**Assessing the Relationship between Cardiovascular and small Airway Disease and Acute events in COPD: the ARCADIA study protocol**

## Study design

The ARCADIA study is a prospective, multicenter, pilot, observational, cohort study that will be conducted in ≥22 pulmonary centers from all over Italy. The goal of this study is to enroll ≥500 patients. The study will consist of an observational period lasting up to 52 weeks, with the possibility of extending the observation up to 3 years for each patient. Between 31 January 2023 and 31 January 2024 patients will be enrolled to the study. The main endpoint will be to assess the risk of CVD in patients with COPD affected by SAD. The secondary endpoints will be to assess mortality, exacerbation risk and exacerbation characteristics in the same patients.

Details of ARCADIA study design can be found in Figure 1.

## Inclusion and exclusion criteria

To participate to the study, inclusion and exclusion criteria have been designated in order to make the population of study participants homogeneous. All criteria are reported in Table 1.

## Patient population and recruitment

The study includes non-invasive investigations normally performed during clinical practice and in the follow-up of COPD patients, in accordance with the availability of each center. After each visit, each center will complete the case report form (CRF) all the variables and parameters subject to statistical analysis will be reported.

The study will be composed of n. 3 visits, in n. 3 times: visit 1 (V1) first patient evaluation at time 0 (T0), the visit will be conducted in presence, visit 2 (V2) at T6±1 month from V1, the visit will be conducted through telephone interview, or if necessary, in presence (6±1 months after V1) and will be characterized by the administration of a questionnaire for the collection of anamnestic data relating to the period which has elapsed since V1; visit 3 (V3) at T12±2

months from V1, similarly to V2, will be conducted through telephone interview, or if necessary, in presence and will be characterized by the administration of a questionnaire for the collection of anamnestic data relating to the period which has elapsed since V2. Detailed information are reported in Table 2.

**Statistical Analyses**

ARCADIA is a cohort, multicenter, observational, prospective, 52-week pilot study. At least ≥22 centers will be involved, and it is estimated that each center will enroll at least ≥30 patients. Total number of patients enrolled in the study will be ≥500.

The main endpoint will be the assessment of the risk of cardiovascular events in patients with COPD and SAD. Secondary endpoints will be assessment of mortality, exacerbation risk, and exacerbation characteristics. The respiratory and cardiovascular functional variables will be evaluated in a descriptive way.

As a pilot study, the sample size calculation cannot be performed and, thus, the statistical analysis will be conducted via Bayesian inference [1,2]. Therefore, the statistical analysis will not be conducted to test the null hypothesis and, consequently, the statistical significance value P will not be calculated. Results will be reported as mean and 95% confidence interval (95%CrI). The Bayesian approach will allow to quantify the probability that the outcomes under study will be more frequent/different in COPD patients with SAD compared to COPD patients without SAD [1,2]. The Bayesian method will also be applied for the management of missing data and for clustering the population based on possible confounding factors, normalizing the results for them [3]. Statistical analysis based on Bayesian inference will be performed using JASP software (V0.16.3).

**Ethics approval and informed consent**

This study will be performed in accordance with the “Comitato Etico Indipendente” of Rome – Fondazione Policlinico Tor Vergata (protocol R.S 259.22), that has approved ARCADIA on 22th of December 2022. In each center that adheres to the study, the ethics approval

preceded the study participant's enrolment. Written informed consent must be obtained from all study participants. Patient's data will not be share out of the investigator's members. The ethics committee operates in accordance with the rules of GCP-ICH (good clinical practice-International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use).

ARCADIA study will be conducted in accordance with internationally accepted strengthening reporting of observational studies in epidemiology (STROBE) quality criteria [4]. The STROBE checklist is reported in supplementary Table 1.

**Data availability**

Personal data will be used confidentially. All data will be pseudonymized through a code that indicates the initials of name and surname's patients, his/her years of birth and two digits that identifies each center (eg: Mario Rossi, born in 1951, from center "01": MARO5101). All participants will receive a unique study identification number that will be safeguarded by the coordinating investigator. Data will be entered into an electronic case report form (eCRF), that will accessible only to the investigators of this study.

## References


[1] E.C. Lee, A.L. Whitehead, R.M. Jacques, S.A. Julious, The statistical interpretation of pilot trials: Should significance thresholds be reconsidered?, BMC Med. Res. Methodol. 14 (2014) 1–8. https://doi.org/10.1186/1471-2288-14-41/FIGURES/2.

[2] A.R. Willan, L. Thabane, Bayesian methods for pilot studies, Clin. Trials. 17 (2020) 414–419. https://doi.org/10.1177/1740774520914306.

[3] Q. Zhou, C. McNeal, L.A. Copeland, J.P. Zachariah, J.J. Song, Bayesian propensity score analysis for clustered observational data, Stat. Methods Appl. 2019 292. 29 (2019) 335–355. https://doi.org/10.1007/S10260-019-00484-8.

[4] E. von Elm, D.G. Altman, M. Egger, S.J. Pocock, P.C. Gøtzsche, J.P. Vandenbroucke, The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies, Int. J. Surg. 12 (2014) 1495–1499. https://doi.org/10.1016/J.IJSU.2014.07.013.

**Table 1.** Inclusion and exclusion criteria of ARCADIA protocol participants.

| Inclusion criteria | Exclusion criteria |
|---|---|
| Clinical and functional diagnosis of CODP | Previous or current history of bronchial asthma |
| FEV1/FVC values <0.7 (after bronchodilatation) and/or FEV1/FVC (or FEV1/VC) <LLN | Restrictive lung disease or interstitial lung disease |
| Clinical stability ≥3 months (no mild moderate or severe exacerbations) | Active or under treatment neoplasms |
| Both genders | Shift of inhalation therapy in the 3 months prior to study entry |
| Age ≥40 years | Inability to perform reliable and repeatable pulmonary function tests |
| Smoking history ≥10 p/y | Oxygen therapy >18 hours a day |
| | Diagnosed with clinically significant bronchiectasis (overt diagnosis of bronchiectasis on chest CT which is the patient's primary diagnosis) |
| | Severe obstructive sleep apnea syndrome (apnea/hypopnea index >30/h) |
| | Pregnancy |

COPD, chronic obstructive pulmonary disease; CT, computed tomography, $FEV_{1:}$ forced expiratory volume in the 1st second; FVC, forced vital capacity; LLN, lower limit of normal; p/y, pack/years; VC, vital capacity.

**Table 2:** Details of the procedures to be carried out during the various phases of the study are shown in table 2.

| **Procedures** | **Visit1 (t0)** | **Visit 2** | **Visit 3** |
|---|---|---|---|
| Evaluation of inclusion/exclusion criteria. | X | | |
| Signed informed consent | X | | |
| Collection of anamnesis | X | | |
| Physiological anamnesis: age, sex, ethnicity, BMI, height, weight, exposure to pneumotoxic substances | X | | |
| Pharmacological anamnesis, if present, cardiological, pneumological, of any other type, according to the predisposition indicated in the CRF | X | | |
| Evaluation of questionnaires: CAT and mMRC | X | | |
| Pathological anamnesis and comorbidities: current or history of smoking, any alpha-1 antitrypsin deficiency, pulmonary comorbidities (year of COPD diagnosis, any previous SARS-CoV2 infection, acute moderate/severe exacerbations of COPD in the previous year ), cardiovascular comorbidities, eg: CHF with preserved or reduced EF, AF, Afib, AA, IHD, SAH, VD, stroke, PT, PCE, non-pulmonological and non-pulmonological comorbidities cardiovascular (diabetes mellitus, chronic renal failure, liver disease, rheumatological pathologies, neoplasms, Charlson Comorbidity Index) | X | | |
| Instrumental and blood tests previously performed: chest CT if performed within 12 months preceding the V1 (it is however possible to perform the chest CT within 6 months after V1 and enter the parameters subsequently), recent blood gas analysis if performed, electrocardiogram and echocardiogram if performed within the 6 months preceding the V1 (it is however possible to perform the electrocardiogram and echocardiogram within the 6 months following the V1 and enter the parameters subsequently), blood tests if performed within the 6 months preceding V1 | X | | |
| Execution of global spirometry with plethysmographic technique (or nitrogen washout), where deemed appropriate with bronchodilatation test, DLCO, SBN2 test, where present in the | X | | |

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|---|---|---|---|
| centre, FOT or IOS, where present in the center, 6MWT in ambient air | | | |
| Administration of a questionnaire for the collection of anamnestic data relating to the period which has elapsed since visit 1 | | X | |
| Inquire about possible AECOPD | | X | X |
| Inquire about hospitalizations | | X | X |
| Inquire about cardiovascular events | | X | X |
| Inquire about SARS-CoV2 infections | | X | X |
| Possible need to modify/introduce specific pneumological therapy with respect to V1 | | X | |
| Possible need to modify/introduce specific diuretic or cardiological therapy with respect to V1 | | X | |
| Possible need for modification/introduction of antibiotic or corticosteroid therapy with respect to V1 | | X | |
| Administration of a questionnaire for the collection of anamnestic data relating to the period which has elapsed since visit 2 | | | X |
| Possible need to modify/introduce specific pneumological therapy with respect to V2 | | | X |
| Possible need to modify/introduce specific diuretic or cardiological therapy with respect to V2 | | | X |
| Possible need for modification/introduction of antibiotic or corticosteroid therapy with respect to V2 | | | X |

AA, atrial arrhythmias; AECOPD, acute exacerbations of COPD; AF, atrial flutter; AFib, atrial fibrillation; BMI, body mass index; CAT, CHF, chronic heart failure; COPD assessment test; COPD, chronic obstructive pulmonary disease; CRF, case report form; CT, computed tomography; DLCO, diffusion lunge carbon monoxide; EF, ejection fraction; FOT, forced oscillation technique; IHD, ischemic heart disease; IOS, impulse oscillometry system; mMRC, modified British medical research council; PCE, previous cardiovascular events; PT, pulmonary thromboembolism; SAH, systemic arterial hypertension; SARS-CoV2, severe acute respiratory syndrome coronavirus 2; SBN2 test, single breath nitrogen test; VD, vascular disease; V1, visit 1; V2 visit 2; V3 visit 3; 6MWT, six-minute walk test.

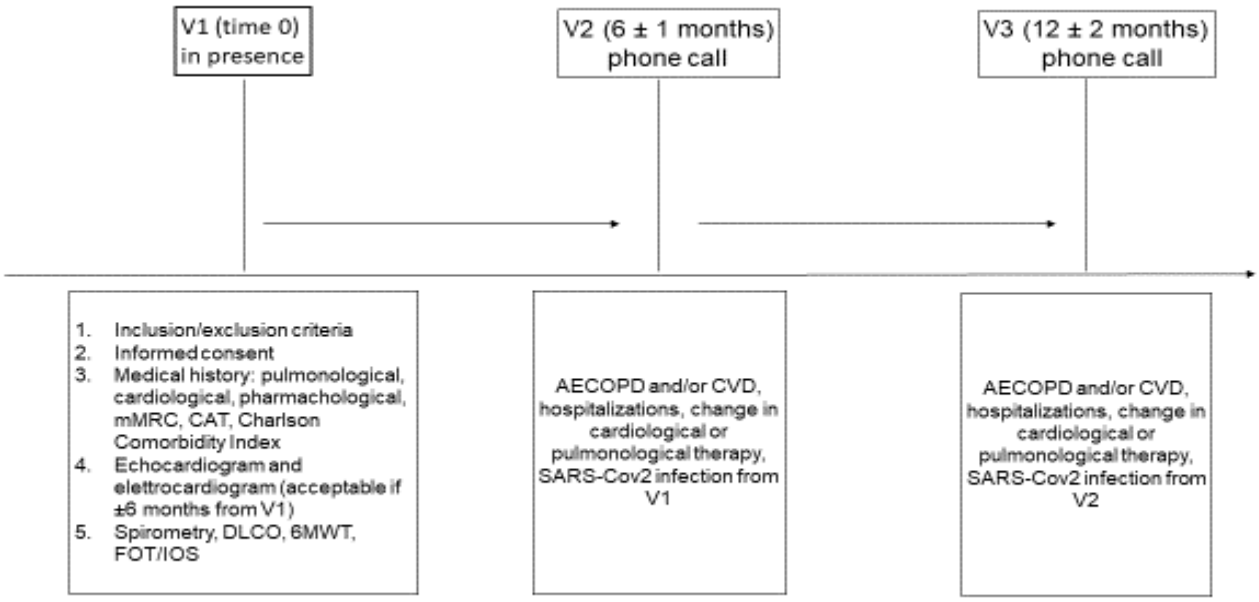


**Figure 1.** Overview of ARCADIA study design. Each panel represents a phase of the study with the relative clinic evaluation carried out on the patients. ARCADIA, assessing the relationship between cardiovascular and small airway disease and acute events in COPD; CAT, COPD assessment test; CVD, cardiovascular disease; DLCO, diffusion lunge carbon monoxide; FOT, forced oscillation technique; IOS, impulse oscillometry system; mMRC, modified British medical research council; V1, visit 1; V2, visit 2; V3, visit 3; 6MWT, six-minute walk test.