SUPPLEMENTAL MATERIAL

Data S1.

Supplemental Methods

Data quality and completeness (9)

The analysis framework includes a dedicated data quality assurance process during data integration in the GENERATOR HF DataMart.

In broad terms, we adopt a validation scheme using evidence from different data sources with the guidance of clinicians, who also conduct independent incremental checks on the quality of the results.

As an example, the assessment of comorbidities could be considered. First, to exploit information from unstructured data in several medical records (such as clinical diaries, nurse diaries, consultancies, diagnostic exams) the clinical team supports data scientists with an annotation phase on a large set of sample documents. The clinical team provides keywords, representative example sentences, indirect evidence included in the documents, which are used by the technical team to implement machine-learning algorithms, i.e. Natural Language Processing (NLP), in order to identify the presence/absence of such comorbidity in the clinical history of a specific patient. Such methods do not imply just the parsing of specific sentences, since the algorithms help identifying semantically equivalent sentences associated to the variable (comorbidity in this example), through the so called 'topic models', and supports the elimination of confounding factors, such as occurrence of negations, reference to familiarities or risk factors.

Once the data scientists have generated a first round of NLP-based identification of comorbidities, a new sample set is used to test the procedure. These new cases are shared with the clinical team in order to perform an independent check, which allows to identify any potential defects generated by the machine learning model, through which the technical team can improve the accuracy of such algorithms.

Then the cross-check validation is performed, which makes use of independent data; for most cases, the occurrence of a comorbidity is associated with well-defined critical ranges for specific laboratory values (such as: glycated hemoglobin, creatinine). This validation, performed on a significant set of test cases, allows to further improve the identification method and adjudicate comorbidities with a high degree of accuracy.

Once the HF Data Mart is built based on the above steps, clinicians have the possibility to control overall consistency with aggregated type of analysis, by using the dashboard linked to the datamart, where they can select subgroups of patients (e.g., the ones characterized with a specific comorbidity) and analyze the distribution of relevant clinical data for such populations.

Finally, as a technical step to evaluate the data quality of the extracted data, we sample several subsets of data (both in patients and variable sets), and we calculate quantitative variable distributions and binary variable incidences among samples. Then, we perform statistical tests to ensure low statistical differences among them and the overall consistency of the entire dataset.

Table S1. Contraindications and cautions of recommended medications according to the European Society of Cardiology Guidelines on Heart Failure 2021

ACEi/ARNi/ARB	
Contraindications	
History of angioedema	
Bilateral renal artery stenosis	
Pregnancy	Female gender and age less than 50 years
ACEi/ARB/ARNi adverse reaction	Known allergic reaction/other adverse reaction to ACEi/ARB/ARNi
Cautions	
Hyperkalaemia	Potassium>5.0 mEq/L
Significant renal dysfunction	eGFR<30 ml/min/1.73m2 or Creatinine>2.5 mg/dL
Hypotension	Systolic blood pressure<90 mmHg or symptomatic hypotension
β-blocker	
Contraindications	
AV block II/III without permanent pacemaker	Second or third degree of AV block (in the absence of a permanent pacemaker)
Critical limb ischaemia	
Asthma	
β-blocker adverse reaction	Known allergic reaction/other adverse reaction to β-blocker
Cautions	
NYHA IV	
Heart block	Heart rate<50 bpm
Hypotension	Systolic blood pressure<90 mmHg or symptomatic hypotension
Congestion	Raised jugular venous pressure, ascites, marked peripheral edema
MRA	
Contraindications	
MRA adverse reaction	Known allergic reaction/other adverse reaction to MRA
Cautions	
Hyperkalaemia	Potassium>5.0 mEq/L
Significant renal dysfunction	eGFR<30 ml/min/1.73m2 or Creatinine>2.5 mg/dL
SGLT2i	
Contraindications	
SGLT2i adverse condition	Known allergic reaction/other adverse reaction to SGLT2i
Pregnancy	Female gender and age less than 50 years
Significant renal dysfunction	eGFR<20 ml/min/1.73m2
Hypotension	Systolic blood pressure<95 mmHg or symptomatic hypotension
Cautions	
Diabetes Type 1	
Genito-urinary infections	

ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; ARNi, angiotensin receptor–neprilysin inhibitor; MRA,mineralocorticoid receptor antagonists; SGLT2i,Sodium-glucose co-transporter 2 imhibitors; AV, atrioventricular ; NYHA,New York Heart Association

Table S2. Variables definition

Variable	Definition
eGFR	Estimated glomerular filtration rate calculated based on CKD-EPI 2021
Pregnancy	Female gender and age less than 50 years
ACEi/ARB/ARNi adverse reaction	Known allergic reaction/other adverse reaction to ACEi/ARB/ARNi
Hyperkalemia	Potassium>5.0 mEq/L
Significant renal dysfunction [ACEi/ARB/ARNi and β-blocker]	eGFR<30 ml/min/1.73m2 or Creatinine>2.5 mg/dL
Hypotension [ACEi/ARB/ARNi]	Systolic blood pressure<90 mmHg or symptomatic hypotension
AV block II/III without permanent pacemaker	Second or third degree of AV block (in the absence of a permanent pacemaker)
β-blocker adverse reaction	Known allergic reaction/other adverse reaction to β-blocker
NYHA IV	New York Heart Association Class IV
Heart block	Heart rate<50 bpm
Hypotension [β-blocker]	Systolic blood pressure<90 mmHg
Congestion	Raised jugular venous pressure, ascites, marked peripheral edema
MRA adverse reaction	Known allergic reaction/other adverse reaction to MRA
SGLT2i adverse condition	Known allergic reaction/other adverse reaction to SGLT2i
Significant renal dysfunction [SGLT2i]	eGFR<20 ml/min/1.73m2
Hypotension [SGLT2i]	Systolic blood pressure<95 mmHg or symptomatic hypotension
All included variables reported at the date of discharge. ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; ARNi, angiotensin receptor–neprilysin inhibitor; MRA,mineralocorticoid receptor antagonists; NYHA,New York Heart Association;NT-proBNP, N-terminal pro hormone brain natriuretic peptide; SGLT2i,Sodium-glucose co-transporter 2 inhibitors; AV, atrioventricular	

Table S3. Baseline characteristics of the overall population

Variables	Total patients (n = 305)	Missing rate
Demographics/organizational/socioeconomic		
Age (years), median(IQR)	73.0 (63.0,81.0)	0 (0.0%)
Male sex	226 (74.1%)	0 (0.0%)
Education		101 (33.1%)
No education	3 (1.0%)	
Primary	40 (13.1%)	
Secondary	127 (41.6%)	
Higher	34 (11.1%)	
Married	166 (54.4%)	81 (26.6%)
Clinical		
NYHA		237 (77.7%)
I	3 (1.0%)	
II	12 (3.9%)	
III	39 (12.8%)	
IV	14 (4.6%)	
Heart rate (bpm), median (IQR)	73.0 (66.0,80.0)	11 (3.6%)
AV block		0 (0.0%)
I	9 (3.0%)	
II	5 (1.6%)	
III	9 (3.0%)	
Systolic blood pressure (mmHg), median (IQR)	115.0 (110.0,125.0)	11 (3.6%)
BMI(kg/m2), median (IQR)	25.8 (23.0,28.7)	6 (2.0%)
Laboratory values		
Hemoglobin(g/dL), median (IQR)	12.8 (11.0,14.6)	3 (1.0%)
NT-ProBNP(pg/mL), median (IQR)	3744.5 (1337.0,9818.5)	29 (9.5%)
eGFR (ml/min/1.73m2), median (IQR)	61.5 (40.0,80.0)	2 (0.7%)
Potassium (mEq/L), median (IQR)	4.1 (4.0,4.4)	2 (0.7%)
History and comorbidities		
Diabetes	93 (30.5%)	0 (0.0%)
Pulmonary disease	82 (26.9%)	0 (0.0%)
Malignant disease	58 (19.0%)	0 (0.0%)
Hypertension	198 (64.9%)	0 (0.0%)
Hepatic disease	5 (1.6%)	0 (0.0%)
Treatment		
β-blockers	285 (93.4%)	0 (0.0%)
ACEi	42 (13.8%)	0 (0.0%)
ARB	37 (12.1%)	0 (0.0%)
ARNi	129 (42.3%)	0 (0.0%)
MRA	99 (32.5%)	0 (0.0%)
SGLT2i	14 (4.6%)	0 (0.0%)
Diuretics	273 (89.5%)	0 (0.0%)
Digoxin	19 (6.2%)	0 (0.0%)
Statin	148 (48.5%)	0 (0.0%)
Acetylsalicylic acid (ASA)	81 (26.6%)	0 (0.0%)

All included variables reported at the date of discharge. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blockers; ARNi, angiotensin receptor–neprilysin inhibitor; BMI, body mass index; eGFR, estimated glomerular filtration rate; IQR,interquartile range; MRA, mineralocorticoid receptor antagonists; NYHA,New York Heart Association; NT-proBNP, N-terminal pro hormone brain natriuretic peptide; SGLT2i, Sodium-glucose co-transporter 2 inhibitors; AV, atrioventricular

Table S4. Prevalence of contraindications and cautions according to drug type

Pillar	Total patients (n = 305)	Prescribed	Not prescribed	Missing rate (%) (n = 305)
ACEi/ARB/ARNi		208 (68.2%)	97 (31.8%)	-
Contraindications				-
History of angioedema	0, (0.0%)	0, (0.0%)	0, (0.0%)	Not estimable
Bilateral renal artery stenosis	0, (0.0%)	0, (0.0%)	0, (0.0%)	Not estimable
Pregnancy	3, (1.0%)	3, (1.4%)	0, (0.0%)	0, (0.0%)
ACEi/ARB/ARNi adverse reaction	2, (0.7%)	1, (0.5%)	1, (1.0%)	Not estimable
Cautions				
Hyperkalemia	20, (6.6%)	9, (4.3%)	11, (11.3%)	2 (0.7%)
Significant renal dysfunction	40, (13.1%)	7, (3.4%)	33, (34.0%)	2 (0.7%)
Hypotension	36, (11.8%)	16, (7.7%)	20, (20.6%)	11 (3.6%)
β-blocker		285 (93.4%)	20 (6.6%)	-
Contraindications				
AV block II/III without permanent pacemaker	3, (1.0%)	3, (1.1%)	0, (0.0%)	Not estimable
Critical limb ischaemia	17, (5.6%)	15, (5.3%)	2.0, (10.0%)	Not estimable
β-blocker adverse reaction	1, (0.3%)	1, (0.4%)	0, (0.0%)	Not estimable
Cautions				-
NYHA IV	14, (4.6%)	13, (4.6%)	1, (5.0%)	Not estimable
Heart block	2, (0.7%)	0, (0.0%)	2, (10.0%)	11 (3.6%)
Hypotension	0, (0.0%)	0, (0.0%)	0, (0.0%)	11 (3.6%)
Congestion	5, (1.6%)	5, (1.8%)	0, (0.0%)	Not estimable
Asthma	13, (4.3%)	13, (4.6%)	0, (0.0%)	Not estimable
MRA		99 (32.5%)	206 (67.5%)	-
Contraindications				-
MRA adverse reaction	0, (0.0%)	0, (0.0%)	0, (0.0%)	Not estimable
Cautions				
Hyperkaliemia	20, (6.6%)	5, (1.6%)	15, (7.3%)	2 (0.7%)
Significant renal dysfunction	40, (13.1%)	11, (3.6%)	29, (14.1%)	2 (0.7%)
SGLT2i		14 (4.6%)	291 (95.4%)	-
Contraindications				-
SGLT2i adverse condition	0, (0.0%)	0, (0.0%)	0, (0.0%)	Not estimable
Pregnancy	3, (1.0%)	0, (0.0%)	3, (1.0%)	0, (0.0%)
Significant renal dysfunction	19, (6.2%)	0, (0.0%)	19, (6.5%)	2 (0.7%)
Hypotension	46, (15.1%)	1, (7.1%)	45, (15.5%)	11 (3.6%)
Cautions				-
Diabetes Type 1	0, (0.0%)	0, (0.0%)	0, (0.0%)	Not estimable
Genito-urinary infections	15, (4.9%)	0, (0.0%)	15, (5.2%)	Not estimable

ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; ARNi, angiotensin receptor–neprilysin inhibitor; MRA, mineralocorticoid receptor antagonists; SGLT2i, Sodium-glucose co-transporter 2 imhibitors; AV, atrioventricular ; NYHA,New York Heart Association
Not estimable = information not available due to unstructured data

Table S5. Variables significantly dependent on outcomes.

Variable	Type	Statistical Test	p-value	Outcome
Age (years)	Numerical	Kruskal-Wallis	0.000	ACEi/ARB/ARNi
NT-ProBNP (pg/mL)	Numerical	Kruskal-Wallis	0.000	ACEi/ARB/ARNi
Hemoglobin (g/dL)	Numerical	Kruskal-Wallis	0.000	ACEi/ARB/ARNi
eGFR (ml/min/1.73m2)	Numerical	Kruskal-Wallis	0.000	ACEi/ARB/ARNi
Hyperkalemia	Categorical	Chi-squared	0.042	ACEi/ARB/ARNi
Hypotension	Categorical	Chi-squared	0.002	ACEi/ARB/ARNi
eGFR<30 (ml/min/1.73m2)	Categorical	Chi-squared	0.000	ACEi/ARB/ARNi
Pillar number	Categorical	Chi-squared	0.000	ACEi/ARB/ARNi
Pillar number	Categorical	Chi-squared	0.000	β-blocker
NT-ProBNP (pg/mL)	Numerical	Kruskal-Wallis	0.018	Re-hospitalization within 30 days
Hemoglobin (g/dL)	Numerical	Kruskal-Wallis	0.017	Re-hospitalization within 30 days
eGFR (ml/min/1.73m2)	Numerical	Kruskal-Wallis	0.036	Re-hospitalization within 30 days
Pillar number	Categorical	Chi-square	0.000	Re-hospitalization within 30 days
NT-ProBNP (pg/mL)	Numerical	Kruskal-Wallis	0.000	Pilar number
Hemoglobin (g/dL)	Numerical	Kruskal-Wallis	0.020	Pilar number
eGFR (ml/min/1.73m2)	Numerical	Kruskal-Wallis	0.000	Pilar number
eGFR<30 (ml/min/1.73m2)	Categorical	Chi-squared	0.000	Pilar number
Critical limb ischaemia	Categorical	Chi-squared	0.003	Pilar number
Diabetes	Categorical	Chi-squared	0.007	Pilar number

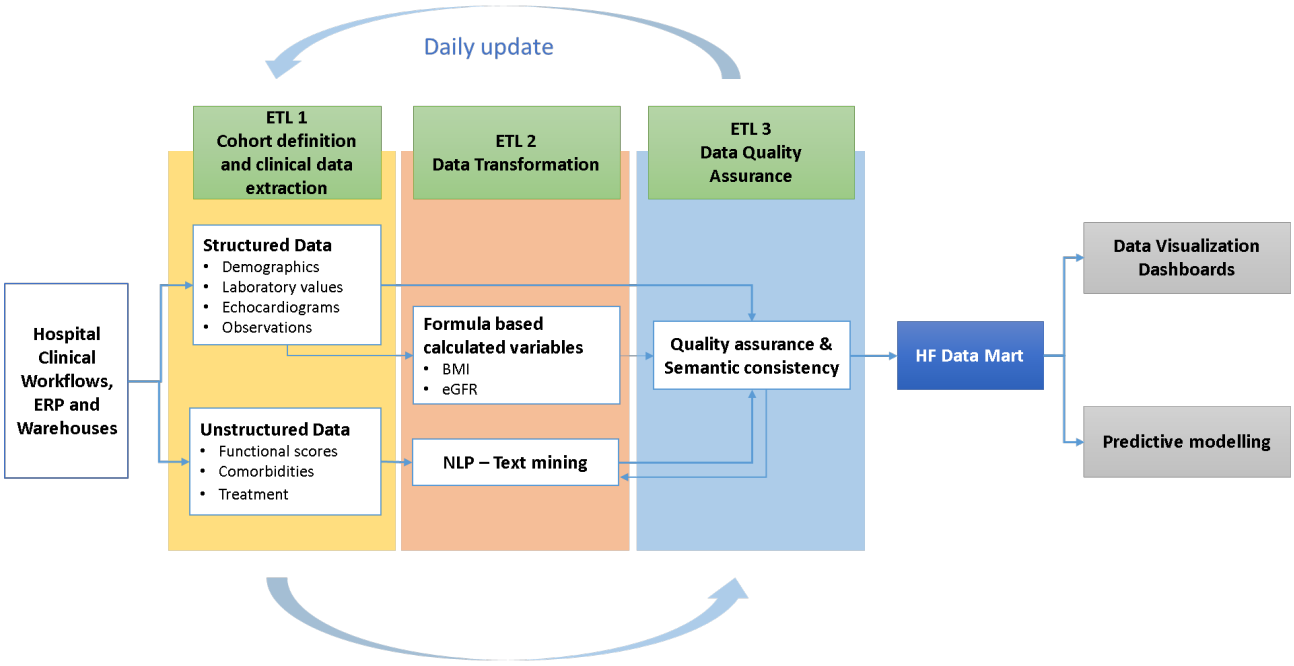
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor–neprilysin inhibitor; eGFR, estimated glomerular filtration rate; NYHA,New York Heart Association; NT-proBNP, N-terminal pro hormone brain natriuretic peptide;

Table S6. Predictors of prescription of Renin-angiotensin system inhibitors/Angiotensin receptor neprilysin inhibitor

Renin-angiotensin system inhibitors/Angiotensin receptor neprilysin inhibitor				
	Unadjusted OR (95% CI)	**Adjusted OR (95% CI)**	**p-value**	**Baseline**
eGFR<30 ml/min/1.73m2 (Yes vs No)	0.07 (0.03,0.16)	0.08 (0.03,0.19)	0.000/0.000	**68.2%**
Hypotension (Yes vs No)	0.32 (0.16,0.65)	0.29 (0.13,0.64)	0.002/0.002	
Hyperkalemia (Yes vs No)	0.36 (0.14,0.89)	0.42 (0.14,1.24)	0.028/0.115	
Diabetes (Yes vs No)	0.60 (0.36,1.00)		0.048	
Age (Per 1 year increase)	0.95 (0.93,0.98)	0.96 (0.94,0.99)	0.000/0.002	
NT-ProBNP (Per 100 pg/mL increase)	0.99 (0.99,1.00)		0.000	
Hemoglobin (Per 1g/dL increase)	1.25 (1.12,1.40)		0.000	
eGFR (Per 10 ml/min/1.73m2 increase)	1.48 (1.31,1.67)		0.000	

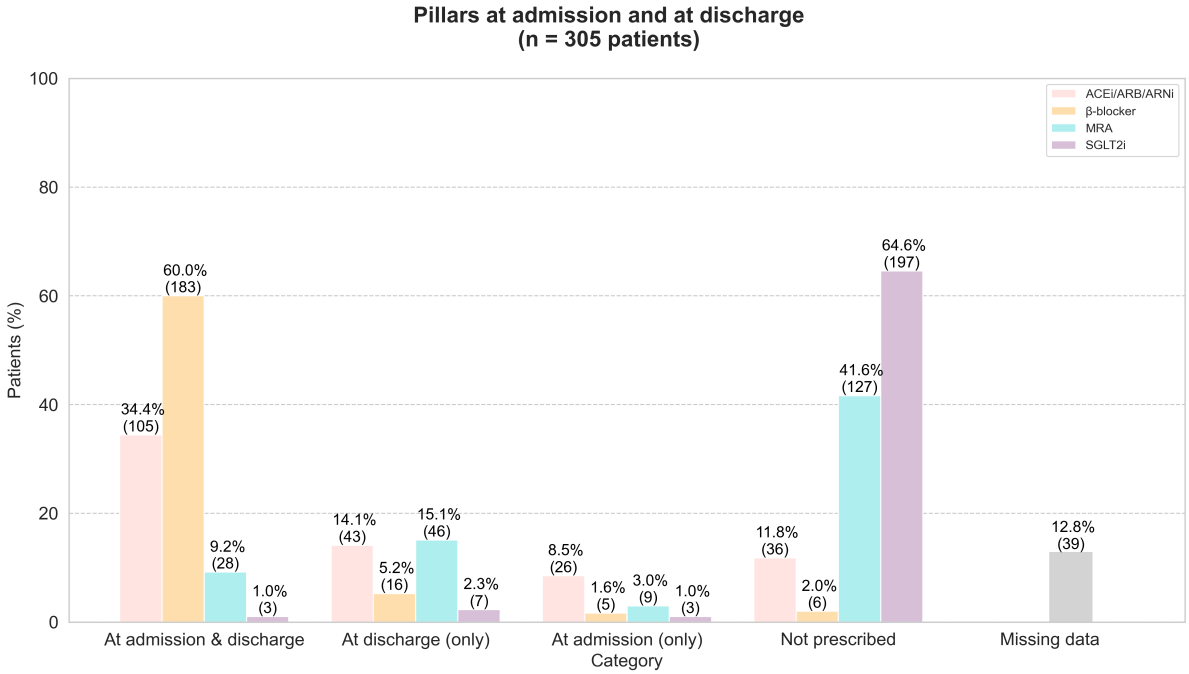
eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro hormone brain natriuretic peptide; OR, odds ratio.

Figure S1. Data extraction workflow



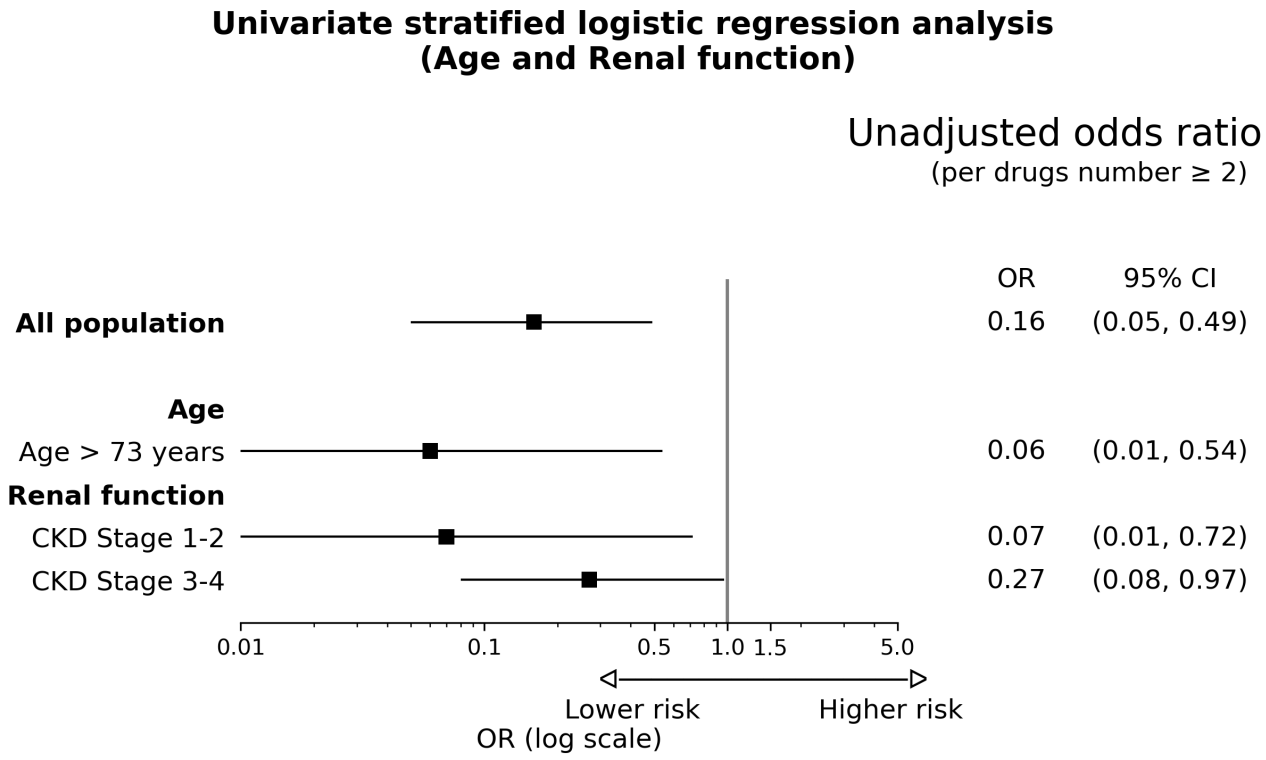
ERP, Enterprise resource planning; ETL, Extract Transform Load; BMI, Body Mass Index; NYHA, New York Heart Association; NLP, Natural Language Processing; eGFR, estimated glomerular filtration rate; HF, Heart Failure

Figure S2. Trajectories of drugs use at admission and at discharge



ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; ARNi, angiotensin receptor–neprilysin inhibitor; MRA, mineralocorticoid receptor antagonists; SGLT2i, Sodium-glucose co-transporter 2 inhibitors.

Figure S3. Univariate stratified analysis for the 30-day risk of readmission



CI = confidence intervals, CKD = Chronic kidney disease, OR = odds ratio