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## SPANISH JOURNAL OF MEDICINE REVIEWERS 2021

# Performance of the Panbio COVID-19 Rapid Antigen Test Device for infection control purposes

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## Abstract

**Objective:** We assessed the performance characteristics of the Panbio COVID-19 Rapid Antigen Test Device in field conditions and its potential use as a point-of-care test for isolation and cohorting patients at risk. **Methods:** We reviewed our laboratory records from January 2021 to May 2021 to identify subjects with a Panbio COVID-19 Rapid Antigen Test Device (index test) and a real-time reverse transcriptase-polymerase chain reaction (RT-PCR) (reference test) test carried out on the same date. **Results:** In total, 634 subjects met inclusion criteria. Three (0.2%) samples of the index test were not interpretable. A total of 51 (8.08%) subjects had SARS-CoV-2 infection. The index test had sensitivity 78.85% (95% CI: 66.30-88.94%), specificity 91.58% (95% CI: 89.02-93.71), and accuracy 90.54% (95% CI: 87.99-92.70%). A total of 11 (1.73%) subjects (one asymptomatic, five with respiratory symptoms, and five with pneumonia) had a false-negative result of the index test with median (range) cycle threshold RT-PCR of 25 (21-30), indicating the presence of high viral load in the nasopharyngeal sample. **Conclusions:** The Panbio COVID-19 Rapid Antigen Test Device cannot replace SARS-CoV-2 RT-PCR for infection control purposes.

**Key words:** Coronavirus infections/\*diagnosis. Sensitivity and specificity. COVID-19 testing.

## Introduction

The pandemic caused by coronavirus 2 (SARS-CoV-2) continues to challenge the health systems. One of the basic strategies in controlling the pandemic is identifying cases and contacts to carry out their isolation<sup>1</sup>.

Due to its high sensitivity and specificity, the gold standard for diagnosing SARS-CoV-2 infection recommended by the WHO and FDA is detecting the virus by the real-time reverse transcriptase-polymerase chain reaction (RT-PCR)<sup>2,3</sup>. However, RT-PCR is a laboratory procedure that requires sophisticated equipment and trained personnel to perform the test. The turnaround time varies according to geographical location and proximity to the testing laboratory. Sometimes there

have been delays in completing the RT-PCR tests due to demand overload or lack of reagents.

Antigen detection tests for the diagnosis of SARS-CoV-2 infection have lower diagnostic performance than the detection of the virus by RT-PCR<sup>4</sup>. However, they can be used as point-of-care tests for SARS-CoV-2 disease with the results available in 15 min. Several commercial antigen detection kits for SARS-CoV-2 diagnosis are available<sup>5</sup>, and one of the most commonly used is the Panbio COVID-19 Rapid Antigen Test Device. Compared with RT-PCR, the manufacturer claimed a sensitivity of 98.1% and a specificity of 99.8% in 508 symptomatic subjects. Furthermore, during the epidemic, the Panbio COVID-19 Rapid Antigen Test

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Device performance reproduced manufacturer results<sup>6</sup>. However, in field conditions, the performance characteristics have not been thoroughly evaluated. Moreover, the Panbio COVID-19 Rapid Antigen Test used as a surrogate marker of SARS-CoV-2 transmission capability is unknown.

The purpose of our study was to evaluate in field conditions the diagnostic performance of the Panbio COVID-19 Rapid Antigen Test Device compared with RT-PCR for SARS-CoV-2. We also assessed the potential use of the Panbio COVID-19 rapid antigen test for infection control purposes to isolate and cohort cases and high-risk contacts.

## Methods

### Study setting

We carried out the study in a 280-bed hospital belonging to the National Health System (Generalitat Valenciana) that serves a registered population of 190,000 inhabitants on the east coast of Spain.

### Study design

We have followed the recommendations of the STARD guideline for reporting Diagnostic Studies in preparing the document<sup>7</sup>.

We carried out a retrospective study reviewing our Clinical Microbiology Department data between January and May 2021. We selected for the study those subjects who had the Panbio COVID-19 Rapid Test Device (Abbott Abbott Diagnostic GmbH, Jena, Germany) and the RT-PCR (Genesig<sup>®</sup> COVID-19 2G Real-Time PCR Assay) carried out in nasopharyngeal samples on the same day. Trained healthcare professionals collected nasopharyngeal swabs.

### Population

We included adult and pediatric populations if they had COVID-19 symptoms lasting for < 7 days or subjects exposed to a patient with SARS-CoV-2 infection. We collected from the Clinical Microbiology Department records information about the primary complaint, results of rapid antigen test, and RT-PCR.

### Rapid diagnostic antigen testing

The Panbio™ COVID-19 Ag Rapid Test Device (index test) is a membrane-based immunochromatography

assay that detects the nucleocapsid protein of SARS-CoV-2 in nasopharyngeal samples<sup>8</sup>. For the procedures, we followed the manufacturer's recommendations. Tests results were recorded after 15 min of assay initiation by one observer. Only the control line and no test line within the result window indicated a negative result. The presence of the test line and the control line within the result window, regardless of which line appeared first, showed a positive result. The result was invalid if the control line was not visible within the result window after performing the test.

### RT-PCR testing

We tested nasopharyngeal swab samples as the reference test by RT-PCR (Genesig<sup>®</sup> COVID-19 2G Real-Time PCR Assay)<sup>9</sup>. This multiplex assay is a CE marked, *in vitro* diagnostic, real-time, RT-PCR intended for the qualitative detection of nucleic acid from SARS-CoV-2 (ORF1ab and S gene targets) in nasopharyngeal swabs, oropharyngeal swabs, and sputum specimens. Amplification and detection were performed for 45 cycles on a Biorad CFX96 thermocycler (Biorad Laboratories); the manufacturer's software automatically determined the threshold cycle (Ct). A positive result was defined as amplification of any of the two SARS-CoV-2 genes. We used a cycle threshold value < 30 to determine clinically relevant concentrations of SARS-CoV-2 since culturing of SARS-CoV-2 was not possible at Ct-values above 29<sup>10</sup>.

### Statistical analysis

We expressed continuous variables as mean and standard deviation and categorical variables as frequency and percentage. Using the RT-PCR results as the reference test, we calculated the performance characteristics of the Panbio COVID-19 Rapid Antigen Test Device. All statistical analyses were performed with the R program (R 4.1.0 for Windows).

### Ethics statement

The Research Commission approved the study of our center. As it was a retrospective study, the patients' informed consent was not considered necessary by the Research Commission. The treatment of personal data was governed by organic law 15/1999 and Royal Decree 1720/2007 for its protection.

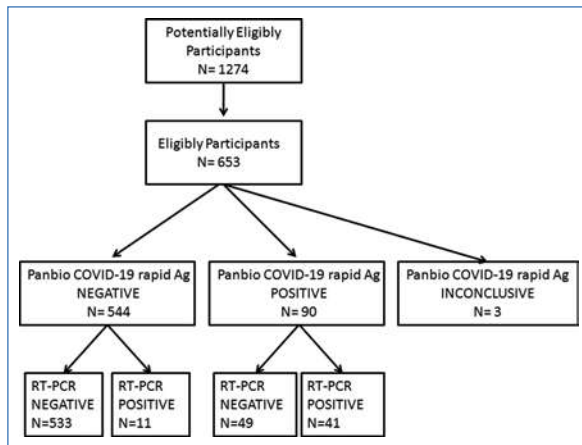


Figure 1. Patient flow chart.

## Results

### Participants

From a total of 1274 eligible participants with matched pairs of the index and reference test, we found 634 (49.8%) subjects with enough clinical information (Fig. 1). All participants had a time interval between symptoms onset to the sampling of fewer than 7 days. Subjects' mean age was 59-year-old; 53.9% were women. The most frequently chief complaints were shortness of breath and a combination of fever, cough, and shortness of breath (Table 1).

### Test results

The index test was positive in 41 (78.84%) subjects with RT-PCR cycle threshold values lower than 30, and it was negative in 533 (91.58%) subjects with RT-PCR cycle threshold values 30 or greater (Table 2). The overall accuracy was 90.54%.

We found 11 individuals with negative index tests and positive RT-PCR showing median (range) values of cycle threshold values of 25 (21-29), indicating SARS-CoV-2 at high concentrations. Ten out of 11 subjects were symptomatic, six had lung infiltrates, and five required hospital admission due to severe symptoms. Among patients with false-negative results, the Panbio COVID-19 antigen testing was carried out at a median of 1.5 days (range 1-7 days) after the onset of symptoms.

There were 49 (7.72%) subjects with false-positive index tests who had no amplification of SARS-CoV-2 gene targets after 45 cycles ( $n = 48$ ) or had a cycle threshold value of 31 (1 case). Among the 49 subjects,

25 had symptoms suggesting respiratory tract infection, and 24 were high-risk contacts.

### Overall performance of Panbio COVID-19 antigen test

We estimated the performance characteristics of the index test overall and in symptomatic and high-risk asymptomatic contacts (Table 3). The SARS-CoV-2 infection prevalence in our study population was 8.20%, with minor differences between symptomatic (8.47%) and high-risk asymptomatic subjects (7.66%). The test's sensitivity was fair, ranging from 72.22% to 93.75%, and the specificity was high, ranging from 87.05% to 93.83%, depending on the population studied symptomatic or asymptomatic, respectively (Table 3). Overall, the index test showed a high negative predictive value, between 97.33% and 99.41%.

### Discussion

We evaluated the performance of the Panbio COVID-19 Rapid Antigen Test Device in field conditions in Spain. For a disease prevalence of approximately 8%, the Panbio COVID-19 rapid antigen test showed an acceptable sensitivity of 78.85% with reasonable specificity of 88.69% compared with RT-PCR. The test performed better to rule out than in COVID-19 in this population with low disease prevalence. However, 11 (0.20%) subjects with false-negative Panbio COVID-19 rapid antigen test had Ct values of RT-PCT that indicated the possible infectivity of the clinical specimen.

Other field evaluations of the Panbio COVID-19 rapid antigen test have reproduced our performance results. In studies carried out in primary health centers, Albert et al.<sup>11</sup> showed a sensitivity of 79.6% with a specificity of 100%, and Bulilete et al.<sup>12</sup> found similar sensitivity (71.4%) and specificity (99.8%) for a prevalence of disease around 10%. The study carried out by Albert et al. also showed that in subjects with negative antigen tests and positive RT-PCR, the SARS-CoV-2 could not be cultured from nasopharyngeal samples<sup>10</sup>. In contrast, our study suggests that symptomatic patients with negative Panbio COVID-19 rapid antigen test and positive RT-PCR could transmit the infection. We found that patients had symptoms for < 7 days, and five required hospitalization due to disease severity. According to SARS-CoV-2 viral dynamics, our patients were in the time frame of maximum risk of contagious infection<sup>13</sup>. Unfortunately, viral culture was not possible at our

**Table 1.** Characteristics of the patients included in the study

| Characteristic  | RT-PCR                |                      |                    | p     |
|---|-----------------------|----------------------|--------------------|-------|
|   | Negative<br>(n = 582) | Positive<br>(n = 52) | Total<br>(n = 634) |       |
| Age, mean (SD), years                                 | 59.2 ± 23.0           | 57.0 ± 21.5          | 59.0 ± 22.9        | 0.507 |
| Age category — no (%)                                 |                       |                      |                    | 0.252 |
| < 15 years  | 3 (0.51)              | 0                    | 3 (0.47)           |       |
| 15-65 years   | 313 (53.78)           | 34 (65.38)           | 347 (54.73)        |       |
| > 65 years  | 266 (45.70)           | 18 (34.62)           | 284 (44.79)        |       |
| Sex — no (%)  |                       |                      |                    | 0.608 |
| Men   | 271 (46.56)           | 21 (40.38)           | 292 (46.06)        |       |
| Women   | 311 (53.43)           | 31 (59.62)           | 342 (53.94)        |       |
| Chief complaint — no (%)                              |                       |                      |                    |       |
| Shortness of breath                                   | 129 (22.16)           | 9 (17.30)            | 138 (21.77)        | 0.429 |
| Fever, cough, and shortness of breath                 | 96 (16.49)            | 17 (32.69)           | 113 (17.82)        | 0.007 |
| Fever   | 69 (11.86)            | 4 (6.89)             | 73 (11.51)         | 0.385 |
| General malaise                                       | 44 (7.56)             | 3 (5.77)             | 47 (7.41)          | 0.685 |
| Cough   | 12 (2.06)             | 1 (1.72)             | 13 (2.05)          | 0.964 |
| Headache  | 8 (1.37)              | 0                    | 8 (1.26)           | 0.438 |
| Chest pain  | 7 (1.20)              | 0                    | 7 (1.10)           | 0.486 |
| Confusion   | 4 (0.68)              | 1                    | 5 (0.79)           | 0.405 |
| Seizures  | 4 (0.68)              | 0                    | 4 (0.64)           | 0.663 |
| Diarrhea  | 2 (0.34)              | 0                    | 2 (0.32)           | 0.815 |
| Loss of smell   | 1 (0.17)              | 1 (1.72)             | 2 (0.32)           | 0.164 |
| Hemoptysis  | 1 (0.17)              | 0                    | 1 (0.16)           | 0.903 |
| Contact with another person with respiratory symptoms | 205 (35.22)           | 16 (30.76)           | 209 (32.96)        | 0.528 |

SD: standard deviation.

**Table 2.** Pan COVID-19 antigen test results according to the RT-PCR cycle threshold

|  | RT-PCR Ct     |                   |                   |                  |                |
|--|---------------|-------------------|-------------------|------------------|----------------|
|  | < 20 (n = 14) | 20- < 25 (n = 25) | 25- < 30 (n = 13) | 30- < 35 (n = 4) | ≥ 35 (n = 578) |
| Panbio COVID-19 Antigen test positive result | 13 (92.86)    | 21 (84)           | 7 (53.85)         | 1 (25)           | 48 (8.31)      |
| Panbio COVID-19 Antigen test negative result | 1 (7.14)      | 4 (16)            | 6 (46.15)         | 3 (75)           | 530 (91.69)    |

Ct: cycle threshold.

**Table 3.** Overall diagnostic performance of Panbio COVID-19 antigen test

| Statistic, value (95%CI)     | All subjects<br>(n = 634) | Symptomatic subjects<br>(n = 425) | Asymptomatic high-risk contacts<br>(n = 209) |
|------------------------------|---------------------------|-----------------------------------|--|
| Disease prevalence, %        | 8.20 (6.19-10.62)         | 8.47 (6.00-11.53)                 | 7.66 (4.44-12.13)                            |
| Sensitivity, %               | 78.85 (65.30-88.94)       | 72.22 (54.81-85.80)               | 93.75 (69.77-99.84)                          |
| Specificity, %               | 91.58 (89.02-93.71)       | 93.83 (90.96-96.01)               | 87.05 (81.47-91.44)                          |
| Positive likelihood ratio    | 9.36 (6.92-12.68)         | 11.71 (7.56-8.13)                 | 7.24 (4.91-10.66)                            |
| Negative likelihood ratio    | 0.23 (0.14-0.39)          | 0.30 (0.17-0.50)                  | 0.07 (0.01-0.48)                             |
| Positive predictive value, % | 45.56 (38.20-53.11)       | 52.00 (41.16-62.65)               | 37.50 (28.95-46.91)                          |
| Negative predictive value, % | 97.98 (96.63-98.79)       | 97.33 (95.56-98.41)               | 99.41 (96.18-99.91)                          |
| Accuracy, %                  | 90.54 (87.99-92.70)       | 92.00 (89.00-94.40)               | 87.56 (82.31-91.71)                          |

CI: confidence interval.

institution to investigate the presence of a viable virus. The SARS-CoV-2 RNA threshold associated with a viable virus in culture is around  $> 5.9 \log_{10}$  genome copies/mL of the sample, equivalent to an RT-PCR cycle threshold value  $< 30$ <sup>14-16</sup>.

We also found approximately 8% of discordant positive index test and negative reference test results, about 50% of these patients had respiratory tract symptoms. False-positive results can occur if reading tests results are done later than 20 min or in case of infection by SARS-CoV, which was considered highly unlikely<sup>8</sup>. We cannot provide alternate explanations for these false-positive results.

There is limited information on Panbio COVID-19 rapid antigen test performance to identify SARS-CoV-2 in infected asymptomatic individuals. In our study, we carried out a subanalysis in asymptomatic high-risk subjects. In a total of 16 (7.65%) individuals testing positive by RT-PCR, 15 (93.75%) yielded positive results with the rapid antigen test. The Panbio COVID-19 rapid antigen test's overall sensitivity and specificity were 93.75% (95% CI; 69.77-99.84%) and 87.05% (95% CI; 81.47-91.44%), respectively. Our results showed a better sensitivity value than the reported by Torres et al. (48.1%) or by Linares et al. (54.5%) in similar cohorts<sup>17,18</sup>. These differences could lie in the timing of sample collection, or the kinetics of SARS-CoV-2 load in symptomatic and asymptomatic individuals.

A recent meta-analysis including 29 studies and 17,171 COVID-19 subjects evaluated the clinical performance of rapid antigen tests<sup>19</sup>. The overall pooled sensitivity was 78.5% for symptomatic and 54.5% for asymptomatic subjects, and the pooled specificity was 99.4%. The Panbio COVID-19 rapid antigen test showed the highest sensitivity compared to Abbott BinaxNOW™, Standard™, and Biocredit™. Furthermore, the meta-analysis showed that sensitivity was 82.0% when the symptom onset was  $< 5$  days but decreased to 75.1% when the test was used later in the course of the disease. Besides time from symptom onset, another source of heterogeneity was the country of the study. Studies in African and Asian countries showed a decreased sensitivity compared to European and North-American studies, possibly related to a repetitive freeze-thaw process during transportation. The article suggests using kit utilization from local manufacturers to improve the performance of the test. An additional source of heterogeneity was the type of sample collected, being nasopharyngeal swabs the most sensitive compared with saliva.

Among the limitations of our study were the relatively low number of SARS-CoV-2 infections included and lacked precise information regarding the timing of exposure. Therefore, we could not correlate laboratory results with disease courses. However, the study's added value reflects the real-life performance of the Panbio COVID-19 Rapid Antigen Device as a point-of-care test. Due to the lower sensitivity of the Panbio COVID-19 Rapid Antigen Device, RT-PCR would be the preferred diagnostic test. Due to its high specificity, these rapid antigen test results could be helpful to rule out COVID-19. Nevertheless, a small proportion of negative results of the Panbio COVID-19 rapid antigen test can happen in subjects with symptoms in a period of infectivity.

In summary, the performance characteristics of Panbio COVID-19 rapid antigen test indicated that it should not be used as an infection control point-of-care test to decide isolation and cohort of patients. The high transmissibility of new variants of SARS-CoV-2, the lack of a specific treatment, and the potential severity of COVID-19 require a point-of-care test with better performance. Therefore, RT-PCR remains the gold standard for deciding cohorting and isolating patients at risk of SARS-CoV-2 infection.

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## Conflicts of interest

The authors declare that there is no conflict of interest.

## Ethical disclosures

**Protection of human and animal subjects.** The authors declare that no experiments were performed on humans or animals for this study.

**Confidentiality of data.** The authors declare that they have followed the protocols of their work center on the publication of patient data.

**Right to privacy and informed consent.** The authors declare that no patient data appear in this article.

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## Epidemiology, clinical and prognostic factors in Spanish patients with heart failure: The RICA-2 registry

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### Abstract

**Introduction:** Heart failure (HF) is a syndrome of epidemic proportions and one of the main reasons for hospitalization worldwide. Different scientific societies have risen interest in the creation of their own registries to study the characteristics and prognosis of these patients. Each registry covers a part of the spectrum of this heterogeneous syndrome and is useful to address questions that are difficult to answer in clinical trials. The RICA-2 is a national registry created by the Heart Failure Working Group of the Spanish Society of Internal Medicine and offers an Internal Medicine perspective of this pathology. **Objectives:** The main objective is to assess clinical and epidemiological characteristics and prognostic factors among patients with HF. Secondary objectives include: (1) To determine clinical/epidemiological/phenotypic characteristics and prognosis specifically in patients with HF and preserved left-ventricle ejection fraction (LVEF); (2) To examine how functional status, cognition, frailty, and nutrition influence the prognosis of patients with HF; (3) To assess congestion and strategies to achieve decongestion during the acute decompensation phase. **Methods:** A multicentre, prospective, observational cohort study including patients with HF attended in Spanish Internal Medicine Departments. Patients will be recruited in the acute decompensation phase or in the stable phase in the outpatient setting, including *de novo* and chronically decompensated patients. Patients will be included regardless of HF aetiology, LVEF values and comorbidities. **Conclusions:** Our work is a prospective study that aims to improve knowledge regarding epidemiology and prognosis in patients with HF, with focus on functionality, cognition, frailty, nutrition, and congestion phase.

**Key words:** Heart failure. Congestive heart failure. Epidemiology. Frailty. Nutrition. Registries.

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## Introduction

Heart failure (HF) is a clinical syndrome of epidemic proportions in developed countries and is a major health problem due to its incidence, prevalence, mortality, and consumption of resources<sup>1,2</sup>. HF registries have become powerful tools that provide valuable epidemiological data and contribute decisively to the understanding of this syndrome<sup>3</sup>. The information collected in most of these registries include demographic data, patients' comorbidities, diagnosis and classification of the disease, mortality and hospitalization rates, prescribed medication, among others<sup>4</sup>. To the best of our knowledge, there are three large HF registries in Spain, one developed from the perspective of Cardiology (REDINSCOR registry)<sup>5</sup>, another one from the Emergency Medicine and Emergencies (EAHFE registry)<sup>6</sup> and finally a registry from the perspective of Internal Medicine (RICA registry)<sup>7</sup>. A large number of publications from these registries have contributed to improve the understanding of HF mainly on its clinical, epidemiological, and prognostic aspects. They have also shown the different points of view of the three main specialties that care for these patients in hospital clinical practice (Cardiology, Internal Medicine, and Emergency Medicine) on a syndrome defined by its heterogeneous and complex nature<sup>8,9</sup>.

Over the past 13 years, the RICA registry has included more than 7,000 patients and a lot of scientific work has been carried out based on its data that has been communicated through almost 50 scientific publications (in national and international indexed journals), or in more than 50 scientific national and international communications in medical meetings. On the other hand, HF has undergone notable changes in the last decade, in clinical and epidemiological aspects, diagnostic criteria, and therapeutic targets, which require updating the initial research questions and modifying the necessary variables to be able to answer these questions. For these reasons, the Research Committee of the RICA registry belonging to the Heart Failure and Atrial Fibrillation Working Group of the Spanish Society of Internal Medicine decided to update the RICA registry by creating a new one named RICA-2. The main objective of this registry is to continue investigating the clinical and epidemiological characteristics of HF but (unlike the RICA) it aims to provide more knowledge in some areas that are highly prevalent in Internal Medicine such as HF with preserved ejection fraction (HFpEF), the geriatric evaluation (including functionality, cognition, and frailty), the nutritional status and finally the

**Table 1.** Inclusion and exclusion criteria

| Inclusion criteria   |
|--|
| 1. Age equal to or greater than 18 years   |
| 2. Patients diagnosed with HF following the recommendations of the European HF Guidelines <sup>a,b10</sup>   |
| 3. Patients will be included in the decompensation phase (defined as the need to administer parenteral loop diuretic, either in hospitalization or in the HF Units) or in the stable phase in the outpatient setting                                     |
| 4. Both <i>de novo</i> and chronically decompensated patients will be included   |
| 5. Patients will be included regardless of the HF etiology, LVEF values, and comorbidities   |
| 6. Patients must sign an informed consent for inclusion in the study   |
| Exclusion criteria   |
| There are no specific exclusion criteria and only those patients who do not strictly comply with the inclusion criteria, those who do not give their informed consent to participate and / or those patients who cannot be followed up will be excluded. |

<sup>a</sup>Diagnostic criteria: 1) Symptoms ± Signs; 2) LVEF value (to be classified as HFrEF, HFmrEF or HFpEF) and in case of HFpEF; 3) Objective evidence of cardiac structural and/or functional abnormalities consistent with the presence of LV diastolic dysfunction/raised LV filling pressures, including raised natriuretic peptides.

<sup>b</sup>Natriuretic peptide cut offs: in the non-acute setting 35 pg/mL for BNP and 125 pg/mL for NT-proBNP. In the acute setting 100 pg/mL for BNP and NT-proBNP values depend on age: > 450 pg/mL if aged < 55 years, > 900 pg/mL if aged between 55 and 75 years and >1800 pg/mL if aged > 75 years.  
HF: heart failure; HFrEF: heart failure with reduced ejection fraction; HFmrEF: heart failure with mid-range ejection fraction; HFpEF: heart failure with preserved ejection fraction; LVEF: left-ventricle ejection fraction.

assessment and treatment of congestion during the decompensation phase.

## Methods

### Design and study population

This is a nationwide, prospective, multicentre, observational cohort study. Patients will be recruited from the Internal Medicine Departments of Spanish hospitals whose researchers are members of the Heart Failure and Atrial Fibrillation Working Group of the Spanish Society of Internal Medicine.

### Patient selection and inclusion/exclusion criteria

The inclusion of patients will be done prospectively and consecutively. Each center will be assigned a minimum number of patients to include each year tailored to the size of the hospital. Only those patients who strictly meet the diagnostic criteria for HF of the European Guidelines will be included<sup>10</sup>. The rest of the inclusion and exclusion criteria are detailed in [Table 1](#).

## Objectives

The main objective of the study is to know the clinical and epidemiological characteristics and the prognostic factors of patients with HF treated in the Spanish Internal Medicine Departments. Secondary objectives include: (1) To determine the clinical, epidemiological, phenotypic, and prognostic characteristics of patients with HFpEF; (2) To examine how functional status, cognition, and frailty influence the prognosis of patients with HF; (3) To analyze the nutritional status of patients with HF and to know how malnutrition influences the prognosis of these patients; and (4) To determine which are the best tools to assess congestion, as well as the best strategies to achieve decongestion in patients with HF during the acute decompensation phase.

## Study variables and data collection

Study visits consist of an inclusion visit at baseline, a 30-day follow-up visit (only for patients included after an acute HF decompensation), and two follow-up visits at one year and two years after inclusion. Additional visits, whenever necessary and according to clinical judgment are allowed. Most of the study variables will be collected during the inclusion visit and are detailed in Table 2. Briefly, the following parameters will be collected: demographic data, HF-related variables, comorbidities, social, functional, and cognitive status, variables related to frailty and nutrition, variables related to the acute HF decompensation episode and its management, analytical parameters, and treatments (at baseline and during the acute decompensation phase). Data will be collected through an electronic medical record, which contains the database, accessed with a personal password. Confidentiality will be preserved since no personal data will be stored.

## Sample size

A sample size calculation has not been performed as the RICA-2 will be an “open” HF registry with five different objectives. Based on the experience of the researchers in the development of the RICA registry, we estimate the inclusion of 1,000 patients per year with the objective of including at least 5,000 patients in a period of 5 years. In order to achieve this inclusion rate, the same recruitment strategy used in other studies of our working group will be followed and consists

**Table 2.** Study variables at inclusion and follow-up visits

| Inclusion visit                                  |   |
|--|---|
| Demographic variables                            | Age<br>Gender   |
| Body composition estimate                        | Body mass index   |
| HF-related variables                             | HF etiology<br>NYHA scale<br>Previous admissions for AHF<br>Previous ED visits for AHF  |
| Comorbidities <sup>7</sup>                       | Charlson Comorbidity Index  |
| Social variables                                 | Place of living and caregiver needs   |
| Functional status <sup>16</sup>                  | Barthel Index   |
| Cognitive status <sup>15</sup>                   | Delirium<br>Pfeiffer test   |
| Frailty <sup>14</sup>                            | FRAIL scale<br>Clinical Frailty Scale   |
| Advanced HF and palliative care <sup>23</sup>    | EPICter score   |
| Nutritional status <sup>18,19</sup>              | Nutritional Risk Screening 2002<br>Mini Nutritional Assessment<br>CONUT score   |
| Acute HF decompensation variables <sup>*22</sup> | EVEREST score<br>Precipitating factors<br>Pharmacological treatment<br>Non-pharmacological measures<br>Outcomes   |
| Analytical parameters <sup>10</sup>              | Blood cell count<br>Biochemical parameters**<br>Natriuretic peptides<br>Cardiac Troponin<br>Carbohydrate antigen 125 <sup>21</sup><br>Iron metabolism parameters<br>Vitamin D<br>Urine analysis** |
| Complementary procedures                         | Electrocardiogram<br>Echocardiogram parameters<br>Chest X-ray<br>Lung and inferior vena cava ultrasound<br>Other cardiologic procedures***  |
| Cardiac amyloidosis diagnostic criteria          | ESC working group on myocardial and pericardial diseases criteria <sup>24</sup>   |
| Baseline treatment                               | HF-related medications<br>Other medications   |
| Follow-up visits                                 |   |
| Outcomes   | Vital status and causes of death<br>Hospitalizations for AHF and other causes<br>ED visits for AHF<br>Outpatient clinic visits  |

(Continue)

**Table 2.** Study variables at inclusion and follow-up visits (Continued)

| Follow-up visits      |   |
|-----------------------|---|
| Analytical parameters | Blood cell count<br>Kidney function<br>Electrolytes<br>Natriuretic peptides |
| Treatment             | Optimization of prognostic-modifying treatment for HF                       |

\*Only in patients included during and acute decompensation but not for those included in a stable phase.

\*\*Including glucose, kidney function (urea, creatinine, and glomerular filtration rate estimates using CKD-EPI formula), uric acid, electrolytes (sodium, potassium, chloride, magnesium), blood gasometry parameters, c-reactive protein, liver enzymes, lipids (total cholesterol, LDL, HDL, triglycerides), albumin. Urine analysis includes sodium, potassium, chloride, and albumin-to-creatinine ratio.

\*\*\*Including: coronary angiography, myocardial perfusion SPECT, cardiac scintigraphy with <sup>99m</sup>Tc-DPD.

AHF: acute heart failure; CONUT: Controlling Nutritional Status; ED: Emergency Department; ESC: European Society of Cardiology; HF: heart failure; NYHA: New York Heart Association.

of assigning to each center a minimum number of patients to be included each year which is proportional to the centers' number of beds.

### Statistical analysis

There is no single statistical methodology for the different studies that will be carried out with the RICA-2 registry. Every study will have its own methodology depending on the research question to be answered (and it will be detailed in a timely manner when it is necessary to present results). We can foresee that most studies will be descriptive, univariate, and multivariate comparative studies (using regression analysis) as well as survival analysis using Kaplan Meier curves and Cox regression analysis.

### Ethical aspects

The patients included in this study will be treated following usual medical care, since being an observational study does not modify the usual clinical practice. The study will be carried out in accordance with the Declaration of Helsinki. The study has been approved by the Clinical Research Ethics Committee of the Dr. Josep Trueta University Hospital in Girona and an informed consent will be obtained from all participating subjects.

### Discussion

Despite advances in the knowledge of HF and the development of new treatments that improve its prognosis, this syndrome, with a high prevalence and

incidence, continues to be a determinant of poor prognosis and presents high morbidity and mortality<sup>11</sup>. The need to keep promoting knowledge to continue improving our patients has served as a stimulus to work in this direction and is what has led the Heart Failure and Atrial Fibrillation working group to propose this new RICA-2 registry. In this new version, apart from revisiting epidemiological aspects, the authors have decided to focus on answering more specific questions about which there is currently less evidence and which can help to enhance awareness, especially in those patients with HFpEF.

### Clinical, epidemiological, phenotypic characteristics, and prognosis in heart failure with preserved ejection fraction

HFpEF is not even present a clear clinical entity. It is a mixture of cardiovascular, metabolic, renal, and geriatric conditions<sup>12</sup>. A rational focus on the improvement of the outcomes of patients with HFpEF may be to tackle the patients according to the conditions that led them to seek medical counseling. In this regard, a phenotype-oriented approach to HF and, in particular, to HFpEF could be interesting mainly if these presumable phenotypes lead to new therapeutic approaches<sup>13</sup>.

### Functional status, cognition and frailty on patients with heart failure

Persons with HF are more likely to be frail and suffer cognitive impairment than their age-matched equivalents without HF<sup>14</sup>. The reasons for this are not well known and may be linked to hemodynamic, vascular, and inflammatory changes that take place as heart failure progresses. Frailty, denoted by an increased physiologic vulnerability to stressors, may induce sickly persons with HF to exacerbation and worsening of this entity due to greater liability to the harmful pathophysiologic responses in HF, such as inflammation and autonomic dysfunction. Deepening the knowledge of the role of frailty in patients with HF can be useful to find mechanisms that attenuate the poor prognosis that its presence imposes on the patients. In addition, cognitive impairment many times associated to frailty, and highly prevalent in older people with HF adds a worse prognosis to these patients as was reported in our previous registry RICA<sup>15</sup>. The understanding of this association will be also a new reason for studying it in the new RICA-2. Finally, functional status was already studied previously<sup>16</sup>. Previous data from the RICA registry

showed that severe functional disability existed in more than half of older patients admitted because of a HF decompensation. For this population, preadmission Barthel index was a robust predictor of short-term mortality. It would be worthy to analyze again this aspect in the sample of this new registry.

### **Nutrition and heart failure**

Cachexia and malnutrition are significant complications of numerous diseases such as chronic kidney disease and severe HF. Malnutrition in HF is associated with loss of muscles, fat, and bone mass. Its causes can be due to decreased intake, increased metabolic rate, and cytokine dysfunction involving several molecules such as tumor necrosis factor-alpha, cortisol, epinephrine, renin as well as aldosterone. Drugs used in the treatment of HF such as diuretics or beta-blockers may suppose the loss of micronutrients and water-soluble vitamins. On the other hand, it is not clear what method is the best to assess nutritional status in patients whose weight and body mass index may be overestimated as a consequence of a congestive situation and biochemical tests such as albumin has also limitations because its variation with several non-nutritional factors such as status of hydration (states of overhydration lead to overestimation and dehydration leads to underestimation of serum albumin)<sup>17</sup>. The question is not trivial, since the state of malnutrition has prognostic repercussions both in outpatients<sup>18</sup> where it will be evaluated and in patients with acute decompensation<sup>19</sup> where we will also evaluate it.

### **Assessment of congestion and strategies to achieve decongestion**

Congestion is defined as the signs and symptoms of extracellular fluid accumulation, established by an increase in left-sided cardiac filling pressure<sup>20</sup>. The mechanisms that produce this status beyond a progressive accumulation of sodium and water deserve a thorough study of their causes, development, or markers. In this regard, we included the study of the role to detect congestion and its prognosis of the carbohydrate antigen 125 (CA 125)<sup>21</sup>. CA 125 is synthesized by serous epithelial cells as reaction to congestion and/or inflammatory stimulus. In recent years, increasing evidence has raised indicating that plasma levels of this glycoprotein could be useful as a biomarker in HF.

On the other hand, congestion is directly related to acute decompensation of HF. This aspect, crucial in the

timeline progression of HF, will be also evaluated in the new RICA-2. The underlying cardiac disease, the clinical presentation and precipitating factors may be very variable. Therefore, the pathophysiology of acute HF is highly heterogeneous. In addition, current management of acute HF is mostly symptomatic, led on decongestive drugs, at best tailored according to the initial hemodynamic status but with little regard to the underlying pathophysiological particularities. As a consequence, acute HF is linked to high mortality and hospital readmissions. As there is an unmet need for increased individualization of in-hospital tackle, including treatments targeting the causative factors, and continuation of treatment after hospital discharge to improve long-term outcomes<sup>22</sup>, we decided to include these aspects to widely research it.

Finally, other relevant aspects of HF are going to be included in the registry. It is of interest the approach of patients with advanced HF. A previous study of this working group showed a high prevalence of advanced disease and a low use of palliative care along with new criteria for defining it<sup>23</sup>. In this new registry, we will prove its validity in that new population. Furthermore, we will also aim to study the characteristics of an emerging entity as cardiac amyloidosis<sup>24</sup> in the setting of internal medicine wards.

### **Conclusions**

RICA-2 is a prospective study that aims to improve knowledge regarding epidemiology and prognosis in patients with HF, with special attention to relevant aspects such as functionality, cognition, frailty, nutrition, and congestion phase without forgetting other emergent topics such as advanced HF and cardiac amyloidosis.

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### **Conflicts of interest**

The authors declare that they have no conflicts of interest.

### **Ethical disclosures**

**Protection of human and animal subjects.** The authors declare that no experiments were performed on humans or animals for this study.

**Confidentiality of data.** The authors declare that no patient data appear in this article.

**Right to privacy and informed consent.** The authors declare that no patient data appear in this article.

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# Atrial fibrillation and dementia: Relationship, physiopathological mechanisms, and anticoagulant treatment

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## Abstract

Atrial fibrillation (AF) and dementia are highly prevalent pathologies. In the past two decades, multiple observational studies have been published that demonstrate the causal relationship between AF and dementia. These pathologies share common vascular risk factors such as those included in CHA<sub>2</sub>DS<sub>2</sub>-VASC score. Several physiopathological mechanisms have been involved, among the theories proposed to date are: clinical stroke and silent brain infarction, cerebral hypoperfusion and vascular inflammation. Although dementia is not a contraindication for oral anticoagulation, this population is still undertreated due to fear of hemorrhagic events. More and more studies propose that the benefit of anticoagulation in patients with dementia and AF outweighs the hemorrhagic risk, due to the reduction of morbidity and mortality with a net clinical benefit. Concerning the association between effective anticoagulation therapy and the risk of developing dementia, there are data that suggest a possible beneficial effect, however, we need larger scale studies to evaluate the real influence of anticoagulant treatment in prevention of dementia. Some studies showed a borderline significant association between the use of direct oral anticoagulants and the tendency to decrease cognitive impairment when compared with warfarin therapy. There are three ongoing clinical trials to clarify whether the type and use of anticoagulants are related to the development of cognitive decline.

**Key words:** Atrial fibrillation. Dementia. Cognitive decline. Oral anticoagulation. Direct oral anticoagulants.

## Introduction

The aging of the population worldwide is leading to the care of patients with increasing complexity, multiple pathologies, and comorbidities, such as dementia or atrial fibrillation (AF).

Dementia is a global health concern as its prevalence increases with age. The Alzheimer's Disease International (ADI) 2019 report estimates that over 50 million of people are affected by dementia and this prevalence will triple by 2050<sup>1</sup>. The proportion of deaths in the general population older than 64 years that could

be prevented, if dementia was eliminated, is > 10%<sup>2</sup>. The most frequent type of dementia is AD, followed by vascular dementia (VaD)<sup>3</sup>, being responsible for 60% and 20% of dementia cases, respectively<sup>4</sup>.

AF is also becoming an increasing health problem as it primarily affects the elderly, with an estimated incidence of 43.6 million globally<sup>5</sup>. It is the most common arrhythmia encountered in clinical practice and it has been associated with significant morbidity and mortality from all causes, especially in the oldest population<sup>6</sup>. There is sufficient evidence to establish that AF could be responsible

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for an increased incidence of dementia, probably related not only to stroke but also to cerebral hypoperfusion and other pathophysiological mechanisms (by a factor of 1.4 in a mixed population)<sup>7</sup>. Known risk factors for dementia are also considered risk factors for AF, such as old age, diabetes, chronic kidney disease, sleep apnea, hypertension, heart failure, heavy alcohol consumption, and coronary heart disease<sup>8</sup>. If AF plays a role in the development of cognitive decline, one might wonder if anticoagulant treatment could help prevent dementia, and actually there is growing evidence about the veracity of this fact<sup>9</sup>.

This article will review the most relevant and recent evidence on the relationship between AF and dementia, including the impact of anticoagulation as a preventive treatment for dementia.

### AF as an independent risk factor of dementia

Already in the late 90s, an article was published that highlighted the relationship between AF and dementia, the Rotterdam Scan Study<sup>10</sup>. This observational study found that dementia is twice as common in patients with AF compared to those patients without it (odds ratio [OR]: 2.3; 95% confidence interval [CI]: 1.4-3.7). Furthermore, despite excluding patients with a previous history of stroke, the relationship between AF and dementia was maintained (OR: 2.3; 95% CI: 1.4-3.8). Since then, numerous studies have been published on whether dementia is related to AF even without a previous history of stroke.

As an example, a prospective observational study was published in 2010 with a large sample size that included 37,000 patients<sup>11</sup>. Over the 5-year study period of follow-up, Bunch et al. reported an increased incidence of dementia among patients with AF, even after adjusting for prior stroke. In the same way, a longitudinal study of 5,150 older adults without prior stroke published in 2013 observed that patients who develop AF had a faster cognitive decline than those who did not have incident AF<sup>12</sup>. An interesting fact of the Bunch et al. study is that the highest risk of dementia was observed in the youngest group (< 70 years). Another study published in 2015 with a 20-year follow-up reported not only the statistically significant relationship between AF and dementia but also the strongest association in younger patients<sup>13</sup>. Finally, a cohort study of 262,611 patients recently published in 2019 compared patients with incident AF with AF-free patients, finding a higher risk of dementia in the AF group, with the presence of previous stroke being an exclusion

criterion of the study<sup>14</sup>. In addition to observational studies, several meta-analyses have demonstrated an increased risk of dementia in AF patients regardless of the presence of previous stroke<sup>15-18</sup> (Table 1).

Interestingly, dementia and AF share common vascular risk factors<sup>8</sup>. The CHA2DS2-VASC score (congestive heart failure; hypertension; age > 75; diabetes mellitus; prior stroke, TIA, or thromboembolism; vascular disease; age 65-74 years; sex category) includes various cardiovascular risk factors and it has been observed that the higher the CHA2DS2-VASC score, the higher the incidence of AF<sup>19</sup>. Similarly, the risk of dementia increases as the CHA2DS2-VASC score is higher<sup>20</sup>.

### Pathophysiologic mechanisms responsible for AF leading to dementia

the mechanisms underlying the relationship between AF and dementia are not fully understood. Two main mechanisms have been proposed: silent brain infarction (SBI) and reduced and intermittent cerebral hypoperfusion<sup>8,21,22</sup>.

SBI is defined as radiological evidence of focal arterial ischemia without any obvious clinical correlation. AF seems to be an independent risk factor for SBI<sup>23</sup>. In an observational study published in 2013, the prevalence of SBI in patients with AF was compared with those in sinus rhythm<sup>24</sup>, with approximately 90% involving at least one area of cerebral ischemia in the AF group. Among those patients with AF, worse cognitive performance was observed when compared with the control group. Brain microinfarcts are considered a common form of vascular brain damage of ischemic origin and have also been related to cognitive decline<sup>25,26</sup>. As it happens with SBI, AF is considered an independent risk factor for cerebral microinfarcts<sup>27</sup>. Other brain lesions on MRI have been proposed to explain the association between FA and dementia, such as microbleeds or white matter lesions<sup>28</sup>. Microbleeds are of particular interest because patients with AF usually need lifelong oral anticoagulation. In a study that included 1,737, the different lesions on MRI in patients with FA and their relationship with cognitive impairment were studied, with SBI showing a statistically significant relationship with cognitive impairment. This was not the case for other brain lesions characteristic of dementia such as microbleeds or white matter lesions, but it should be noted that up to 22% of AF patients had microbleeds and more than 50% had white matter lesions<sup>29</sup>.

**Table 1.** Published studies on atrial fibrillation and dementia relationship

| First author (Ref.)                   | Study design             | Cohort characteristics                                   | Main findings  |
|---------------------------------------|--------------------------|--|--|
| Ott et al., 1997 <sup>8</sup>         | Prospective cohort study | n = 6,584<br>age 69.2 ± 9.1 years<br>follow-up 3 years   | AF as an independent risk factor for dementia, OR: 2.3 (95% CI: 1.4-3.8)   |
| Bunch et al., 2010 <sup>9</sup>       | Prospective cohort study | n = 10,161<br>age 60.6 ± 17.9 years<br>follow-up 5 years | AF as an independent risk factor for dementia, with the highest risk in the younger group (<70), OR: 2.30 (p < 0.01)   |
| Kwok et al., 2011 <sup>13</sup>       | Meta-analysis            | n = 46,637<br>studies 15                                 | AF was associated with a significant increase in dementia, OR: 2.0 (95% CI: 1.4-2.7)   |
| Santageli et al., 2012 <sup>14</sup>  | Meta-analysis            | n = 77,668<br>studies 8                                  | AF was independently associated with increased risk of incident dementia, HR: 1.42 (95% CI: 1.17-1.72)   |
| Thacker et al., 2013 <sup>10</sup>    | Prospective cohort study | n = 5,150<br>age 73.0 ± 5.4 years<br>follow-up 7 years   | AF as an independent risk factor for cognitive decline, with a decline of -3.0 points (95% CI: -4.1-1.8) in 3MSE scores  |
| Udompanich et al., 2013 <sup>15</sup> | Meta-analysis            | n = 78,190<br>studies 11                                 | Among cross-sectional studies, AF was associated with increased risk of dementia, OR: 2.3 (95% CI: 1.4-3.7)  |
| Kalatarian et al., 2013 <sup>16</sup> | Meta-analysis            | n = 79,997<br>studies 21                                 | AF was significantly associated with the risk of developing cognitive impairment RR: 1.40 (95% CI: 1.19, 1.64), independently of stroke RR: 1.34 (95% CI: 1.13-1.58) |
| De Bruijn et al., 2015 <sup>11</sup>  | Prospective cohort study | n = 6,514<br>age 68.3 ± 8.5 years<br>follow-up 20 years  | AF as an independent risk factor in < 67, HR: 1.81 (95% CI: 1.11-2.94)   |
| Kim et al., 2019 <sup>12</sup>        | Prospective cohort study | n = 262,611<br>age 70.7 ± 5.4 years<br>follow-up 8 years | AF as an independent risk factor for dementia, HR: 1.27 (95% CI: 1.18-1.37)  |

CI: confidence interval; OR: odds ratio; HR: hazard ratio; MMSE: Modified Mini-Mental state examination; AF: atrial fibrillation; RR: relative risk.

More than two decades ago, a cross-sectional study was carried out which observed that in patients with chronic heart failure, lower left ventricular ejection fraction was an independent risk factor for cognitive impairment<sup>30</sup>. Since then, observational studies with similar results have been published, relating cognitive impairment to reduced cardiac output even in the absence of heart failure or only in the presence of subclinical diastolic dysfunction<sup>30-34</sup>. AF could lead to cognitive decline through decreased cerebral perfusion<sup>35</sup>. An observational study was carried out in patients with chronic heart failure, in which lower cerebral perfusion was observed in patients with AF, a fact that was related to cognitive impairment<sup>36</sup>. Not only the reduction in cardiac output seems to be related to cognitive decline but also the beat-to-beat variability that occurs in AF. To analyze the effect of ventricular heart rate response (VRR) in AF patients, an observational study followed 358 participants with mild cognitive

impairment and stratified them into moderate VRR (50-90 beats) and low/high (< 50/> 90 beats). In the low/high VRR group, the progression to dementia was higher when compared to the moderate VRR group<sup>37</sup>. If AF leads to cognitive impairment through cerebral hypoperfusion, one might consider whether restoring sinus rhythm would have an effect on the development of dementia. An observational study published in 2011 analyzed whether the treatment of AF with catheter ablation impacted on long-term events, finding similar risk rates for dementia between ablation treated patients and patients without AF, compared to worse outcomes for untreated AF patients<sup>38</sup>. In another recent study from 2020, a cohort of 9,119 patients treated with catheter ablation was compared to patients on medical treatment, encountering decreased dementia risk in the ablation group<sup>39</sup>. Studies are still needed to draw conclusions about the positive influence of catheter ablation over dementia as other studies with conflicting results have also been published<sup>40-42</sup>.



In addition to cerebral ischemia and cerebral hypoperfusion as pathophysiological mechanisms for the development of dementia in patients with AF, other mechanisms have been proposed. Vascular inflammation is one of the most prominent theories. In both the Rotterdam and Framingham studies, published in the 2000s, the elevation of inflammatory proteins was associated with an increased risk of dementia<sup>43,44</sup>. Likewise, a recent meta-analysis found that elevated inflammatory proteins are associated with a higher risk of all forms of dementia<sup>45</sup>. The inflammatory response has also been related to AF, acting both as a trigger for AF and as a perpetuator of it, generating a pro-inflammatory substrate that, in turn, would help in the development of thrombosis with the consequent prognostic implication<sup>46-49</sup>. In relation to what was previously described above, considering inflammation as another additional etiological mechanism of dementia in patients with AF becomes a plausible and interesting option<sup>8,21,22,50</sup>.

Finally, genetic factors have also been considered as a possible mechanism for dementia in AF patients with genetic variations in PITX2, ZFH3 genes being the most relevant<sup>51</sup>. The genetic influence may be the explanation of the higher risk for developing dementia in younger patients with AF.

### Influence of oral anticoagulants in the risk of developing dementia

Compared with the general population with AF, people with AF and dementia have twice the risk of stroke<sup>52</sup>, and 12-47% increased death risk<sup>53</sup>. Underuse of oral anticoagulants in people with dementia may contribute to increased risk of stroke and mortality<sup>54-56</sup>. A meta-analysis of 21 studies demonstrated that people with AF and dementia have a 52% lower rate of receiving warfarin than those without dementia<sup>57</sup>. Underuse of oral anticoagulants may be due to the possibility of increasing the bleeding risk in people with dementia. A meta-analysis indicated 41% increased risk of intracranial bleeding in the population with dementia, possibly because of the high prevalence of cerebral amyloid angiopathy<sup>58</sup>. Moreover, patients with dementia are older and frailer and have higher rates of other comorbidities, polymedication, and risk of falls, which lead to underuse of anticoagulation<sup>59</sup>. However, oral anticoagulants are still a main pillar for stroke prevention therapy and are strongly recommended by current guidelines<sup>5</sup> and dementia is not a contraindication for therapy with oral anticoagulants. A retrospective study from CardioCHUVI-FA registry, included

221 patients with AF, aged 85 or over, with moderate-severe dementia and showed that oral anticoagulation was significantly linked with lower embolic risk, higher bleeding risk, but there were no differences in global mortality<sup>60</sup>. In a cohort study from the Swedish dementia Registry, only 2,143 patients (26%) received oral anticoagulant treatment. Patients with warfarin treatment presented lower risk for ischemic stroke and mortality, and small increase of bleeding rates than those without treatment<sup>61</sup>. Therefore, what was previously commented supports the fact that anticoagulation treatment is necessary to improve morbidity and mortality of patients with AF and dementia. Cognitive function should not be the only aspect for starting or maintaining anticoagulation. This decision should be based on a comprehensive geriatric evaluation<sup>62</sup>. This decision should be reassessed periodically. Only in very advanced stages should avoiding or withdrawing anticoagulation be considered<sup>63,64</sup>.

Moreover, a Chinese observational study that included 3,284 patients with AF aged 65-85 years, concluded that warfarin therapy was associated with a decrease in new-onset dementia in comparison with those who did not receive treatment or with those who received aspirin. Female gender, age  $\geq 75$  years, and high CHA<sub>2</sub>DS<sub>2</sub>-VASC score were related to higher risk of dementia<sup>65</sup>. Another retrospective cohort study, with 84,521 AF patients, showed that those treated with oral anticoagulants had a 10% lower risk of cognitive decline/dementia compared with those without treatment. Furthermore, dual therapy, oral anticoagulants plus antiplatelet agent, was related to a higher risk of dementia in comparison with no treatment<sup>66</sup>. On the other hand, a small prospective cohort study carried out in the United Kingdom demonstrated that there was no apparent effect of anti-thrombotic therapy in the development of cognitive decline in patients with non-valvular AF<sup>67</sup>. A randomized controlled trial that included 973 patients aged  $\geq 75$  years with AF was randomly assigned to warfarin (n = 488; target international normalized ratio, 2-3) or aspirin (n = 485; 75 mg/d) concluded that there was no evidence that anticoagulation supply clinically important protection over aspirin against cognitive decline as measured by the Mini-Mental State Examination (MMSE) in AF during 2.7 years of follow-up<sup>68</sup>. However, potential confounding in these observational studies limits confidence in a cause-effect relationship.

A systematic review and meta-analysis that included one randomized controlled trial and five observational studies concluded that anticoagulation therapy in patients with AF reduces risk of developing dementia

or cognitive impairment by 20% in comparison with no treatment, but conditioned by study limitations and heterogeneity<sup>69</sup>. Another systematic review that included 19 studies compared oral anticoagulation versus antiplatelet therapy and change in MMSE score from baseline with a follow-up of 5.9 years. Results indicated a difference in favor of anticoagulation (mean difference: 0.90; 95% CI: 0.29-1.51), according to the observed trend in the single RCT included (mean difference MMSE: 0.80; 95% CI: -0.07 to 1.67). However, the pooled OR suggested no association with incident dementia, comparing anticoagulant to antiplatelet therapy (two studies, OR: 1.23; 95% CI: 0.80-1.91) or no treatment (three studies, OR: 0.89; 95% CI: 0.47-1.69). The analyses showed no definitive evidence of cognitive benefit or harm from anticoagulation but it seems that there exists a potential benefit of oral anticoagulation in comparison with antiplatelet overtime<sup>70,71</sup>.

Further, in patients anticoagulated with warfarin, a higher percentage in the therapeutic range (TTR) was associated with lower risk of dementia<sup>69</sup>. Another retrospective study, involving 2,605 chronically anticoagulated patients with warfarin for AF, showed that patients with low percentage in TTR had an increased risk of dementia<sup>72</sup>. An observational population-based study, that included 2,800 patients with incident AF, also investigated the association between percentage of TTR during warfarin therapy and the risk of dementia. After an average follow-up of 5 years, incident dementia diagnosis occurred in 357 patients (12.8%). After adjusting for confounders, warfarin therapy was associated with a reduced incidence of dementia (HR: 0.80; 95% CI: 0.64-0.99). However, only those in the two highest quartiles of TTR were associated with lower risk of dementia. The risk of dementia diminishes with a reduction in time spent in sub and supratherapeutic international normalized ratio range, so effective anticoagulation may prevent cognitive impairment in patients with AF<sup>73</sup>.

In the same vein, a retrospective study of national registries of Sweden, which included 444,106 patients with diagnosis of AF, showed that anticoagulant therapy was associated with a 29% decrease in the risk of dementia as compared to patients without anticoagulant treatment<sup>74</sup>. Another study was carried out from the same database, which is interesting. Patients with a baseline CHA<sub>2</sub>DS<sub>2</sub>-VASC score more than 1 (without counting female sex) and patients with previous diagnosis of intracranial bleeding or dementia were excluded of this retrospective study. From the 91,254 patients, 43% were receiving oral anticoagulants at baseline and they presented lower risk of dementia after adjustment

for death. With respect to the composite brain protection endpoint (new diagnosis of ischemic stroke, intracranial bleeding, and dementia), anticoagulation treatment was associated with a 12% lower risk in patients aged more than 65 years. Therefore, patients older than 65 seem to benefit from oral anticoagulants in an independent way of CHA<sub>2</sub>DS<sub>2</sub>-VASC score<sup>75</sup> (Table 2).

In summary, there is still scarce evidence, concerning the association between anticoagulation treatment and the risk of developing dementia. However, it seems that effective anticoagulation in patients with AF prevents the onset of dementia and decreases the developing of cognitive decline, but we need larger scale studies to evaluate the real influence of thromboprophylaxis in cognitive function.

### **Comparative studies between vitamin K antagonists (VKAs) versus direct oral anticoagulants (DOACs)**

As previously commented, SBI and microbleed, as well as, clinical stroke appears to be the principal mechanism of the association of AF and cognitive decline, but the role of anticoagulation type to prevent development of dementia is not well known.

Meta-analyses, clinical trials, and observational registries show that the efficacy and safety of DOACs are similar or superior to those of VKAs<sup>59</sup>. In accordance with the aforementioned, worsening cognitive function in patients with VKAs has been linked to insufficient time in the therapeutic range. However, DOACs have a more predictable and stable anticoagulation level, which is one of the reasons why they probably decrease the development of cognitive impairment. On the other hand, anticoagulation with DOACs, in comparison with VKAs, seems to reduce the risk of microbleeds and major intracranial hemorrhages, also implicated in the appearance and progression of dementia<sup>59,76</sup>.

In a retrospective study of the large Swedish registry (2006-2014), there was no significant difference in dementia risk, comparing warfarin therapy with DOACs when performing propensity analysis. The dementia incidence rates per 100 years were lower with DOACs versus warfarin therapy (1.13 vs. 2.26) and this is because of potential residual confounding related to comorbidities and selective prescribing<sup>77</sup>. This also occurred in the Danish nationwide cohort study that included 33,617 patients with non-valvular AF who initiated new oral anticoagulants and compared rates of new-onset dementia by age and anticoagulant treatment. The group of DOACs users that were 80 years

Table 2. Studies on impact of oral anticoagulation on cognitive function in AF patients

| First author (Ref.)                  | Study design   | Cohort characteristics   | Main findings  |
|--------------------------------------|--|--|--|
| Cobas Paz et al., 2020 <sup>60</sup> | Retrospective cohort study   | n = 3,549<br>age 88.8 ± 3.2 years<br>follow-up 2.8 ± 1.7 years | Anticoagulation was associated with lower embolic risk and higher bleeding risk both in patients with dementia [HR] <sub>embolisms</sub> 0.36; 95% CI: 0.15-0.84; [HR] <sub>bleeding</sub> 2.44; 95% CI: 1.04-5.71. Anticoagulation was associated with lower mortality only in patients without dementia (HR: 0.63; 95% CI: 0.53-0.75)  |
| Subic et al., 2018 <sup>61</sup>     | Prospective cohort study   | n = 8,096<br>age 82.3 ± 6.5 years<br>follow-up 1.74 years      | Warfarin treatment in patients with dementia was associated with a lower risk for IS (HR: 0.76; 95% CI: 0.59-0.98), antiplatelets were associated with increased risk (HR: 1.25; 95% CI: 1.01-1.54) compared to no treatment. For any cause hemorrhage, higher risk with warfarin (HR: 1.28; 95% CI: 1.03-1.59) compared to antiplatelets  |
| Wong et al., 2020 <sup>65</sup>      | Prospective cohort study   | n = 3,284<br>age 76.4 ± 5.3 years<br>follow-up 3.6 years       | Incidence of dementia was 1.04%/year (no therapy), 0.69%/year (aspirin), and 0.14%/year (warfarin). Warfarin use was associated with significantly lower risk of dementia (HR: 0.14; 95% CI: 0.05-0.36; p < 0.001)   |
| Mongkhon et al., 2020 <sup>66</sup>  | Retrospective cohort study   | n = 84,521<br>follow-up 5.9 years                              | OAC treatment was associated with lower risk of dementia/CI compared to no OAC treatment (HR: 0.90; 95% CI: 0.85-0.95; p < 0.001) or antiplatelets (HR: 0.84; 95% CI: 0.79-0.90; p < 0.001). Dual therapy (OAC plus an antiplatelet agent) was associated with higher risk of dementia/CI compared with no treatment (HR: 1.17; 95% CI: 1.05-1.31; p = 0.006)                          |
| Park et al., 2007 <sup>67</sup>      | Prospective cohort study   | n = 938<br>age 75.6 years<br>follow-up 3 years                 | Analysis of change in cognitive function between baseline and follow-up at 12 and 36 months revealed no clinically important differences between cases and controls nor between subgroups on aspirin, warfarin, or neither.  |
| Mavaddat et al., 2014 <sup>68</sup>  | Prospective randomized open-label trial  | n = 973<br>age 81.5 ± 4.3 years<br>follow-up 33 months         | Not significantly improved cognition in warfarin-treated AF patients. Adjusted analysis for baseline short orientation-memory-concentration test, age, sex, and previous stroke or TIA   |
| Moffitt et al., 2016 <sup>69</sup>   | Meta-analysis of randomized controlled trials regarding cognition or dementia in AF patients | n = 15,876<br>follow-up 5.9 years                              | Potential benefit of anticoagulation in comparison to controls with antiplatelet therapy in patients with AF (or atrial flutter) overtime  |
| Jacobs et al., 2014 <sup>72</sup>    | Retrospective population-based study   | n = 2,605<br>age 73.7 ± 10.8 years<br>follow-up 4 years        | Low time in the therapeutic range increases the risk of incident dementia HR 5.34 (95% CI: 2-12), adjusted for age, sex, HTN, hyperlipidemia, diabetes mellitus, smoking, CHF, CAD, coronary bypass, myocardial infarction, renal failure.   |
| Madhavan et al., 2018 <sup>73</sup>  | Prospective population-based study   | n = 2,800<br>age 71.2 years<br>follow-up 5.0 ± 3.7 years       | After adjusting for confounders, warfarin therapy was associated with a reduced incidence of dementia HR: 0.80; 95% CI: 0.64-0.99). Only those in the two highest quartiles of TTR were associated with lower risk of dementia. Warfarin therapy for AF is associated with a 20% reduction in risk of dementia. Increasing TTR on warfarin is associated with reduced risk of dementia |
| Friberg et al., 2018 <sup>74</sup>   | Retrospective registry study   | n = 444,106<br>age 74.7 years<br>follow-up 8 years             | Anticoagulant treatment at baseline was associated with 29% lower risk of dementia than patients without treatment (HR: 0.71; 95% CI: 0.68-0.74)   |
| Friberg et al., 2019 <sup>75</sup>   | Retrospective study of cross-matched national registries                                     | n = 91,254<br>age 59 years<br>follow-up 4.7 ± 2.8 years        | Composite brain protection endpoint, OAC was associated with an overall 12% lower risk (HR: 0.88; 95% CI: 0.72-1.00). This apparent benefit was restricted to patients aged > 65 years. Low-risk AF patients who take OAC have a lower risk of dementia than those who do not use it.  |

AF: atrial fibrillation; HR: hazard ratio; IS: ischemic stroke; OAC: oral anticoagulation; CI: cognitive impairment; HTN: hypertension; CHF: chronic heart failure; TIA: transient ischemic attack; CAD: coronary artery disease.

**Table 3.** Meta-analysis non-Vitamin K antagonist oral anticoagulants and cognitive impairment in atrial fibrillation. Comparative studies between VKAs versus DOACs. Randomized trials and database studies (modified from Zang et al.<sup>81</sup>)

| Study (year)   | Intervention   | Patients (n)   | Comparison                     | Patients (n) | Follow-up  | Reported cognition impairment  |
|--|--|----------------|--------------------------------|--------------|------------|--|
| RE-LY (2009)<br>Connolly et al.,<br>2009 <sup>84</sup>             | Dabigatran<br>110 mg/12 h<br>Dabigatran<br>150 mg/12 h | 5,983<br>6,059 | Warfarin                       | 5,998        | 2.0 years  | Amnesia; cognitive disorder; dementia; dementia Alzheimer's type; global amnesia; memory impairment; Parkinson's disease; Parkinsonism; vascular dementia  |
| ROCKET-AF (2011)<br>Patel et al., 2011 <sup>85</sup>               | Rivaroxaban<br>20 mg                                   | 7,111          | Warfarin                       | 7,125        | 1.9 years  | cognitive disorder; dementia; dementia Alzheimer's type; Parkinson's disease; Parkinsonism; vascular dementia; senile dementia; sensory disturbance; frontotemporal dementia; altered state of consciousness |
| ARISTOTLE (2011)<br>Granger et al.,<br>2011 <sup>86</sup>          | Apixaban<br>5 mg/12 h                                  | 9,088          | Warfarin                       | 9,052        | 1.52 years | Amnesia; cognitive disorder; dementia, dementia Alzheimer's type; global amnesia; Parkinson's disease; vascular dementia   |
| AVERROES (2011)<br>Connolly et al.,<br>2011 <sup>87</sup>          | Apixaban<br>5 mg/12 h                                  | 2,798          | Acetylsalicylic acid 81-324 mg | 2,780        | 1.1 years  | Dementia; Parkinson's disease  |
| ENGAGE AF-TIMI48 (2013)<br>Giugliano et al.,<br>2013 <sup>88</sup> | Edoxaban<br>60 mg<br>Edoxaban<br>30 mg                 | 7,002<br>7,002 | Warfarin                       | 7,012        | 2.8 years  | Amnesia; cognitive disorder; dementia; dementia Alzheimer's type; Parkinson's disease; Parkinsonism; vascular dementia; senile dementia; amnesic disorder; dementia with Lewy bodies                         |
| AXAFA-AFNET 5 (2018)<br>Kirchhof et al.,<br>2018 <sup>89</sup>     | Apixaban<br>5 mg/12 h                                  | 318            | Vitamin K antagonist           | 315          | 0.25 years | Cognitive dysfunction  |
| Jacobs et al.,<br>2016 <sup>69</sup>                               | DOACs  | 2,627          | Warfarin                       | 2,627        | 0.67 years | Dementia (Alzheimer's disease, vascular, senile, and non-specified)  |
| Friberg, et al.,<br>2018 <sup>67</sup>                             | DOACs  | 7,349          | Warfarin                       | 7,349        | 3.4 years  | Dementia   |

DOACs: direct oral anticoagulants.

and older had significantly higher dementia rates in comparison with warfarin users, may be in relation to residual confounding related to comorbidities and selective prescribing. This real-world observational study suggests that there was no difference between DOACs and well-managed treatment with warfarin<sup>78</sup>.

Besides, a new user retrospective cohort study included 2,399 patients with AF and cognitive impairment or dementia. Patients with all forms of dementia AD, VaD, mixed dementias, frontotemporal dementia, and Lewy body dementia were represented in the study. The patients who started DOACs (42%) were older and had increased prevalence of prior ischemic stroke, transient ischemic attack, or systemic embolism

and also had higher chronic comorbidity burden compared with warfarin users (58%). This study concluded that people with AF and dementia who initiated on DOACs had reduced risk of intracranial bleeding, but had an increased risk of all-cause mortality and gastrointestinal bleeding compared with warfarin users. Probably, in this study, there exists an impact of residual confounding in the fact of assigning DOACs to frailer and older patients<sup>79</sup>.

A previous study compared the risk of dementia incidence across patients with AF starting different oral anticoagulants in patients from two US healthcare claim databases (MarketScan 2007-2015 and Optum Clinformatics 2009-2015). Patients with AF starting

DOACs had lower rates of incident dementia in comparison with warfarin users, without differences between specific DOACs. However, these results should be interpreted with caution because of the possibility of confounding by indication and the nonrandomized study design<sup>80</sup>.

In line with the above, another meta-analysis of 97,595 patients with AF of randomized controlled trials and real-world studies indicated that the use of DOACs could decrease the risk of develop cognitive impairment in comparison to Vitamin K antagonists (VKAs)/acetylsalicylic acid. Out of the total patients, 55,337 (56.7%) were receiving DOACs and 42,258 (43.3%) were receiving VKAs and the primary outcome was a composite of any cognitive impairment. The results showed a borderline significant association between the use of DOACs and the tendency to decrease cognitive impairment when compared with VKAs/acetylsalicylic acid (HR 0.80; 95% CI: 0.63-0.98 for fixed effects model; HR 0.77; 95% CI: 0.53-1.01 for random effects model)<sup>81</sup> (Table 3). Taking into account previous, further investigation is needed, more RCTs and real-world studies are essential to obtain robust results.

Most therapies used to stop cognitive decline are ineffective, so the primary prevention is the key. The possible preventive strategies in the context of AF are the rhythm control with the objective of improving brain perfusion and the anticoagulation treatment. There are three ongoing clinical trials to clarify whether the type and use of anticoagulants are related to the development of cognitive decline. BRAIN AF is a blinded randomized trial that will assess the effect of DOACs on cognitive function in patients that otherwise would not justify oral anticoagulation (ClinicalTrials.gov NCT02387229). The CAF trial will compare cognition scores and rates of dementia in patients with AF, randomized to dabigatran etexilate versus dose-adjusted warfarin (INR 2.0-3.0) (ClinicalTrials.gov NCT03061006). Finally, another trial called GIRAF, Cognitive Impairment Related to AF Prevention, will evaluate if DOACs, compared to warfarin, ameliorate cognitive function (ClinicalTrials.gov NCT 01994265)<sup>82,83</sup>.

## Conclusions

There is a causal relationship between AF and dementia, independently of stroke. Ischemia and hypoperfusion cerebral and vascular inflammation are the main pathophysiological mechanisms. Anticoagulation of patients with AF could prevent the onset of dementia and DOACs seem to decrease the

development of cognitive decline compared to Vitamin K antagonists, but large-scale studies are needed.

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## Conflicts of interest

The authors declare that they have no conflicts of interest.

## Ethical disclosures

**Protection of human and animal subjects.** The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

**Confidentiality of data.** The authors declare that they have followed the protocols of their work center on the publication of patient data.

**Right to privacy and informed consent.** The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

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