

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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Supplementary Appendix

Blockers of the renin-angiotensin system and the risk of Covid-19 infection

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Table of Contents

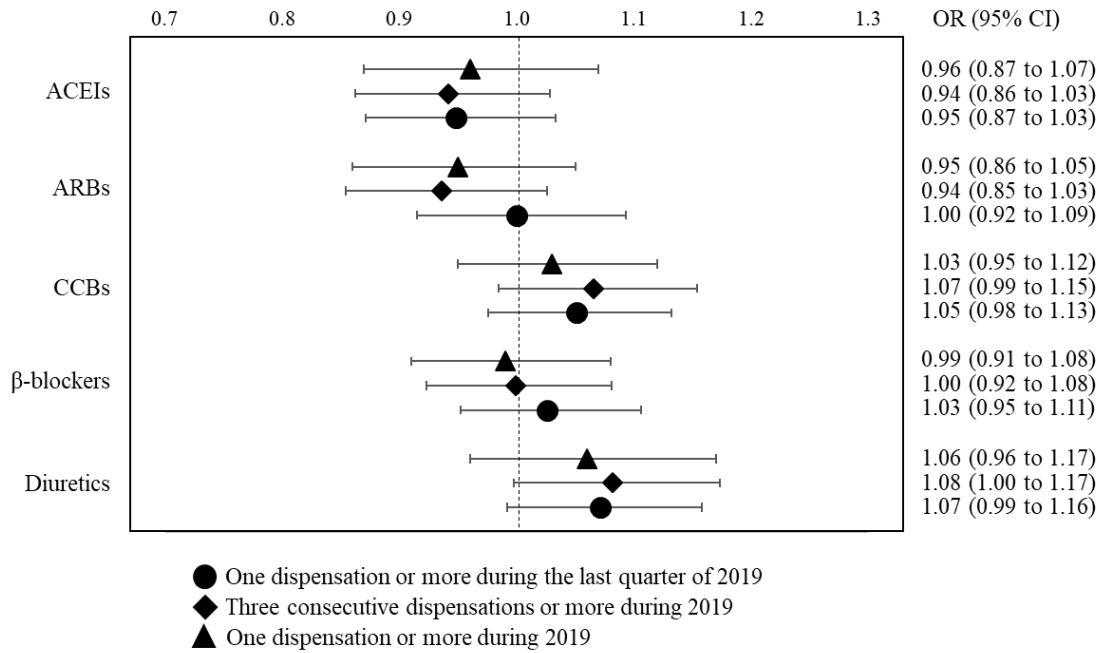
Calculating individual Chronic Related Score	3
Figure S1. Adjusted odds ratios (OR), and 95% confidence intervals (CI), of infection from Covid-19 associated with use of antihypertensive agents during different time windows in the year 2019. Data refer to patients with residence in Lombardy (Italy) included in the study from February 21 until March 11 2020	4
Table S1. Diagnostic and therapeutic codes used in the current study for drawing records and fields from Healthcare Utilization databases	5
Table S2. ARBs, ACEIs, other antihypertensive drugs, drugs for a variety of other diseases, and other features of men and women with diagnosis of infection from Covid-19 (cases) and corresponding matched controls	7
Table S3. Adjusted odds ratios, and 95% confidence intervals, of Covid-19 infection associated with use of non-antihypertensive drugs and other features, according with the severity of clinical manifestations (mild-moderate and critical/fatal), sex and age at diagnosis (< 60 and ≥ 60 years) ..	10
Table S4. ARBs, ACEIs, other antihypertensive drugs, drugs for a variety of other diseases, and other features of younger (age < 60 years) and older (age ≥ 60 years) patients with diagnosis of infection from Covid-19 (cases) and corresponding matched controls.....	12
Table S5. ARBs, ACEIs, other antihypertensives drugs, drugs for a variety of other diseases, and other features of patients with diagnosis of infection from Covid-19 (cases) and corresponding matched controls according with the severity of clinical manifestations (mild-moderate and critical/fatal)	14
Table S6. Adjusted odds ratios, and 95% confidence intervals, of infection from Covid-19 associated with use of blockers of the renin-angiotensin system, according with the period on which Covid-19 cases were diagnosed (before and after 26th February, 2020).....	17

Calculating individual Chronic Related Score

The list of predictors used for calculating CReSc, and the corresponding weights, is reported in the original paper [1]. Briefly, the presence of 31 diseases / conditions was traced from footprints left by NHS beneficiaries through diagnostic and procedure codes in private and public hospital records, drugs dispensed in community pharmacies or in hospital setting, outpatient visits and diagnostic tests performed laboratories accredited from the NHS, and co-payment exemptions for diagnosed chronic diseases. A string with 31 values was built for each beneficiary, so that each disease / condition was indexed as 1 whether a footprint suggestive of its presence was left at least once within two years prior to the index year, 0 otherwise. A weight was assigned to each disease according to how much it predicted the outcome (i.e., 5-year mortality). Finally, CReSc was calculated by categorising the individual sum of the string values into 1 of the 5 categories denoting a progressive worsening comorbidity status. The CReSc performances, which were tested through NHS beneficiaries from Lombardy Region, showed (i) an area under the receiver operating characteristic curve of 0.730, (ii) a net reclassification ability improved of 44% to 52% with respect to other scores (such as the Charlson Comorbidity Index), and (iii) a remarkable calibration of observed and predicted 5-year probability.

[1] Rea F, Corrao G, Ludergnani M, Cajazzo L, Merlino L. A new population-based risk stratification tool was developed and validated for predicting mortality, hospital admissions, and health care costs. *J Clin Epidemiol* 2019;116:62-71

Figure S1. Adjusted odds ratios (OR), and 95% confidence intervals (CI), of infection from Covid-19 associated with use of antihypertensive agents during different time windows in the year 2019. Data refer to patients with residence in Lombardy (Italy) included in the study from February 21 until March 11 2020



Footnote. ACEI: Angiotensin converting enzyme inhibitors; ARB: Angiotensin II receptor blockers; CCB: Calcium channel blocker. Odds ratios, and 95% confidence intervals, estimated by fitting conditional logistic regression. Estimates were fully adjusted for drug therapies and comorbidities listed in Table 1

Table S1. Diagnostic and therapeutic codes used in the current study for drawing records and fields from Healthcare Utilization databases

	Codes
Drugs †	
Antihypertensive classes	
ACEIs	C09A, C09BA, C09BB, C09BX01
ARBs	C09C, C09DA, C09DB
CCBs	C08C, C08D, C08E, C08G, C09BB, C09BX01, C09DB
Diuretics	C03, C07B, C07C, C07D, C08G, C09BA, C09BX01, C09DA
Thiazide/Thiazide-like	C03A, C03B, C07B, C07C, C09BA, C09BX01, C09DA
Loop	C03C
MRA	C03DA
β-blockers	C07A, C07B, C07C, C07D
Oral antidiabetic drugs	A10B
Metformin	A10BA02
Sulfonylureas	A10BB
DPP-4 inhibitors	A10BH
GLP-1 agonists	A10BJ
SGLT2 inhibitors	A10BK
Thiazolidinediones	A10BG
Other oral antidiabetic	A10BD, A10BF, A10BX
Insulin	A10A
Lipid-lowering drugs	C10
Antiplatelet drugs	B01AC
Oral anticoagulant agents	B01AA, B01AE, B01AF
Digitalis	C01AA
Nitrates	C01DA
Drugs for respiratory disease	
LABA	R03AC12, R03AC13, R03AC18, R03AC19, R03AK06, R03AK07, R03AK08, R03AK10, R03AK11, R03AL03, R03AL04, R03AL05, R03AL06, R03AL09
SABA	R03AC02, R03AC03, R03AC04, R03CC02, R03CC04, R03AL01, R03AL02
Inhaled corticosteroids	R03BA01, R03BA05, R03BA03, R03BA02, R03BA08
Other medicaments	R03BB01, R03BB02, R03BB04, R03BC01, R03BC03, R03DA04, R03DC01, R03DC03
Immunosuppressant agents	H02AB, L01BA01, L01XC, L04AA10, L04AD, L04AX03
Non-steroidal anti-inflammatory drugs	M01A
Non-selective COX inhibitors	M01AA, M01AB, M01AC, M01AE, M01AG, M01AX

Selective COX2 inhibitors M01AH

Comorbidities and associated procedures †

Cardiovascular disease	390.x – 459.x
Coronary artery disease	410.x-414.x
Percutaneous coronary intervention	00.66, 36.01, 36.02, 36.03, 36.05, 36.06, 36.07 (procedure codes)
Heart failure	402.01, 402.11, 402.91, 428.x
Respiratory diseases	460 – 519.x
Chronic obstructive pulmonary disease	490-492.x, 494.x, 496
Asthma	493.x
Kidney disease	584.x – 586
Chronic kidney disease	585.x
Dialysis §	K03A
Cancer	140.x – 239.x

ACEI: Angiotensin converting enzyme inhibitors; ARB: Angiotensin II receptor blockers; CCB: Calcium channel blocker; MRA: Mineralocorticoid receptor antagonists; DPP-4: Dipeptidyl peptidase 4; GLP-1: Glucagon-like peptide-1; SGLT2: Sodium-glucose co-transporter 2; LABA: Long-acting β -agonists; SABA Short-acting β -agonists

† According to the ATC (Anatomical-Therapeutic-Chemical) classification system

‡ According to the ICD-9-CM (International Classification of Disease, 9th Revision) system

§ According to the regional outpatients services coding

Table S2. ARBs, ACEIs, other antihypertensive drugs, drugs for a variety of other diseases, and other features of men and women with diagnosis of infection from Covid-19 (cases) and corresponding matched controls

	Cases (N=2,303)	Women Controls (N=11,357)	Relative difference	Cases (N=3,969)	Men Controls (N=19,402)	Relative difference
Age, years						
Mean (SD)	66 (14)	66 (14)	MV	68 (12)	68 (12)	MV
Drugs†						
Antihypertensive drugs	1,247 (54.2%)	5,173 (45.6%)	+15.9%	2,385 (60.1%)	10,146 (52.3%)	+13.0%
ACEIs	451 (19.6%)	1,956 (17.2%)	+12.1%	1,051 (26.5%)	4,613 (23.8%)	+10.2%
ARBs	486 (21.1%)	2,076 (18.3%)	+13.4%	908 (22.9%)	3,834 (19.8%)	+13.6%
CCBs	467 (20.3%)	1,814 (16.0%)	+21.2%	979 (24.7%)	4,112 (21.2%)	+14.1%
Diuretics	716 (31.1%)	2,710 (23.9%)	+23.3%	1,186 (29.9%)	4,710 (24.3%)	+18.8%
Thiazide/Thiazide-like	429 (18.6%)	1,918 (16.9%)	+9.3%	675 (17.0%)	3,156 (16.3%)	+4.4%
Loop	317 (13.8%)	821 (7.2%)	+47.5%	554 (14.0%)	1,590 (8.2%)	+41.3%
MRA	82 (3.6%)	211 (1.9%)	+47.8%	157 (4.0%)	527 (2.7%)	+31.3%
β-blockers	657 (28.5%)	2,458 (21.6%)	+24.1%	1,169 (29.5%)	4,665 (24.0%)	+18.4%
Monotherapy	368 (16.0%)	1,677 (14.8%)	+7.6%	699 (17.6%)	3,226 (16.6%)	+5.6%
Combination therapy	879 (38.2%)	3,496 (30.8%)	+19.4%	1,686 (42.5%)	6,920 (35.7%)	+16.0%
Oral antidiabetic drugs	244 (10.6%)	848 (7.5%)	+29.5%	617 (15.6%)	2,310 (11.9%)	+23.4%
Metformin	169 (7.3%)	638 (5.6%)	+23.5%	459 (11.6%)	1,693 (8.7%)	+24.6%
Sulfonylureas	64 (2.8%)	192 (1.7%)	+39.2%	150 (3.8%)	589 (3.0%)	+19.7%
DPP-4 inhibitors	29 (1.3%)	89 (0.8%)	+37.8%	60 (1.5%)	224 (1.2%)	+23.6%
GLP-1 agonists	20 (0.9%)	46 (0.4%)	+53.4%	45 (1.1%)	149 (0.8%)	+32.3%
SGLT2 inhibitors	12 (0.5%)	25 (0.2%)	+57.8%	35 (0.9%)	84 (0.4%)	+50.9%
Thiazolidinediones	12 (0.5%)	27 (0.2%)	+54.4%	23 (0.6%)	68 (0.4%)	+39.5%
Other oral antidiabetic	63 (2.7%)	204 (1.8%)	+34.3%	156 (3.9%)	621 (3.2%)	+18.6%
Insulin	111 (4.8%)	231 (2.0%)	+57.8%	227 (5.7%)	632 (3.3%)	+43.1%
Lipid-lowering drugs	571 (24.8%)	2,305 (20.3%)	+18.1%	1,357 (34.2%)	5,528 (28.5%)	+16.7%
Antiplatelet drugs	400 (17.4%)	1,259 (11.1%)	+36.2%	963 (24.3%)	3,609 (18.6%)	+23.3%
Oral anticoagulant agents	211 (9.2%)	583 (5.1%)	+44.0%	432 (10.9%)	1,590 (8.2%)	+24.7%
Digitalis	35 (1.5%)	71 (0.6%)	+58.9%	31 (0.8%)	99 (0.5%)	+34.7%

Nitrates	67 (2.9%)	142 (1.3%)	+57.0%	134 (3.4%)	482 (2.5%)	+26.4%
Drugs for respiratory disease as a whole	343 (14.9%)	1,187 (10.5%)	+29.8%	600 (15.1%)	1,983 (10.2%)	+32.4%
LABA	171 (7.4%)	528 (4.7%)	+37.4%	337 (8.5%)	999 (5.2%)	+39.4%
SABA	103 (4.5%)	342 (3.0%)	+32.7%	165 (4.2%)	538 (2.8%)	+33.3%
Inhaled corticosteroids	186 (8.1%)	655 (5.8%)	+28.6%	313 (7.9%)	1,003 (5.2%)	+34.5%
Other drugs for respiratory disease	103 (4.5%)	203 (1.8%)	+60.0%	155 (3.9%)	411 (2.1%)	+45.8%
Immunosuppressant agents	344 (14.9%)	1,130 (10.0%)	+33.4%	458 (11.5%)	1,581 (8.2%)	+29.4%
Non-steroidal anti-inflammatory drugs	437 (19.0%)	1,972 (17.4%)	+8.5%	599 (15.1%)	2,607 (13.4%)	+11.0%
Non-selective COX inhibitors	345 (15.0%)	1,646 (14.5%)	+3.3%	519 (13.1%)	2,268 (11.7%)	+10.6%
Selective COX2 inhibitors	123 (5.3%)	517 (4.6%)	+14.8%	129 (3.3%)	522 (2.7%)	+17.2%
Comorbidities and associated procedures						
Cardiovascular disease	551 (23.9%)	1,731 (15.2%)	+36.3%	1,340 (33.8%)	4,948 (25.5%)	+24.5%
Coronary artery disease	87 (3.8%)	260 (2.3%)	+39.4%	386 (9.7%)	1,259 (6.5%)	+33.3%
Percutaneous coronary intervention	41 (1.8%)	115 (1.0%)	+43.1%	203 (5.1%)	708 (3.7%)	+28.7%
Heart failure	110 (4.8%)	210 (1.9%)	+61.3%	213 (5.4%)	549 (2.8%)	+47.3%
Respiratory diseases	196 (8.5%)	465 (4.1%)	+51.9%	455 (11.5%)	1,251 (6.5%)	+43.8%
Chronic obstructive pulmonary disease	52 (2.3%)	98 (0.9%)	+61.8%	136 (3.4%)	335 (1.7%)	+49.6%
Asthma	12 (0.5%)	18 (0.2%)	+69.6%	6 (0.2%)	17 (0.1%)	+42.0%
Kidney disease	82 (3.6%)	188 (1.7%)	+53.5%	229 (5.8%)	630 (3.3%)	+43.7%
Chronic kidney disease	48 (2.1%)	86 (0.8%)	+63.7%	133 (3.4%)	307 (1.6%)	+52.8%
Dialysis	13 (0.6%)	10 (0.1%)	+84.4%	36 (0.9%)	44 (0.2%)	+75.0%
Cancer	367 (15.9%)	1,446 (12.7%)	+20.1%	724 (18.2%)	3,193 (16.5%)	+9.8%
Chronic Related Score[†]						
0	899 (39.1%)	5,549 (48.9%)	-25.2%	1,217 (30.7%)	7,502 (38.7%)	-26.1%
1	581 (25.2%)	2,964 (26.1%)	-3.5%	869 (21.9%)	4,661 (24.0%)	-9.7%
2	373 (16.2%)	1,555 (13.7%)	+15.5%	744 (18.7%)	3,301 (17.0%)	+9.2%
3	189 (8.2%)	630 (5.5%)	+32.4%	487 (12.3%)	1,828 (9.4%)	+23.2%
4	261 (11.3%)	659 (5.8%)	+48.8%	652 (16.4%)	2,110 (10.9%)	+33.8%

MV: Matching variables; SD: Standard deviation; ACEI: Angiotensin converting enzyme inhibitors; ARB: Angiotensin II receptor blockers; CCB: Calcium channel blocker; MRA: Mineralocorticoid receptor antagonists; DPP-4: Dipeptidyl peptidase 4; GLP-1: Glucagon-like peptide-1; SGLT2: Sodium-glucose co-transporter 2; LABA: Long-acting β -agonists; SABA Short-acting β -agonists

[†] At least one prescription during the year 2019

‡ Chronic Related Score is a new index of patients' clinical profile derived from inpatient and outpatient services provided by the Regional Health Service and validated for outcome prediction [28]. Five categories of progressively worsening clinical profile are considered

1 **Table S3.** Adjusted odds ratios, and 95% confidence intervals, of Covid-19 infection associated with use of non-antihypertensive drugs and
 2 other features, according with the severity of clinical manifestations (mild-moderate and critical/fatal), sex and age at diagnosis (< 60 and ≥
 3 60 years)

	Odds ratio (95% confidence interval) [§]					
	Mild-moderate (5,655 cases / 27,790 controls)	Critical/fatal (617 cases / 2,969 controls)	Women (2,303 cases / 11,357 controls)	Men (3,969 cases / 19,402 controls)	Age < 60 years (1,932 cases / 9,615 controls)	Age ≥ 60 years (4,340 cases / 21,144 controls)
Drugs[†]						
Oral antidiabetic drugs	1.04 (0.94 to 1.15)	1.23 (0.96 to 1.59)	1.05 (0.88 to 1.26)	1.08 (0.96 to 1.20)	0.85 (0.63 to 1.15)	1.09 (0.99 to 1.21)
Insulin	1.35 (1.15 to 1.58)	1.52 (1.06 to 2.17)	1.58 (1.22 to 2.05)	1.29 (1.09 to 1.53)	1.09 (0.68 to 1.76)	1.42 (1.22 to 1.65)
Lipid-lowering drugs	1.01 (0.93 to 1.09)	1.10 (0.89 to 1.36)	1.01 (0.88 to 1.14)	1.04 (0.95 to 1.14)	0.94 (0.76 to 1.16)	1.04 (0.96 to 1.12)
Antiplatelet drugs	1.17 (1.06 to 1.28)	1.30 (1.02 to 1.65)	1.41 (1.21 to 1.64)	1.11 (0.99 to 1.23)	0.91 (0.65 to 1.27)	1.21 (1.10 to 1.33)
Oral anticoagulant agents	1.16 (1.03 to 1.31)	1.19 (0.89 to 1.60)	1.43 (1.16 to 1.76)	1.06 (0.93 to 1.21)	1.55 (0.96 to 2.51)	1.15 (1.03 to 1.30)
Digitalis	1.24 (0.89 to 1.73)	1.22 (0.56 to 2.64)	1.42 (0.90 to 2.25)	1.04 (0.68 to 1.58)	0.72 (0.06 to 8.89)	1.26 (0.93 to 1.71)
Nitrates	1.04 (0.86 to 1.27)	0.97 (0.63 to 1.50)	1.37 (0.99 to 1.89)	0.92 (0.75 to 1.14)	0.16 (0.02 to 1.21)	1.06 (0.89 to 1.27)
Drugs for respiratory disease	1.29 (1.18 to 1.41)	1.02 (0.78 to 1.34)	1.19 (1.03 to 1.37)	1.30 (1.17 to 1.44)	1.25 (1.04 to 1.50)	1.26 (1.14 to 1.39)
Immunosuppressant agents	1.26 (1.15 to 1.38)	1.68 (1.30 to 2.18)	1.38 (1.20 to 1.58)	1.26 (1.13 to 1.41)	1.35 (1.12 to 1.62)	1.30 (1.18 to 1.43)
NSAIDs	1.08 (0.99 to 1.17)	0.96 (0.75 to 1.24)	1.04 (0.92 to 1.17)	1.08 (0.98 to 1.19)	0.84 (0.71 to 1.00)	1.13 (1.04 to 1.23)
Comorbidities and associated procedures						
Cardiovascular disease	1.02 (0.92 to 1.13)	0.92 (0.71 to 1.19)	1.00 (0.84 to 1.19)	1.01 (0.90 to 1.13)	1.15 (0.87 to 1.52)	1.00 (0.90 to 1.10)
Respiratory diseases	1.34 (1.19 to 1.52)	1.54 (1.14 to 2.07)	1.38 (1.12 to 1.70)	1.37 (1.20 to 1.56)	1.69 (1.28 to 2.22)	1.33 (1.18 to 1.51)
Kidney disease	1.04 (0.85 to 1.28)	1.51 (1.00 to 2.29)	1.12 (0.78 to 1.63)	1.16 (0.94 to 1.43)	0.83 (0.37 to 1.87)	1.15 (0.96 to 1.39)
Cancer	1.07 (0.96 to 1.20)	0.87 (0.65 to 1.16)	1.12 (0.93 to 1.34)	1.01 (0.89 to 1.15)	1.15 (0.89 to 1.47)	1.02 (0.91 to 1.14)
Chronic Related Score[‡]						
0	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)
1	1.18 (1.07 to 1.30)	1.56 (1.09 to 2.22)	1.23 (1.06 to 1.43)	1.16 (1.03 to 1.31)	1.21 (1.03 to 1.42)	1.17 (1.04 to 1.32)
2	1.35 (1.20 to 1.52)	1.81 (1.23 to 2.67)	1.35 (1.11 to 1.63)	1.36 (1.18 to 1.56)	1.46 (1.15 to 1.86)	1.35 (1.18 to 1.54)
3	1.50 (1.29 to 1.75)	2.23 (1.44 to 3.47)	1.54 (1.20 to 1.98)	1.52 (1.28 to 1.81)	1.26 (0.82 to 1.96)	1.57 (1.34 to 1.84)
4	1.53 (1.29 to 1.82)	2.08 (1.29 to 3.37)	1.71 (1.30 to 2.25)	1.52 (1.25 to 1.85)	1.44 (0.82 to 2.52)	1.57 (1.32 to 1.87)

- 1 ACEI: Angiotensin converting enzyme inhibitors; ARB: Angiotensin II receptor blockers; CCB: Calcium channel blocker; NSAIDs: Non-steroidal anti-inflammatory drugs
- 2 † At least one prescription during the year 2019
- 3 ‡ Chronic Related Score is a new index of patients' clinical profile derived from inpatient and outpatient services provided by the Regional Health Service and validated for outcome
4 prediction [28]. Five categories of progressively worsening clinical profile are considered
- 5 § Odds ratios of Covid-infection risk associated with exposure to treatments and comorbidities. No exposure was considered as reference, unless otherwise reported. Estimates were
6 obtained by fitting conditional logistic regression. Estimates were unadjusted and full adjusted for drugs and comorbidities listed in the Table

Table S4. ARBs, ACEIs, other antihypertensive drugs, drugs for a variety of other diseases, and other features of younger (age < 60 years) and older (age ≥ 60 years) patients with diagnosis of infection from Covid-19 (cases) and corresponding matched controls

	Age < 60 years			Age ≥ 60 years		
	Cases (N=1,932)	Controls (N=9,615)	Relative difference	Cases (N=4,340)	Controls (N=21,144)	Relative difference
Women	875 (45%)	4,348 (45%)	MV	1,428 (33%)	7,009 (33%)	MV
Drugs†						
Antihypertensive drugs	519 (26.9%)	1,871 (19.5%)	+27.6%	3,113 (71.7%)	13,448 (63.6%)	+11.3%
ACEIs	197 (10.2%)	757 (7.9%)	+22.8%	1,305 (30.1%)	5,812 (27.5%)	+8.6%
ARBs	201 (10.4%)	719 (7.5%)	+28.1%	1,193 (27.5%)	5,191 (24.6%)	+10.7%
CCBs	189 (9.8%)	595 (6.2%)	+36.7%	1,257 (29.0%)	5,331 (25.2%)	+13.0%
Diuretics	171 (8.9%)	572 (6.0%)	+32.8%	1,731 (39.9%)	6,848 (32.4%)	+18.8%
Thiazide/Thiazide-like	135 (7.0%)	473 (4.9%)	+29.6%	969 (22.3%)	4,601 (21.8%)	+2.5%
Loop	31 (1.6%)	86 (0.9%)	+44.3%	840 (19.4%)	2,325 (11.0%)	+43.2%
MRA	11 (0.6%)	30 (0.3%)	+45.2%	228 (5.3%)	708 (3.4%)	+36.3%
β-blockers	206 (10.7%)	693 (7.2%)	+32.4%	1,620 (37.3%)	6,430 (30.4%)	+18.5%
Monotherapy	218 (11.3%)	871 (9.1%)	+19.7%	849 (19.6%)	4,032 (19.1%)	+2.5%
Combination therapy	301 (15.6%)	1,000 (10.4%)	+33.2%	2,264 (52.2%)	9,416 (44.5%)	+14.6%
Oral antidiabetic drugs	72 (3.7%)	315 (3.3%)	+12.1%	789 (18.2%)	2,843 (13.5%)	+26.0%
Metformin	58 (3.0%)	283 (2.9%)	+2.0%	570 (13.1%)	2,048 (9.7%)	+26.3%
Sulfonylureas	11 (0.6%)	53 (0.6%)	+3.2%	203 (4.7%)	728 (3.4%)	+26.4%
DPP-4 inhibitors	2 (0.1%)	14 (0.2%)	-40.7%	87 (2.0%)	299 (1.4%)	+29.5%
GLP-1 agonists	11 (0.6%)	34 (0.4%)	+37.9%	54 (1.2%)	161 (0.8%)	+38.8%
SGLT2 inhibitors	6 (0.3%)	21 (0.2%)	+29.7%	41 (0.9%)	88 (0.4%)	+55.9%
Thiazolidinediones	2 (0.1%)	9 (0.1%)	+9.6%	33 (0.8%)	86 (0.4%)	+46.5%
Other oral antidiabetic	14 (0.7%)	67 (0.7%)	+3.8%	205 (4.7%)	758 (3.6%)	+24.1%
Insulin	26 (1.4%)	96 (1.0%)	+25.8%	312 (7.2%)	767 (3.6%)	+49.5%
Lipid-lowering drugs	171 (8.9%)	722 (7.5%)	+15.2%	1,757 (40.5%)	7,111 (33.6%)	+16.9%
Antiplatelet drugs	72 (3.7%)	270 (2.8%)	+24.7%	1,291 (29.8%)	4,598 (21.8%)	+26.9%
Oral anticoagulant agents	30 (1.6%)	62 (0.6%)	+58.5%	613 (14.1%)	2,111 (10.0%)	+29.3%
Digitalis	1 (0.1%)	2 (0.0%)	+59.8%	65 (1.5%)	168 (0.8%)	+47.0%
Nitrates	1 (0.1%)	18 (0.2%)	-261.7%	200 (4.6%)	606 (2.9%)	+37.8%

Drugs for respiratory disease as a whole	183 (9.5%)	649 (6.8%)	+28.7%	760 (17.5%)	2,521 (11.9%)	+31.9%
LABA	88 (4.6%)	266 (2.8%)	+39.3%	420 (9.7%)	1,261 (6.0%)	+38.4%
SABA	58 (3.0%)	184 (1.9%)	+36.3%	210 (4.8%)	696 (3.3%)	+32.0%
Inhaled corticosteroids	98 (5.1%)	339 (3.5%)	+30.5%	401 (9.2%)	1,319 (6.2%)	+32.5%
Other drugs for respiratory disease	38 (2.0%)	68 (0.7%)	+64.0%	220 (5.1%)	546 (2.6%)	+49.1%
Immunosuppressant agents	187 (9.7%)	638 (6.6%)	+31.5%	615 (14.2%)	2,073 (9.8%)	+30.8%
Non-steroidal anti-inflammatory drugs	187 (9.7%)	967 (10.1%)	-3.9%	849 (19.6%)	3,612 (17.1%)	+12.7%
Non-selective COX inhibitors	156 (8.1%)	855 (8.9%)	-10.1%	708 (16.3%)	3,059 (14.5%)	+11.3%
Selective COX2 inhibitors	39 (2.0%)	180 (1.9%)	+7.3%	213 (4.9%)	859 (4.1%)	+17.2%
Comorbidities and associated procedures						
Cardiovascular disease	165 (8.5%)	528 (5.5%)	+35.7%	1,726 (39.8%)	6,151 (29.1%)	+26.9%
Coronary artery disease	29 (1.5%)	112 (1.2%)	+22.4%	444 (10.2%)	1,407 (6.7%)	+35.0%
Percutaneous coronary intervention	21 (1.1%)	86 (0.9%)	+17.7%	223 (5.1%)	737 (3.5%)	+32.2%
Heart failure	14 (0.7%)	22 (0.2%)	+68.4%	309 (7.1%)	737 (3.5%)	+51.0%
Respiratory diseases	91 (4.7%)	214 (2.2%)	+52.8%	560 (12.9%)	1,502 (7.1%)	+45.0%
Chronic obstructive pulmonary disease	10 (0.5%)	11 (0.1%)	+77.9%	178 (4.1%)	422 (2.0%)	+51.3%
Asthma	3 (0.2%)	3 (0.0%)	+79.9%	15 (0.4%)	32 (0.2%)	+56.2%
Kidney disease	17 (0.9%)	38 (0.4%)	+55.1%	294 (6.8%)	780 (3.7%)	+45.5%
Chronic kidney disease	9 (0.5%)	15 (0.2%)	+66.5%	172 (4.0%)	378 (1.8%)	+54.9%
Dialysis	6 (0.3%)	4 (0.0%)	+86.6%	43 (1.0%)	50 (0.2%)	+76.1%
Cancer	177 (9.2%)	691 (7.2%)	+21.6%	914 (21.1%)	3,948 (18.7%)	+11.3%
Chronic Related Score[‡]						
0	1,268 (65.6%)	7,151 (74.4%)	-13.3%	848 (19.5%)	5,900 (27.9%)	-42.8%
1	414 (21.4%)	1,689 (17.6%)	+18.0%	1,036 (23.9%)	5,936 (28.1%)	-17.6%
2	175 (9.1%)	559 (5.8%)	+35.8%	942 (21.7%)	4,297 (20.3%)	+6.4%
3	43 (2.2%)	139 (1.4%)	+35.1%	633 (14.6%)	2,319 (11.0%)	+24.8%
4	32 (1.7%)	77 (0.8%)	+51.7%	881 (20.3%)	2,692 (12.7%)	+37.3%

MV: Matching variables; ACEI: Angiotensin converting enzyme inhibitors; ARB: Angiotensin II receptor blockers; CCB: Calcium channel blocker; MRA: Mineralocorticoid receptor antagonists; DPP-4: Dipeptidyl peptidase 4; GLP-1: Glucagon-like peptide-1; SGLT2: Sodium-glucose co-transporter 2; LABA: Long-acting β -agonists; SABA Short-acting β -agonists

[†] At least one prescription during the year 2019

[‡] Chronic Related Score is a new index of patients' clinical profile derived from inpatient and outpatient services provided by the Regional Health Service and validated for outcome prediction [28]. Five categories of progressively worsening clinical profile are considered

Table S5. ARBs, ACEIs, other antihypertensives drugs, drugs for a variety of other diseases, and other features of patients with diagnosis of infection from Covid-19 (cases) and corresponding matched controls according with the severity of clinical manifestations (mild-moderate and critical/fatal)

	Mild-moderate infection			Critical/fatal infection		
	Cases (N=5,655)	Controls (N=27,790)	Relative difference	Cases (N=617)	Controls (N=2,969)	Relative difference
Age, years						
Mean (SD)	66 (13)	66 (13)	MV	75 (10)	75 (10)	MV
Women	2,165 (38%)	10,691 (38%)	MV	138 (22%)	666 (22%)	MV
Drugs†						
Antihypertensive drugs	3,185 (56.3%)	13,565 (48.8%)	+13.3%	447 (72.5%)	1,754 (59.1%)	+18.5%
ACEIs	1,305 (23.1%)	5,742 (20.7%)	+10.5%	197 (31.9%)	827 (27.9%)	+12.8%
ARBs	1,227 (21.7%)	5,257 (18.9%)	+12.8%	167 (27.1%)	653 (22.0%)	+18.7%
CCBs	1,230 (21.8%)	5,124 (18.4%)	+15.2%	216 (35.0%)	802 (27.0%)	+22.8%
Diuretics	1,638 (29.0%)	6,473 (23.3%)	+19.6%	264 (42.8%)	947 (31.9%)	+25.5%
Thiazide/Thiazide-like	991 (17.5%)	4,464 (16.1%)	+8.3%	113 (18.3%)	610 (20.6%)	-12.2%
Loop	706 (12.5%)	2,044 (7.4%)	+41.1%	165 (26.7%)	367 (12.4%)	+53.8%
MRA	186 (3.3%)	625 (2.3%)	+31.6%	53 (8.6%)	113 (3.8%)	+55.7%
β-blockers	1,556 (27.5%)	6,213 (22.4%)	+18.8%	270 (43.8%)	910 (30.7%)	+30.0%
Monotherapy	977 (17.3%)	4,445 (16.0%)	+7.4%	90 (14.6%)	458 (15.4%)	-5.8%
Combination therapy	2,208 (39.1%)	9,120 (32.8%)	+16.0%	357 (57.9%)	1,296 (43.7%)	+24.6%
Oral antidiabetic drugs	723 (12.8%)	2,753 (9.9%)	+22.5%	138 (22.4%)	405 (13.6%)	+39.0%
Metformin	539 (9.5%)	2,037 (7.3%)	+23.1%	89 (14.4%)	294 (9.9%)	+31.4%
Sulfonylureas	171 (3.0%)	682 (2.5%)	+18.8%	43 (7.0%)	99 (3.3%)	+52.2%
DPP-4 inhibitors	65 (1.2%)	267 (1.0%)	+16.4%	24 (3.9%)	46 (1.6%)	+60.2%
GLP-1 agonists	58 (1.0%)	174 (0.6%)	+39.0%	7 (1.1%)	21 (0.7%)	+37.7%
SGLT2 inhibitors	40 (0.7%)	101 (0.4%)	+48.6%	7 (1.1%)	8 (0.3%)	+76.3%
Thiazolidinediones	32 (0.6%)	84 (0.3%)	+46.6%	3 (0.5%)	11 (0.4%)	+23.8%
Other oral antidiabetic	184 (3.3%)	708 (2.6%)	+21.7%	35 (5.7%)	117 (3.9%)	+30.5%
Insulin	277 (4.9%)	747 (2.7%)	+45.1%	61 (9.9%)	116 (3.9%)	+60.5%
Lipid-lowering drugs	1,656 (29.3%)	6,861 (24.7%)	+15.7%	272 (44.1%)	972 (32.7%)	+25.7%
Antiplatelet drugs	1,145 (20.3%)	4,208 (15.1%)	+25.2%	218 (35.3%)	660 (22.2%)	+37.1%

Oral anticoagulant agents	541 (9.6%)	1,860 (6.7%)	+30.0%	102 (16.5%)	313 (10.5%)	+36.2%
Digitalis	55 (1.0%)	145 (0.5%)	+46.4%	11 (1.8%)	25 (0.8%)	+52.8%
Nitrates	165 (2.9%)	530 (1.9%)	+34.6%	36 (5.8%)	94 (3.2%)	+45.7%
Drugs for respiratory disease as a whole	846 (15.0%)	2,832 (10.2%)	+31.9%	97 (15.7%)	338 (11.4%)	+27.6%
LABA	460 (8.1%)	1,352 (4.9%)	+40.2%	48 (7.8%)	175 (5.9%)	+24.2%
SABA	239 (4.2%)	791 (2.9%)	+32.7%	29 (4.7%)	89 (3.0%)	+36.2%
Inhaled corticosteroids	437 (7.7%)	1,487 (5.4%)	+30.8%	62 (10.1%)	171 (5.8%)	+42.7%
Other drugs for respiratory disease	230 (4.1%)	527 (1.9%)	+53.4%	28 (4.5%)	87 (2.9%)	+35.4%
Immunosuppressant agents	727 (12.9%)	2,558 (9.2%)	+28.4%	75 (12.2%)	153 (5.2%)	+57.6%
Non-steroidal anti-inflammatory drugs	934 (16.5%)	4,105 (14.8%)	+10.6%	102 (16.5%)	474 (16.0%)	+3.4%
Non-selective COX inhibitors	778 (13.8%)	3,519 (12.7%)	+8.0%	86 (13.9%)	395 (13.3%)	+4.6%
Selective COX2 inhibitors	224 (4.0%)	924 (3.3%)	+16.1%	28 (4.5%)	115 (3.9%)	+14.7%
Comorbidities and associated procedures						
Cardiovascular disease	1,599 (28.3%)	5,723 (20.6%)	+27.2%	292 (47.3%)	956 (32.2%)	+32.0%
Coronary artery disease	386 (6.8%)	1,292 (4.7%)	+31.9%	87 (14.1%)	227 (7.7%)	+45.8%
Percutaneous coronary intervention	202 (3.6%)	720 (2.6%)	+27.5%	42 (6.8%)	103 (3.5%)	+49.0%
Heart failure	263 (4.7%)	634 (2.3%)	+51.0%	60 (9.7%)	125 (4.2%)	+56.7%
Respiratory diseases	546 (9.7%)	1,482 (5.3%)	+44.8%	105 (17.0%)	234 (7.9%)	+53.7%
Chronic obstructive pulmonary disease	158 (2.8%)	367 (1.3%)	+52.7%	30 (4.9%)	66 (2.2%)	+54.3%
Asthma	14 (0.3%)	34 (0.1%)	+50.6%	4 (0.7%)	1 (0.0%)	+94.8%
Kidney disease	244 (4.3%)	690 (2.5%)	+42.5%	67 (10.9%)	128 (4.3%)	+60.3%
Chronic kidney disease	138 (2.4%)	334 (1.2%)	+50.8%	43 (7.0%)	59 (2.0%)	+71.5%
Dialysis	43 (0.8%)	43 (0.2%)	+79.7%	6 (1.0%)	11 (0.4%)	+61.9%
Cancer	949 (16.8%)	4,014 (14.4%)	+13.9%	142 (23.0%)	625 (21.1%)	+8.5%
Chronic Related Score‡						
0	2,008 (35.5%)	12,182 (43.8%)	-23.5%	108 (17.5%)	869 (29.3%)	-67.2%
1	1,327 (23.5%)	6,889 (24.8%)	-5.6%	123 (19.9%)	736 (24.8%)	-24.4%
2	989 (17.5%)	4,280 (15.4%)	+11.9%	128 (20.8%)	576 (19.4%)	+6.5%
3	577 (10.2%)	2,121 (7.6%)	+25.2%	99 (16.1%)	337 (11.4%)	+29.3%
4	754 (13.3%)	2,318 (8.3%)	+37.4%	159 (25.8%)	451 (15.2%)	+41.1%

MV: Matching variables; SD: Standard deviation; ACEI: Angiotensin converting enzyme inhibitors; ARB: Angiotensin II receptor blockers; CCB: Calcium channel blocker; MRA: Mineralocorticoid receptor antagonists; DPP-4: Dipeptidyl peptidase 4; GLP-1: Glucagon-like peptide-1; SGLT2: Sodium-glucose co-transporter 2; LABA: Long-acting β -agonists; SABA Short-acting β -agonists

† At least one prescription during the year 2019

‡ Chronic Related Score is a new index of patients' clinical profile derived from inpatient and outpatient services provided by the Regional Health Service and validated for outcome prediction [28]. Five categories of progressively worsening clinical profile are considered

Table S6. Adjusted odds ratios, and 95% confidence intervals, of infection from Covid-19 associated with use of blockers of the renin-angiotensin system, according with the period on which Covid-19 cases were diagnosed (before and after 26th February, 2020)

	Odds ratio (95% confidence interval) [§]	
	February 25 and before	February 26 and after
ACEIs	0.92 (0.58 to 1.48)	0.98 (0.88 to 1.08)
ARBs	0.80 (0.50 to 1.30)	0.96 (0.86 to 1.06)

ACEIs: Angiotensin converting enzyme inhibitors; ARBs: Angiotensin II receptor blockers

[§] Odds ratios of Covid-infection risk associated with drug use. No use was considered as reference. Estimates were obtained by fitting conditional logistic regression. Estimates were unadjusted and full adjusted for drugs and comorbidities listed in the Table 1