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Supplemental material

Insulin treatment in patients with diabetes mellitus and heart failure in the era of new antidiabetic medications.

Brief title: *Insulin and new antidiabetics in heart failure*

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- **ANNEX 1**

Anatomical Therapeutic Chemical Classification (ATC code)

Medications	ATC-code
GLP-1 RA	A10BX04; A10BX07; A10BX10; A10BX13; A10BX14; A10BJ*
SGLT-2i	A10BK*; A10BX09; A10BX11; A10BX12; A10BD15; A10BD16; A10BD19; A10BD20; A10BD21
Insulin	A10A*; A10AB*; A10AE*; A10AC*; A10AD*
Biguanide- (Metformin)	A10BA*; A10BD01; A10BD02; A10BD03; A10BD05; A10BD07; A10BD08; A10BD10; A10BD11; A10BD13; A10BD14; A10BD15; A10BD16; A10BD17; A10BD18; A10BD20
Sulfonylureas	A10BB*; A10BD01; A10BD02; A10BD04; A10BD06
Meglitinides	A10BX02; A10BX03; A10BX08; A10BD14;
Glitazones	A10BG*; A10BD03; A10BD04; A10BD05; A10BD06; A10BD09; A10BD12
Alpha-glucosidase inhibitors –(Acarbose)	A10BF*; A10BD17
DDP-4i	A10BH*; A10BD07; A10BD08; A10BD09; A10BD10; A10BD11; A10BD12; A10BD13;

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	A10BD18; A10BD19; A10BD21; A10BH51
Antihypertensive agents	C02*; C03*; C03; C04*; C07*; C08*, C09*; C10BX03; C10BX09
ACE-I/ARBs	C09*; C10BX10
Lipid lowering agents	C10*
Antiplatelets	N02BA01; B01AC*; C10BX08; C10BX02; C10BX05; C10BX01;
Sucubitril-valsartan	CO9DXO4
Antiarrhythmics	C01B
Digitalis	C01A
Calcium antagonist	C08
Nitrates	C01DA
Ivabradine	C01EB17
GLP-1 RA: glucagon-like peptide-1 receptor agonist; SGLT-2i: sodium glucose cotransporter 2 inhibitors; DPP-4i: dipeptidyl peptidase-4 inhibitors; ACE-I: angiotensin-converting enzyme inhibitors; ARBs: angiotensin II receptor agonist blockers	

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ANNEX 2

COMORBIDITY (in the previous five years before entry in the study)

Diagnosis	ICD-9CM
Cerebrovascular disease	433.01; 433.11; 433.21; 433.31; 433.81; 433.91; 434.01 434.91; 430; 431; 432; 432.0; 432.1; 432.9; 435; 435.0; 435.1; 435.2; 435.3; 435.8; 435.9; 435.9; 436; 433.10; 433.20; 433.30; 38.11; 38.12; 433; 433.0; 433.00; 433.1; 433.10; 433.2; 433.20; 433.3; 433.30; 433.8; 433.80; 433.9; 433.90; 434; 434.0; 434.00; 434.9; 434.90; 437; 437.0; 437.1
Acute myocardial infarction	410.x; 412
Other ischemic disease	413.x; 414.x
Heart failure	428.x; 398.91; 402.01; 402.11; 402.91; 404.01; 404.03; 404.11; 404.13; 404.91; 404.93
Atrial fibrillation	427.31; 427.32
Cardiovascular interventions	36.x
Endovascular valve replacement or Heart valve replacement or Annuloplasty	35.x

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\or Valvuloplasty	
Device therapy	37.62; 37.65; 37.66; 37.67; 37.68; 0050; 0051; 0053; 0054; 37.94; 37.96; 37.97; 37.98; 37.94; 37.96; 37.97; 37.98; 0050; 0051; 0053; 0054; 37.71; 37.74; 37.82; 37.83; 37.85; 37.87; 37.89
Peripheral vascular disease	440.2; 440.20; 440.21; 440.22; 440.23; 440.24; 440.29; 440.3; 440.30; 440.3; 440.32; 443.81; 250.7; 250.70; 250.71; 250.72; 250.73; 39.50; 38.18; 38.08; 39.90; 39.25; 39.26; 39.29
Lower limb complication	736 .70; 707.1; 440.23; 707.1; 84.13; 84.15; 84.17; 84.11; 84.12; 730.06; 730.07; 730.16; 730.17; 730.26; 730.27; 730.86; 730.87; 730.96; 730.97; 681.1; 681.10; 681.9; 682.6; 682.7; 711.97; 785.4; 440.24
Pulmonary embolism	415.1; 415.11; 415.19
Renal disease	585.x; V451; 39.95; 54.98; V561; V562; V563; V563.1; V563.2; 38.95; 39.27; 39.42; 39.43; 581.81

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Neuropathy	350; 350.0; 350.1; 350.2; 350.8; 350.9; 351; 351.0; 351.1 351.8; 351.9; 354; 354.0; 354.1; 354.2; 354.3; 354.4; 354.5 354.8; 354.9; 355; 355.0; 355.1; 355.2; 355.3; 355.4; 355.5; 355.6; 355.7; 355.71; 355.79; 355.8; 355.9; 378.51; 378.52; 378.53; 378.54; 357.2; 337.1
Diabetic retinopathy	362.0; 362.01; 362.02; 362.01 + 14.24; 362.02 + 14.24; 362.55; 361; 364.42; 365.63; 369.xx
Chronic obstructive pulmonary disease	491.x;492.x;493.x; 494.x;496.x;518.81; 518.83; 518.84
Cancer	140 -165, 170 -208, 210 - 239, 2592

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ANNEX 3

ICD-9CM code of study clinical events

Diagnosis	ICD-9CM code
Heart failure	428.x; 398.91; 402.01; 402.11; 402.91; 404.01; 404.03; 404.11; 404.13; 404.91; 404.93
Acute myocardial infarction	410.x; 412
Stroke (ischemic, hemorrhagic)	[433.01; 433.11; 433.21; 433.31; 433.81; 433.91; 434.01; 434.91; 430; 431; 432; 432.0; 432.1; 432.9
Renal failure	585.x; V451; 39.95; 54.98; V561; V562; V563; V563.1; V563.2; 38.95; 39.27; 39.42; 39.43; 581.81
Unstable angina	411; 411.0; 411.1; 411.8; 411.81; 411.89

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ANNEX 4

ICD-9CM code of safety events

Diagnosis	ICD-9CM code
Hypoglycemia	2510; 2512
Ketoacidosis	2501; 25010; 25011; 25012; 25013
Diabetic coma	25030; 25031; 25032; 25033
Lower limb amputations	8411; 8412; 8413; 8415; 8417
Renal failure	584; 5845; 5846; 5847; 5848; 5849
Syncope	9921; 7802
Bone fractures	800; 829

ANNEX 5.

Sensitivity analyses.

The consistency in treatment association with outcomes was assessed in: i) propensity matched cohorts, ii) unmatched and matched propensity cohort (MPC) of subjects without a history of renal disease and iii) as SGLT-2i received first marketing authorization approval in Italy in 2014, to homogenize the calendar years and the follow-up; it was considered first-time antidiabetic agent uses between 1 January 2015 and 31 December 2018 in propensity matched cohorts, then a Kaplan-Meier analysis for death from any cause and first hospitalization for HF was conducted.

In i) and ii) cohorts time-to-first event analysis was conducted using multivariable Cox proportional hazard models; HRs and 95% CI for each outcome was estimated, comparing the effects of GLP-1RA, SGLT-2i and other-AHAs versus insulin; in MPC hazard ratios (HRs) were adjusted for variables with standardized differences >10%.

Propensity score matching

Participants were matched on the logit of the propensity score using callipers of width equal to 0.1 of the standard deviation of the logit of the estimated propensity score. GLP-1 RA, SGLT-2i and other-AHAs cohorts were matched with insulin in a 1:1 ratio using variables related to outcomes of interest: age classes (50-59; 60-64; 65-69; 70-74; 75-79; >80), sex, stroke, myocardial infarction, atrial fibrillation, renal disease, chronic obstructive pulmonary disease, cancer, duration of diabetes, and the Drug Derived Complexity Index (DDCI), a proxy of comorbidities (1).

The adequacy (congruency) of PSM was assessed from the standardized mean differences (SMD) of post-matching patients' characteristics: good balance is conventionally set at SMD <0.10 (2).

The baseline characteristics of matched populations of subjects according to treatment status (SGLT-2i, GLP-1RA, Other-AHAs vs insulin), from 2010 to 2018, are presented in the three tables below: [A]. SGLT-2i vs insulin, [B]: GLP-1RA vs Insulin, [C] Other-AHAs vs Insulin.

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TABLES [(A), (B), (C)]: Baseline characteristics of matched populations of subjects with diabetes and heart failure according to treatment status, from 2010 to 2018. [A]. SGLT-2i vs insulin, [B]: GLP-1RA vs Insulin, [C] Other-AHAs vs Insulin.

Matching variables related to outcomes of interest: age classes, sex, year of entry in the cohort, haemorrahgic and ischemic stroke, myocardial infarction, atrial fibrillation, chronic obstructive pulmonary disease, cancer, DDCI, duration of diabetes.

(A)

Variable	Apulia			Lombardy		
	SGLT-2i (414)	Insulin (414)	Standardized differences	SGLT-2i (715)	Insulin (715)	Standardized differences
Mean age, mean± SD	70.5 ± 7.8	71.1 ± 8.5	-0.07	71.3 ± 7.6	72.4 ± 9.1	-0.12
Age categories, n (%)						
50-59 yr	42 (10.14)	41 (9.90)	0.01	49 (6.85)	55 (7.69)	0.10
60-64 yr	49 (11.84)	48 (11.59)		75 (10.49)	82 (11.47)	
65-69 yr	86 (20.77)	87 (21.01)		151 (21.12)	118 (16.50)	
70-74 yr	103 (24.88)	103 (24.88)		187 (26.15)	190 (26.57)	
75-79 yr	81 (19.57)	81 (19.57)		151 (21.12)	157 (21.96)	
80+	53 (12.80)	54 (13.04)		102 (14.27)	113 (15.80)	
Gender (female), n (%)	168 (40.6)	167 (40.3)	0.00	236 (33.0)	240 (33.6)	-0.01
Comorbidities, n (%)						
Cerebrovascular disease	89 (21.5)	61 (14.7)	0.17	84 (11.7)	85 (11.8)	0.00
- Stroke	18 (4.4)	10 (2.4)	0.11	20 (2.8)	27 (3.8)	-0.05
Ischemic heart disease						
- Myocardial infarction	112 (27.1)	108 (26.1)	0.02	183 (25.6)	202 (28.2)	-0.05
-Other coronary disease	210 (50.7)	184 (44.4)	0.12	344 (48.1)	321 (44.9)	0.06
Atrial fibrillation	107 (25.9)	106 (25.6)	0.01	207 (28.9)	203 (28.4)	0.01
Peripheral vascular disease	72 (17.4)	61 (14.7)	0.07	95 (13.3)	98 (13.7)	-0.01
Lower limb complication	4 (1.0)	10 (2.4)	-0.11	24 (3.3)	31 (4.2)	-0.05
Pulmonary embolism	1 (0.2)	6 (1.5)	-0.13	3 (0.4)	10 (1.4)	-0.10
Renal failure	59 (14.3)	100 (24.2)	-0.25	57 (8.0)	183 (25.6)	-0.48
Neuropathy	22 (5.3)	6 (1. 5)	0.21	38 (5.3)	12 (1.7)	0.19
Diabetic retinopathy	1 (0.2)	2 (0.5)	-0.04	4 (0.5)	4 (0.5)	0.00
Chronic obstructive pulmonary disease	101 (24.4)	125 (30.2)	-0.13	136 (19.0)	135 (18.9)	0.00
Cancer	46 (11.1)	45 (10.9)	0.01	70 (9.8)	62 (8.7)	-0.01
DDCI Index, median [Q1-Q3]	8 [7-10]	8 [7-10]	0.02	8 [7-10]	8 [6-10]	0.01
Number of hospital admission, median [Q1-Q3]	3 (2-5)	3 (2-5)	0.09	3 [2-5]	3 [2-6]	-0.15
History of diabetes, n (%)						
0-4 yr	2 (0.5)	2 (0.5)	0.14	63 (8.3)	68 (9.0)	0.04
5-9 yr	83 (20.1)	84 (20.3)		188 (24.8)	199 (26.2)	
10+yr	329 (79.5)	328 (79.2)		507 (66.9)	491 (64.8)	
Median [Q1-Q3]	10	10	-0.01	10	10	0.12

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	[8-10]	[9-10]		[8-10]	[8-10]	
Cardiovascular interventions, n (%)						
Percutaneous coronary intervention/ Coronary artery by-pass/ Other revascularizations	34 (8.2)	52 (12.6)	-0.14	85 (11.9)	83 (11.6)	0.00
Heart valve replacement/ Annuloplasty/Valvuloplasty	11 (2.7)	28 (6.8)	-0.19	47 (6.6)	41 (5.7)	0.03
Device therapy, n (%)						
Ventricular assist device	1 (0.2)	0 (0.0)	0.07	0 (0.0)	2 (0.3)	-0.07
Implantable cardioverter defibrillator	38 (9.2)	47 (11.4)	-0.07	49 (6.8)	67 (9.4)	-0.09
Cardiac resynchronization therapy	15 (3.6)	10 (2.4)	0.07	65 (9.1)	57 (8.0)	0.04
Pacemaker implantation	28 (6.8)	29 (7.0)	-0.01	42 (5.9)	57 (8.0)	-0.08
Antihyperglycemic drugs						
GLP-1RA	5 (1.2)	1 (0.2)	0.11	10 (1.3)	3 (0.4)	0.10
SGLT-2i	0 (0.0)	0 (0.0)	0.00	0 (0.0)	0 (0.0)	0.00
Other-AHAs	394 (95.8)	409 (98.8)	-0.21	670 (93.7)	702 (98.2)	-0.22
Insulin	288 (69.6)	0 (0.0)	2.13	496 (69.4)	0 (0.0)	2.1
Metformin	373 (90.1)	364 (87.9)	0.07	626 (87.5)	624 (87.3)	-0.00
Sulfonylureas	154 (37.2)	218 (52.7)	-0.31	393 (55.0)	502 (70.2)	-0.32
Glinides	156 (37.7)	192 (46.4)	-0.17	115 (16.1)	215 (30.1)	-0.33
Glitazones	63 (15.)	58 (14.0)	0.03	112 (15.6)	100 (14.0)	0.02
Acarbose	47 (11.4)	34 (8.2)	0.11	65 (9.1)	69 (9.6)	-0.01
DDP4-inhibitor	147 (35.5)	132 (31.9)	0.07	197 (27.5)	247 (34.5)	-0.15
No Antihyperglycemic drugs	0 (0.0)	5 (0.0)	0.15	5 (0.7)	13 (1.8)	0.10
Other medications of interest (in the previous 12 months)						
ACE-I/ARBS	337 (81.4)	313 (75.6)	0.14	607 (84.9)	568 (79.4)	0.14
Sacubitril-valsartan	0 (0.0)	0 (0.0)	0.00	9 (1.2)	5 (0.7)	0.05
Beta blockers	318 (76.8)	269 (65.0)	0.26	577 (80.7)	526 (73.6)	0.17
Diuretics	304 (73.4)	309 (74.6)	-0.03	587 (82.1)	568 (79.4)	0.06
Mineralocorticoid receptor antagonist	152 (36.7)	155 (37.4)	-0.02	276 (38.6)	251 (35.1)	0.07
Antiarrhythmics	49 (11.8)	72 (17.4)	-0.16	104 (14.5)	130 (18.2)	-0.09
Digital drugs	43 (10.4)	48 (11.6)	-0.04	60 (8.4)	47 (6.6)	0.06
Ca-antagonists	108 (26.1)	100 (24.2)	0.04	255 (35.6)	281 (39.3)	-0.07
Nitrates	56 (13.5)	43 (10.4)	0.09	139 (19.4)	144 (20.1)	-0.01
Ivabradine	43 (10.4)	38 (9.2)	0.04	64 (8.9)	69 (9.6)	0.02
Lipid lowering drugs	348 (84.1)	296 (71.5)	0.30	577 (80.7)	485 (67.8)	0.29
Antiplatelet drugs	312 (75.4)	290 (70.1)	0.12	460 (64.3)	434 (60.7)	0.07
Anticoagulant drugs	118 (28.5)	116 (28.0)	0.02	224 (31.3)	233 (32.6)	-0.02

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(B)

Variable	Apulia			Lombardy		
	GLP1-RA (444)	Insulin (444)	Standardized differences	GLP1-RA (758)	Insulin (758)	Standardized differences
Mean age, mean± SD	68.1 ± 8.3	69.1 ± 8.9	-0.12	69.5 ± 8.4	69.7 ± 9.2	-0.01
Age categories, n (%)						
50-59 yr	71 (15.99)	63 (14.19)		98 (12.93)	103 (13.59)	
60-64 yr	83 (18.69)	82 (18.47)		126 (16.62)	142 (18.73)	
65-69 yr	101 (22.75)	97 (21.85)	0.06	146 (19.26)	150 (19.79)	0.01
70-74 yr	90 (20.27)	97 (21.85)		160 (21.11)	156 (20.58)	
75-79 yr	60 (13.51)	58 (13.06)		129 (17.02)	109 (14.38)	
80+	39 (8.78)	47 (10.59)		99 (13.06)	98 (12.93)	
Female), n (%)	194 (43.7)	176 (39.6)	0.08	288 (37.9)	250 (33.1)	0.09
Comorbidities, , n (%)						
Cerebrovascular disease	67 (15.1)	90 (20.3)	-0.13	79 (10.4)	96 (12.6)	-0.07
-Stroke	14 (3.2)	22 (5.0)	-0.09	20 (2.6)	24 (3.2)	-0.03
Ischemic heart disease						
-Myocardial infarction	104 (23.4)	102 (23.0)	0.01	155 (20.4)	168 (22.0)	-0.04
-Other coronary disease	190 (42.8)	205 (46.2)	-0.07	339 (44.7)	314 (41.4)	0.06
Atrial fibrillation	125 (28.2)	121 (27.3)	0.02	232 (30.6)	245 (32.3)	-0.03
Peripheral vascular disease	110 (24.8)	83 (18.7)	0.15	95 (12.5)	130 (17.1)	-0.11
Lower limb complication	21 (4.7)	8 (1.8)	0.16	27 (3.5)	41 (5.4)	-0.08
Pulmonary embolism	4 (0.9)	4 (0.9)	0.00	7 (0.9)	10 (1.3)	-0.03
Renal failure	94 (21.2)	93 (21.0)	0.01	118 (15.6)	176 (23.2)	-0.19
Neuropathy	24 (5.1)	7 (1.6)	0.21	34 (4.5)	20 (2.6)	0.09
Diabetic retinopathy	0 (0.0)	3 (0.7)	-0.11	1 (0.1)	4 (0.5)	-0.06
Chronic obstructive pulmonary disease	136 (30.6)	142 (32.0)	-0.03	185 (24.4)	154 (20.3)	0.09
Cancer	50 (11.3)	35 (7.9)	0.11	81 (10.7)	80 (10.5)	0.00
Cardiovascular interventions, n (%)						
Percutaneous coronary intervention/ Coronary artery by-pass/ Other revascularizations	47 (10.6)	58 (13.1)	-0.07	122 (16.1)	127 (16.7)	-0.02
Heart valve replacement/ Annuloplasty/Valvuloplasty	15 (3.4)	18 (4.1)	-0.03	42 (5.5)	50 (6.5)	-0.04
Device therapy, n (%)						
Ventricular assist device	2 (0.5)	3 (0.7)	-0.03	1 (0.1)	2 (0.3)	-0.02
Implantable cardioverter defibrillator	28 (6.3)	51 (11.5)	-0.18	74 (9.7)	68 (9.0)	0.02
Cardiac resynchronization therapy	17 (3.8)	15 (3.4)	0.02	33 (4.3)	45 (5.9)	-0.07
Pacemaker implantation	25 (5.6)	23 (5.2)	0.02	47 (6.2)	55 (7.2)	-0.04
DDCI Index, median [IQR]	9 [7-10]	8 [7-10]		8 [7-10]	8 [7-10]	0.05
Number of hospital admissions, median [IQR]	4 [2-6]	4 [2-6]	0.08	4 [2-6]	4 [2-6]	-0.10

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History of diabetes, n (%)						
0-4 yr	31 (7.0)	19 (4.3)		63 (8.3)	68 (9.0)	
5-9 yr	142 (32.0)	131 (29.50)	0.14	188 (24.8)	199 (26.2)	0.04
10+yr	271 (61.0)	294 (66.2)		507 (66.9)	491 (64.8)	
Median [Q1-Q3]	10 [8-10]	10 [9-10]	-0.01	10 [8-10]	10 [8-10]	0.12
Antihyperglycemic drugs						
GLP-1RA	0 (0.0)	5 (1.1)	-0.15	0 (0.0)	3 (0.4)	-0.08
SGLT-2i	0 (0.0)	0 (0.0)	0.00	0 (0.0)	0 (0.0)	0.00
Other-AHAs	432 (97.3)	441 (99.3)	-0.15	737 (97.2)	740 (97.6)	-0.02
Insulin	241 (54.3)	0 (0.0)	1.54	396 (52.2)	0 (0.0)	1.47
Metformin	416 (93.7)	407 (91.7)	0.08	691 (91.1)	660 (87.1)	0.12
Sulfonylureas	201 (45.3)	283 (63.7)	-0.37	486 (64.1)	547 (72.1)	-0.17
Glinides	180 (40.5)	197 (44.4)	-0.08	179 (23.4)	236 (31.1)	-0.17
Glitazones	113 (25.5)	79 (17.8)	0.18	196 (25.8)	104 (13.7)	0.30
Acarbose	35 (7.9)	38 (8.6)	-0.02	85 (11.1)	63 (8.3)	0.09
DDP4-inhibitors	148 (33.3)	111 (25.0)	0.18	233 (30.7)	184 (24.3)	0.14
None	0 (0.0)	3 (0.7)	0.11	2 (0.3)	18 (2.4)	0.18
Other medications of interest (in the previous 12 months)						
ACE-I/ARBS	377 (84.9)	369 (83.11)	0.05	644 (84.9)	609 (80.3)	0.12
Sacubitril-valsartan	0 (0.0)	0 (0.0)	0.00	5 (0.6)	3 (0.4)	0.03
Beta blockers	309 (69.6)	300 (67.6)	0.04	580 (76.5)	562 (74.1)	0.05
Diuretics	356 (80.2)	332 (74.77)	0.13	653 (86.1)	606 (79.9)	0.15
Mineralocorticoid receptor antagonists	157 (35.4)	170 (38.3)	-0.06	287 (37.8)	275 (36.3)	0.03
Antiarrhythmics	63 (14.2)	81 (18.2)	-0.11	120 (15.8)	135 (17.8)	-0.05
Digital drugs	41 (9.2)	65 (14.6)	-0.16	57 (7.5)	75 (9.9)	0.08
Ca-antagonists	122 (27.5)	137 (30.9)	-0.07	281 (37.0)	298 (39.3)	0.04
Nitrates	71 (16.0)	85 (19.1)	-0.08	177 (23.3)	178 (23.4)	0.00
Ivabradine	28 (6.3)	30 (6.8)	-0.02	55 (7.2)	58 (7.6)	0.01
Lipid lowering drugs	362 (81.5)	314 (70.7)	0.25	586 (77.3)	492 (64.9)	0.27
Antiplatelet drugs	308 (69.4)	326 (73.4)	-0.08	496 (65.4)	466 (61.5)	0.08
Anticoagulant drugs	130 (29.3)	122 (27.5)	0.04	250 (33.1)	227 (32.6)	0.06

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(C)

Variable	Apulia			Lombardy		
	Insulin (5009)	Other_AHAs (5009)	Standardized differences	Other-AHAs (7043)	Insulin (7043)	Standardized differences
Mean age, mean± SD	77.6 ± 8.9	77.6 ± 8.5	0.00	78.8 ± 8.7	78.7 ± 8.5	0.01
Age categories, n (%)						
50-59 yr	186 (3.71)	132 (2.64)		171 (2.58)	182 (2.58)	
60-64 yr	267 (5.33)	253 (5.05)		295 (4.19)	315 (4.47)	
65-69 yr	483 (9.64)	498 (9.94)		529 (7.51)	529 (7.95)	
70-74 yr	705 (14.07)	767 (15.31)	-0.07	981 (13.93)	981 (13.80)	0.06
75-79 yr	1052 (21.00)	1076 (21.48)		1460 (20.73)	1460 (20.64)	
80+	2316 (46.24)	2283 (45.58)		3607 (51.21)	3607 (50.55)	
Female), n (%)	2568 (51.3)	2536 (50.6)	0.01	3220 (45.7)	3147 (44.7)	0.02
Comorbidities,, n (%)						
Cerebrovascular disease	1160 (23.2)	1249 (25.0)	-0.04	1201 (17.1)	1293 (18.4)	-0.03
-Stroke	251 (5.0)	238 (4.8)	0.01	273 (3.8)	321 (4.5)	0.00
Ischemic heart disease						
-Myocardial infarction	1099 (21.9)	1124 (22.4)	-0.01	1685 (23.9)	1684 (23.9)	-0.00
-Other coronary disease	2042 (40.8)	2211 (44.1)	-0.07	2801 (39.7)	2730 (38.7)	-0.00
Atrial fibrillation	1851 (37.0)	1890 (37.7)	-0.02	2735 (38.8)	2737 (38.8)	-0.00
Peripheral vascular disease	902 (18.0)	961 (19.2)	-0.03	874 (12.4)	1030 (14.6)	-0.06
Lower limb complication	99 (2.0)	114 (2.3)	-0.02	241 (3.4)	270 (3.8)	-0.02
Pulmonary embolism	36 (0.7)	31 (0.6)	0.01	99 (1.4)	120 (1.7)	-0.02
Renal failure	1531 (30.6)	1259 (25.1)	0.12	1542 (21.9)	1892 (26.8)	-0.11
Neuropathy	130 (2.6)	216 (4.3)	-0.09	279 (3.9)	224 (3.2)	0.04
Diabetic retinopathy	12 (0.2)	30 (0.6)	-0.05	22 (0.3)	22 (0.3)	0.00
Chronic obstructive pulmonary disease	2013 (40.2)	2035 (40.6)	-0.01	1472 (20.9)	1517 (21.5)	-0.01
Cancer	819 (16.4)	872 (17.4)	-0.03	1187 (16.8)	1171 (16.6)	0.00
DDCI Index, median [Q1-Q3]	9 (7-11)	9 (7-11)	0.01	8 [7,10]	8 [6.10]	0.03
Number of hospital admissions, median [Q1-Q3]	4 (2-6)	4 (2-7)	-0.06	4 [2,6]	4 [2,6]	-0.01
History of diabetes, n (%)						
0-4 yr	856 (17.1)	916 (18.3)	0.04	906 (12.8)	947 (13.4)	0.15
5-9 yr	2289 (45.7)	2195 (43.8)		1930 (27.4)	1887 (26.6)	
10+yr	1864 (37.2)	1898 (37.9)		4207 (60.0)	4219 (60.0)	
Median [Q1-Q3]	9 6-10	9 6-10	0.07	10 7-10	10 7-10	0.05
Cardiovascular interventions, n (%)						
Percutaneous coronary intervention/ Coronary artery by-pass/ Other revascularizations	535 (10.7)	542 (10.8)	-0.00	963 (13.7)	967 (13.7)	-0.00
Heart valve replacement/ Annuloplasty/Valvuloplasty	165 (3.3)	152 (3.0)	0.01	400 (5.7)	341 (4.8)	0.03
Device therapy, n (%)						

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Ventricular assist device	4 (0.1)	1 (0.02)	0.02	2 (0.0)	2 (0.0)	0.00
Implantable cardioverter defibrillator	382 (7.6)	370 (7.4)	0.01	402 (5.7)	436 (6.2)	-0.02
Cardiac resynchronization therapy	98 (2.0)	106 (2.1)	-0.01	260 (3.7)	258 (3.6)	0.01
Pacemaker implantation	373 (7.5)	432 (8.6)	-0.04	751 (10.6)	641 (9.1)	0.05
Antihyperglycemic drugs						
GLP-1RA	15 (0.3)	17 (0.3)	-0.01	17 (0.2)	17 (0.2)	0.00
SGLT-2i	0 (0.0)	0 (0.0)	0.00	0 (0.0)	0 (0.0)	0.00
Other AHAs	4850 (96.8)	4166 (83.2)	0.46	5999 (85.2)	6792 (96.4)	-0.39
Insulin	0 (0.0)	1710 (34.1)	-1.02	0 (0.0)	1693 (24.0)	0.71
Metformin	4284 (85.5)	3401 (67.9)	0.42	4473 (63.5)	5744 (81.5)	-0.27
Sulfonylureas	3356 (67.0)	2491 (49.7)	0.35	3835 (54.4)	5329 (75.6)	-0.39
Glinides	2177 (43.5)	598 (11.9)	0.75	574 (8.1)	2538 (36.0)	-0.53
Glitazones	711 (14.2)	337 (6.7)	0.24	265 (3.7)	765 (10.8)	-0.20
Acarbose	351 (7.0)	2 (0.04)	0.38	5 (0.1)	517 (7.3)	0.39
DDP4-inhibitor	599 (12.0)	16 (0.3)	0.49	20 (0.3)	929 (13.2)	-0.53
None	159 (3.2)	487 (9.7)	0.27	599 (8.5)	251 (3.5)	-0.20
Other medications of interest (in the previous 12 months)						
ACE-I/ARBS	4047 (80.8)	4187 (83.6)	-0.07	5609 (79.6)	5647 (80.2)	-0.01
Sacubitril-valsartan	0 (0.0)	0 (0.0)	0.00	8 (0.1)	8 (0.1)	0.00
Beta blockers	2773 (55.4)	2860 (57.1)	-0.03	4524 (64.2)	4578 (65.0)	-0.01
Diuretics	4079 (81.4)	4068 (81.2)	0.01	5852 (83.1)	5765 (81.8)	0.03
Mineralocorticoid receptor antagonists	1857 (37.1)	1662 (33.2)	0.08	2294 (32.6)	2322 (33.0)	-0.01
Antiarrhythmics	909 (18.2)	854 (17.1)	0.03	1276 (18.1)	1198 (17.0)	0.02
Digital drugs	1180 (23. 6)	1121 (22.4)	0.03	1034 (14.6)	1016 (14.8)	-0.01
Ca-antagonists	1670 (33.3)	1658 (33.1)	0.01	2658 (37.7)	2732 (38.8)	-0.02
Nitrates	1307 (26.1)	1420 (28.4)	-0.05	2458 (34.9)	2356 (33.4)	0.03
Ivabradine	192 (3.8)	185 (3.7)	0.01	252 (3.6)	267 (3.8)	-0.01
Lipid lowering drugs	2982 (59.5)	3105 (62.0)	-0.05	3985 (56.6)	4017 (57.0)	-0.01
Antiplatelet drugs	3398 (67.8)	3512 (70.1)	-0.05	4368 (62.0)	4286 (60.8)	0.02
Anticoagulant drugs	1329 (26.5)	1344 (26.8)	-0.01	2427 (34.4)	2305 (32.7)	0.03

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SUPPLEMENTARY REFERENCES

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2. Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. Stat Med 2009;28:3083–3107.

SUPPLEMENTARY TABLES

Supplementary Table 1A. Sensitivity analysis. Hazard ratios (CI 95%) for clinical events in matched cohorts from the Apulia region

	SGLT-2i *(414)*	Insulin *(414)*		GLP-1RA *(444)*	Insulin *(444)*		Other-AHAs *(5009)*	Insulin *(5009)*	
	IR/100 person year n (%)	IR/100 person year n (%)	**HR (CI 95%)**	IR/100 person year n (%)	IR/100 person year n (%)	**HR (CI 95%)**	IR/100 person year n (%)	IR/100 person year n (%)	**HR (CI 95%)**
Death from any cause	15 (2.83)	113 (9.95)	**0.24 (0.13-0.43)**	62 (4.69)	113 (9.95)	**0.44 (0.32-0.61)**	2460 (13.73)	2849 (18.51)	**0.78 (0.74-0.82)**
First hospitalization for heart failure	45 (9.19)	107 (11.95)	**0.68 (0.45-1.01)**	76 (6.59)	107 (11.95)	**1.00 (0.41-2.43)**	1440 (9.77)	170 (1.12)	**0.91 (0.85-0.98)**
Renal failure	3 (0.57)	21 (1.95)	**0.30 (0.08-1.08)**	9 (0.69)	21 (1.95)	**0.38 (0.19-0.74)**	359 (2.10)	283 (1.91)	**0.84 (0.73-0.97)**
All Stroke	2 (0.38)	12 (1.08)	**0.64 (0.10-4.05)**	9 (0.69)	12 (1.08)	**0.18 (0.04-0.75)**	147 (0.83)	46 (0.30)	**0.77 (0.61-0.96)**
Myocardial infarction	8 (1.52)	25 (2.29)	**0.53 (0.21-1.33)**	16 (1.24)	25 (2.29)	**0.60 (0.44-0.82)**	264 (1.52)	1399 (11.40)	**0.82 (0.69-0.97)**
MACE3	25 (4.78)	118 (12.55)	**0.32 (0.20-0.52)**	73 (5.86)	118 (12.55)	**0.43 (0.32-0.58)**	2655 (15.46)	3048 (20.86)	**0.78 (0.74-0.82)**
MACE4	71 (14.87)	206 (25.11)	**0.54 (0.40-0.73)**	126 (11.42)	206 (25.11)	**0.47 (0.37-0.59)**	3211 (23.01)	3572 (31.01)	**0.78 (0.75-0.82)**
IR, crude incidence rate. HR adjustment for covariates with a standardized difference >10%: a) SGLT-2i vs insulin (cerebrovascular disease, stroke, other coronary disease, cardiovascular interventions, endovascular valve replacement or heart valve replacement /annuloplasty /valvuloplasty, lower limb complication, pulmonary embolism, renal failure, neuropathy, chronic obstructive pulmonary disease); b) GLP-1RA vs insulin (age classes (50-59, 60-64, 65-69, 70-74, 75-79, >80), cerebrovascular disease, myocardial infarction, implantable cardioverter defibrillator, peripheral artery disease, lower limb complication, diabetic neuropathy, diabetic retinopathy, cancer); c) other-AHAs vs insulin (renal disease). MACE, major adverse clinical event									

Supplementary Table 1B. Sensitivity analysis. Hazard ratios (CI 95%) for clinical events in matched cohorts from the Lombardy region

	SGLT-2i *(715)*	Insulin *(715)*		GLP-1RA *(758)*	Insulin *(758)*		Other-AHAs *(7043)*	Insulin *(7043)*	
	IR/100 person year n (%)	IR/100 person year n (%)	HR (CI 95%)	IR/100 person year n (%)	IR/100 person year n (%)	HR (CI 95%)	IR/100 person year n (%)	IR/100 person year n (%)	HR (CI 95%)
Death from any cause	52 (5.0)	154 (16.0)	0.37 (0.26-0.51)	166 (6.8)	294 (13.9)	0.50 (0.40-0.60)	4090 (19.4)	4395 (22.7)	0.87 (0.84-0.91)
First hospitalization for heart failure	76 (7.7)	138 (16.7)	0.51 (0.38-0.68)	182 (8.9)	226 (13.47)	0.72 (0.59-0.87)	2314 (13.7)	2392 (16.0)	0.89 (0.84-0.95)
Renal failure	1 (0.1)	32 (3.4)	-	24 (1.0)	57 (2.9)	0.45 (0.28-0.72)	310 (1.5)	427 (2.3)	0.75 (0.64-0.86)
All Stroke	4 (0.2)	8 (0.6)	0.50 (0.14-1.70)	8 (0.3)	13 (0.6)	0.55 (0.22-1.36)	166 (0.8)	179 (0.9)	0.85 (0.69-1.05)
Myocardial infarction	19 (1.9)	23 (2.0)	0.73 (0.39-1.38)	43 (1.9)	44 (2.1)	0.97 (0.63-1.48)	403 (2.0)	460 (2.45)	0.82 (0.72-0.92)
MACE3	59 (5.7)	142 (15.1)	0.44 (0.32-0.60)	181 (7.8)	291 (14.3)	0.57 (0.46-0.66)	3862 (18. 9)	4009 (21.6)	0.89 (0.86-0.93)
MACE4	120 (12.6)	224 (27.8)	0.50 (0.40-0.64)	281 (14.9)	381 (23.6)	0.67 (0.57-0.77)	4447 (27.1)	4639 (32.5)	0.87 (0.83-0.90)

IR, crude incidence rate. HR adjustment for covariates with a standardized difference >10%: a) SGLT-2i vs insulin (age classes (50-59, 60-64, 65-69, 70-74, 75-79, >80); renal disease; neuropathy; pulmonary embolism), b) GLP-1RA vs insulin (renal disease; peripheral artery disease); c) other-AHAs vs insulin (renal disease). MACE, major adverse clinical event

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Supplemental material

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Supplementary Table 2. Sensitivity analysis: incidence rates (IRs) and hazard ratios (HRs) in subjects without history of renal disease in the 5 years before study entry in whole cohorts. (A) APULIA (9980), (B) LOMBARDY (15871).

	SGLT-2i (460)	Insulin (4826)	SGLT-2i vs Insulin	GLP-1RA (360)	Insulin (4826)	GLP-1RA vs Insulin	Other-AHAs (4334)	Insulin (4826)	Other-AHAs vs Insulin
Events	IRx100py	IRx100py	HR (95% CI)	IRx100py	IRx100py	HR (95% CI)	IRx100py	IRx100py	HR (95% CI)
Death from any cause	14 (2.55)	2447 (17.30)	**0.23 (0.14-0.39)**	44 (3.85)	2447 (17.30)	**0.40 (0.29-0.54)**	1945 (10.90)	2447 (17.30)	**0.69 (0.65-0.73)**
First hospitalization for heart failure	41 (7.97)	1215 (10.54)	**0.65 (0.47-0.91)**	59 (5.91)	1215 (10.54)	**0.63 (0.48-0.82)**	1170 (7.83)	1215 (10.54)	**0.85 (0.78-0.92)**
Renal failure	2 (0.36)	201 (1.46)	*	6 (0.56)	201 (1.46)	**0.38 (0.17-0.87)**	192 (1.10)	201 (1.46)	0.83 (0.68-1.02)
All stroke	2 (0.37)	138 (0.99)	0.47 (0.11-2.01)	7 (0.62)	138 (0.99)	0.89 (0.41-1.95)	125 (0.71)	138 (0.99)	0.82 (0.64-1.05)
Myocardial infarction	9 (1.66)	253 (1.85)	0.62 (0.31-1.28)	14 (1.26)	253 (1.85)	0.51 (0.24-1.08)	228 (1.32)	253 (1.85)	0.83 (0.69-1.00)
MACE3	25 (4.62)	2636 (19.54)	**0.34 (0.23-0.51)**	57 (5.17)	2636 (19.54)	**0.44 (0.34-0.58)**	2127 (12.34)	2636 (19.54)	**0.70 (0.66-0.74)**
MACE4	69 (13.77)	3169 (29.24)	**0.55 (0.43-0.71)**	99 (10.36)	3169 (29.24)	**0.51 (0.42-0.63)**	2630 (18.59)	3169 (29.24)	**0.72 (0.68-0.76)**

(A) **APULIA.** Multivariate analyses were adjusted for age classes (50-59, 60-64, 65-69, 70-74, 75-79, >80), sex, index year, myocardial infarction, stroke, atrial fibrillation, chronic obstructive pulmonary disease, cancer, diabetes history, DDCI index. *: HR (95% CI) was not included since SGLT-2is in years 2015-2018 were not indicated in patients with renal dysfunction.

	SGLT-2i (725)	Insulin (7982)	SGLT-2i vs Insulin	GLP-1RA (641)	Insulin (7982)	GLP-1RA vs Insulin	Other-AHAs (6433)	Insulin (7982)	Other-AHAs vs Insulin
Events	IRx100py	IRx100py	HR (95% CI)	IRx100py	IRx100py	HR (95% CI)	IRx100py	IRx100py	HR (95% CI)
Death from any cause	46 (4.42)	4483 (21.44)	**0.27 (0.19-0.35)**	139 (6.35)	4483 (21.44)	**0.47 (0.40-0.56)**	3603 (16.70)	4483 (20.82)	**0.81 (0.78-0.85)**
First hospitalization for heart failure	73 (7.56)	2396 (14.49)	**0.50 (0.48-0.63)**	153 (8.34)	2396 (14.49)	**0.68 (0.57-0.81)**	2011 (11.46)	2396 (14.49)	**0.88 (0.83-0.93)**
Renal failure*	-	-	*	15 (0.69)	207 (1.00)	**0.56 (0.31-0.94)**	145 (0.67)	207 (1.00)	**0.76 (0.61-0.95)**
All stroke	4 (0.38)	198 (0.95)	0.58 (0.17-1.44)	6 (0.27)	198 (0.95)	**0.37 (0.14-0.78)**	155 (0.72)	198 (0.95)	**0.77 (0.62-0.96)**
Myocardial infarction	17 (1.65)	455 (2.26)	0.80 (0.46-1.31)	38 (1.84)	455 (2.26)	1.09 (0.76-1.52)	361 (1.72)	455 (2.26)	**0.85 (0.73-0.98)**
MACE3	62 (6.05)	4703 (23.64)	**0.32 (0.25-0.41)**	167 (8.11)	4703 (23.64)	**0.53 (0.45-0.62)**	3765 (18.20)	4703 (23.64)	**0.81 (0.77-0.85)**
MACE4	121 (12.83)	5491 (34.83)	**0.41 (0.34-0.50)**	254 (14.99)	5491 (34.83)	**0.61 (0.53-0.69)**	4354 (25.80)	5491 (34.83)	**0.80 (0.77-0.84)**

(B) **LOMBARDY.** Multivariate analyses were adjusted for age classes (50-59, 60-64, 65-69, 70-74, 75-79, >80), sex, index year, myocardial infarction, stroke, atrial fibrillation, chronic obstructive pulmonary disease, cancer, diabetes history, DDCI index. *: HR (95% CI) was not included since SGLT-2is in years 2015-2018 were not indicated in patients with renal dysfunction.

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Supplementary Table 3. Sensitivity analysis: incidence rates (IRs) and hazard ratios (HRs) in subjects without history of renal disease in the 5 years before study entry in propensity matched cohorts. (A) APULIA, (B) LOMBARDY.

	SGLT-2i (355)	Insulin (314)	SGLT-2i vs Insulin	GLP-1RA (350)	Insulin (351)	GLP-1RA vs Insulin	Other-AHAs (3750)	Insulin (3478)	Other-AHAs vs Insulin
Events	IRx100py	IRx100py	HR (95% CI)	IRx100py	IRx100py	HR (95% CI)	IRx100py	IRx100py	HR (95% CI)
Death from any cause	10 (2.14)	37 (9.69)	**0.20 (0.10-0.40)**	44 (3.88)	78 (8.28)	**0.44 (0.30-0.66)**	1714 (11.98)	1863 (16.38)	**0.75 (0.70-0.80)**
First hospitalization for heart failure	34 (7.81)	47 (14.41)	**0.60 (0.38-0.93)**	58 (5.85)	78 (10.21)	**0.66 (0.46-0.93)**	1026 (8.60)	930 (10.19)	**0.87 (0.80-0.96)**
Renal failure]	2 (0.43)	4 (1.05)	*	6 (0.54)	10 (1.09)	0.58 (0.18-1.83)	155 (1.11)	157 (1.43)	**0.79 (0.64-0.99)**
All stroke	2 (0.43)	1 (0.26)	1.39 (0.13-15.30)	7 (0.62)	9 (0.97)	1.16 (0.42-3.26)	106 (0.75)	119 (1.06)	**0.72 (0.55-0.93)**
Myocardial infarction	8 (1.73)	11 (2.92)	0.56 (0.22-1.41)	14 (1.27)	18 (1.95)	0.51 (0.24-1.08)	194 (1.39)	203 (1.85)	**0.77 (0.63-0.93)**
MACE3	20 (4.35)	47 (12.51)	**0.35 (0.21-0.59)**	57 (5.20)	95 (10.47)	**0.51 (0.36-0.70)**	1861 (13.53)	2016 (18.66)	**0.74 (0.70-0.79)**
MACE4	57 (13.47)	86 (26.61)	**0.52 (0.37-0.73)**	98 (10.33)	151 (21.51)	**0.52 (0.40-0.67)**	2295 (20.30)	2413 (28.25)	**0.74 (0.70-0.79)**

(A) APULIA. HR adjustment for covariates with a standardized difference >10%: a) SGLT-2i vs insulin (cerebrovascular disease, stroke, other coronary disease, cardiovascular interventions, endovascular valve replacement or heart valve replacement /annuloplasty /valvuloplasty, lower limb complication, pulmonary embolism, renal failure, neuropathy, chronic obstructive pulmonary disease); b) GLP-1RA vs insulin (age classes (50-59, 60-64, 65-69, 70-74, 75-79, >80), cerebrovascular disease, myocardial infarction, implantable cardioverter defibrillator, peripheral artery disease, lower limb complication, diabetic neuropathy, diabetic retinopathy, cancer); c) other-AHAs vs insulin (renal disease). MACE, major adverse clinical event. *: HR (95% CI) was not included since SGLT-2is in years 2015-2018 were not indicated in patients with renal dysfunction.

	SGLT-2i (658)	Insulin (532)	SGLT-2i vs Insulin	GLP-1RA (640)	Insulin (582)	GLP-1RA vs Insulin	Other-AHAs (5501)	Insulin (5151)	Other-AHAs vs Insulin
Events	SGLT-2i IRx100py	Insulin IRx100py	HR (95% CI)	GLP-1RA IRx100py	Insulin IRx100py	HR (95% CI)	Other-A IRx100py	Insulin IRx100py	HR (95% CI)
Death from any cause	44 (4.44)	107 (14.31)	**0.32 (0.22-0.46)**	139 (6.35)	218 (12.95)	**0.48 (0.38-0.59)**	3027 (17.58)	3097 (21.03)	**0.84 (0.80-0.88)**
First hospitalization for heart failure	72 (7.87)	94 (14.47)	**0.54 (0.40-0.74)**	153 (8.34)	157 (11.25)	**0.75 (0.60-0.93)**	1696 (12.12)	1643 (14.27)	**0.87 (0.81-0.94)**
Renal failure	-	-	-	15 (0.69)	21 (1.27)	0.54 (0.28-1.06)	134 (0.78)	160 (1.11)	**0.71 (0.56-0.89)**
All stroke	4 (0.40)	7 (0.97)	0.46 (0.13-1.58)	6 (0.27)	10 (0.60)	0.43 (0.15-1.19)	124 (0.72)	146 (1.00)	**0.73 (0.57-0.93)**
Myocardial infarction	16 (1.63)	19 (2.60)	0.61 (0.31-1.19)	38 (1.84)	28 (1.78)	1.13 (0.70-1.85)	305 (1.82)	304 (2.15)	0.86 (0.74-1.00)
MACE3	59 (6.05)	125 (17.26)	**0.36 (0.26-0.48)**	167 (8.12)	241 (15.04)	**0.53 (0.44-0.64)**	3164 (19.16)	3238 (23.17)	**0.83 (0.79-0.87)**
MACE4	118 (13.20)	183 (28.83)	**0.47 (0.37-0.59)**	254 (14.99)	306 (22.86)	**0.64 (0.54-0.76)**	3665 (27.22)	3742 (34.21)	**0.81 (0.77-0.85)**

(B) LOMBARDY. HR adjustment for covariates with a standardized difference >10%: a) SGLT-2i vs insulin (age classes (50-59, 60-64, 65-69, 70-74, 75-79, >80); renal disease; neuropathy; pulmonary embolism), b) GLP-1RA vs insulin (renal disease; peripheral artery disease); c) other-AHAs vs insulin (renal disease). MACE, major adverse clinical event.

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Supplementary Table 4A. Frequency of antihyperglycemic drugs prescribed in 12 months before entering the study

	Apulia				Lombardy			
	SGLT-2i (531)	**GLP-1RA** (459)	**Insulin** (7027)	**Other-AHAs** *(5704)*	**SGLT-2i** *(786)*	**GLP-1RA** *(759)*	**Insulin** *(10 950)*	**Other-AHAs** *(8159)*
Insulin	345 (65.0)	226 (49.2)	0 (0.0)	1546 (27.1)	521 (66.3)	343 (45.2)	0 (0.0)	1387 (17.0)
Metformin	399 (75.1)	362 (78.9)	4985 (70.9)	3101 (54.4)	508 (64.6)	543 (71.5)	7112 (65.0)	3910 (47.9)
Sulfonylureas	106 (20.0)	127 (27.6)	3231 (46.0)	1887 (33.1)	230 (29.3)	328 (43.2)	6343 (57.9)	3048 (37.4)
DPP4-i	114 (21.5)	131 (28.5)	2760 (39.3)	455 (8.0)	122 (15.5)	182 (24.0)	1591 (14.5)	15 (0.2)
Glinides	106 (20.0)	120 (26.1)	852 (12.1)	10 (0.2)	67 (8.5)	112 (14.8)	3403 (31.1)	418 (5.1)
Glitazones	33 (6.2)	49 (10.7)	521 (7.4)	159 (2.8)	48 (6.1)	85 (11.2)	687 (6.3)	112 (1.4)
Acarbose	23 (4.3)	21 (4.6)	378 (5.4)	1 (0.0)	31 (3.9)	53 (7.0)	722 (6.6)	3 (0.0)
GLP-1RA	5 (0.9)	0 (0.0)	11 (0.2)	11 (0.2)	4 (0.5)	0 (0.0)	19 (0.2)	7 (0.1)
SGLT-2i	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

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Supplementary Table 4B. Frequency of antihyperglycemic drugs prescribed in the 12 months after entering the study (sum: pts who continued + pts who added-on antihyperglycemic drugs

	Apulia				Lombardy			
	SGLT-2i *(531)*	GLP-1 RA *(459)*	Insulin *(7027)*	Other-AHAs *(5704)*	SGLT-2i *(786)*	GLP-1 RA *(759)*	Insulin *(10 950)*	Other-AHAs *(8159)*
Insulin	352 (66.3)	206 (44.9)	7027 (100.0)	1539 (27.0)	548 (69.7)	345 (45.5)	10 950 (100.0)	1284 (15.7)
Metformin	405 (76.3)	335 (73.0)	2104 (29.9)	3129 (54.9)	525 (66.8)	481 (63.4)	2402 (21.9)	3768 (46.2)
Sulfonylureas	47 (8.9)	96 (20.9)	917 (13.1)	1251 (21.3)	104 (13.2)	254 (33.5)	1924 (17.6)	2363 (29.0)
DPP4-i	34 (6.4)	37 (8.1)	693 (9.9)	1149 (20.1)	51 (6.5)	55 (7.3)	1182 (10.8)	1521 (18.6)
Glinides	54 (10.2)	99 (21.6)	1871 (26.6)	2911 (51.0)	30 (3.8)	73 (9.6)	2020 (18.5)	3742 (45.9)
Glitazones	8 (1.5)	19 (4.1)	137 (2.0)	377 (6.6)	18 (2.3)	40 (5.3)	119 (1.1)	299 (3.7)
Acarbose	19 (3.6)	18 (3.9)	286 (4.1)	773 (13.6)	25 (3.2)	46 (6.1)	491 (4.5)	1046 (12.8)
GLP-1 RA	16 (3.0)	459 (100.0)	3 (0.04)	8 (0.1)	23 (2.9)	759 (100.0)	6 (0.05)	3 (0.04)
SGLT-2i	531 (100.0)	7 (1.5)	0 (0.0)	0 (0.0)	786 (100.0)	11 (1.5)	0 (0.0)	0 (0.0)

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Supplementary Table 5. Insulin defined daily doses three years after starting treatment with SGLT-2i or GLP-1RA in Apulia region
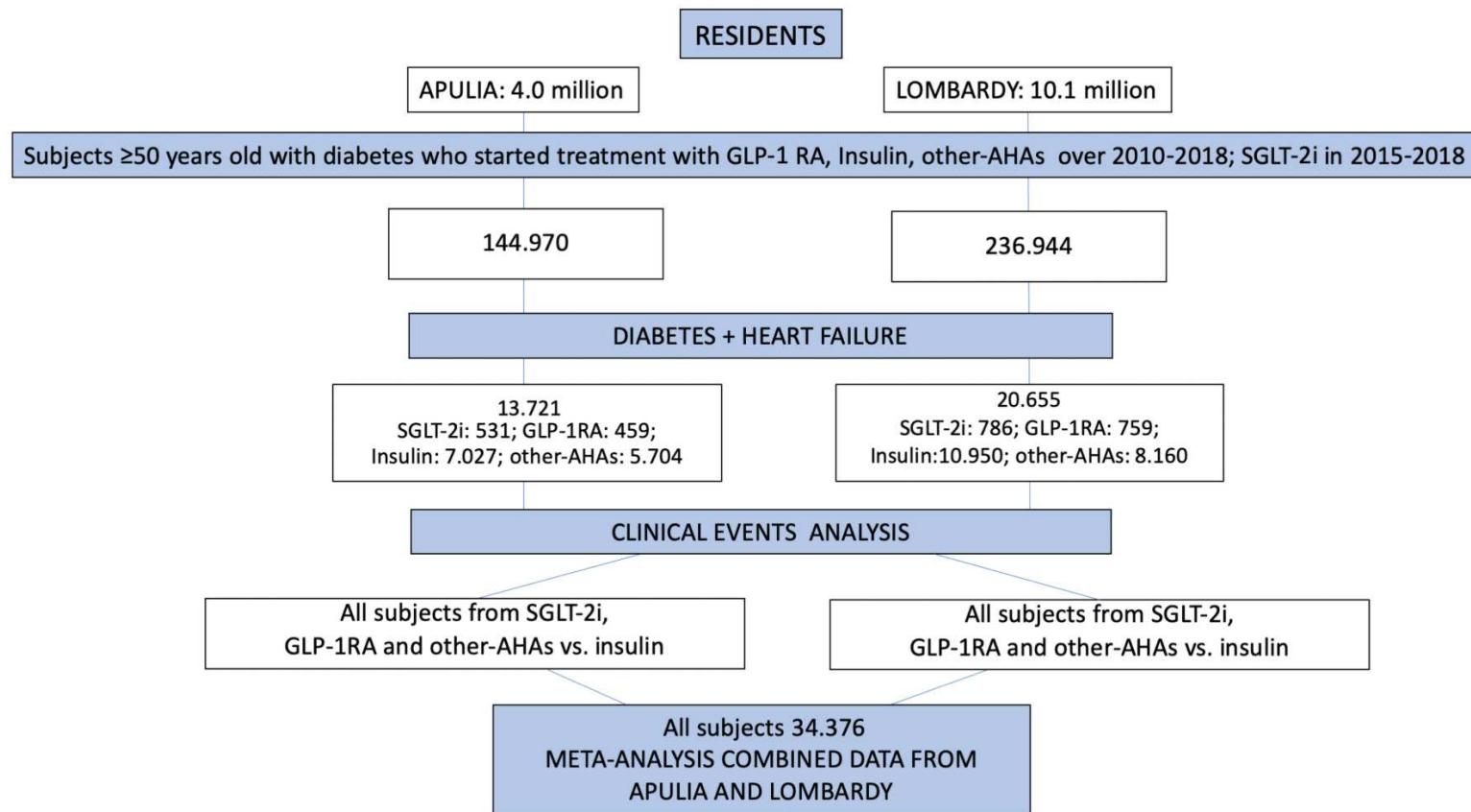
	Insulin DDD				
	Reduced	**Mantained**	**Increased**	**Total patients**	**Chi^2 test***
	n (%)	*n* (%)	*n* (%)	*n*	*p value*
SGLT-2i	124 (51.0)	26 (10.7)	93 (38.3)	243	*<0.001*
GLP-1RA	120 (62.5)	16 (8.3)	56 (29.2)	192	0.75
TOTAL, ^	244 (56.1)	42 (9.7)	149 (34.2)	435	0.01

* Chi^2 test: Reduced vs. Maintained +Increased. DDD, defined daily dose

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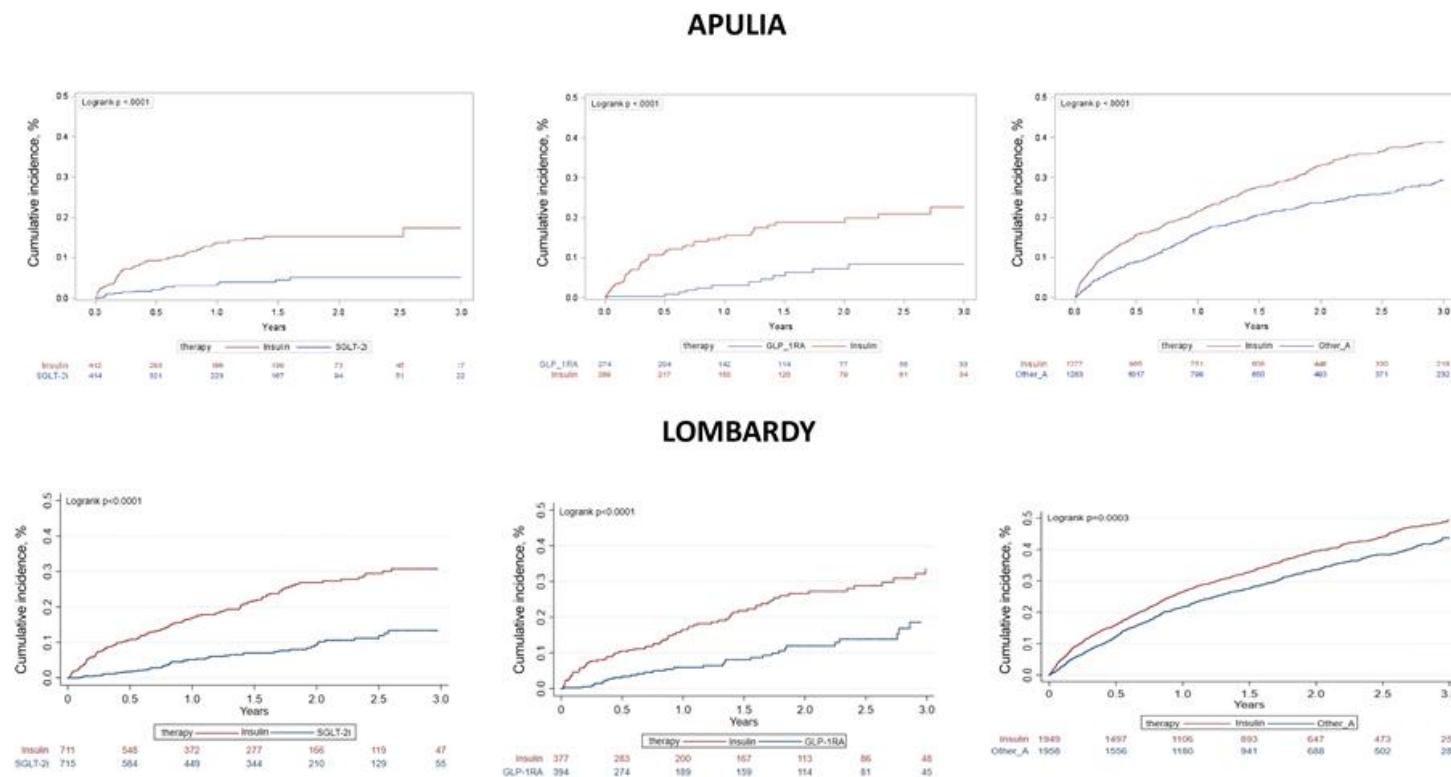
Supplementary Table 6. Insulin defined daily dose reduction in alive patients during three years of follow-up. Cardiovascular events and renal failure incidence rate ratio three-years pre and three-years post SGLT-2i or GLP-1RA treatment initiation, in Apulia region.

| Events	SGLT-2i (n= 124)			GLP-1RA (*n*= 120)		
	PRE	**POST**	**IRR (CI 95%)**	**PRE**	**POST**	**IRR (CI 95%)**
	IRx100 p/y *n (%)*	IRx100 p/y *n (%)*		IRx100 p/y *n (%)*	IRx100 p/y *n (%)*	
Heart Failure	74 (5.5)	26 (2.9)	0.53 (0.34-0.82)	85 (6.5)	57 (3.5)	0.54 (0.38-0.75)
Renal failure	3 (0.2)	3 (0.4)	1.50 (0.30-7.43)	3 (0.2)	7 (0.4)	1.87 (0.48-7.23)
Stroke	3 (0.2)	3 (0.4)	1.50 (0.30-7.43)	0	14 (0.9)	/
Myocardial infarction	30 (2.2)	2 (0.3)	0.10 (0.02-0.42)	34 (2.6)	9 (0.6)	0.21 (0.10-0.44)
PRE, three-years pre SGLT-2i or GLP-1RA treatment start; POST, three-years post SGLT-2i or GLP-1RA treatment initiation; IRR, incidence rate ratio.						
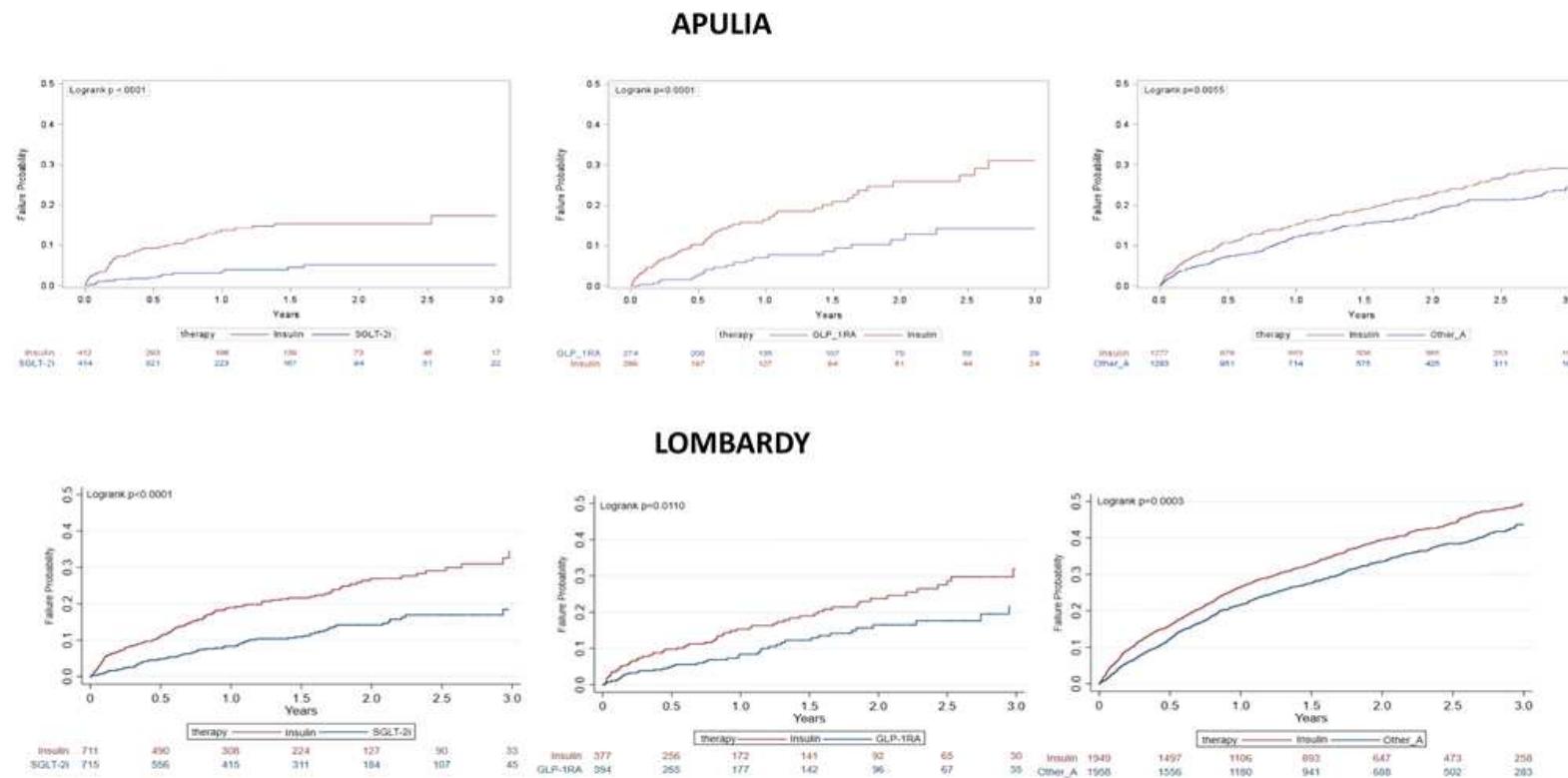
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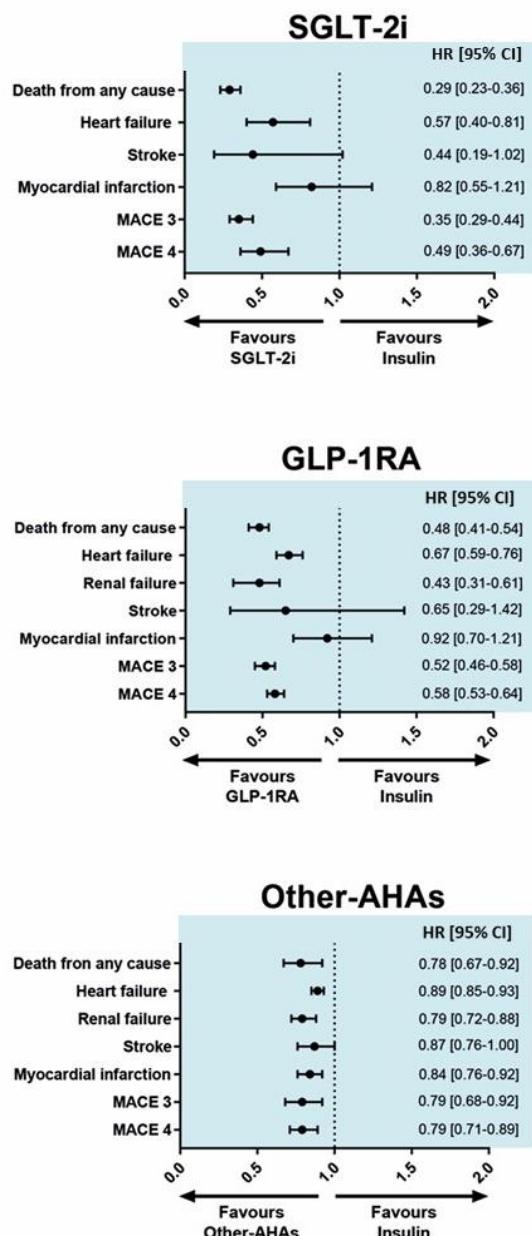
Supplementary Figure 1. Study diagram

Supplementary Figure 2. Kaplan-Meier curves of incidence of death from any cause, for the comparison of SGLT-2i, GLP1-RA and other-AHAs with insulin in propensity matched cohorts of subjects treated in the frame time 2015-2018 in Apulia and Lombardy.

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Supplementary Figure 3. Kaplan-Meier curves of incidence of first hospitalization for heart failure, for the comparison of SGLT-2i, GLP1-RA and other-AHAs with insulin in propensity matched cohorts of subjects treated in the frame time 2015-2018 in Apulia and Lombardy.

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Supplementary Figure 4. Meta-analysis from combined data from Apulia and Lombardy regions (34.376 subjects) comparing the effects of SGLT-2i, GLP-1RA and Other-AHAs with insulin treatment, on the selected outcomes.

Age classes (50-59, 60-64, 65-69, 70-74, 75-79, >80), sex, index year, myocardial infarction, ischemic or haemorrhagic stroke, atrial fibrillation, chronic obstructive pulmonary disease, cancer, renal disease, diabetes history, DDCI index were considered as confounding variables.

Plotted points are the pooled Apulia, Lombardy region HR for each outcome and the horizontal lines represent the 95% CIs. HR, hazard ratio.

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Supplementary Figure 5

Frequency of insulin treatment in the SGLT-2i, GLP1-RA and other-AHA cohorts, 12 months before study entry, those who started in the 12 months after study entry and those who continued insulin for 12 months more.

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