

# THE LANCET

## Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

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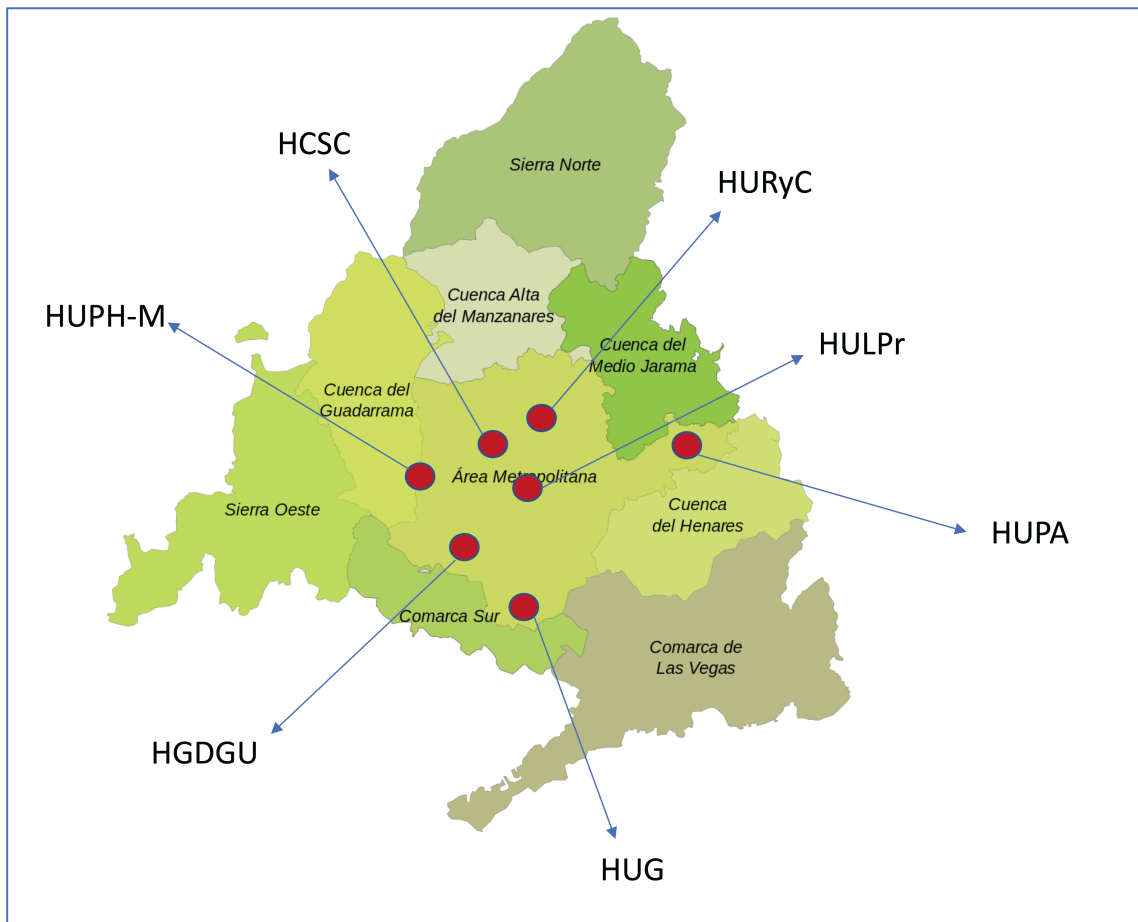
## **APPENDIX**

### **USE OF RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM INHIBITORS AND RISK OF COVID-19 REQUIRING ADMISSION TO HOSPITAL: A CASE- POPULATION STUDY**

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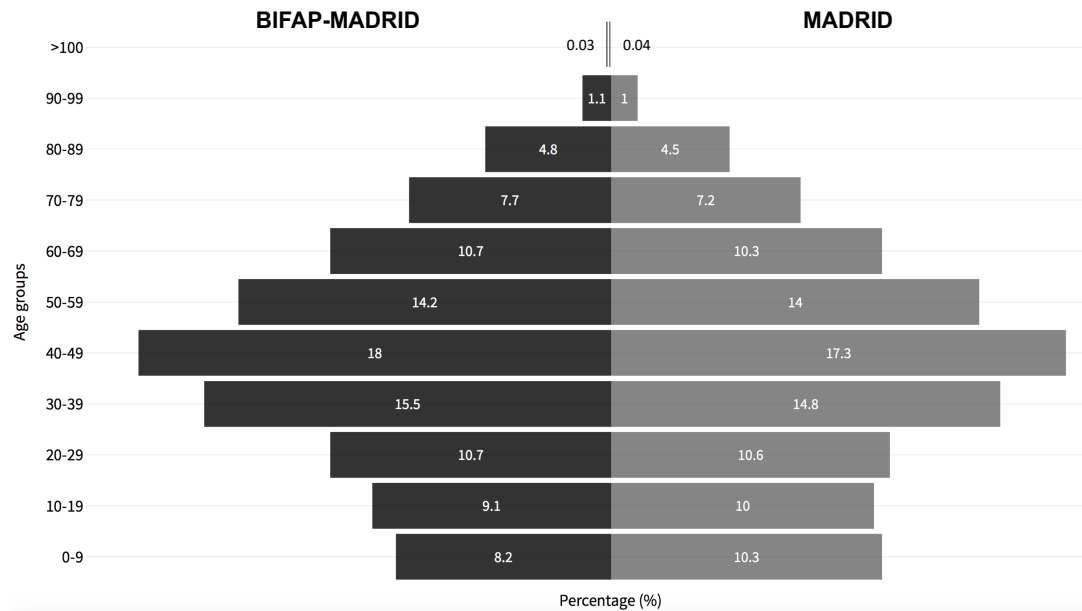
## Appendix p 2: Distribution of hospitals taking part in the study



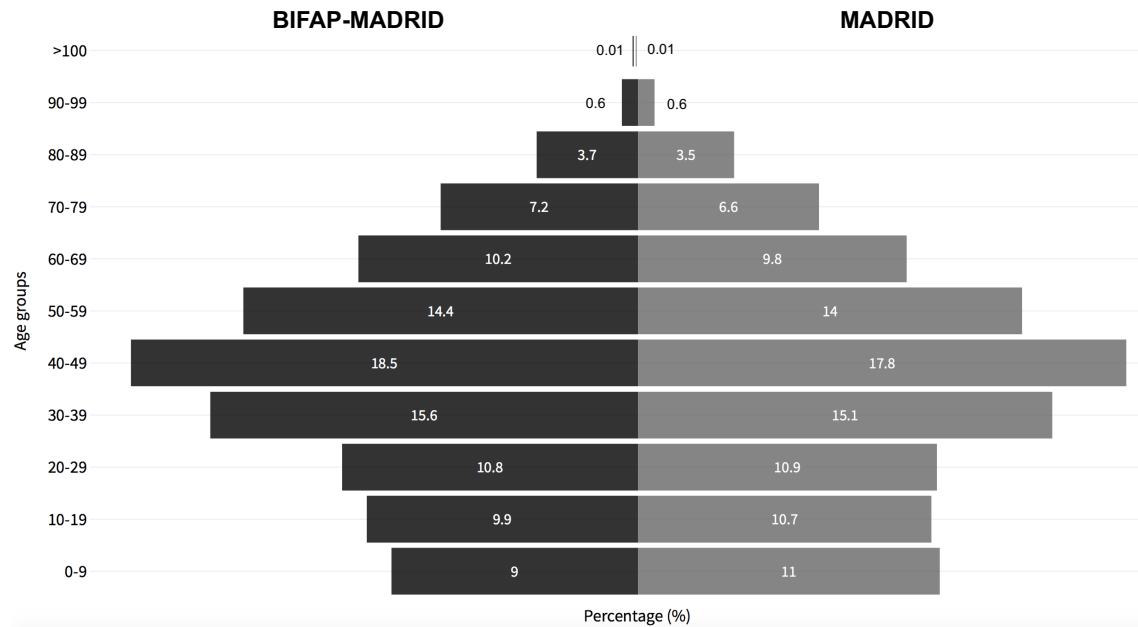
- HURyC: Hospital Universitario Ramón y Cajal (Madrid)  
HULPr: Hospital Universitario de La Princesa (Madrid)  
HUPA: Hospital Universitario Príncipe de Asturias (Alcalá de Henares)  
HUG: Hospital Universitario de Getafe (Getafe)  
HGDGU: Hospital General de la Defensa "Gómez Ulla" (Madrid)  
HUPH-M: Hospital Universitario Puerta de Hierro (Majadahonda)  
HCSC: Hospital Clínico San Carlos (Madrid)

**Appendix pp 3-4. Distribution by age and gender of BIFAP patients from Madrid (BIFAP-MADRID) as compared to Madrid population census (MADRID).**

**Both genders**

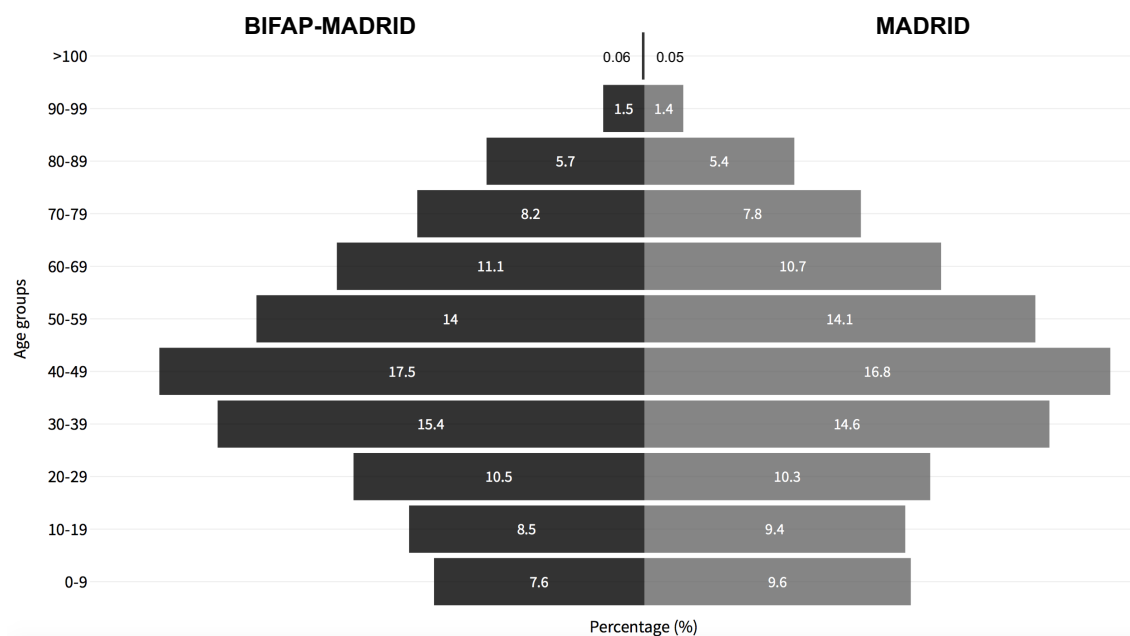


**Males**



**Appendix pp 3-4 (continued). Distribution by age and gender of BIFAP patients from Madrid (BIFAP-MADRID) as compared to Madrid population census (MADRID).**

**Females**

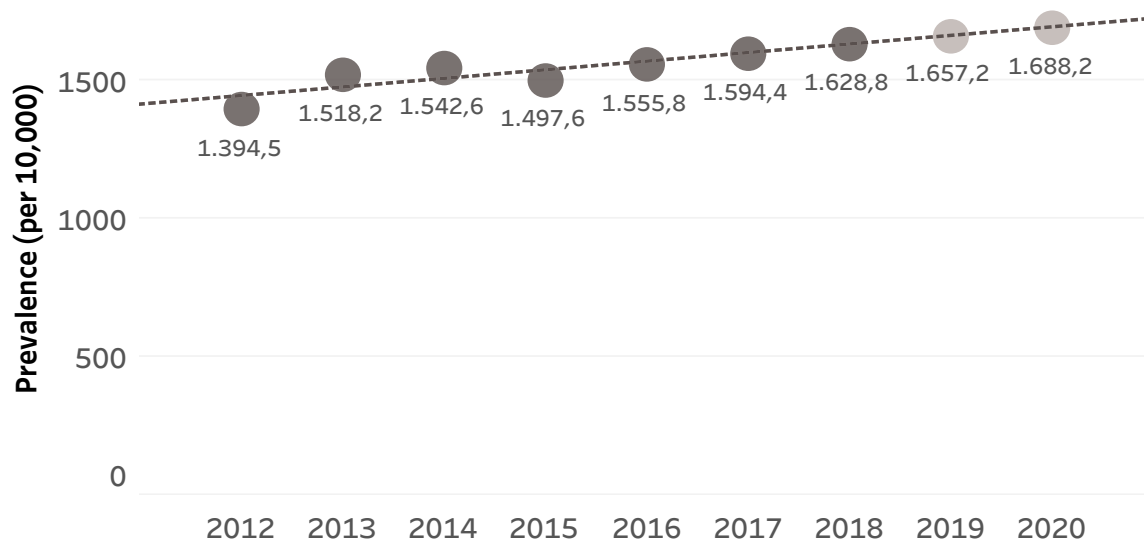


**Appendix pp 5-7: Trends of use prevalence of different antihypertensive subgroups. It is shown the forecasted values for 2019 and 2020, as well as the ratio 2020/2018 (used as correction factor). Data are shown in number of users per 10,000 patients with records in BIFAP.**

### RENIN-ANGIOTENSIN SYSTEM BLOCKERS (RAS)

Method: Linear ; R2 = 0.79

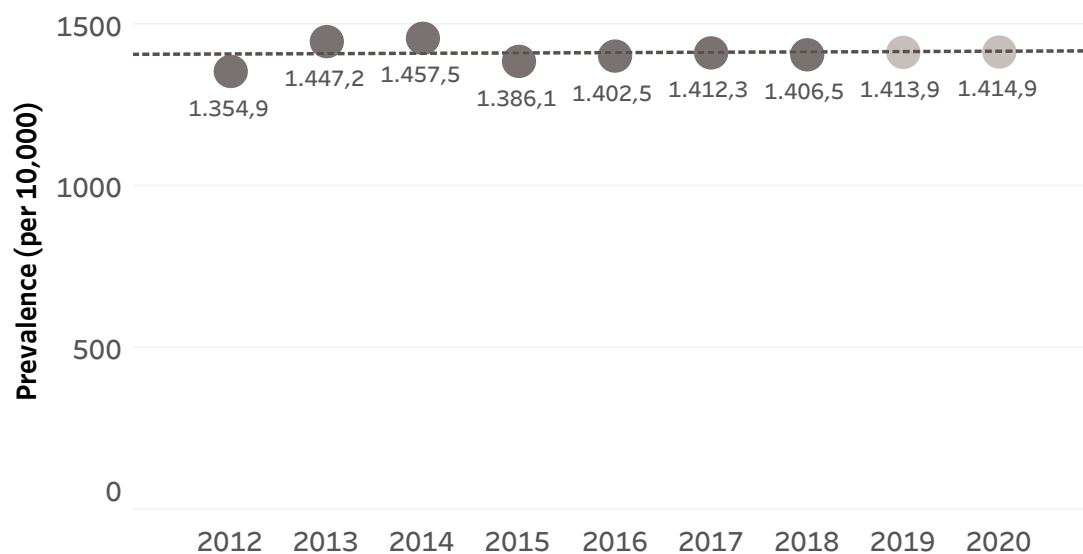
Correction Factor (2020 / 2018) = 1.04



### OTHER ANTIHYPERTENSIVE DRUGS

Method: Linear ; R2 = 0.01

Correction Factor (2020 / 2018) = 1.01

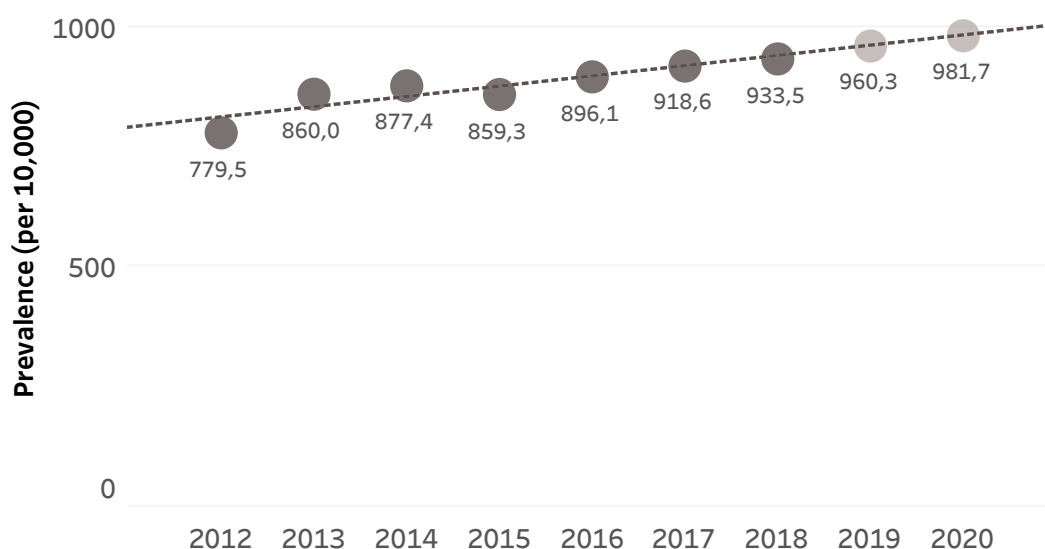


**Appendix pp 5-7 (continued): Trends of use prevalence of different antihypertensive subgroups. It is shown the forecasted values for 2019 and 2020, as well as the ratio 2020/2018 (used as correction factor). Data are shown in number of users per 10,000 patients with records in BIFAP.**

### ANGIOTENSIN CONVERTING ENZYME INHIBITORS (ACEI)

Method: Linear ; R2 = 0.83

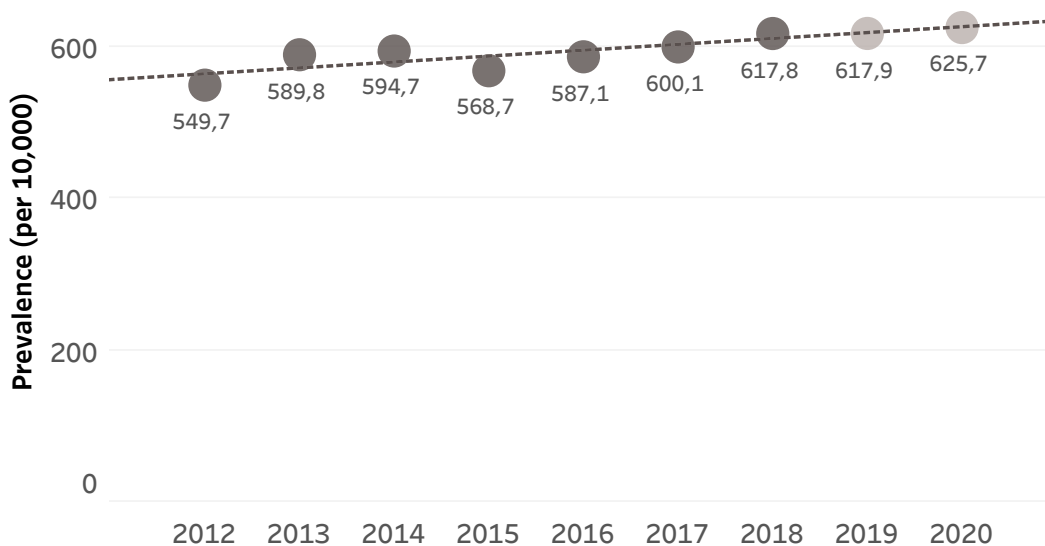
Correction Factor (2020 / 2018) = 1.05



### ANGIOTENSIN RECEPTOR BLOCKERS (ARB)

Method: Linear ; R2 = 0.58

Correction Factor (2020 / 2018) = 1.01

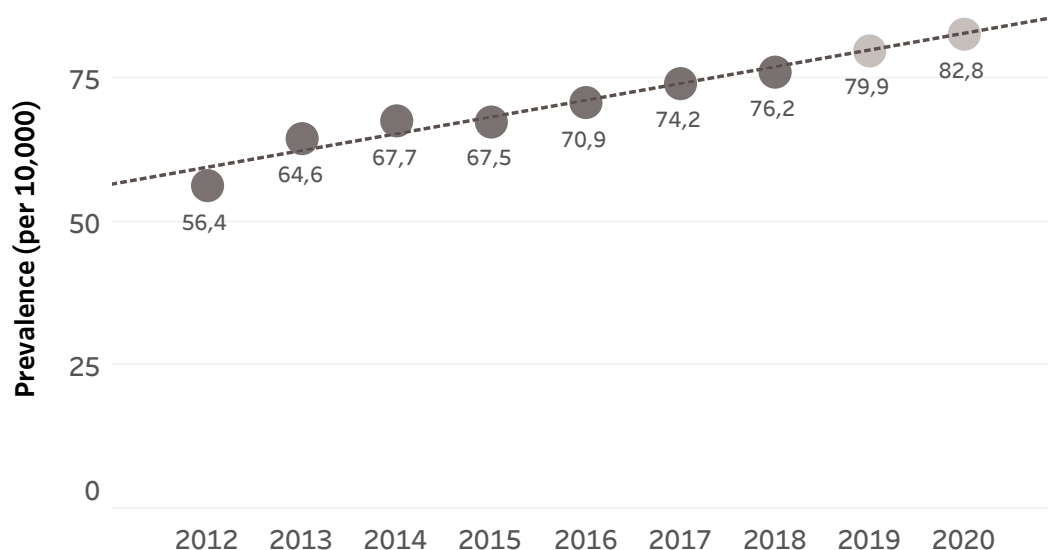


**Appendix pp 5-7 (continued): Trends of use prevalence of different antihypertensive subgroups. It is shown the forecasted values for 2019 and 2020, as well as the ratio 2020/2018 (used as correction factor). Data are shown in number of users per 10,000 patients with records in BIFAP.**

**ALDOSTERONE ANTAGONISTS (AA)**

Method: Linear ; R2 = 0.92

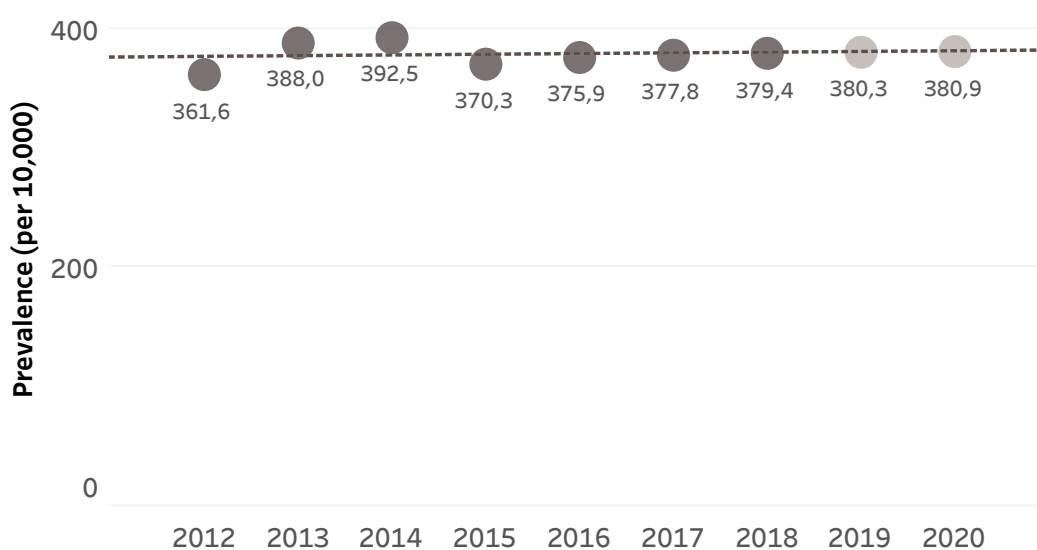
Correction Factor (2020 / 2018) = 1.09



**CALCIUM CHANNEL BLOCKERS (CCB)**

Method: Linear ; R2 = 0.01

Correction Factor (2020 / 2018) = 1.0





**Appendix p 8: Antihypertensive drugs included in the study and their respective ATC codes.**

<b>Antihypertensive drugs</b>	<b>ATC codes</b>
ACE inhibitors	C09AA, C09B, C10BX04, C10BX06, C10BX07, C10BX11, C10BX12, C10BX13, C10BX14, C10BX15, C10BX17.
Angiotensin II receptor blockers	C09CA, C09D, C10BX10, C10BX16
Renin inhibitors	C09X, C09DX02
Aldosterone antagonists	C03DA, C03EA04, C03EA06, C03EA13
Calcium channel blockers	C08, C07FB, C09BB, C09BX01, C09BX03, C09BX04, C09DB, C09DX01, C09DX03, C09DX06, C09DX07, C09XA53, C09XA54, C10BX03, C10BX07, C10BX09, C10BX11, C10BX14
Diuretics	C03A, C03B, C03C, C03DB, C03E, C03X, C02L, C07B, C07C, C07D, C08GA, C09BA, C09BX01, C09BX03, C09DA, C09DX01, C09DX03, C09DX06, C09DX07, C09XA52, C09XA54, C10BX13
Beta-blocking agents	C07A, C07B, C07C, C07D, C07E, C07F, C09BX02, C09BX04, C09DX05
Alpha-blockers	C02CA

**Appendix p 9. Risk of COVID-19 requiring hospital admission and current use of Renin-Angiotensin-Aldosterone System (RAAS) inhibitors as compared to non-use of any antihypertensive drug.**

Antihypertensive drug use	Cases (%) N=1139	Controls (%) N=11390	Crude OR* (95%CI)	Adjusted OR** (95%CI)
Non-use	487 (42.8)	6439 (56.5)	1 (Ref.)	1 (Ref.)
<b>Current use of RAAS inhibitors</b>	497 (43.6)	3822 (33.6)	1.99 (1.72-2.31)	1.71 (1.46-2.01)
<i>ACEIs</i>	240 (21.1)	2192 (19.2)	1.68 (1.41-2.00)	1.47 (1.22-1.77)
Monotherapy	82 (7.2)	757 (6.7)	1.61 (1.25-2.08)	1.54 (1.19-1.99)
Combinations	158 (13.9)	1435 (12.6)	1.72 (1.40-2.10)	1.44 (1.16-1.79)
<i>ARBs</i>	237 (20.8)	1552 (13.6)	2.36 (1.98-2.83)	2.02 (1.67-2.44)
Monotherapy	38 (3.3)	328 (2.9)	1.76 (1.23-2.51)	1.61 (1.12-2.31)
Combinations	199 (17.5)	1224 (10.8)	2.54 (2.10-3.07)	2.13 (1.73-2.61)
<i>AAs</i>	19 (1.7)	71 (0.6)	4.38 (2.59-7.39)	3.10 (1.80-5.34)
<i>RIs</i>	1 (0.1)	7 (0.1)	2.32 (0.28-18.90)	1.92 (0.23-15.84)
<b>Current use of OADs</b>	155 (13.6)	1129 (9.9)	2.13 (1.73-2.61)	1.82 (1.47-2.26)
<i>CCBs</i>	55 (4.8)	372 (3.3)	2.29 (1.69-3.12)	1.96 (1.43-2.69)
<i>Diuretics</i>	60 (5.3)	442 (3.9)	2.12 (1.57-2.85)	1.79 (1.32-2.43)
<i>BBAs</i>	37 (3.3)	293 (2.6)	1.93 (1.35-2.77)	1.68 (1.16-2.43)
<i>ABs</i>	3 (0.3)	22 (0.2)	2.11 (0.62-7.16)	1.96 (0.57-6.71)

\* Crude OR actually means adjusted only for the matching variables.

\*\* Adjusted for the matching variables plus antecedents of diabetes, dyslipidaemia, ischaemic heart disease, heart failure, atrial fibrillation, thromboembolic disease, cerebrovascular accident, chronic obstructive pulmonary disease, asthma, cancer and chronic renal failure

**Abbreviations:** AAs: Antagonists of aldosterone; ACEIs: Angiotensin-converting enzyme inhibitors; ABs: Alpha-blockers; ARBs: Angiotensin II receptor blockers; BBAs: Beta-blocking agents; CCBs: Calcium-channel blockers; OADs: Other antihypertensive drugs; OR: Odds ratio; RAAS: Renin-Angiotensin-Aldosterone System; RIs: Renin inhibitors.

**Note:** In this table, the different pharmacological classes examined are mutually exclusive categories, so that patients who used combinations are counted only once, applying the following criteria: ACEIs includes current users of any angiotensin converting enzyme inhibitor, alone or combined with any other antihypertensive drug (in fixed-dose combinations or in different medicinal products); ARBs includes current users of any angiotensin II receptor blocker (ARB), alone or combined with any other antihypertensive drug different from ACEIs (in fixed-dose combinations or in different medicinal products); AAs includes current users of any antagonist of aldosterone, alone or combined with any other antihypertensive drug different from ACEIs and ARBs (in fixed-dose combinations or in different medicinal products); OADs includes calcium channel blockers, diuretics, beta-blockers, and alpha-blockers, alone or combined (excluding RAAS inhibitors, either in fixed-dose combinations or in different medicinal products).

**Appendix p 10. Risk of COVID-19 requiring hospital admission and current use of Renin-Angiotensin-Aldosterone System (RAAS) inhibitors as compared to current use of Calcium Channel Blockers (CCBs).**

	Cases (%) N=1139	Controls (%) N=11390	Crude OR	Adjusted OR*
<b>Current use of OADs</b>	155 (13.6)	1129 (9.9)	..	..
<i>CCBs</i>	55 (4.8)	372 (3.3)	1 (Ref.)	1 (Ref.)
<i>Diuretics</i>	60 (5.3)	442 (3.9)	0.92 (0.62-1.37)	0.91 (0.61-1.36)
<i>Beta-blocking agents</i>	37 (3.3)	293 (2.6)	0.84 (0.54-1.32)	0.86 (0.55-1.34)
<i>Alpha-blockers</i>	3 (0.3)	22 (0.2)	0.92 (0.26-3.20)	1.00 (0.29-3.52)
<b>Current use of RAAS inhibitors</b>	497 (43.6)	3822 (33.6)	0.87 (0.64-1.17)	0.87 (0.65-1.18)
<i>ACEIs</i>	240 (21.1)	2192 (19.2)	0.73 (0.53-0.99)	0.74 (0.54-1.02)
Monotherapy	82 (7.2)	757 (6.7)	0.70 (0.48-1.00)	0.78 (0.54-1.13)
Combinations	158 (13.9)	1435 (12.6)	0.74 (0.53-1.03)	0.73 (0.52-1.01)
<i>ARBs</i>	237 (20.8)	1552 (13.6)	1.02 (0.75-1.40)	1.02 (0.74-1.40)
Monotherapy	38 (3.3)	328 (2.9)	0.76 (0.49-1.18)	0.81 (0.52-1.27)
Combinations	199 (17.5)	1224 (10.8)	1.09 (0.79-1.51)	1.07 (0.77-1.49)
<i>AAs</i>	19 (1.7)	71 (0.6)	1.90 (1.06-3.39)	1.57 (0.86-2.84)
<i>RIs</i>	1 (0.1)	7 (0.1)	1.00 (0.12-8.30)	0.97 (0.12-8.12)
<b>Non-use</b>	487 (42.8)	6439 (56.5)	0.44 (0.32-0.59)	0.51 (0.37-0.70)

\* Crude OR actually means adjusted only for the matching variables.

\*\* Adjusted for the matching variables plus antecedents of diabetes, dyslipidaemia, ischaemic heart disease, heart failure, atrial fibrillation, thromboembolic disease, cerebrovascular accident, chronic obstructive pulmonary disease, asthma, cancer and chronic renal failure.

**Abbreviations:** AAs: Antagonists of aldosterone; ACEIs: Angiotensin-converting enzyme inhibitors; ABs: Alpha-blockers; ARBs: Angiotensin II receptor blockers; BBAs: Beta-blocking agents; CCBs: Calcium-channel blockers; OADs: Other antihypertensive drugs; OR: Odds ratio; RAAS: Renin-Angiotensin-Aldosterone System; RIs: Renin inhibitors.

**Note:** In this table, the different pharmacological classes examined are mutually exclusive categories, so that patients who used combinations are counted only once, applying the following criteria: ACEIs includes current users of any angiotensin converting enzyme inhibitor, alone or combined with any other antihypertensive drug (in fixed-dose combinations or in different medicinal products); ARBs includes current users of any angiotensin II receptor blocker (ARB), alone or combined with any other antihypertensive drug different from ACEIs (in fixed-dose combinations or in different medicinal products); AAs Includes current users of any antagonist of aldosterone, alone or combined with any other antihypertensive drug different from ACEIs and ARBs (in fixed-dose combinations or in different medicinal products); OADs includes calcium channel blockers, diuretics, beta-blockers, and alpha-blockers, alone or combined (excluding RAAS inhibitors, either in fixed-dose combinations or in different medicinal products).

**Appendix p 11. Risk of COVID-19 requiring hospital admission and current use of Renin-Angiotensin System (RAS) inhibitors as compared to current use of other antihypertensive drugs (OADs) (main analysis).** In this analysis, aldosterone antagonists (AAs) and renin inhibitors (RIs) are not included among RAAS inhibitors.

Antihypertensive drug use	Cases (%) N=1139	Controls (%) N=11390	Crude OR* (95%CI)	Adjusted OR** (95%CI)
<b>Current use of OADs***</b>	155 (13.6)	1129 (9.9)	1 (Ref.)	1 (Ref.)
<b>Current use of RAS inhibitors</b>	477 (41.9)	3744 (32.9)	0.92 (0.75-1.11)	0.92 (0.76-1.12)
<i>ACEIs</i>	240 (21.1)	2192 (19.2)	0.78 (0.63-0.97)	0.80 (0.64-1.00)
Monotherapy	82 (7.2)	757 (6.7)	0.75 (0.57-1.00)	0.83 (0.62-1.12)
Combinations	158 (13.9)	1435 (12.6)	0.80 (0.63-1.01)	0.78 (0.62-0.99)
<i>ARBs</i>	237 (20.8)	1552 (13.6)	1.11 (0.89-1.38)	1.10 (0.88-1.37)
Monotherapy	38 (3.3)	328 (2.9)	0.82 (0.56-1.20)	0.87 (0.60-1.28)
Combinations	199 (17.5)	1224 (10.8)	1.18 (0.94-1.48)	1.15 (0.92-1.45)
<b>AAs</b>	19 (1.7)	71 (0.6)	2.04 (1.20-3.49)	1.68 (0.97-2.91)
<b>RIs</b>	1 (0.1)	7 (0.1)	1.08 (0.13-8.86)	1.04 (0.13-8.62)
<b>Non-use</b>	487 (42.8)	6439 (56.5)	0.47 (0.38-0.58)	0.55 (0.44-0.68)

\* Crude OR actually means adjusted only for the matching variables.

\*\* Adjusted for the matching variables plus antecedents of diabetes, dyslipidaemia, ischaemic heart disease, heart failure, atrial fibrillation, thromboembolic disease, cerebrovascular accident, chronic obstructive pulmonary disease, asthma, cancer and chronic renal failure.

**Abbreviations:** AAs: Antagonists of aldosterone; ACEIs: Angiotensin-converting enzyme inhibitors; ABs: Alpha-blockers; ARBs: Angiotensin II receptor blockers; BBAs: Beta-blocking agents; CCBs: Calcium-channel blockers; OADs: Other antihypertensive drugs; OR: Odds ratio; RAAS: Renin-Angiotensin-Aldosterone System; RIs: Renin inhibitors.

**Note:** In this table, the different pharmacological classes examined are mutually exclusive categories, so that patients who used combinations are counted only once, applying the following criteria: ACEIs includes current users of any angiotensin converting enzyme inhibitor, alone or combined with any other antihypertensive drug (in fixed-dose combinations or in different medicinal products); ARBs includes current users of any angiotensin II receptor blocker (ARB), alone or combined with any other antihypertensive drug different from ACEIs (in fixed-dose combinations or in different medicinal products); AAs Includes current users of any antagonist of aldosterone, alone or combined with any other antihypertensive drug different from ACEIs and ARBs (in fixed-dose combinations or in different medicinal products); OADs includes calcium channel blockers, diuretics, beta-blockers, and alpha-blockers, alone or combined (excluding RAAS inhibitors, either in fixed-dose combinations or in different medicinal products).

**Appendix p 12. Risk of COVID-19 requiring inpatient admission and current use of Renin-Angiotensin System (RAS) inhibitors as compared to current use of other antihypertensive drugs (OADs) by severity.** In this analysis, aldosterone antagonists (AAs) and renin inhibitors (RIs) are not included among RAAS inhibitors.

Fatal and ICU cases			
	Cases (N=393)	Controls (N=3930)	Adjusted OR* (95%CI)
Males	264 (67.2)	2640 (67.2)	Matched
Age (y), mean ( $\pm$ SD)	75.3 (12.3)	75.3 (12.3)	Matched
Current use of:	..	..	..
<i>OADs</i> **	64 (16.3)	484 (12.3)	1 (Ref.)
<i>RAS inhibitors</i> ***	206 (52.4)	1560 (39.7)	1.06 (0.78-1.44)
<i>ACEIs</i>	101 (25.7)	905 (23.0)	0.92 (0.65-1.29)
<i>ARBs</i>	105 (26.7)	655 (16.7)	1.25 (0.89-1.77)
<i>Non-use</i>	114 (29.0)	1854 (47.2)	0.48 (0.34-0.69)

Less severe cases			
Current use of:	Cases (N=746)	Controls (N=7460)	Adjusted OR* (95%CI)
Males	431 (57.8)	4310 (57.8)	Matched
Age (y), mean ( $\pm$ SD)	65.8 (15.9)	65.8 (15.9)	Matched
Current use of:	..	..	..
<i>OADs</i> **	91 (12.2)	645 (8.7)	1 (Ref.)
<i>RAS inhibitors</i> ***	271 (36.3)	2184 (29.3)	0.84 (0.65-1.09)
<i>ACEIs</i>	139 (18.6)	1287 (17.3)	0.74 (0.56-0.99)
<i>ARBs</i>	132 (17.7)	897 (12.0)	0.99 (0.74-1.33)
<i>Non-use</i>	373 (50.0)	4585 (61.5)	0.57 (0.43-0.75)

\* Adjusted for the matching variables plus antecedents of diabetes, dyslipidaemia, ischaemic heart disease, heart failure, atrial fibrillation, thromboembolic disease, cerebrovascular accident, chronic obstructive pulmonary disease, asthma, cancer and chronic renal failure

\*\* Including calcium channel blockers, beta-blocking agents, diuretics and alpha-blockers

\*\*\* Including ACEIs and ARBs

**Abbreviations:** ACEIs: Angiotensin-converting enzyme inhibitors; ARBs: Angiotensin II receptor blockers; OADs: Other anti-hypertensive drugs; OR: Odds ratio; RAAS: Renin-Angiotensin-Aldosterone System.

**Note:** In this table, the different pharmacological classes examined are mutually exclusive categories, so that patients who used combinations are counted only once, applying the following criteria: ACEIs include current users of any angiotensin converting enzyme inhibitor, alone or combined with any other antihypertensive drug (in fixed-dose combinations or in different medicinal products); ARBs include current users of any angiotensin II receptor blocker (ARB), alone or combined with any other antihypertensive drug different from ACEIs (in fixed-dose combinations or in different medicinal products); OADs include calcium channel blockers, diuretics, beta-blockers, and alpha-blockers, alone or combined (excluding RAAS inhibitors, either in fixed-dose combinations or in different medicinal products).

**Appendix p 13. Comorbidity pattern associated with different antihypertensive drugs use, as well as non-use (of any antihypertensive drug), among controls.**

	<b>RAAS inhibitors (N=3828)</b>	<b>ACEIs (N=2192)</b>	<b>ARBs (N=1552)</b>	<b>OADs (N=1129)</b>	<b>CCBs (N=372)</b>	<b>Non-users (N=6439)</b>
<b>Male</b>	2427 (63·5)	1472 (67·2)	908 (58·5)	660 (58·5)	191 (65·2)	3863 (60·0)
<b>Age (y), mean (± SD)</b>	76·0 (10·3)	75·5 (10·4)	76·5 (10·0)	77·8 (10·1)	78·6 (10·2)	63·4 (16·3)
<b>Hypertension</b>	3486 (91·2)	1986 (90·6)	1451 (93·5)	823 (72·9)	314 (84·4)	1335 (20·7)
<b>Diabetes</b>	1258 (32·9)	698 (31·8)	532 (34·3)	283 (25·1)	91 (24·5)	770 (12·0)
<b>Dyslipidaemia</b>	2158 (56·5)	1236 (56·4)	887 (57·2)	538 (47·7)	202 (54·3)	834 (13·0)
<b>Ischaemic heart disease</b>	510 (13·3)	299 (13·6)	194 (12·5)	169 (15·0)	57 (15·3)	183 (2·8)
<b>Heart failure</b>	252 (6·6)	117 (5·3)	109 (7·0)	85 (7·5)	23 (6·2)	63 (1·0)
<b>Atrial fibrillation</b>	492 (12·9)	257 (11·7)	199 (12·8)	267 (23·6)	68 (18·3)	211 (3·3)
<b>Thromboembolic disease</b>	126 (3·3)	72 (3·3)	49 (3·2)	45 (4·0)	18 (4·8)	119 (1·9)
<b>Cerebrovascular accident</b>	279 (7·3)	144 (6·6)	123 (7·9)	97 (8·6)	40 (10·8)	193 (3·0)
<b>COPD</b>	421 (11·0)	232 (10·6)	176 (11·3)	145 (12·8)	45 (12·1)	357 (5·5)
<b>Asthma</b>	221 (5·8)	108 (4·9)	107 (6·9)	68 (6·0)	26 (7·0)	341 (5·3)
<b>Cancer</b>	663 (17·4)	375 (17·1)	274 (17·7)	216 (19·1)	80 (21·5)	694 (10·8)
<b>Chronic Renal Failure</b>	344 (9·0)	169 (7·7)	162 (10·4)	117 (10·4)	50 (13·4)	112 (1·7)

**Abbreviations:** SD: Standard Deviation; COPD: Chronic obstructive pulmonary disease; RAAS: Renin-Angiotensin-Aldosterone System; ACEIs: Angiotensin-converting enzyme inhibitors; ARBs: Angiotensin II receptor blockers; CCBs: Calcium-channel blockers; OADs: other antihypertensive drugs.