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A retrospective multicentre European study

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Association of Statin and/or Renin-Angiotensin-Aldosterone System modulating therapy with mortality in adults with diabetes admitted to hospital with COVID-19: A Retrospective Multicentre European study.

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Running Title

Association of Statin and/or Renin-Angiotensin-Aldosterone System modulating therapy with mortality in adults with diabetes admitted to hospital with COVID-19: A Multicentre European study.

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Table 1

Details of study contributors can be found in the supplementary material.

Structured abstract:

Background & Aims:

To assess the impact of pre-admission renin-angiotensin-aldosterone system inhibitor (RAASi) and statin use on mortality following COVID-19 hospitalization in adults with pre-existing diabetes.

Methods:

Retrospective cohort study of adults with diabetes admitted to ninety-nine participating hospitals in the United Kingdom, France and Spain during the first wave of the COVID-19 pandemic. Logistic regression models adjusted for demographic factors and comorbidity were used to describe associations with mortality in hospital or within 28 days of admission and individual or combined RAASi and statin therapy prescription followed by a country level meta-analysis.

Results:

Complete data were available for 3474 (42.6%) individuals. Prescribing patterns varied by country: 25-50% neither RAASi nor statin therapy, 14-36% both RAASi and statin therapy, 9-24% RAASi therapy alone, 12-36% statin alone. Overall, 20-37% of patients died within 28 days. Meta-analysis found no evidence of an association between mortality and prescription of RAASi therapy (OR 1.09, CI 0.78-1.52 (I^2 22.2%)), statin (OR 0.97, CI 0.59-1.61 (I^2 72.9%)) or both (OR 1.14, CI 0.67-1.92 (I^2 78.3%)) compared to those prescribed neither drug class.

Conclusions:

This large multicentre, multinational study found no evidence of an association between mortality from COVID-19 infection in people with diabetes and use of either RAASi, statin or combination therapy. This provides reassurance that clinicians should not change their RAASi and statin therapy prescribing practice in people with diabetes during the COVID-19 pandemic.

Abbreviations:

Renin-angiotensin-aldosterone system inhibitor (RAASi)

Angiotensin-converting enzyme-2 (ACE-2)

Angiotensin-converting enzyme inhibitors (ACEi)

Angiotensin II receptor blockers (ARB)

United Kingdom (UK)

Association of British Clinical Diabetologist (ABCD)

Oxford University Hospitals NHS Foundation Trust (OUH)

Middle East and North African (MENA)

Chronic kidney disease (CKD)

Confidence interval (CI)

Acute respiratory distress syndrome (ARDS)

Research Highlights:

1. No association between COVID-19 related mortality and use of renin-angiotensin-aldosterone system inhibitor or statin therapy in people with diabetes
2. There was no evidence of an association dependent on ethnicity or type of diabetes
3. Significant variation in renin-angiotensin-aldosterone system inhibitor and statin use across Europe, variable mortality needs further exploration
4. This study reassures clinicians to continue prescribing both statin and renin-angiotensin-aldosterone system inhibitor therapy throughout COVID-19 pandemic.

INTRODUCTION:

The COVID-19 pandemic has been one of the biggest human catastrophes of the modern age; killing almost 5 million people in 2 years and being one of the leading causes of death in the USA in 2021^{1,2}. The SARS-CoV-2 viral infection, initially identified in China in December 2019, rapidly became a global pandemic, reaching Europe in January 2020³. Almost two years on, the pandemic continues with new variants emerging.

The main intracellular entry point into humans for the SARS-CoV-2 virus is the spike protein that binds to angiotensin-converting enzyme-2 (ACE-2) receptor. ACE-2 shows homology to ACE, a key player in the renin-angiotensin-aldosterone system (RAAS), suggesting hypothetical benefits and harms for people using medications affecting RAAS. Statin use has also been proposed as modulating COVID-19 infectivity through its upregulation of ACE2 and pleiotropic effect on oxidative stress⁴.

International guidance for management of both type 1 and type 2 diabetes advocates the use of angiotensin-converting enzyme inhibitors (ACEi) or angiotensin II receptor blockers (ARB) as first line agents to manage hypertension and reduce deterioration of diabetic nephropathy⁵. Additionally, the use of statin therapy is advocated for both primary and secondary prevention of cardiovascular mortality and morbidity in these higher risk populations. The COVID-19 pandemic has disproportionately affected people with diabetes, raising questions as to whether certain pharmacological agents have played a contributory role⁶. Recent studies have indicated that glucose-lowering agents are safe to use during COVID-19 but large study data on the use of both RAASi and statins in people with diabetes are lacking⁷. This study aims to address the uncertainty of benefit and harm on the concomitant use of statin and RAASi therapy in adults with pre-existing type 1 and type 2 diabetes hospitalised with COVID-19 infection, using data from a multicentre, multinational study across Europe (France, Spain and United Kingdom (UK)).

RESEARCH DESIGN AND METHODS

Study design and participants

Retrospective data from hospitalized adults with pre-existing diabetes and concomitant COVID-19 infection were collected in the UK, France and Spain. Adults with

hyperglycaemia at admission, but not pre-existing or subsequent diagnosis of diabetes (based on WHO criteria) were excluded from analysis⁸. Further descriptions of each nation's dataset have been published previously⁹⁻¹².

United Kingdom: Association of British Clinical Diabetologist (ABCD) COVID-19 audit

ABCD COVID-19 audit collects data retrospectively from hospitals across the UK. Clinicians submit data for adults with pre-existing type 1 and type 2 diabetes infected with COVID-19. The audit is registered with Oxford University Hospitals NHS Foundation Trust (OUH) and a Data Protection Impact Assessment was carried out and approved by the OUH Caldicott Guardian and the Public Benefit and Privacy Panel in Scotland (reference 2021-0111). The NHS supports audit with clear guidance for the contributing centres on the use of routine clinical practice data submitted in anonymized form via the secure NHS network¹².

France: CORONADO (CORONAVirus-SARS-CoV-2 and Diabetes Outcomes)

The CORONADO study set out to describe the phenotypic characteristics and prognosis of people with diabetes admitted with COVID-19 between March 10 and April 10, 2020^{10,11}. CORONADO is a retrospective study from French hospitals volunteering to share data on hospitalized COVID-19 patients with diabetes. The study was sponsored by Nantes University Hospital and designed in accordance with the Declaration of Helsinki. It obtained all regulatory approvals.

Spain:

The six hospitals in the HM Hospitales group collected anonymized observational data for people infected with COVID-19 during the first wave. This dataset is made available to researchers via "[Covid Data Save Lives](#)"⁹. The electronic hospital health records were collected for admitted persons including pre-existing disease status, medication use, demographic and outcome. A subset of people with pre-existing diabetes from this cross-sectional database was used in this study. Before access was granted, a formal petition, specific study protocol, and ethics committee approval were obtained. The study was approved by the Ethics Committee of the Primary Health Care University Research Institute (IDIAP) Jordi Gol, Barcelona (approval number: 20/089-PCV).

Data collection: Definitions and Outcomes

Demographic data included: age, gender and type of diabetes. UK and France collected ethnicity data (White/Europid, Black/African, Asian/Asian, Other/Middle East and North African (MENA)). Medication use at point of admission was collected with particular focus on those medications associated with diabetes or diabetes-related comorbidities. This study focused on statin, ACEi and ARB use.

Microvascular disease (including retinopathy, neuropathy and nephropathy) was collected for the French and UK cohorts. The Spanish cohort collected presence of chronic kidney disease (CKD) alone based on clinical coding record. CKD was defined by eGFR <60ml/min or presence of macroalbuminuria. To improve homogeneity of the data and reduce collinearity we reported on CKD only. Macrovascular disease was collected for all datasets and included a diagnosis of cardiovascular, peripheral vascular or cerebrovascular disease.

The primary outcome was death. French data was collected to day 28 of admission, Spanish and UK data included outcome to conclusion of hospital episode.

Statistical Analysis

We conducted complete-case analyses and reported descriptive statistics comparing the complete dataset to those excluded due to missing variables. Clinical characteristics were reported as frequency and percentages for categorical variables, and as mean and standard deviation for continuous variables. Multivariable logistic regression models were used to obtain odds ratios for the outcome variable, death. The main exposure was RAASi use, statin use, or both, and associations were estimated using as a reference category neither RAASi nor Statin. Potential confounders were ethnicity, CKD, macrovascular complications, hypertension, gender and type of diabetes (categorical) and age (continuous). Logistic regressions were performed using R in each contributing country; country-specific odds ratios were then pooled in a random-effects DerSimonian and Laird meta-analysis, with estimates stratified by model adjustment. Heterogeneity across studies was evaluated using the statistic I^2 . Results are reported with 95% confidence interval (CI) and P-values of less than 0.05 were considered statistically significant.

RESULTS:

The UK ABCD COVID-19 audit collected data on 3007 people with diabetes from twenty-five hospitals between March and October 2020. Of these 1849 individuals (61.4%) had

complete data required for this study and were included in this analysis. CORONADO investigators collected data on 2843 people from 68 hospitals with 1219 (43%) having complete data set. Spanish investigators collected data on 2310 individuals at six hospital sites, the majority without hyperglycaemia or diabetes. There was complete data for 406 Spanish individuals (18%) with pre-existing diabetes.

Comparison of the complete dataset to that with missing data showed no difference in mean age, gender, ethnicity or type of diabetes across all three countries (Supplementary material Table 1). Ethnicity data were not available for the Spanish cohort.

The final dataset included 3474 individuals with diabetes and COVID-19 infection. One thousand- and nineteen (29.3%) people died. Characteristics of the study populations including prescribing patterns and mortality by country are shown in Table 1.

Output from individual logistic regression models for each country were combined in a meta-analysis and showed no significant association between death and use of either RAASi or statin therapy with considerable heterogeneity (Fig. 1). The overall odds ratio for RAASi use and mortality was 1.09 after adjusting for age, gender, type of diabetes, presence of macrovascular disease, CKD and hypertension and ethnicity (model 4), however this did not reach significance (CI 0.78-1.52) with little evidence of heterogeneity (I^2 22.2%). Similar non-significant association was seen for statin use (OR 0.97, CI 0.59-1.61) after further adjustment for ethnicity in UK and French cohorts with high heterogeneity (Fig. 1) (I^2 72.9%). Combined use of statin and RAASi therapy had similar non-significant association (OR 1.14, CI 0.67-1.92) with high heterogeneity (Fig. 1) (I^2 78.3%)

DISCUSSION:

This is the first multinational European retrospective study to specifically investigate the outcomes of hospitalized adults with pre-existing diabetes and COVID-19 in relation to prior use of RAASi and statin therapy. We found no significant association between the prior use of RAASi or statin and the primary outcome of death in the meta-analysis, although the findings for statins were highly heterogeneous between the participating countries. The findings remained non-significant after adjusting for age, gender, diabetes type, hypertension, macrovascular disease and CKD. Further adjustment for ethnicity in two of the nations' data had no further impact on the findings.

COVID-19 infection is associated with poorer outcome for those with long-term conditions, such as diabetes, and several potential mechanisms have been proposed^{6,9}. This paper specifically examined medications used by many people with diabetes (type 1 and 2) for the prevention of diabetic complications and, therefore, the potential detrimental or beneficial effect of these medications on outcomes for this specific population. It uses large heterogeneous real world datasets to draw clinically relevant conclusions.

Early use of statin therapy is globally advocated to prevent diabetes complications however the proportions receiving statin prescriptions in our study cohort varied between 26% in Spain and 61% in the UK⁸. Current guidance does not advise stopping statin therapy during intercurrent illness.

Prior to the COVID-19 pandemic, secondary analysis of a randomised, placebo-controlled trial in acute respiratory distress syndrome (ARDS) showed improved survival with simvastatin treatment in a sub-group of participants with hyperinflammatory state¹³. This raises a hypothetical benefit from statin use in populations with high inflammatory burden, such as type 2 diabetes, due to potential suppression of the hyperinflammatory response triggered by SARS-CoV-2 infection. Observational studies of statin therapy and COVID-19 infection support this. A US study showed reduced severity of COVID-19 infection where statins were used within 1 month prior to admission with faster recovery in those without severe disease, whilst another study found 12% reduced risk of in-hospital mortality in a diabetes subset^{4,14}. A large Chinese retrospective sub-study found reduced COVID-19 related mortality associated with statin use (5.2% v 9.4% death rate) but no additional effect of additive RAASi therapy¹⁵.

Our analysis revealed high heterogeneity in mortality for those using statin therapy, with differences in the relationship in France compared to both Spain and UK. The CORONADO statin therapy outcomes are surprising and oppose other evidence¹⁶. Strandberg and Kivimäki suggested that they may be outlier findings¹⁷. Closer review of this French cohort reveals a higher burden of macrovascular disease, CKD and hypertension¹⁶. However the mortality was considerably lower in the French than the UK cohort, suggesting unmeasured differences may explain these opposing relationships, such as diabetes stage or severity, diabetes therapies, smoking status, socioeconomic status or national healthcare systems.

Antecedent statin use with an associated lower lipid profile on admission has been associated with lower 30-day mortality in a general USA population¹⁸. A meta-analysis of adults with COVID-19 infection found almost 50% mortality risk reduction associated with in-hospital use of statin in a mixed patient population, but no benefit from statin use pre-admission¹⁹. In a population with high diabetes prevalence (44%), similar beneficial results were found with in-hospital statin use²⁰. However, a recent meta-analysis of 25 studies, including 33% people with diabetes, found benefit of statin therapy only in chronic use prior to admission²¹. Our study did not examine either inflammatory markers or lipid levels, nor collect data on duration of prior use of statin and/or continuation of therapy on admission, which may have explained national differences.

Mounting evidence suggests beneficial or neutral effects of statin therapy but further investigation is needed in diabetes-specific populations of in-hospital and pre-admission statin use in relation to mortality and ICU admission. At least 34 randomised controlled trials using lipid-lowering medications are currently underway in general populations, including 14 using statins (both high and low dose with patients in and out of intensive care settings)²².

The potential pleiotropic interactions between statin therapy and COVID-19 include effects on inflammatory response and ACE2 protein. One may anticipate more conclusive evidence from therapies exclusively affecting ACE2 protein, and therefore SARS-CoV-2 transmission and infection, such as RAASi. To date, evidence from cohort studies and a global meta-analysis of over 19,000 people show no increased risk of SARS-CoV-2 infection or COVID-19 disease severity for those taking RAASi^{23,24}. In fact, meta-analysis of over 33,000 people found beneficial effect of RAASi use on disease severity²⁵. A UK primary care prospective study also observed reduced disease severity but reported ethnic disparities in association between RAASi use and SARS-CoV-2 positivity, with those from Caribbean or Black-African ethnic groups having increased risk of infection compared to White²⁶. Within our diabetes-specific population, with 43% RAASi use overall (Supplementary Table 1), there was no significant association with mortality, including after adjusting for ethnicity. These findings are in keeping with a meta-analysis of people with co-existent hypertension and COVID-19, which showed a beneficial effect of RAASi use that was not modulated by diabetes in meta-regression²⁷.

RAASi treatment may be interrupted to minimise potential nephrotoxic effects²⁸. Further research is required to investigate whether stopping RAASi is appropriate in the face of COVID-19 infection. As with statin therapy, this research is in progress, but it will be important to look at the diabetes-specific population where prescribing indications differ²⁹.

This study has clinical relevance to the general practitioner, diabetologist and their patients. It provides reassurance about continued outpatient use of RAASi and statin therapy during the pandemic, with no significant association with increased mortality or disease severity in those prescribed them. The multinational and demographically diverse datasets allow for wider generalisability of findings.

Our study is limited by the heterogeneity of data collection methods across the nations due to use of databases not initially created in collaboration to answer the study question and, therefore, by some missing data. The meta-analysis combines a larger dataset to provide an overall relationship of association, rather than causality, but masks heterogeneity across nations. Markers of inflammation and lipid levels were not collected, as well as other potential confounding factors such as smoking status, body mass index and diabetes duration. Lastly, drug histories were often collected from health records, rather than being confirmed with individuals, introducing the possibility of error in the context of access to pharmacies being restricted during pandemic lockdowns.

CONCLUSION:

This large multinational study of people with diabetes requiring hospitalisation for COVID-19 infection demonstrates no significant association with the pre-admission use of statin and/or RAAS inhibitor therapy with mortality. It provides reassurance to clinicians who have continued prescribing RAAS inhibitors throughout the pandemic despite publicity surrounding unadjusted associations between statin therapy and poor outcomes from COVID-19. Further studies, including randomised controlled trials, are required to provide further reassurance. These studies should consider prescribing indications specific to diabetes, such as microalbuminuria, which may produce conflicting results to those seen in the general population.

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We are grateful to all the people who collected the data for this study, to Ben Maylor and Joanne Miksza for data template development, and to Melissa Cull of the ABCD secretariat for administrative support.

Data availability: Data is available on request from corresponding author and/or national study leads.

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No potential conflicts of interest relevant to this article were reported.

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All other authors declare no competing interests.

Author Contributions:

MW, PG, SaH and BC designed the CORONADO study.

RRe, EGW, SHW, SoH, BCTF, REJR, PN, KV, YR and KK designed the ABCD COVID-19 National audit. YR conducted the statistical analysis for the ABCD study. FZ conducted the meta-analysis. SoH, KK and SW drafted the first version of the manuscript. All authors approved the final manuscript. SoH and KK are the guarantors of this work.

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	UK ABCD N=1849				France CORONADO N=1219				Spain HM Hospitales N=406			
	Neither RAASi nor Statin (n=547, 29.6%)	Statin alone (n=669, 36.2%)	RAASi alone (n=163, 8.8%)	RAASi and Statin (n=470, 25.4%)	Neither RAASi nor Statin (n=310, 25.4%)	Statin alone (n=194, 15.9%)	RAASi alone (n=279, 22.9%)	RAASi and Statin (n=436, 35.8%)	Neither RAASi nor Statin (n=203, 56.7%)	Statin alone (n=50, 12.3%)	RAASi alone (n=96, 23.6%)	RAASi and statin (n=57, 14%)
Age (mean, SD) years	72 (16)	72 (13)	72 (14)	71 (12)	69.2 (15.9)	73.3 (11.7)	71.8 (13.3)	71.3(10.9)	73.5 (13.0)	77.1 (10.3)	74.5 (11.0)	77.0 (9.74)
Men n (%)	314 (57%)	428 (64%)	93 (57%)	301 (64%)	176 (56.8%)	125 (64.4%)	166 (59.5%)	278 (63.8%)	123 (60.6%)	30 (60.0%)	61 (63.5%)	36 (63.2%)
Ethnicity:												
White	421 (77%)	428 (64%)	117 (72%)	320 (68%)	181 (58.4%)	123 (63.4%)	164 (58.8%)	253 (58%)	NA	NA	NA	NA
Asian	57 (10%)	119 (18%)	18 (11%)	78 (17%)	18 (5.8%)	6 (3.1%)	5 (1.8%)	14 (3.2%)				
Black	31 (6%)	44 (7%)	5 (3%)	24 (5%)	58 (18.7%)	21 (10.8%)	55 (19.7%)	65 (14.9%)				
Other	38 (7%)	78 (11%)	23 (14%)	48 (10%)	53 (17.1%)	44 (22.7%)	55 (19.7%)	104 (23.9%)				
Type of diabetes												
Type 1	40 (7%)	29 (4%)	9 (6%)	19 (4%)	19 (6.1%)	4 (2.1%)	6 (2.2%)	12 (2.8%)	2 (0.99%)	2 (4.00%)	0 (0.00%)	0 (0.00%)
Type 2	507 (93%)	640 (96%)	154 (94%)	451 (96%)	291 (93.9%)	190 (97.9%)	273 (97.8%)	424 (97.2%)	201 (99.0%)	48 (96.0%)	96 (100%)	57 (100%)
Presence of CKD	130 (24%)	186 (28%)	32 (20%)	114 (24%)	119 (38.4%)	100 (51.5%)	141 (50.5%)	212 (48.6%)	15 (7.39%)	13 (26.0%)	16 (16.7%)	7 (12.3%)

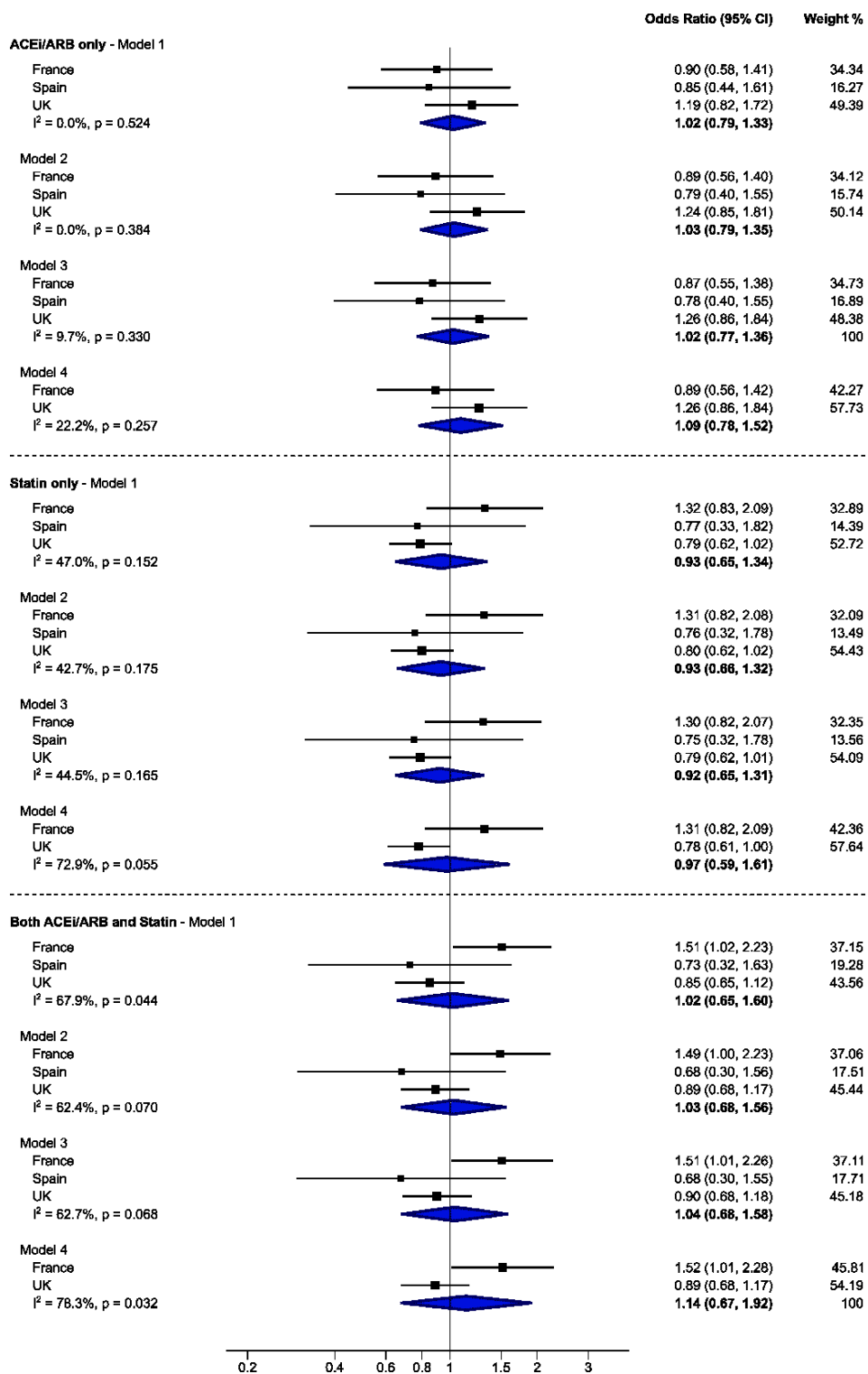
Presence of macrovascular disease	184 (34%)	260 (39%)	69 (42%)	218(46%)	87 (28.1%)	100 (51.5%)	101 (36.2%)	243 (55.7%)	35 (17.2%)	23 (46.0%)	13 (13.5%)	24 (42.1%)
Presence of hypertension	326 (60%)	427 (64%)	142 (87%)	403 (86%)	184 (59.4%)	146 (75.3%)	266 (95.3%)	409 (93.8%)	111 (54.7%)	33 (66.0%)	89 (92.7%)	53 (93.0%)
Death	212 (39%)	229 (34%)	70 (43%)	165 (35%)	55 (17.7%)	49 (25.3%)	49 (17.6%)	111 (25.5%)	42 (20.7%)	9 (18.0%)	18 (18.8%)	10 (17.5%)

Table 1. Characteristics of people with diabetes and COVID-19 infection by combinations of medication prescription per country;

United Kingdom (UK), France and Spain. Abbreviations used: Chronic kidney disease (CKD), renin-angiotensin-aldosterone-system

inhibitors (RAASi)

Figure 1: Country-specific and pooled odds ratios



Legend: Odds ratio of death associated with use of either renin-angiotensin-aldosterone system inhibitor (RAASi)(indicated as ACEi/ARB), Statin or combined therapy in each

country and overall (random-effects meta-analysis). I^2 indicates heterogeneity in the estimates. The baseline level for odds ratio estimates is the category “neither on ACEi/ARB nor on Statin”.

Odds Ratio estimates adjusted for:

Model 1 – Admission age, gender, Type of diabetes, presence of macrovascular complications

Model 2 – Model 1 + Hypertension

Model 3 – Model 2 + CKD

Model 4 – Model 3 + Ethnicity

Spain is excluded from Model 4 due to lack of ethnicity data.