemoglobin (mmol/mol), mean (SD)	50.0 (16.9)
Creatinine (mg/dL), mean (SD)	1.2 (0.9)
eGFR (ml/min/1.73 m2), mean (SD)	75.5 (29.9)
Patients with Proteinuria, n (%)	90 (0.6)

STARTING FROM THE SAMPLE POPULATION OF **6 MILLION OF HEALTH-ASSISTED INDIVIDUALS**,**217,658 PATIENTS WITH CKD HAVE BEEN IDENTIFIED** DURING INCLUSION PERIOD.

IN LINE WITH PUBLISHED EVIDENCES[1], THE MAIN COMORBIDITIES FOUND WERE:

HYPERTENSION (71%)
HYPERLIPIDEMIA (41%)
DIABETES (30%)
CKD (29%)
OTHER CV DISASE (26%)

References:
[1]Baechli C, Koch D, Bernet S, Gut L, Wagner U, Mueller B, Schuetz P, Kutz A. Association of comorbidities with clinical outcomes in patients after acute myocardial infarction. Int J Cardiol Heart Vasc. 2020 Jun 10;29:100558.

KEY- MESSAGES

VALUE MESSAGES SUPPORTED BY PRESENT EVIDENCE GENERATION

VALUES MESSAGES supported by the present evidence generation are:

In patients with Heart Failure (HF) - type II diabetes mellitus (T2D) - Chronic Kidney Diseases (CKD) – Acute Myocardial Infarction (AMI) in un selected Italian population.

❖ **FREQUENCY OF COMORBIDITIES** In line with published evidences, the main comorbidities found were:

- **HF PATIENTS:** HYPERTENSION (91%) CKD (51%) CV DISEASE (47%) HYPERLIPIDEMIA (43%) COPD (36%) DIABETES (35%)
- **CKD PATIENTS:** HYPERTENSION (85%) - HYPERLIPIDEMIA (39%) - DIABETES (29%) - CV DISEASE (27%) - COPD (36%)
- **T2D PATIENTS:** HYPERTENSION (78%) - HYPERLIPIDEMIA (50%) - CV DISEASE (17%) - CKD (16%)
- **AMI PATIENTS:** HYPERTENSION (71%) - HYPERLIPIDEMIA (41%) - DIABETES (30%) - CKD (29%) - OTHER CV DISASE (26%)

❖ **OUTCOMES** the findings from this analysis evaluated during the first 12 months of follow-up. Although a direct comparison with literature data was complicated as published data regarding outcomes are often presented in particular patient settings depending on the presence of specific comorbidities, treatments and clinical characteristics, Data obtained from our analysis are generally consistent with findings of outcomes of published studies.

- **HF PATIENTS**
  - ALL CAUSE HOSPITALIZATIONS: 51%
  - HF HOSPITALIZATION: 26%
  - MORTALITY: 26%
- **CKD PATIENTS**
  - ALL CAUSE HOSPITALIZATIONS: 47%
  - MORTALITY:15%
  - END-STAGE KIDNEY DISEASE: 7.7% of patients had a EGFR change ≥ 40% from baseline value.
- **T2D PATIENTS**
  - ALL CAUSE HOSPITALIZATIONS: 16.8%
  - HF HOSPITALIZATION: 2.1%
  - MORTALITY:4.4%.
  - END-STAGE KIDNEY DISEASE: 10% of patients had a EGFR change ≥ 40% from baseline value.

❖ **HEALTHCARE CONSUMPTIONS AND COSTS**

In the three different populations of analysis, in line with the literature, the results elaborated highlight how the cost of hospitalizations had the greatest impact on the total medical costs.

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Real World Evidence in Italy in Patients with Cardio-Renal-Metabolic sindrome (CRM)

Retrospective Observational Study from an Italian Administrative Database

Report 23/11/2023

Delitti in materia di violazione del diritto d'autore (Art. 25-novies, D.Lgs. n. 231/2001) [articolo aggiunto dalla L. n. 99/2009]

- Messa a disposizione del pubblico, in un sistema di reti telematiche, mediante connessioni di qualsiasi genere, di un'opera dell'ingegno protetta, o di parte di essa (art. 171, legge n.633/1941 comma 1 lett. a) bis)
- Reati di cui al punto precedente commessi su opere altrui non destinate alla pubblicazione qualora ne risulti offeso l'onore o la reputazione (art. 171, legge n.633/1941 comma 3)
- Abusiva duplicazione, per trarne profitto, di programmi per elaboratore; importazione, distribuzione, vendita o detenzione a scopo commerciale o imprenditoriale o concessione in locazione di programmi contenuti in supporti non contrassegnati dalla SIAE; predisposizione di mezzi per rimuovere o eludere i dispositivi di protezione di programmi per elaboratori (art. 171-bis legge n.633/1941 comma 1)
- Riproduzione, trasferimento su altro supporto, distribuzione, comunicazione, presentazione o dimostrazione in pubblico, del contenuto di una banca dati; estrazione o reimpiego della banca dati; distribuzione, vendita o concessione in locazione di banche di dati (art. 171-bis legge n.633/1941 comma 2)
- Abusiva duplicazione, riproduzione, trasmissione o diffusione in pubblico con qualsiasi procedimento, in tutto o in parte, di opere dell'ingegno destinate al circuito televisivo, cinematografico, della vendita o del noleggio di dischi, nastri o supporti analoghi o ogni altro supporto contenente fonogrammi o videogrammi di opere musicali, cinematografiche o audiovisive assimilate o sequenze di immagini in movimento; opere letterarie, drammatiche, scientifiche o didattiche, musicali o drammatico musicali, multimediali, anche se inserite in opere collettive o composite o banche dati; riproduzione, duplicazione, trasmissione o diffusione abusiva, vendita o commercio, cessione a qualsiasi titolo o importazione abusiva di oltre cinquanta copie o esemplari di opere tutelate dal diritto d'autore e da diritti connessi; immissione in un sistema di reti telematiche, mediante connessioni di qualsiasi genere, di un'opera dell'ingegno protetta dal diritto d'autore, o parte di essa (art. 171-ter legge n.633/1941)
- Mancata comunicazione alla SIAE dei dati di identificazione dei supporti non soggetti al contrassegno o falsa dichiarazione (art. 171-septies legge n.633/1941)
- Fraudolenta produzione, vendita, importazione, promozione, installazione, modifica, utilizzo per uso pubblico e privato di apparati o parti di apparati atti alla decodificazione di trasmissioni audiovisive ad accesso condizionato effettuate via etere, via satellite, via cavo, in forma sia analogica sia digitale (art. 171-octies legge n.633/1941).

Torna all'inizio