# Asthma, COPD, and overlap in a national cohort: ACO on a gradient

Arnaud Bourdin, Carey Suehs, Grégory Marin, Isabelle Vachier, Eric Matzner-Løber, Pascal Chanez, Nicolas Molinari

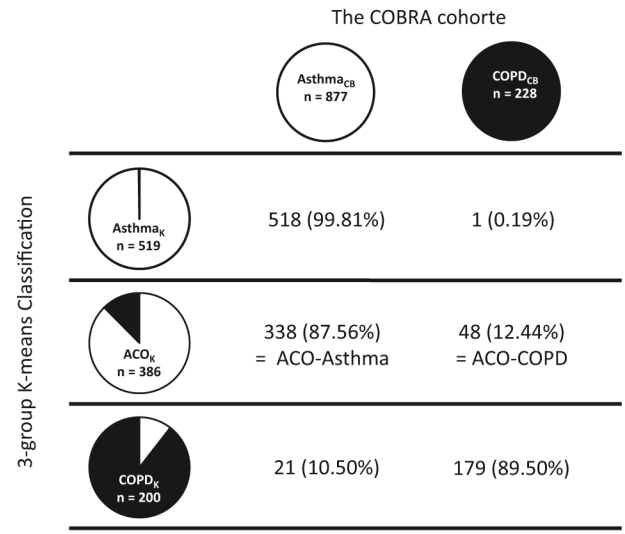


**FIG 1**. Patients originally diagnosed with asthma/COPD in the French national observational cohort of patients with asthma and COPD, termed "COBRA," were reclassified via K-means clustering into (1) a new Asthma$_K$ group, (2) an Asthma-COPD-Overlap group (ACO$_K$), and (3) a new COPD group (COPD$_K$). Designated by "CB," the COBRA cohort prospectively enrolls patients with asthma and COPD from 15+ expert centers in France. Initial diagnoses were made by participating physicians. Asthma and COPD were defined according to GINA (symptom history and 200 mL/12% reversibility) and GOLD criteria, respectively. The presented ACO classification is solely the result of the clustering algorithm. The number (%) of COBRA patients falling into each K-means group are provided. The ACO$_K$ group is further subdivided into "ACO-Asthma" and "ACO-COPD" groups. *GINA*, Global Initiative for Asthma; *GOLD*, Global Initiative for Chronic Obstructive Lung Disease.

*Arnaud Bourdin, MD, PhD*[a,b]
*Carey M. Suehs, PhD*[a,c]
*Gregory Marin, PhD*[c]
*Isabelle Vachier, PhD*[a]
*Eric Matzner-Lober, PhD*[d]
*Pascal Chanez, MD, PhD*[e,f]
*Nicolas Molinari, PhD*[b,c,g]
*on behalf of the COBRA Consortium**

## Asthma, COPD, and overlap in a national cohort: ACO on a gradient

*To the Editor:*

Asthma and chronic obstructive pulmonary disease (COPD) are characterized as distinct entities, though the clinical reality encountered by physicians includes a complex mixture of heterogeneous, overlapping states. In older patients (typically older than 40 years), distinguishing between them becomes difficult because patients can increasingly share characteristics of either disease, resulting in "asthma-COPD overlap" (ACO).[1]

Diagnosing ACO has been justified by reports of poorer outcomes for "intermediate" patients when compared with those who have clear diagnoses of asthma or COPD alone.[1,2] Treatment options and responses may also differ, notably by the fact that patients with ACO have been found to better respond to inhaled corticosteroids as compared with patients with COPD.[3,4] However, certain authors have expressed concern when blurring the lines between asthma and COPD, citing the potential for overmedication as a concern,[5-7] as well as the lack of studies supporting specific treatments for intermediate groups.[5,8] Nevertheless, the ability to easily identify an expected "poor-outcome" group via overlapping asthma and COPD clinical characteristics would be of great utility for clinicians.[8] In addition, an important part of nosology is identifying diseases with similar outcomes: testing whether or not the requalification of patients with asthma and COPD into an ACO group more accurately identifies subgroups in terms of prognosis may represent one argument justifying this refined classification.

Given this context, we sought to verify the presence of disease severity in association with ACO using the French national Bronchial Obstruction and Asthma Cohort

**TABLE I.** Outcomes (at the end of follow-up) for the $Asthma_K$, $ACO_K$ (divided into ACO-Asthma and ACO-COPD groups according to initial diagnosis), and $COPD_K$ groups

| Variable | $Asthma_K$ (n = 519) | $ACO_K$ (N = 386) | | $COPD_K$ (n = 200) | *P* value | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | ACO-asthma (n = 338) | ACO-COPD (n = 48) | | $Asthma_K$ vs $COPD_K$ | $ACO_K$ vs $asthma_K$ | $ACO_K$ vs $COPD_K$ | ACO-asthma vs $asthma_K$ | ACO-COPD vs $COPD_K$ |
| $FEV_1$ pre-β2 (L) | 2.40 (1.63 to 3.06) | 2.02 (1.54 to 2.59) | | 1.48 (0.95 to 2.09) | <.001 | <.001 | <.001 | <.001 | <.001 |
| | | 2.06 (1.54 to 2.59) | 1.98 (1.49 to 2.61) | | | | | | |
| $FEV_1$ pre-β2 (% predicted) | 80 (64 to 94) | 80 (64 to 97) | | 58 (38 to 77) | <.001 | .660 | <.001 | .427 | <.001 |
| | | 81 (65 to 97) | 71 (58 to 97) | | | | | | |
| FVC pre-β2 (L) | 3.36 (2.55 to 4.15) | 2.93 (2.44 to 3.63) | | 2.89 (2.31 to 3.51) | <.001 | <.001 | .246 | <.001 | .179 |
| | | 2.91 (2.41 to 3.62) | 3.08 (2.52 to 3.77) | | | | | | |
| FVC pre-β2 (% predicted) | 96 (83 to 108) | 95 (82 to 109) | | 84 (70 to 103) | <.001 | .962 | <.001 | .570 | .371 |
| | | 96 (82 to 110) | 90 (82 to 101) | | | | | | |
| $FEV_1$/FVC (% predicted) | 69 (60 to 78) | 69 (59 to 79) | | 53 (40 to 62) | <.001 | .549 | <.001 | .966 | <.001 |
| | | 69 (59 to 79) | 64 (54 to 76) | | | | | | |
| $FEV_1$ post-β2 (L) | 2.53 (1.77 to 3.22) | 2.16 (1.67 to 2.69) | | 1.56 (1.01 to 2.20) | <.001 | <.001 | <.001 | <.001 | .002 |
| | | 2.16 (1.69 to 2.69) | 2.08 (1.61 to 2.61) | | | | | | |
| $FEV_1$ post-β2 (% predicted) | 85 (68 to 98) | 85 (67 to 100) | | 61 (40 to 80) | <.001 | .500 | <.001 | .249 | <.001 |
| | | 86 (67 to 100) | 74 (62 to 98) | | | | | | |
| % Reversibility: $100 \times \frac{FEV_{1\ post-\beta2(L)} - FEV_{1\ pre-\beta2(L)}}{FEV_{1\ pre-\beta2(L)}}$ | 6.74 (2.66 to 13.90) | 6.67 (2.14 to 14.77) | | 4.65 (0.00 to 12.18) | .003 | .959 | .006 | .522 | .519 |
| | | 7.00 (3.09 to 15.95) | 5.40 (−0.31 to 7.21) | | | | | | |
| Annualized change in $FEV_1$ (% variation) | 0.62 (−6.30 to 8.60) | 1.70 (−6.40 to 9.86) | | −1.16 (−3.86 to 1.48) | .203 | .582 | .067 | .644 | .174 |
| | | 1.89 (−6.50 to 9.86) | 1.51 (−2.29 to 40.79) | | | | | | |
| No. of exacerbations during the last 12 mo of follow-up | | | | | | | | | |
| 0 | 272 (54.73) | 198 (55.00) | | 101 (53.16) | .263 | .622 | .414 | .921 | .388 |
| | | 169 (53.82) | 29 (63.04) | | | | | | |
| 1 | 100 (20.12) | 69 (19.17) | | 45 (23.68) | | | | | |
| | | 62 (19.75) | 7 (15.22) | | | | | | |
| 2 | 125 (25.15) | 93 (25.83) | | 44 (23.16) | | | | | |
| | | 83 (26.43) | 10 (21.74) | | | | | | |
| No. of hospitalizations during the last 12 mo of follow-up | 0 (0 to 1) | 0 (0 to 0) | | 0 (0 to 0) | .010 | .117 | .147 | .042 | .418 |
| | | 0 (0 to 0) | 0 (0 to 0) | | | | | | |
| Emergency department admission during the last 12 mo of follow-up | 125 (25.77) | 69 (19.88) | | 21 (11.23) | <.001 | .282 | .004 | .212 | .367 |
| | | 66 (21.85) | 3 (6.67) | | | | | | |
| Intensive care unit admission during the last 12 mo of follow-up | 25 (5.17) | 8 (2.46) | | 6 (10.53) | .374 | .019 | 1.00 | .088 | .171 |
| | | 8 (2.66) | 0 (0) | | | | | | |

Descriptive statistics are presented as medians (interquartile range) for quantitative variables and as numbers (percentage) for qualitative variables. *P* values indicate Mann-Whitney, $\chi^2$, or Fisher exact test results for the indicated comparisons.

*FVC*, Forced vital capacity.

("COBRA"), which is composed of prospective data (including satisfactory follow-up >2 years) for 877 patients with asthma (the $Asthma_{CB}$ group) and 228 patients with COPD (the $COPD_{CB}$ group; see Fig 1). COBRA was approved by the local Ethics Committee (*Comité de Protection des Personnes d'Ile de France*; reference no. 0811738) and written informed consent was gathered for all participants at inclusion. K-means clustering for 3 *a priori* groups on clinical characteristics (age at symptom onset, atopy, coughing, smoking, spirometry, family history of asthma, shortness of breath at rest) reclassified the $Asthma_{CB}$ and $COPD_{CB}$ group patients into 3 new groups (the "K" groups in Fig 1). The intermediate group, that is, the $ACO_K$ group, was further subdivided into ACO-Asthma and ACO-COPD groups according to the patient's original diagnosis (as demonstrated in Fig 1). Of note, K-means clustering well identified groups, underlining the validity of current classifications. Those patients who were reclassified were mainly originally from the $Asthma_K$ group. Baseline parameters (age, skin prick tests, smoking parameters, hospitalizations before inclusion, airflow parameters, % reversibility, and baseline medications) were well in line with a disease gradient starting with the $Asthma_K$ group, intermediate values for the $ACO_K$ group, and ending with the $COPD_K$ group.

As concerns outcomes at the end of follow-up (ranging from a median [interquartile range] of 1.90 [0.45-3.54] years for $COPD_K$ group patients to 2.07 [0.48-3.99] years for $Asthma_K$ group patients), most outcome variables (as presented in Table I) were associated with significant group differences that were in line with the same gradient starting at the $Asthma_K$ group going toward the $COPD_K$ group, with ACO groups demonstrating intermediate values. These "gradient variables" included all measured airflow parameters (all $FEV_1$, forced vital capacity, $FEV_1$/forced vital capacity, and % reversibility variables) as well as the number of hospitalizations and emergency department admission frequencies during the last 12 months of follow-up. No significant differences (or trends) between groups that would support increased outcome severity in association with ACO groups were observed. There was a tendency for the $ACO_K$ group to have higher annualized change in $FEV_1$ (% variation) values as compared with the $COPD_K$ group. Intensive care unit admissions during the last 12 months of follow-up occurred among a significantly smaller percentage of $ACO_K$ group patients as compared with $COPD_K$ group patients. A similar tendency was found for ACO-Asthma group patients versus $Asthma_K$ group patients. None of the ACO-Asthma versus $Asthma_K$ or ACO-COPD versus $COPD_K$ comparisons, which minimize potential confounding due to initial diagnostic group, provided evidence of particularly severe disease in association with ACO. At a glance, reclassifying asthma as ACO was not detrimental in terms of prognosis, whereas changing COPD to ACO more often identified a subgroup with better outcomes.

Like all cohort studies, the present work is limited by its observational nature and will need to be reproduced by other teams for confirmation. Nevertheless, the large size and broad population covered provide a new and valuable insight into the ACO debate. As stated in the Global Initiative for Asthma/Global Initiative for Chronic Obstructive Lung Disease guidelines, ACO does not represent a single disease.[1] The intermediate position of patients with ACO on an asthma-to-COPD gradient supports and helps explain this plurality. Previous observations implying particularly severe disease in patients with ACO might be relevant only relative to patients with asthma, who are on the "less severe" side of the gradient. It also implies that the development of a treatment algorithm for patients with ACO is going to involve more than simply screening on clinical characteristics.

In conclusion, clustering patients according to the simultaneous presence of clinical signs for both asthma and COPD resulted in an "overlap" group whose outcomes and disease severity were generally intermediate on an asthma-to-COPD gradient, with poorer lung function and outcomes on the COPD side of the gradient. Overlap was not associated with particularly severe outcomes beyond this gradient, at least not in the relatively highly medicated, secondary-care COBRA cohort. We propose that although sharing overlap signs may not be sufficient to induce severe disease, perhaps the inverse is truer. It may be that patients with particularly severe obstructive lung disease are more likely to have complex phenotypes. In any case, using clinical characteristics to screen for patients with ACO may not have any utility in certain populations. Given the multifacetted nature of the spectrum, further effort should be focused on detailed patient profiling and personalized medicine.

*Arnaud Bourdin, MD, PhD*[a,b]
*Carey M. Suehs, PhD*[a,c]
*Gregory Marin, PhD*[c]
*Isabelle Vachier, PhD*[a]
*Eric Matzner-Lober, PhD*[d]
*Pascal Chanez, MD, PhD*[e,f]
*Nicolas Molinari, PhD*[b,c,g]
*on behalf of the COBRA Consortium**

From [a]the Department of Respiratory Diseases, Montpellier University Hospitals, Arnaud de Villeneuve Hospital, Montpellier Cedex, France; [b]INSERM U 1046, Arnaud de Villeneuve Hospital, Crastes de Paulet Building, Montpellier, France; [c]the Department of Medical Information, Montpellier University Hospitals, La Colombière Hospital, Montpellier Cedex, France; [d]Continuing Education ENSAE-ENSAI (CEPE), Rennes University 2, France; [e]the Department of Respiratory Diseases, Public Assistance - The Hospitals of Marseilles, Nord Hospital, Chemin des Bourrely, Marseille Cedex, France; [f]INSERM CNRS U1067 UMR7733, Aix Marseille University, Marseille, France; and [g]Alexander Grothendieck Institut at Montpellier, CNRS, Montpellier University, France. E-mail: a-bourdin@chu-montpellier.fr.

*The COBRA Consortium: Michel Aubier, Cindy Barnig, Patrick Berger, Jean-François Bervar, Raphaël Borie, Karine Botturi, Arnaud Bourdin, Arnaud Chambellan, Pascal Chanez, Cécile Chenivesse, Bruno Crestani, Frédéric De Blay, Gilles Devouassoux, Marie-Christine Dombret, Daniel Dusser, Gilles Garcia, Patrick Germaud, Pierre-Olivier Girodet, Philippe Godard, Jesus Gonzalez, Bruno Housset, Gérard Huchon, Marc Humbert, Annick Joly, Sylvie Leroy, Antoine Magnan, Bernard Maitre, Hervé Mal, Jean Pierre Mallet, Charles-Hugo Marquette, Roger Marthan, Nicolas Molinari, Megguy Morisset, Catherine Neukirch, Annaig Ozier, Anais Pipet, Marina Pretolani, Alain Proust, Anne Prudhomme, Chantal Raherison, Patrice Ray, Nicolas Roche, Arnaud Scherpereel, Thomas Similowski, Camille Taille, Gabriel Thabut, Isabelle Tillie, Anne Tsicopoulos, Isabelle Vachier, Muriel Varrin, Benoît Wallaert, and Lidwine Wemeau.

The COBRA cohort was financed by Inserm, CHU de Nîmes, LEGS POIX, GSK, AstraZeneka, and Chiesi. These funding sources played no part in the present analysis.

Disclosure of potential conflict of interest: A. Bourdin, as an advisory board member, congress participant, or study investigator, has previously received honoraria, grants, or other forms of support from AstraZeneca, GSK, Boeringher Ingelheim, Novartis, Teva, Regeneron, Chiesi, Actelion, Gilead, and Roche. None of the latter participated in or had any influence over the present analysis or manuscript. P. Chanez, as an

advisory board member, consultant, or lecturer, has previously received honoraria or grants from Boehringer Ingeheim, Almirall, Centocor, GSK, MSD, AstraZeneca, Novartis, Teva, Chiesi, Shering Plough, and Amu. None of the latter participated in or had any influence over the present analysis or manuscript. The rest of the authors declare that they have no relevant conflicts of interest.

## REFERENCES


1. Global Initiative for Chronic Obstructive Lung Diseases. GINA-GOLD. Diagnosis of diseases of chronic airflow limitation: asthma, COPD and asthma-COPD overlap syndrome (ACOS). 2015. Available at: http://ginasthma.org/asthma-copd-and-asthma-copd-overlap-syndrome-acos/. Accessed January 19, 2017.
2. de Marco R, Pesce G, Marcon A, Accordini S, Antonicelli L, Bugiani M, et al. The coexistence of asthma and chronic obstructive pulmonary disease (COPD): prevalence and risk factors in young, middle-aged and elderly people from the general population. PLoS One 2013;8:e62985.
3. Barrecheguren M, Esquinas C, Miravitlles M. The asthma-COPD overlap syndrome: a new entity? COPD Res Pract 2015. Available at: http://www.copdrp.com/content/1/1/8. Accessed January 19, 2017.
4. Chanez P, Vignola AM, O'Shaugnessy T, Enander I, Li D, Jeffery PK, et al. Corticosteroid reversibility in COPD is related to features of asthma. Am J Respir Crit Care Med 1997;155:1529-34.
5. Postma DS, Rabe KF. The asthma-COPD overlap syndrome. N Engl J Med 2015; 373:1241-9.
6. Pavord ID, Shaw DE, Gibson PG, Taylor DR. Inflammometry to assess airway diseases. Lancet Lond Engl 2008;372:1017-9.
7. Magnussen H, Watz H, Kirsten A, Decramer M, Dahl R, Calverley PMA, et al. Stepwise withdrawal of inhaled corticosteroids in COPD patients receiving dual bronchodilation: WISDOM study design and rationale. Respir Med 2014;108: 593-9.
8. Hahn D. Distinct clinical phenotypes of airways disease: a primary-care clinician perspective. Eur Respir J 2010;35:459, author reply 459-60.