CONFLICT OF INTEREST DISCLOSURE

Disclosure. Luca Degli Esposti reports no conflicts of interest in this work.

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Cardiovascular Events And Mortality In Type-2 Diabetic Patients Under Second-Line Treatment With Hypoglycemic Agents: An Italian Real-World Study

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BACKGROUND AND OBJECTIVES

- Patients with **type 2 diabetes (T2D)** are characterized by a **two-fold higher risk of developing cardiovascular disease**, respect to non-diabetic population [1].
- International guidelines for the management of T2D patients recommend **metformin as a first-line glucose-lowering agent** [2].
- Metformin **failure occurs in over 50%** of T2D patients treated [3].
- In recent years, **new generation antidiabetic therapies** have become available as **second-line therapeutic treatments**; several studies have shown a clinical benefit of these therapies (characterized by a high cost) on **mortality** and **cardiovascular risk** in T2D patients [3].
- **The aim of the present study was to evaluate the incidence and risk of major adverse cardiovascular events (MACE) and all-cause mortality in T2D patients with metformin failure in second-line treatment with hypoglycemic drugs, using real-world data in Italy.**

References:
[1] Shin J-I. Curr Diab Rep. 2019 Aug;19(8):54
[2] American Diabetes Association. Diabetes Care. 20151;38:S41–8.
[3] Brown JB, et al. Diabetes Care. 2010 Mar 1;33(3):501–6.

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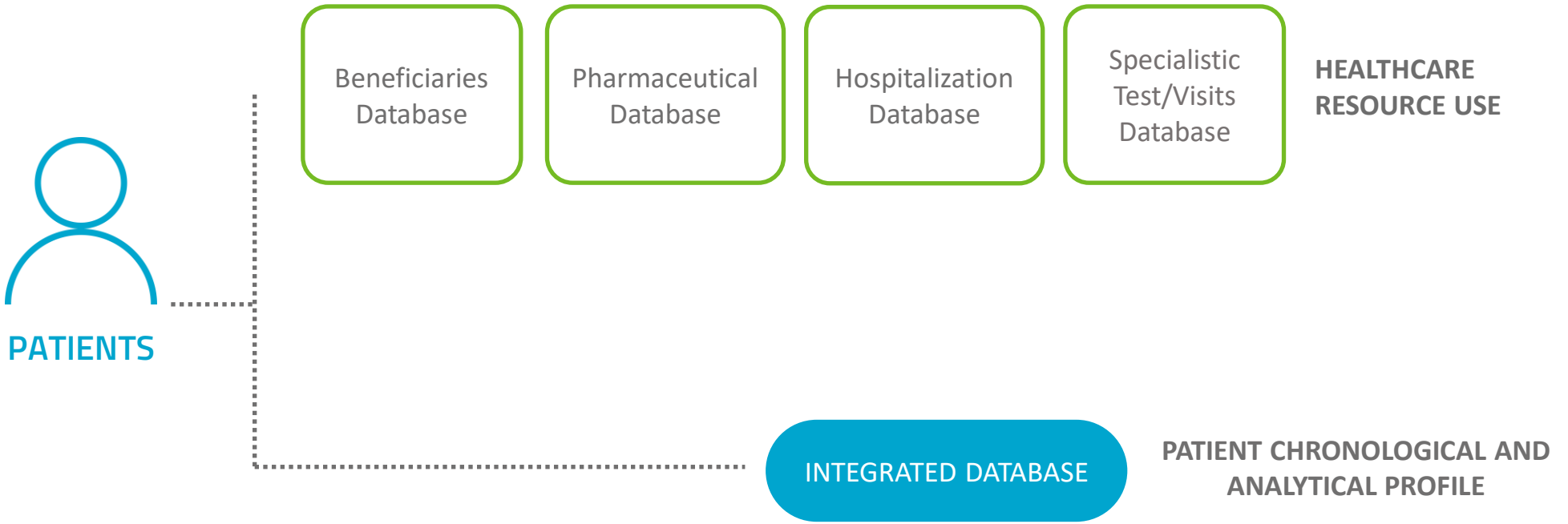
METHODS
DATA SOURCE

A ***retrospective study*** was conducted using administrative databases from a sample of Italian Local Health Units.



"The integration of administrative datasets makes it possible to represent the patient's entire clinical history and not just individual prescriptions. The analyzes were conducted on exclusively anonymous data in full compliance with privacy regulations. Clicon s.r.l. has obtained the approval as per legislation by all the Ethics Committees to analyze these data. The results are exclusively in aggregated form and never attributable to a single institution, department, doctor, individual, or individual prescribing behaviors. The study was conducted in full compliance with current legislation for retrospective studies."

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METHODS
STUDY POPULATION AND COHORTS DEFINITION

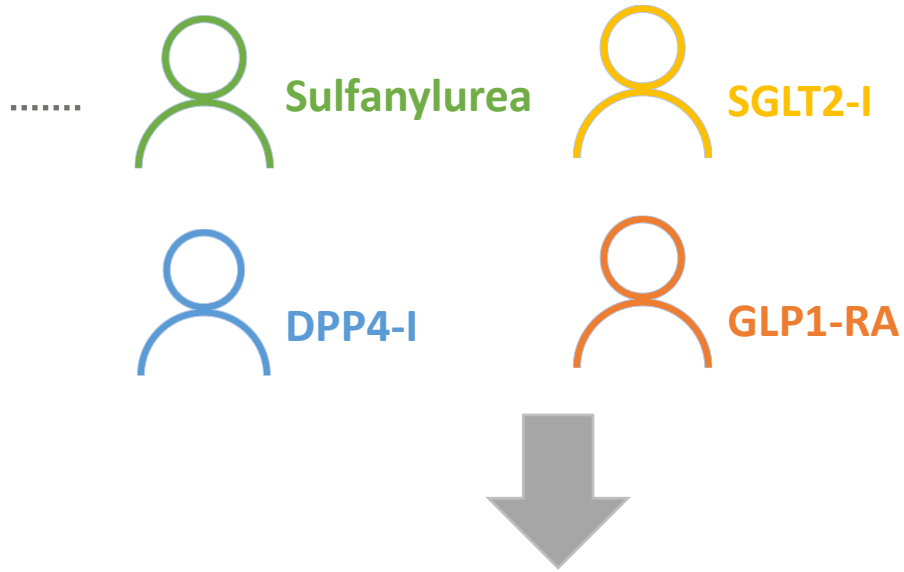
INCLUSION CRITERIA

During **01/2015-12/2017**, all adult T2D patients who failed metformin therapy and in **second-line with the following hypoglycemic drugs (**alone or combined with metformin) were included:

- sulfonylureas (Sulf),
- dipeptidyl peptidase inhibitors (DPP4I),
- glucagon-like-peptide-1 receptor agonists (GLP1-RA),
- inhibitors of the sodium/glucose-2 co-transporter (SGLT-2I).

Index-date: first prescription date within inclusion period.
Follow-up: from index-date to end of 2019.

*Based on the type of drug prescribed at the index date, the patients were divided into **4 cohorts**:*



Propensity score matching (PSM) was then applied to minimized selection bias therefore reducing potential unbalances among the cohorts.

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RESULTS

BASELINE CHARACTERISTICS OF INCLUDED PATIENTS

- ✓ Among the **18,818 patients included** (mean age 65.6 years, 57.5% male) **40.3% had Sulfanylurea** as second-line, **36.1% DPP4-I**, **15.3% SGLT2-I**, **8.3% GLP-1-RA**.
- ✓ The most frequent observed comorbidities were **hypertension** (74-78%), **dyslipidaemia** (51-64%); **anti-inflammatory agents** were used by 28-29% of patients and **anti-platelets** by 32-49% of patients.
- ✓ After applying the PSM, all statistically significant differences between the demographic and clinical characteristics among the cohorts were abated.

	Sulfonylureas	DPP4-I	SGLT2-I	GLP1-RA	P value
N	7,588	6,795	2,874	1,561	
Age (mean, SD)	67.6 (12.0)	67.5 (11.6)	59.8 (9.7)	57.7 (10.4)	<0.001
Male (n, %)	4,171 (55.0)	3,994 (58.8)	1,767 (61.5)	886 (56.8)	<0.001
Charlson index (mean, SD)	0.7 (1.1)	0.7 (0.9)	0.5 (0.7)	0.6 (0.8)	<0.001
- Charlson index = 0 ((n, %)	4,157 (54.8)	3,638 (53.5)	1,681 (58.5)	904 (57.9)	<0.001
- Charlson index = 1 (n, %)	2,428 (32.0)	2,269 (33.4)	900 (31.3)	505 (32.4)	
- Charlson index >= 2 (n, %)	1,003 (13.2)	888 (13.1)	293 (10.2)	152 (9.7)	
CV hospitalization (n, %)	447 (5.9)	652 (9.6)	157 (5.5)	76 (4.9)	<0.001
Hypertension (n, %)	5,769 (76.0)	5,316 (78.2)	2,166 (75.4)	1,161 (74.4)	<0.001
Dyslipidaemia (n, %)	3,884 (51.2)	4,349 (64.0)	1,800 (62.6)	885 (56.7)	<0.001
COPD (n, %)	1,248 (16.4)	1156 (17.0)	452 (15.7)	265 (17.0)	0.598
Antiinflammatory agents (n, %)	2,176 (28.7)	1959 (28.8)	823 (28.6)	432 (27.7)	1.000
Anti-platelet agents (n, %)	2,967 (39.1)	3292 (48.4)	1,151 (40.0)	495 (31.7)	<0.001
Metformine combination (n, %)	5,144 (67.8)	5449 (80.2)	2,461 (85.6)	1,267 (81.2)	<0.001

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RESULTS-
BASELINE CHARACTERISTICS OF INCLUDED PATIENTS POST PSM

	Sulfonylureas	DPP4-I	SGLT2-I	GLP1-RA	P value
N	1,487	1,488	1,488	1,489	
Age (mean, SD)	58.9 (11.4)	58.8 (10.8)	58.3 (9.6)	58.0 (10.3)	0.064
Male (n, %)	876 (58.9)	911 (61.2)	856 (57.5)	863 (58.0)	0.226
Charlson index (mean, SD)	0.5 (0.8)	0.6 (0.8)	0.5 (0.7)	0.5 (0.8)	0.494
- Charlson index = 0 ((n, %)	871 (58.6)	850 (57.1)	875 (58.8)	864 (58.0)	0.964
- Charlson index = 1 (n, %)	486 (32.7)	498 (33.5)	477 (32.1)	484 (32.5)	
- Charlson index >= 2 (n, %)	130 (8.7)	140 (9.4)	136 (9.1)	141 (9.5)	
CV hospitalization (n, %)	57 (3.8)	77 (5.2)	64 (4.3)	71 (4.8)	0.436
Hypertension (n, %)	1,097 (73.8)	1,105 (74.3)	1,109 (74.5)	1,110 (74.5)	1.000
Dyslipidaemia (n, %)	837 (56.3)	914 (61.4)	882 (59.3)	867 (58.2)	0.050
COPD (n, %)	229 (15.4)	228 (15.3)	235 (15.8)	245 (16.5)	1.000
Antiinflammatory agents (n, %)	412 (27.7)	430 (28.9)	416 (28.0)	413 (27.7)	1.000
Anti-platelet agents (n, %)	464 (31.2)	492 (33.1)	481 (32.3)	487 (32.7)	0.989
Metformine combination (n, %)	1,198 (80.6)	1,229 (82.6)	1,236 (83.1)	1,221 (82.0)	0.421

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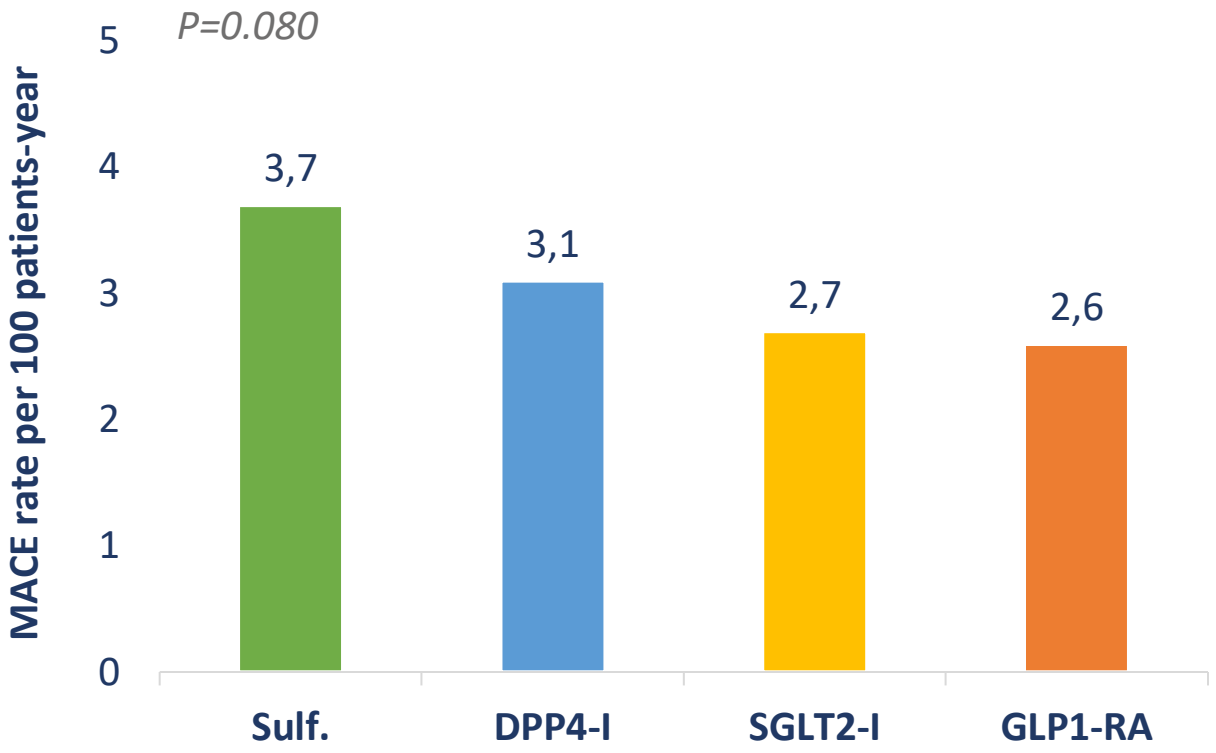
RESULTS

MACE INCIDENCE RATE PER 100 PATIENTS-YEAR, AFTER PSM



✓After PSM, a trend (not statistically significant) of a **slightly higher incidence of MACE events** in patients treated with **sulfonylureas** (3.7 per 100 patient/year) compared to patients treated with **DPP4-I, SGTL2-I, or GLP1-RA** (3.1, 2.7 and 2.6 per 100 patients/year), was observed.

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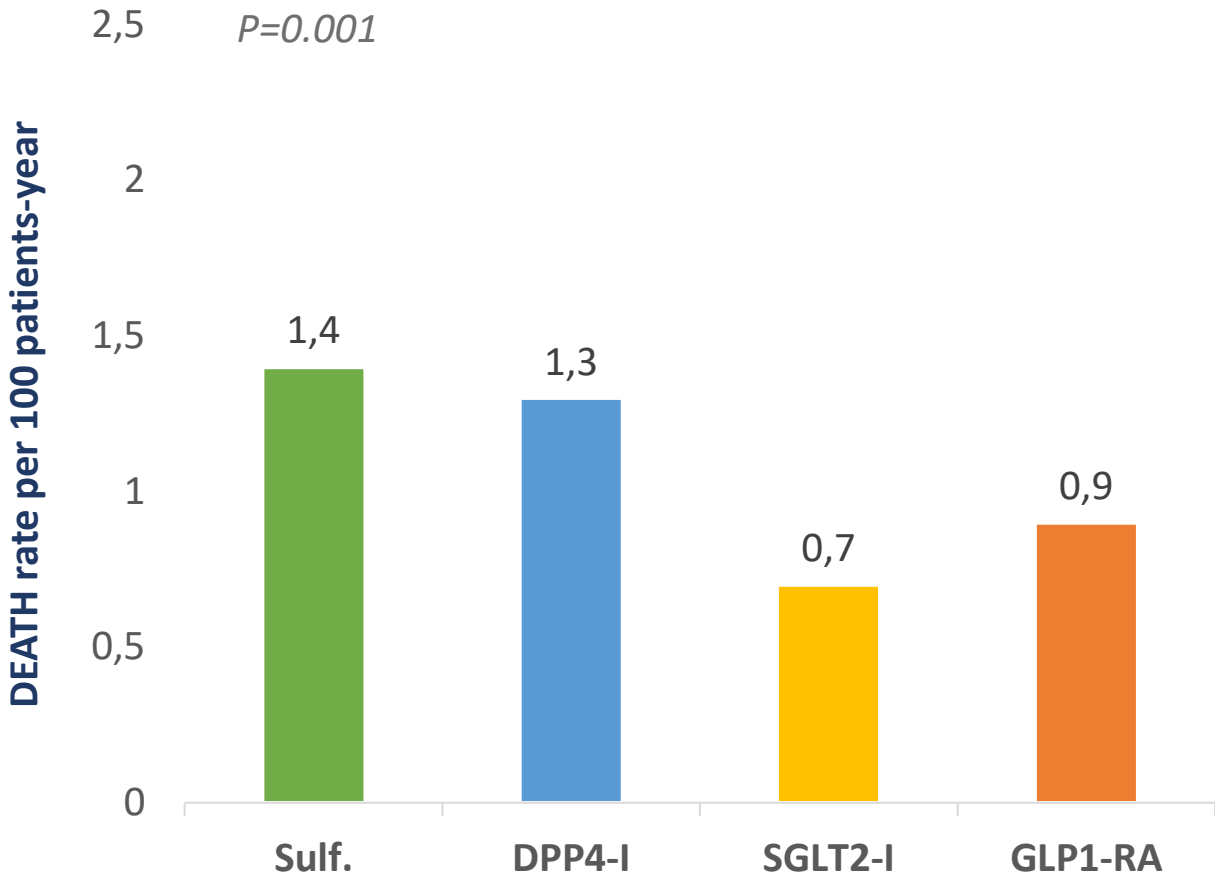
RESULTS

INCIDENCE OF DEATH PER 100 PATIENTS-YEAR, AFTER PSM



✓After PSM, all-cause death incidence rate per 100 person-years was **higher in Sulfanylurea cohort** (1.4) than **DPP4-I (1.3), SGLT2-I (0.7)** and **GLP1-RA (0.9)** (p= 0.001).

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RESULTS

MULTIVARIATE PREDICTIONS OF MACE AND DEATH OCCURRENCE, AFTER PSM

✓Compared to Sulfanylurea patients, **SGLT2-I and GLP1-RA had a 26% (p-value=0.013) and 30% (p-value=0.003) lower risk of MACE events**, respectively.

✓**SGLT2-I and GLP1-RA** patients were also associated to a **lower risk** (**SGLT2I: 52%, p-value=0.001; GLP1-RA:40%, p-value=0.012**) of **all-cause death** rather than Sulfanylurea cohort.

MACE INCIDENCE	HR	95% CI		P value
Sulf.	REF.			
DPP4-I	0.839	0.675	1.043	0.114
SGLT2-I	0.742	0.587	0.939	0.013
GLP1-RA	0.698	0.553	0.882	0.003

DEATH INCIDENCE	HR	95% CI		P value
Sulf.	REF.			
DPP4-I	0.889	0.633	1.248	0.496
SGLT2-I	0.483	0.314	0.741	0.001
GLP1-RA	0.607	0.412	0.895	0.012

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CONCLUSIONS
TAKE-HOME MESSAGE

1. This study provides an evaluation from ***real-world data*** of the clinical profile of **T2D patients in second-line with hypoglycemic agents** after metformin failure in Italian settings of clinical practice.

2. Our findings showed that in matched cohorts, **lower incidences and risks of MACE** and **all-cause death** were observed among patients who received **new generation antidiabetic drugs as second-line medications,** respect to those under sulfanylureas.

3. These data suggest that **evaluating clinical outcomes based on therapeutic interventions** might support health-decision making and could support action **to improve and optimize the prescriptive appropriateness** among type 2 diabetic patients.

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