Sex- and age specific association of new-onset atrial fibrillation with in-hospital mortality in hospitalised COVID-19 patients

Joost A. Offerhaus a,1,3, Linda P.T. Joosten b,1,3, Maarten van Smeden b,3, Marijke Linschoten c,2, Hidde Bleijendaal a,4,2, Robert Tieleman a,3, Arthur A.M. Wilde a,3, Frans H. Rutten b,3, Geert-Jan Geersing b,2,3, Carol Ann Remme a,7,2,3, on behalf of the CAPACITY-COVID collaborative consortium

ABSTRACT

Background: Coronavirus disease 2019 (COVID-19) is a systemic disease with cardiovascular involvement, including cardiac arrhythmias. Notably, new-onset atrial fibrillation (AF) and atrial flutter (AFL) during hospitalisation in COVID-19 patients has been associated with increased mortality. However, how this risk is impacted by age and sex is still poorly understood.

Methods: For this multicentre cohort study, we extracted demographics, medical history, occurrence of electrical disorders and in-hospital mortality from the large international patient registry CAPACITY-COVID. For each electrical disorder, prevalence during hospitalisation was calculated. Subsequently, we analysed the incremental prognostic effect of developing AF/AFL on in-hospital mortality, using multivariable logistic regression analyses, stratified for sex and age.

Results: In total, 5782 patients (64% male; median age 67) were included. Of all patients 11.0% (95% CI 10.2–11.8) experienced AF and 1.6% (95% CI 1.3–1.9) experienced AFL during hospitalisation. Ventricular arrhythmias were rare (<0.8% (95% CI 0.6–1.0)) and a conduction disorder was observed in 6.3% (95% CI 5.7–7.0). An event of AF/AFL appeared to occur more often in patients with pre-existing heart failure. After multivariable adjustment for age and sex, new-onset AF/AFL was significantly associated with a poorer prognosis, exemplified by a two- to three-fold increased risk of in-hospital mortality in males aged 60–72 years, whereas this effect was largely attenuated in older male patients and not observed in female patients.

Conclusion: In this large COVID-19 cohort, new-onset AF/AFL was associated with increased in-hospital mortality, yet this increased risk was restricted to males aged 60–72 years.

1. Introduction

Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) has infected more than 400 million people worldwide, including more than 160 million Europeans, with almost 5.8 million deaths attributed globally to the virus as of February 11th, 2022.[1] With multiple vaccines available as well as the recent increase in immunisation from the omicron variant, which is possibly associated with an overall lower risk
of clinical deterioration, some are optimistic that the end of the coronavirus disease 2019 (COVID-19) pandemic is in sight and that SARS-CoV-2 will become a yearly recurring more endemic virus. However, subsequent waves of new infections with new variants are to be expected in the upcoming years, given the 1) low global vaccination rate of 36%, [2] and global shortage of vaccines, 2) high threshold needed for herd immunity,[3] 3) uncertainties regarding the duration of the immunological effect of the vaccines,[4] 4) high number of intermediate hosts for SARS-CoV-2,[5] and in part due to this, 5) the continuous threat of (more contagious) variants reducing vaccine efficacy.[6] Therefore, research into COVID-19 remains crucial.

Since the start of the pandemic, cardiovascular complications have been increasingly recognised in patients suffering from COVID-19, ranging from vascular damage and cardiac injury to arrhythmias.[7] Arrhythmias in COVID-19 patients may impact significantly on disease progression and outcome. As such, various population-based studies have reported a positive association between atrial fibrillation (AF)/atrial flutter (AFL) and mortality.[8–10] However, these studies did not look at sex-specific influences, nor at the incremental effect of age (on a continuous scale), despite the fact that these parameters are known to influence AF/AFL outcomes in the general population.[11,12]

Therefore, in the large international CAPACITY-COVID dataset (NCT04325412) of 5782 hospitalised COVID-19 patients, using the latest methodology, we explored the relation of AF and AFL to in-hospital mortality, with specific attention for sex- and age-related differences.

2. Methods

2.1. Study design and study population

For the current multicentre cohort study, pseudo-anonymous data generated during routine clinical care retrieved from the international patient registry CAPACITY-COVID (www.capacity-covid.eu) were used.[13] The data within CAPACITY-COVID have been collected by 72 hospitals in 8 European (Belgium, France, Italy, the Netherlands, Spain, Switzerland, Portugal, United Kingdom) and 5 non-European (Egypt, Iran, Israel, Russia, Saudi-Arabia) countries. For this study, patients aged 18 years or older, admitted to any of the participating hospital centres before October 25th, 2020, with a laboratory confirmed SARS-CoV-2 infection during hospitalisation, were included. Readmission(s) from a hospitalisation, were included. Readmission(s) from a hospitalisation. Electrical disorders were detected either through continuous rhythm monitoring or with (an) electrocardiogram(s) and were diagnosed according to the American College of Cardiology (ACC)/American Heart Association (AHA)/Heart Rhythm Society (HRS) 2006 key data elements and definitions for electrophysiological studies and procedures.[14] Types of electrical disorders included AF, AFL, atrial tachycardia, atrioventricular (AV) nodal re-entry tachycardia, non-sustained ventricular tachycardia (nSVT), sustained ventricular tachycardia (sVT), ventricular fibrillation (VF), first degree AV block, second degree AV block, third degree AV block, complete left bundle branch block (LBBB), and complete right bundle branch block (RBBB).

2.2. Data extraction

For this study the following variables were extracted: sex, age, medical history (including history of cardiac electrical disorders), body mass index (BMI), medication, physical examination findings, biomarkers, and follow-up data on the development of electrical disorders, cerebrovascular accident (CVA), pulmonary embolism, and mortality during hospitalisation. Electrical disorders were detected either through continuous rhythm monitoring or with (an) electrocardiogram(s) and were diagnosed according to the American College of Cardiology (ACC)/American Heart Association (AHA)/Heart Rhythm Society (HRS) 2006 key data elements and definitions for electrophysiological studies and procedures.[14] Types of electrical disorders included AF, AFL, atrial tachycardia, atrioventricular (AV) nodal re-entry tachycardia, non-sustained ventricular tachycardia (nSVT), sustained ventricular tachycardia (sVT), ventricular fibrillation (VF), first degree AV block, second degree AV block, third degree AV block, complete left bundle branch block (LBBB), and complete right bundle branch block (RBBB).

2.3. Statistical analyses

Baseline characteristics of patients with COVID-19 disease are reported for the date of hospital admission. Categorical variables are presented as counts and percentages and numerical variables as means with standard deviations or medians with interquartile ranges (IQR), depending on the distribution.

The prevalence of the development of each arrhythmic and conduction disorder during hospitalisation was calculated for the entire follow-up time (i.e. the time from hospital admission to discharge, death or loss to follow-up) and divided into patients without and with a history of that specific arrhythmic or conduction disorder (i.e. new-onset and recurrent, respectively). Only for patients with AF and for patients with AFL, new-onset versus recurrent AF and new-onset versus recurrent AFL were defined as having no history of both AF and AFL versus a history of AF and/or AFL.

To explore the association between all predefined patient characteristics and the development of the most prevalent new-onset arrhythmic disorder (i.e. AF and/or AFL), univariable logistic regression analyses were performed to estimate crude odds ratios (OR) and corresponding 95% confidence intervals (95% CI).

Next, the association between development of new-onset AF and/or AFL during hospitalisation and in-hospital mortality in COVID-19 patients was first examined using univariable logistic regression analysis. Second, multivariable logistic regression analysis was performed with sex, a cubic spline function for age, the development of new-onset AF and/or AFL during hospitalisation, and the interaction between the latter two variables. The results of this analysis were depicted in plots for males and females separately. To explore whether other concomitant comorbidities and/or other known risk factors may have contributed to the observed results, we performed a sensitivity analysis where we additionally adjusted for CHA2DS2-VASc score.

For all analyses, the different AF subtypes (paroxysmal, persistent, and permanent) were merged. All statistical analyses were performed using R version 4.0.2 with the bias reduction in binomial-response generalised linear models (brglm) function in the package ‘brglm’ version 0.7.1, which implements Firth correction reducing finite sample bias in the regression coefficients compared to default maximum likelihood regression.[15] Non-linear relations are graphically displayed using the package ‘rms’ version 6.6.1 and the package ‘ggplot2’ version 3.3.2. In all univariable analyses with age and in all multivariable analyses, a cubic spline function for age (and in the univariable analyses for the association between BMI and new-onset AF and/or AFL also a cubic spline function for BMI) with four knots on recommended locations (on the percentiles 0.05, 0.35, 0.65, and 0.95) was used. [16] Missing data for each variable were reported as percentages in the text or as counts in the corresponding tables. Since missing data was overall limited (e.g. maximum n = 24 in mortality analyses), we proceeded with analyses of complete cases. Associations with two-sided p-values < 0.05 were considered statistically significant.

3. Results

A total of 5782 patients were included in this study. The majority of them were hospitalised in European countries (89.9%). The median duration of hospital admission was 8 (IQR 4–17) days, and 28.8% (n = 1664) of all subjects were admitted to the intensive care unit (ICU). Of the total study population, 63.8% was male and the median age was 67 (IQR 56–76) years. 12.5% (n = 725) had been diagnosed with an arrhythmic event in the past, of which 93.2% (n = 676) consisted of at
least one episode of supraventricular arrhythmia and 7.7% (n = 56) at least one episode of ventricular arrhythmia. Of all patients, 1.7% (n = 96) had been diagnosed with at least one conduction disorder in the past. The most prevalent comorbidity registered was hypertension (47.6%), followed by diabetes mellitus (26.1%), chronic obstructive pulmonary disease (11.1%), renal impairment (10.7%), and prior myocardial infarction (9.2%). A complete list of all baseline characteristics, stratified by new-onset AF/AFL during hospitalisation and history of AF/AFL is presented in Table 1. Baseline characteristics stratified by other arrhythmias and conduction disorders are presented in Supplemental Table S1. All variables had < 3% missing, except for peripheral arterial disease (21.6%), BMI (24.7%), temperature (17.8%), C-reactive protein (12.2%), and white blood cell count (11.4%).

### Table 1

Baseline characteristics of hospitalised COVID-19 patients stratified by new-onset and recurrent atrial fibrillation/atrial flutter.

| Demographics | Total (n = 5782) | No AF/AFL (n = 4712) | New-onset or recurrent AF/AFL (n = 692) | New-onset AF/AFL (n = 420) | Recurrent AF/AFL (n = 271) |
|--------------|-----------------|----------------------|----------------------------------------|---------------------------|---------------------------|
| Age in years | 67 (56–76)      | 64 (54–74)           | 74 (69–81)                             | 73 (66–79)                | 78 (73–83)                |
| Demographics | Male sex (n (%))| 3686 (63.8)          | 2955 (62.7)                            | 482 (69.7)                | 294 (70.0)                | 188 (69.4)                |
| Hypertension | 416 (10.7)      | 0 (0.0)              | 257 (37.2)                             | 0 (0.0)                   | 257 (94.8)                |
| AF/AFL       | 522 (9.2)       | 0 (0.0)              | 223 (3.3)                              | 0 (0.0)                   | 23 (8.5)                  |
| Atrial tachycardia | 21 (0.4) | 12 (0.3)              | 3 (0.4)                               | 3 (0.7)                   | 0 (0.0)                   |
| AV nodal re-entry tachycardia | 22 (0.4) | 15 (0.3)              | 4 (0.6)                               | 1 (0.2)                   | 3 (1.1)                   |
| History of supraventricular tachycardia | 60% | 58% | 62% | 63% | 64% |
| History of ventricular tachycardia | Non-sustained ventricular tachycardia (n (%)) | 21 (0.4) | 12 (0.3) | 7 (1.0) | 4 (1.0) | 3 (1.1) |
| Sustained ventricular tachycardia (n (%)) | 15 (0.3) | 14 (0.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Ventricular fibrillation (n (%)) | 24 (0.4) | 17 (0.4) | 6 (0.9) | 6 (1.4) | 0 (0.0) |
| History of conduction disorders | 1st AV block (n (%)) | 19 (0.3) | 13 (0.3) | 2 (0.3) | 1 (0.2) | 1 (0.4) |
| 2nd AV block (n (%)) | 13 (0.2) | 8 (0.2) | 2 (0.3) | 1 (0.2) | 1 (0.4) |
| 3rd AV block (n (%)) | 26 (0.4) | 16 (0.3) | 2 (0.3) | 1 (0.2) | 1 (0.4) |
| Left bundle branch block (n (%)) | 24 (0.4) | 14 (0.3) | 5 (0.7) | 4 (1.0) | 1 (0.4) |
| Right bundle branch block (n (%)) | 18 (0.3) | 12 (0.3) | 4 (0.6) | 2 (0.5) | 2 (0.7) |
| Other medical history | Heart failure (n (%)) | 315 (5.5) | 156 (3.3) | 88 (12.7) | 23 (5.5) | 64 (23.6) |
| Diabetes mellitus | 1494 (26.1) | 1195 (25.6) | 188 (27.6) | 100 (24.2) | 87 (32.6) |
| (type I or II) (n (%)) | Peripheral arterial disease (n (%)) | 271 (4.9) | 181 (4.9) | 54 (9.8) | 26 (8.0) | 28 (12.6) |
| Myocardial infarction (n (%)) | 522 (9.2) | 374 (8.0) | 81 (11.9) | 47 (11.3) | 34 (12.8) |
| Renal impairment (n (%)) | 620 (10.7) | 414 (8.8) | 123 (17.9) | 58 (13.9) | 65 (24.4) |
| COPD (n (%)) | 643 (11.1) | 487 (10.3) | 97 (14.1) | 53 (12.7) | 44 (16.3) |
| Risk factors | BMI in kg/m² (median (IQR)) | 27.5 (24.6–30.9) | 27.5 (24.6–30.9) | 27.2 (24.5–30.5) | 27.2 (24.7–30.5) | 26.9 (24.1–30.4) |
| Medication | Digoxin (n (%)) | 112 (1.9) | 19 (0.4) | 58 (8.4) | 12 (2.9) | 46 (17.0) |
| Anti-arrhythmic drugs - class I (n (%)) | 28 (0.5) | 6 (0.1) | 12 (1.7) | 0 (0.0) | 12 (4.4) |
| Anti-arrhythmic drugs - class III (n (%)) | 110 (1.9) | 41 (0.9) | 24 (3.5) | 5 (1.2) | 19 (7.0) |
| Anti-arrhythmic drugs - class IV (n (%)) | 64 (1.1) | 39 (0.8) | 15 (2.2) | 5 (1.2) | 10 (3.7) |
| Beta blockers (n (%)) | 1562 (27.0) | 1028 (21.8) | 308 (44.5) | 136 (32.4) | 172 (63.5) |
| Antihypertensive drugs (n (%)) | 2575 (44.6) | 1913 (40.6) | 397 (57.4) | 204 (48.6) | 192 (70.8) |
| Platelet inhibitors (n (%)) | 1270 (22.0) | 1100 (23.4) | 192 (29.1) | 111 (26.4) | 28 (10.3) |
| Anticoagulants (n (%)) | 779 (13.5) | 219 (4.7) | 284 (41.0) | 59 (14.0) | 224 (82.7) |
| Antidiabetic drugs (n (%)) | 1105 (19.1) | 894 (19.0) | 141 (20.4) | 73 (17.4) | 67 (24.7) |

### 3.1. Prevalence of AF/AFL

The prevalence of AF and/or AFL in comparison to other arrhythmias and conduction disorders (recurrent and new-onset) during hospitalisation is summarised in Fig. 1. Of all patients, 12.8% (95% CI 11.9–13.6) (n = 737) experienced an arrhythmic event during hospitalisation, the vast majority being supraventricular (95.9%). AF and AFL were most common, occurring in 12.0% (95% CI 11.2–12.8) (n = 692) of all patients, of which 86.7% (95% CI 84.0–89.1) (n = 600) experienced only AF, 8.5% (95% CI 6.6–10.8) (n = 59) experienced only AFL, and 4.8% (95% CI 3.4–6.6) (n = 33) experienced both AF and AFL. In 60.7% (95% CI 57.0–64.3) (n = 420) of patients the development of AF and/or AFL was new-onset, whereas in the remaining 39.3% (95% CI
AF and/or AFL had been present before hospital admission. Ventricular arrhythmias were rare (0.8% (95% CI 0.6–1.0)) and 50% of them were sVT or VF (n = 23). A conduction disorder during hospitalisation was observed in 6.3% (95% CI 5.7–7.0) (n = 365) of all patients.

### 3.2. Association between patient characteristics and development of new-onset AF and/or AFL

In univariable logistic regression analyses, sex, age, heart failure, hypertension, peripheral arterial disease, prior myocardial infarction, renal impairment, certain drugs, white blood cell count, duration of hospitalisation, and development of pulmonary embolism, showed an increased statistically significant association with the development of AF and/or AFL. Of medical history, heart failure seemed to be most strongly associated with a higher likelihood of developing AF and/or AFL compared to patients without heart failure: OR 1.72 (95% CI 1.05–2.64) (Supplemental Table S2).

### 3.3. Prognostic impact of new-onset AF and/or AFL on in-hospital mortality

In absolute terms, there were only few patients aged < 50 years and > 90 years in our dataset who developed new-onset AF and/or AFL (n = 7 and n = 10, respectively). Because these small numbers could affect the reliability and precision of the point estimates of the outcomes to a high extent, only patients aged ≥ 50 and ≤ 90 years for new-onset AF and/or AFL were included in the mortality analyses.

In univariable logistic regression analyses, we observed that the development of new-onset AF and/or AFL during hospitalisation was associated with increased in-hospital mortality with an unadjusted OR of 1.90 (95% CI 1.52–2.36) (Supplemental Table S3). However, in a multivariable model with sex, age, and new-onset AF and/or AFL as covariates to predict in-hospital mortality, there was only an increased significant association between new-onset AF and/or AFL and in-hospital mortality in males aged between 60 and 72 years (Fig. 2). When extending this model with the CHA²DS²-VASc score in the 24.3%
4.1. Arrhythmogenesis in COVID-19 and the effect of AF on mortality

Several mechanisms may contribute to arrhythmogenesis in the setting of COVID-19. Pre-existing cardiovascular pathologies, such as heart failure and coronary artery disease, may increase the likelihood of myocardial ischaemia in the setting of hypoxemia. Indeed, in our cohort, heart failure, hypertension, and prior myocardial infarction were frequently present and apparently associated with an increased likelihood of developing AF and/or AFL. In addition, SARS-CoV-2 has been linked to a pro-thrombotic and hypercoagulability state in patients, which by itself may promote the development and propagation of AF and/or AFL. Furthermore, the virus may also directly affect the cardiomyocytes through expression of angiotensin-converting enzyme 2, inducing arrhythmogenic conditions such as intracellular ionic dysregulation, apoptosis, and possibly myocarditis. Additionally, potentially pro-arrhythmic therapeutics (including vasopressors and (hydroxy)chloroquine) and electrolyte disturbances in COVID-19 patients can all contribute to arrhythmogenesis. Irrespective of the underlying mechanism, our findings indicate that development of AF and/or AFL might be prognostically unfavourable in COVID-19 patients.

4.2. Sex- and age-dependent effect on AF on mortality

Our study confirms previous (smaller) studies which reported AF/AFL as the most prevalent arrhythmia in COVID-19 patients, in addition to its association with increased mortality. With respect to AF/AFL occurrence, Peltzer et al. and Mountantonakis et al. observed a slightly higher prevalence of AF/AFL compared to our study (16% and 18% compared to 12% respectively), whereas Musikantow et al. found a similar prevalence of 10%. Conversely, Bhatla et al. reported a much lower prevalence of new-onset AF (3.5%), yet in a much smaller dataset of 700 patients.

Similar to our study, Peltzer et al. and Mountantonakis et al. found AF and/or AFL, as well as new-onset AF and/or AFL, to be associated with increased in-hospital mortality. Bhatla et al. did not find such an association between new-onset AF and/or AFL and in-hospital mortality, yet (again) this study included a relatively small dataset with only 25 incident AF cases reported.

Importantly, using the latest prediction methodology (allowing age to remain continuous in all analyses using cubic spline functions), we were – for the first time – able to pinpoint the effect of AF/AFL occurrence on in-hospital mortality to male hospitalised COVID-19 patients aged 60–72 years. In fact, we ruled out an effect of AF/AFL occurrence on mortality in female patients with COVID-19, while in the general population females with AF/AFL have a worse outcome compared to males. As an example, in a male hospitalised COVID-19 patient of 72 years, the occurrence of AF/AFL would increase his risk of mortality from ~15% to ~35%, whereas in a female patient of 65 years this risk remains well below ~15–20%, regardless of AF/AFL development. More importantly, the correlation between age and its interaction with AF and/or AFL follows a non-linear pattern, which is even different for males and females, thus underlining the importance of our statistical approach. As such, our analyses provide a much more granular assessment of the effect of new-onset AF and/or AFL during hospital admission for COVID-19 by better identifying subgroups of patients where the prognostic impact on mortality is most relevant.

4.3. Strengths and limitations

Major strengths of our work include the inclusion of a large international dataset of nearly 6000 hospitalised COVID-19 patients,
allowing to perform sophisticated analyses on the incremental impact of AF/AFL occurrence on in-hospital mortality beyond the effects of age and sex. However, our findings might not be restricted to or typical for COVID-19 patients. For example, a recent study by Muskatontaw et al. shows a similar increase in mortality in hospitalised influenza patients with AF/AFL. [20] This seems to indicate that the found association might be related to a general viral-induced systemic illness rather than specifically COVID-19, suggesting that the findings in this study might be generalised to other patients with viral induced respiratory tract infections (e.g. influenza). Nevertheless, for full appreciation the following topics deserve attention.

First, while our findings show that AF and/or AFL appears prognostically unfavourable, particularly in males, this does not imply a causal relationship. In fact, it could be argued that the development of AF/AFL and its impact on mortality is merely a more general signal of progression of disease severity and accumulation of comorbidities (e.g. exemplified by higher CHA²DS₂-VASc scores), and thus could be considered as an ‘innocent bystander’ in patients experiencing clinical deterioration.

To explore the impact of the development of new-onset AF and/or AFL during hospitalisation on in-hospital mortality when adjusting for concomitant comorbidities and risk factors, we performed a sensitivity analysis with additional adjustment for CHA²DS₂-VASc score. Although this analysis is inherently impacted by a lower degree of statistical robustness due to missing information on the CHA²DS₂-VASc score in 75.7% of patients (n = 2779), it did yield similar inferences (Supplemental Table S3 and S4). Moreover, in our study the majority of AF and/or AFL cases (60.7%) were detected in patients either before ICU admission or in patients never admitted to the ICU (i.e. before widespread increase in disease severity occurred). Although it is possible that the threshold for ICU referral was higher due to limited capacity during the peak of the pandemic, this suggests that (new-onset) AF and/or AFL would at least be an early marker for disease progression. Based on our findings this appears to be prognostically unfavourable, particularly in males aged between 60 and 72 years. Second, although diagnoses were centrally defined, with multicentre studies there is always a risk of heterogeneity due to differences in interpretation among centres. Given that the strategy for rhythm monitoring was defined by the attending physicians, and as a consequence was different per centre, it could well be that electrical disorders may have been underdiagnosed in patients on general wards where continuous rhythm monitoring is not performed. Moreover, grouping the different AF subtypes (paroxysmal, persistent, and permanent) may have resulted in missing subtle disease progression within the AF group. Finally, since only in-hospital death could be recorded, mortality outcome data are limited, and comparison with other studies is hampered by differential follow up due to differences in length of hospital stay.

5. Conclusions

Using a large international database, this study confirms that AF and/or AFL are among the most prevalent electrical disorder in hospitalised COVID-19 patients, and that new-onset AF and/or AFL is associated with a poorer prognosis exemplified by an increased in-hospital mortality. However, this increased mortality risk appears to be restricted to male patients aged between 60 and 72 years, and was not observed in female patients.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments of grant support

The CAPACITY-COVID registry is supported by the Dutch Heart Foundation (2020B006 CAPACITY), the EuroQol Research Foundation, Novartis Global, Sanofi Genzyme Europe, Novo Nordisk Nederland, Servier Nederland, and Daiichi Sankyo Nederland. The Dutch Network for Cardiovascular Research (WCN), a partner within the CAPACITY-COVID consortium, received funding from the Dutch Heart Foundation (2020B006 CAPACITY) for site management and logistic support in the Netherlands. Joost A. Offerhaus is supported by a PhD scholarship form the AMC graduate school. Marijke Linschoten is supported by the Alexandre Suerman Stipend of the University Medical Center Utrecht. Arthur A.M. Wilde and Carol Ann Remme are supported by the CardioVascularResearch Initiative CVON (Dutch Heart Foundation, Dutch Federation of University Medical Centres, ZonMw, and the Royal Netherlands Academy of Sciences; PREDICT2 CVON2018-30).

Acknowledgements

We want to express our gratitude and appreciation to all participating sites and researchers part of the CAPACITY-COVID collaborative consortium. CAPACITY-COVID gratefully acknowledges the following organizations for their assistance in the development of the registry and/or coordination regarding the data registration in the collaborating centres: partners of the Dutch CardioVascular Alliance (DCVA), the Dutch Association of Medical Specialists (FMS), and the British Heart Foundation Centres of Research Excellence. In addition, the consortium is grateful for the endorsement of the CAPACITY-COVID initiative by the European Society of Cardiology (ESC), the European Heart Network (EHN), and the Society for Cardiovascular Magnetic Resonance (SCMR).

Furthermore, the consortium appreciates the endorsement of CAPACITY-COVID as a flagship research project within the National Institute for Health Research (NIHR)/British Heart Foundation (BHF) Partnership framework for COVID-19 research.

CAPACITY-COVID collaborative consortium

Al-Ali AK1, Al-Muhanna FA2, Al-Windy NY3, Almubarak YA4, Alnafie AN5, Alshahrani M6, Alshehri AM7, Anthonio RL8, Asselbergs FW9,10,11, Aujayeb A12, ten Berg JM13, van Boxem AJM14, Captur G11,15, Caputo M16,17, Charlotte K18, Dark P19, De Sutter J20,21, Delsing CE22, Dorman HGR23, Drost JT24, Emans ME25, Ferreira JB26, Gabriël I27, van Gist WH28, Groenemeijer BE29, Haerens-Arends HE30, van der Haydt B31, van der Heijden DJ32, Hellow E33, Hermansides R34, Hermans-van Ast JF35, van Hessen WMJ36, Heymans SRB37,38,39, van der Horst ICC40,41, van Ierssel SH42, Jewell LH43,44, Kearney MT45, van Kesteren HAM46, Kietelaar BLJH47, Konings AMH48, Kopylov PY49, Kuiper AFM50, Kwakkel-van Erp JM51, van der Linden MJM52, Linschoten M53, Linssen GCM54, Macias Ruiz R55, Magdelijn FJH56, Martens FMAC57, McCann GP58, van der Meer P59, Meijis MFL60, Messién P60,61, Monraats PS62, Montagna L62, Moriarty A64, Mosterd A65, Nierop PR66, van Ouwegen-Haneckamp C67, Pinto YM68, Poorthuisse H69, Prasad ST70,71, Reding JR72, Reinganum AC73, Ripley DP70, Salah R72, Saneei E73, Saxena M74, Schapp J80, Schellings DAANM75, Schout A76, Shafee A77, Shore AC78, Siebelink H79, van Smee M80, Smits PC81, Fisters R82, Tessitore E83, Tielemans RG84, Timmermans P Jr85, Tio RA85,93, Tjong FFVY86,94,95, den Uil CA83,44,96, van Craenenbroeck EM87, van Veen HPAA88, Vememan T89, Verschueren DO90, de Vries JK91, van de Wal RMA92, van de Watering DJ93, Westendorp K94, Westendorp PHM95, Weytsiens C96, Wierda E97, Williams B98, Woudstra I99, Wu KW00, Zaal R101, Zaman AG102, van der Zee PM103

Affiliations

1. Department of Clinical Biochemistry, King Faisal Hospital of the University, Imam Abdulrahman Bin Faïsœl University, Alkhobar, Saudi Arabia
2. Department of Internal Medicine, King Faisal Hospital of the University, Imam Abdulrahman Bin Faïsœl University, Alkhobar, Saudi Arabia
Mortality associated with atrial arrhythmias among patients hospitalized with COVID-19, J. Cardiovasc. Electrophysiol. 31 (12) (2020) 3077–3085.

[9] S.E. Mountantonakis, M. Saleh, J. Fishbein, A. Gandomi, M. Lesser, J. Chelico, J. Gabriels, M. Qi, L.M. Epstein, Atrial Fibrillation is an Independent Predictor for In-hospital Mortality in Patients Admitted with SARS-CoV-2 Infection, Hear. Rhythm Heart Rhythm Soc. 18 (4) (2021) 501–507.

[10] A. Bhatla, M.M. Mayer, S. Adusumalli et al., COVID-19 and cardiac arrhythmias, vol. 17, Hear Rhythm Elsevier Inc., 2020, pp. 1439–1444.

[11] E.J. Benjamin, S.S. Virani, C.W. Callaway, et al., Heart Disease and Stroke Statistics—2018 Update: A Report From the American Heart Association, Available from: Circulation [Internet] 137 (2018) https://www.ahajournals.org/doi/10.1161/CIR.0000000000000558.

[12] C.A. Emdin, C.X. Wong, A.J. Hsiao et al., Atrial fibrillation as risk factor for cardiovascular disease and death in women compared with men: systematic review and meta-analysis of cohort studies, BMJ [Internet] 2016, b7013. Available from: https://www.bmj.com/lookup/doi/10.1136/bmj.b7013.

[13] CAPACITY-COVID Collaborative Consortium and LEOS Study Group. Clinical presentation, disease course, and outcome of COVID-19 in hospitalized patients with and without pre-existing cardiac disease: a cohort study across 18 countries. Eur Heart J. 2021 Nov 4;ehab656. doi: 10.1093/eurheartj/ehab656. Epub ahead of print.

[14] A.E. Buxton, H. Calkins, D.J. Callans et al., ACC/AHA/HRS 2006 key data elements and definitions for electrophysiological studies and procedures: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Data Standards (ACC/AHA/HRS Writing Committee to Develop D. Circulation), 2006.

[15] M. van Smeden, J.A.H. de Groot, K.G.M. Moons, G.S. Collins, D.G. Altman, M.J. C. Eijkemans, J.B. Reitsma, No rationale for 1 variable per 10 events criterion for binary logistic regression analysis, BMC Med. Res. Methodol. 16 (1) (2016), https://doi.org/10.1186/s12874-016-0267-5.

[16] F.E. Harrell Jr., Regression modeling strategies: with applications to linear models, logistic and ordinal regression, and survival analysis, 2015.

[17] K. Boonyawat, P. Chantrathammachart, P. Numthavaj, N. Nanthatanti, S. Phusanti, A. Phuphaukrat, P. Niranvuck, P. Angchaisaksiri, Incidence of thromboembolism in patients with COVID-19: a systematic review and meta-analysis, Thromb. J. 2020, https://doi.org/10.1186/s12959-020-00248-5.

[18] M. Gawalko, A. Kapton-Cieślicka, M. Hohl, D. Dobrev, D. Linz, COVID-19 associated atrial fibrillation: Incidence, putative mechanisms and potential clinical implications, UC Hear Vasc. 30 (2020) 1–8.

[19] J.A. Offerhaus, A.A.M. Wilde, C.A. Remme, Prophylactic (hydroxy)chloroquine in COVID-19: Potential relevance for cardiac arrhythmia risk, Heart Rhythm 17 (9) (2020) 1480–1486.

[20] D.R. Musikantow, M.K. Turagam, S. Sartori, E. Chu, I. Kawamura, P. Shivamurthy, M. Bokhari, C. Oates, C. Zhang, C. Pamill, W. Malick, H. Hashemi, T. Ruiz-Maya, M.B. Hadley, J. Gandhi, D. Sperling, W. Whang, J.S. Koruth, M.-N. Langan, A. Sofi, A. Gomes, S. Harcum, S. Cammack, B. Ellsworth, S.R. Dukkipati, A. Bassily-Marcus, R. Kohli-Seth, M.E. Goldman, J.L. Halperin, V. Faster, V.Y. Reddy, Atrial Fibrillation in Patients Hospitalized With COVID-19, JACC Clin. Electrophysiol. [Internet] 7 (9) (2021) 1120–1130.