PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Which patients with chronic obstructive pulmonary disease benefit from the addition of an inhaled corticosteroid to their bronchodilator? A cluster analysis
AUTHORS	DiSantostefano, Rachael; Li, Hao; Rubin, David; Stempel, David

VERSION 1 - REVIEW

REVIEWER	Mapel, Douglas Lovelace Clinic Foundation I have previously worked as a consultant for and received research funding from GlaxoSmithKline.
REVIEW RETURNED	02-Sep-2012

THE STUDY	There are no supplemental documents
GENERAL COMMENTS	Overall this is an excellent project and it is well presented. However, there are several areas of the manuscript that need improvement. Rather than tediously listing the recommended changes, I converted the PDF to a Word file, and inserted my comments and recommended changes using the "track changes" feature

REVIEWER	James F DonohueMD Universityof North Carolina School of Medicne USA Conflict Member Global Steering committee for GSK Zephyr clinical trials in COPD and advisory board
REVIEW RETURNED	02-Oct-2012

GENERAL COMMENTS	A cluster analysis without an "a priori" hypothesis was applied to a large database from 2 pivotal stuies comparing sfc to sal.These 2 studies were used for regulatory approval of SFSC for exacerbations in COPD. 1) Although the numbers are small , is there any signal that the addition of an ICS confers any mortality advantage? These were rather long in duration studies and if there is a cardiac benefit, mortality might be better as seen in TORCH. 2)A dicotomous cut point such as the ATS standard is, as you noted, at 12%. Patients change reversibility status over the course of a long study. Was the reversibility testing based on 1 or multiple measures 3)Comment Line 110; wasn't Advair250/50 the SFC tested in the US studies, not Seretide? 4)Line 187 since the majority are preselected and reported a moderate and not a severe exacerbation in the 12 months prior to study:, any idea if the cluster analysis derived groups would be similar in other COPD populations such as those with <2 or more or

	no exacerbations in the year earlier? 5)As for comorbidity , group 1 had used diuretics. What were the exclusion criteria for cardiac disease in the 2 studies used? Eg recent mi, unstable angina, uncontrolled hypertension or chf? 6)Table 4 are the P values correct? For diuretics there is a difference of100 vs 0 and a P,0.001 the same as antithrombotics with 50.7,32, and 40. It just seems strange

REVIEWER	Wouters, Emiel University Hospital Maastricht, Department of Respiratory Medicine
REVIEW RETURNED	24-Oct-2012

REPORTING & ETHICS	The manuscript describes a post-hoc analysis of data obtained in 3 studies conducted in North America. The authors refer to these papers.
GENERAL COMMENTS	The paper describes a cluster analysis of a pooled chort of COPD patients receiving salmeterol alone or in combination with SFC for 1 year in order to identify clusters of patients who could benefit most from SFC. The authors report the identification of 3 clusters of patients who might benefit from inhaled steroids. Following remarks need to be addressed: 1. Selection bias. The authors have used data of 3 studies. Based on the data summarised in table 2 the included sudy patients had severe COPD and 23 % of these patients were hospitalised at least once in the year before inclusion in the study. Co-morbidity is only assessed based on the medications used. Particularly for this group of severe COPD patients a better characterisation of co-morbidities will be necessary. 2. Reversibility criterium: The authors discuss the limitations of this stratification criterium in the discussion. It can be concluded that reversibility is not a stable characteristic in COPD patients. Furthermore, the authors have used FEV1 reversibility solely as a perecentage of the pre-bronchodilator value. As expected the so-called reversible group in this study is the group with the lowest % predicted FEV1. 3. Diueric users cluster. Although no information is available about the indication of prescription of these drugs, the authors suggest possible mechanisms in order to make links between inhaled steroids and cardiovascular co-morbidity. These hypotheses are interesting, but are a probable overinterpretation of the current findings. Furthermore, as illustrated by the reported study of Garcia-Aymerich hospitalisations and exacerbations in general reflect a heterogeneity of underlying pathology.

REVIEWER	Leonardo M. Fabbri, MD Professor and Director Deparftment of Oncology Haematology and Respiratory Diseases University of Modena and Reggio Emilia, Italy Albeit consult and granted by most pharmas in the field of asthma and COPD, I don't perceive any conflict of interest
REVIEW RETURNED	20-Jan-2013

THE STUDY	There is one reference of a paper just to be accepted in the

	AJRCCM that is particulalry relevant to this paper and NEED to be cited and discussed. At this stage I can only tell you that describes 2 clusters that are very relevant for your paper, ie the "Cardiovascular" and the "Metabolic". I believe you can work on the attached abstract to revise your manuscript (CONFIDENTIALITY MANDATORY) , and I'll send you the full MS as soon as I am allowed to. Clusters of objectified comorbidities and systemic inflammation in patients with chronic obstructive pulmonary disease. RATIONALE: Comorbidities contribute to disease severity in patients with COPD. Multiple comorbidities have been studied separately and mostly on self-reported basis in these patients. The co-existence of objectified comorbidities and the role of low-grade systemic inflammation in their pathophysiology in COPD remains to be elucidated. OBJECTIVES: To objectify 13 clinically important comorbidities, to cluster patients based on their comorbidity-profile and to characterize the clusters in terms of clinical outcome and systemic inflammation. METHODS: 213 patients with COPD (FEV1: 51.2±16.9 % predicted, men: 59%, age: 63.6±7.0 years) were prospectively included. Inflammatory blood biomarkers were determined in all patients. Comorbidities were defined as abnormal values based on well-known cut-offs identified in the peer-reviewed English literature. Self-organizing maps (SOMs) were used to create an ordered representation of the comorbidity data. Based on the created SOMs, clusters have been generated. MEASUREMENTS AND MAIN RESULTS: 97.7% of all patients had ≥1 objectified comorbidity and 53.5% had ≥4 comorbidities. Five different clusters were identified: 1. “Less comorbidity” 2. “Cardiovascular” 3. “Cachectic” 4. “Metabolic” 5. “Psychological” cluster. Comorbidity clusters differed in clinical characteristics but were comparable with respect to disease severity. An increased inflammatory state was observed in the ‘metabolic’ cluster of comorbidities. CONCLUSION: Multimorbidity is common in COPD and different comorbidity clusters can be identified. Low-grade systemic inflammation occurs mostly in the metabolic comorbidity cluster, but is comparable among other comorbidity clusters.

	Statistical analysis must be reviewed by a qualified statistician
RESULTS & CONCLUSIONS	The paper can be improved. Table 3, contaning th key results showing differences in the e clusters should be tasformed or also presented as a figure emphysizing the different effect of SFC over S in the 3 clusters. Discussion should be expanded to include the complex phenotype (It seems to me that most Cluster one have Metabolic syndrome, as they are treated with multiple agent). Also, considere the importance of kidney function for exacerbations (eg Frigola-Capell E, Comin-Colet J, Davins-Miralles J, Gich-Saladich I, Wensing M, Verdú-Rotellar JM. Trends and predictors of hospitalization, readmissions and length of stay in ambulatory patients with heart failure. Rev Clin Esp. 2012 Dec 21.) Two relevant papers to quote are 1) Vanfleteren LE, Franssen FM, Uszko-Lencer NH, Spruit MA, Celis M, Gorgels AP, Wouters EF. Frequency and relevance of ischemic electrocardiographic findings in patients with chronic obstructive pulmonary disease. The American journal of cardiology 2011;108:1669-1674. 2) Barnett K, Mercer SW, Norbury M, Watt G, Wyke S, Guthrie B. Epidemiology of multimorbidity and implications for health care, research, and medical education: A crosssectional study. Lancet 2012.
GENERAL COMMENTS	I would recommend the Authors, who I understand and mainly young scientists, to discuss their paper with some expert pneumologisit, cardiologist, and nephrologist to expand the discussion on their interesting results

REVIEWER	Stelios Loukides University of Athens Medical School Respiratory Medicine Dept Attiko University Hospital Athens Greece
REVIEW RETURNED	24-Jan-2013

THE STUDY	Some issues need clarification mainly how asthma was excluded and when the assesment of reversibility was performed.
GENERAL COMMENTS	I read with interest the current study of DiSantostefano et al. The present study aimed to determine whether cluster analysis which was conducted using data pooled from two clinical trials, could identify patients who benefit from combination treatment with ICS/LABA compared to LABA alone. The study sounds interesting and is in accordance with the latest definition of COPD where it was clearly stated that COPD is a heterogeneous disease. I have some concerns which are mainly attributed to some methodological issues which need clarification before taking a final decision. Specific comments Since the assessment of reversibility is a major characteristic of asthma the authors must comment how they exclude asthmatic subjects from their study. A more detailed methodology is needed since two of the cluster analysis groups are based on reversibility, a characteristic of asthma pathophysiology. As the study consists of pool data from 2 clinical studies it is important for the authors to clarify the time period of the reversibility assessment in relation to study design. At the beginning of the trial, during the trial or at the end. This is somehow important since many confounding factors which are related to different time periods might influence the presented values.

	It is well known that reversibility is not considered as a repeatable characteristic. Furthermore does not identify a group with a different response to treatment. How the authors overcome the already known low repeatability of the reversibility test in patients with COPD? In the discussion section the second paragraph is consisted of many speculations in regard to a possible association between CVD, COPD and the use of ICS. These speculations are not supported either by the current data or/and by a previous one. According to the presented results patients from Cluster 1 benefit from the use of diuretics. At the same time those patients presented with a significant reversibility after BD. If we consider that diuretics might influence the underlying inflammation/hyper-reactivity in asthmatics and combine this evidence with what the authors observed in the current study then the Cluster 1 patients are somehow a complicated group since they share 2 characteristics which are more closely to asthma than COPD. This might explain the difference in response to combination treatment.

REVIEWER	Andriana I Papaioannou, MD. Respiratory Medicine Specialist 3rd Respiratory Medicine Department Sismanogleio General Hospital Athens, Greece I declare that I have no conflict of interest related to the present study
REVIEW RETURNED	27-Jan-2013

GENERAL COMMENTS	The subject of the study is very interesting and provides important information which can be used in clinical practice. I think that the manuscript is well written and provide a clear message. I have some minor comments to make The authors are discussing the differences on the use of medication for comorbid diseases in the three clusters emphasizing mainly in the differences in cardiovascular medication (evidence of the presence of cardiovascular diseases). However, they are not discussing the use of antihistamines. Patients in cluster 1 are receiving antihistamines in a higher percentage compared with clusters 2 and 3 and this difference is statistically significant. ($p=0.0062$). Usually, antihistamines are used for allergic diseases such as allergic rhinitis or hay fever which are very often related with asthma. Although it is mentioned in the methods section that the presence of asthma was excluded from the study participants, I believe that the authors should discuss the use of such medication by the study subjects and its probable relation to the benefit of the use of ICS. They should also discuss this as a potential limitation in this study.

VERSION 1 – AUTHOR RESPONSE

Reviewer & Comment Revision
Reviewer: Douglas Mapel, Lovelace Clinic Foundation I have previously worked as a consultant for and received research funding from GlaxoSmithKline.

I converted the PDF to a Word file, and inserted my comments and recommended changes using the "track changes" feature Thank you for your careful review of the manuscript. We have made most of the stylistic changes you have suggested and clarified questions using tracked changes.
Reviewer: James F DonohueMD
University of North Carolina School of Medicine USA

1) Although the numbers are small, is there any signal that the addition of an ICS confers any mortality advantage? These were rather long in duration studies and if there is a cardiac benefit, mortality might be better as seen in TORCH.

2) A dichotomous cut point such as the ATS standard is, as you noted, at 12%. Patients change reversibility status over the course of a long study. Was the reversibility testing based on 1 or multiple measures

3)Comment Line 110; wasn't Advair250/50 the SFC tested in the US studies, not Seretide?

4)Line 187 since the majority are preselected and reported a moderate and not a severe exacerbation in the 12 months prior to study:, any idea if the cluster analysis derived groups would be similar in other COPD populations such as those with <2 or more or no exacerbations in the year earlier?

5)As for co morbidity , group 1 had used diuretics. What were the exclusion criteria for cardiac disease in the 2 studies used? Eg recent mi, unstable angina, uncontrolled hypertension or chf?

6)Table 4 are the P values correct? For diuretics there is a difference of100 vs. 0 and a P,0.001 the same as antithrombotics with 50.7,32, and 40. It just seems strange
Thank you for your observations during review. Some of these comments resulted in changes to the manuscript and others did not. Regardless, the answers to your questions appear below.

1) No changes to manuscript. One year is insufficient to look at mortality, and number of deaths is too small to draw any conclusions about differences between the groups. There were 6 vs. 4 deaths for

SAL vs. SFC (Anzueto, 2009) and 6 vs. 3 deaths for SAL vs. SFC (Ferguson, 2008). Our endpoint was strictly exacerbation reduction for this analysis.

2) Clarifying comments in methods and discussion added. Reversibility was based on one time point (baseline following 4-week ADVAIR run in), and this limitation is addressed in the discussion. We acknowledge in our discussion section that reversibility can change / have variation, but that increased reversibility is related to greater improvements in lung function, exacerbation, etc. as has been shown by others.

3) These studies were conducted in the US and Canada. The manuscript has been revised to clarify location and the medication name is now ADVAIR/SERETIDE to be consistent with Anzueto and Ferguson publications.

4) We do not have data to support cluster analysis in non-exacerbator population. There are limits to the generalizability – namely, all people here had a history of exacerbation as stated. This was also added to the discussion.

5) We have added to the methods / study description. Subjects were excluded from the study if they had historical or current evidence of clinically significant uncontrolled disease including, that would put the safety of the subject at risk through study participation, or which would affect the efficacy analysis if the disease/condition exacerbated during the study.
• clinically significant cardiac arrhythmias
• uncontrolled/unstable congestive heart failure
• uncontrolled hypertension
• unstable angina
6) We agree that this looked suspicious and have double checked the p-values. These are correct. The large sample size explains why this is significant, and it is a bit awkward to calculate a p-value comparing “all” vs. “none”, It is of course, significant.
Reviewer: Emiel Wouters
University Hospital Maastricht, Department of Respiratory Medicine

1. Selection bias. The authors have used data of 3 studies. Based on the data summarized in table 2 the included study patients had severe COPD and 23 % of these patients were hospitalized at least once in the year before inclusion in the study. Co-morbidity is only assessed based on the medications used. Particularly for this group of severe COPD patients a better characterization of co-morbidities will be necessary.

2. Reversibility criterium: The authors discuss the limitations of this stratification criterium in the discussion. It can be concluded that reversibility is not a stable characteristic in COPD patients.

Furthermore, the authors have used FEV1 reversibility solely as a percentage of the pre-bronchodilator value. As expected the so-called reversible group in this study is the group with the lowest % predicted FEV1.

3. Diuretic users cluster. Although no information is available about the indication of prescription of these drugs, the authors suggest possible mechanisms in order to make links between inhaled steroids and cardiovascular co-morbidity. These hypotheses are interesting, but are a probable over interpretation of the current findings. Furthermore, as illustrated by the reported study of Garcia-Aymerich hospitalizations and exacerbations in general reflect a heterogeneity of underlying pathology.
Thank you for your comments on the manuscript. Some comments on the original study (lack of co-morbidity assessment) cannot be addressed in our analyses as it is secondary data analysis. We address to extent possible in the methods and discussion, including cting your recent manuscripts on co-morbidities (in press) and ECG anomalies in COPD. We hope you find the revised discussion adequate.

1. We have added to our discussion and cited your recent paper on co-morbities and phenotypes in COPD. (in press, Am J Respir Cr Care Med, 2013). As we noted in the discussion section, this cluster analysis was limited to the information collected on the CRF at baseline. Co-morbidities were collected a the body system level only, Medications were determined based on indication when there was more than one ATC category (see clarification in Methods). We agree that this is imperfect characterization of co-morbities as not all co-morbities would be treated or require a medication (and COPD is complex). Nevertheless, medication use with ATC category based on medications is reasonable. This is secondary data and we cannot characterize further. Re: selection bias. Recall also that this is an exacerbator population and generalizability is limited to that group.

2.We have added the effect of reversibility stratum (>12% and 200mL) to the manuscript in methods and discussion, as it was adjusted for in the analysis. We take your points on the limitations of using only 12% reversibility and reversibility in general. The data-driven algorithm chose reversibility, which maximizes treatment differences. The literature supports this differential treatment response despite well-documented limitations (more severe patients in reversible group, taken at baseline, etc). Of note, ~60% of patients in the 12% reversible group also had >200mL improvement in lung function. The >12% cutpoint and limitations is sufficiently addressed in the discussion.

3. We have added additional discussion about the heterogeneity of COPD in our discussion section including your recent paper and a few others suggested by Fabbri. We have also added a reference from the TORCHs study (Calverly, 2010), which showed the potential benefit of ICS on cardiovascular outcomes. We already cite Garcia-Aymerich results in our discussion of the findings . We believe that this is a thorough, balanced discussion.
Reviewer: Leonardo M. Fabbri, MD
Professor and Director
Department of Oncology Haematology and Respiratory Diseases University of Modena and Reggio Emilia, Italy

The paper can be improved. Table 3, containing the key results showing differences in the e clusters should be transformed or also presented as a figure emphasizing the different effect of SFC over S in

the 3 clusters.

Discussion should be expanded to include the complex phenotype (It seems to me that most Cluster one have Metabolic syndrome, as they are treated with multiple agent). Also, consider the importance of kidney function for exacerbations (e.g. Frigola-Capell E, Comin-Colet J, Davins-Miralles J, Gich-Saladich I, Wensing M, Verdú-Rotellar JM. Trends and predictors of hospitalization, readmissions and length of stay in ambulatory patients with heart failure. Rev Clin Esp. 2012 Dec 21.)

Two relevant papers to quote are 1) Vanfleteren LE, Franssen FM, Uszko-Lencer NH, Spruit MA, Celis M, Gorgels AP, Wouters EF. Frequency and relevance of ischemic electrocardiographic findings in patients with chronic obstructive pulmonary disease. The American journal of cardiology 2011;108:1669-1674. 2) Barnett K, Mercer SW, Norbury M, Watt G, Wyke S, Guthrie B. Epidemiology of multimorbidity and implications for health care, research, and medical education: A cross-sectional study. Lancet 2012.

I would recommend the Authors, who I understand and mainly young scientists, to discuss their paper with some expert pneumologist, cardiologist, and nephrologist to expand the discussion on their interesting results Thank you so much for your review and suggestions of references and additional discussion points. We have incorporated this into our discussion as appropriate.

We agree that the graphic tree and exacerbation results would be best combined and have done so in the cluster analysis figure.

We have added the majority of these references to the discussion and consulted as appropriate with experts in the field (co-authors and otherwise) for additional references /thoughts. We have also added to TORCH reference (Calverly, 2010) noting the potential effect of ICS on cardiovascular outcomes.

Reviewer: Stelios Loukides
University of Athens Medical School
Respiratory Medicine Dept Attiko University Hospital
Athens , Greece

Some issues need clarification mainly how asthma was excluded and when the assessment of reversibility was performed.

Specific comments
Since the assessment of reversibility is a major characteristic of asthma the authors must comment how they exclude asthmatic subjects from their study. A more detailed methodology is needed since two of the cluster analysis groups are based on reversibility, a characteristic of asthma pathophysiology.
As the study consists of pool data from 2 clinical studies it is important for the authors to clarify the time period of the reversibility assessment in relation to study design. At the beginning of the trial, during the trial or at the end. This is somehow important since many confounding factors which are related to different time periods might influence the presented values.

It is well known that reversibility is not considered as a repeatable characteristic. Furthermore does not identify a group with a different response to treatment. How the authors overcome the already known low repeatability of the reversibility test in patients with COPD?

In the discussion section the second paragraph is consisted of many speculations in regard to a possible association between CVD, COPD and the use of ICS. These speculations are not supported either by the current data or/and by a previous one.
According to the presented results patients from Cluster 1 benefit from the use of diuretics. At the same time those patients presented with a significant reversibility after BD. If we consider that diuretics might influence the underlying inflammation/hyper-reactivity in asthmatics and combine this evidence with what the authors observed in the current study then the Cluster 1 patients are somehow a complicated group since they share 2 characteristics which are more closely to asthma than COPD. This might explain the difference in response to combination treatment.

Thank you for your comments, particularly on clarification needed regarding asthma and reversibility assessment in the original trials. We agree that the potential for misdiagnosis and mixed disease present a concern in practice and can relate to outcomes. Further, we agree with comments on reversibility and address further in the discussion following your comments. We have added reference to the Dutch hypothesis and potential for mixed disease / overlap.

Patients with a current diagnosis of asthma were excluded based on ATS standards for diagnosis at

the time of the studies. We add this clarification and reference to the methods and discussion – as well as the potential for this study to include mixed disease . As you are aware, the diagnosis of asthma and COPD can be a bit tricky. Patients with COPD can be reversible, and the characteristics of this population are similar to those of other studies. As noted by the ATS publication that was used at the time of the studies -- American Thoracic Society Standards for diagnosis and care of patients with chronic obstructive pulmonary disease and asthma. Am Rev Respir Dis. 1987;136:225–44, "Patients with COPD may have significant reversibility after treatment and patients with asthma may develop airflow obstruction with little to no reversibility. The separation of these overlap patients is often arbitrary and difficult…."

Reversibility
We have clarified timing of reversibility assessment in the methods section. Reversibility was assessed after the run-in period and prior to randomization. Prior to randomization, the subject self-administered 4 puffs (360mcg) of albuterol MDI. Reversibility was determined based on pre-albuterol lung fuction.

We have added the significance of reversibility stratum (>12% and 200mL) to our paper in results, and mention again in discussion. While reversibility has issues of repeatability, etc. the results support what has been noted by others. Patients with more reversibility generally have greater response to treatment. This has been cited by others, and we continue to adjust for reversibility in development programs and secondary data analysis. Our slightly revised discussion section on this point should address the limitations sufficiently.

CVD/COPD/ICS
Indeed, there is evidence in the literature that there are inter-relationships between COPD, CVD and ICS. We have added to Calverly 2010 TORCH paper published in Thorax to the reference section, including some additional mechanistic papers. This relationship has also been seen in asthma in the Nurses' Health Study (Camargo, 2008). There is some evidence that ICS has an effect on cardiovascular outcomes and/or overall mortality.
Reviewer: Andriana I Papaioannou, MD.
Respiratory Medicine Specialist
3rd Respiratory Medicine Department
Sismanogleio General Hospital
Athens, Greece

The authors are discussing the differences on the use of medication for comorbid diseases in the three clusters emphasizing mainly in the differences in cardiovascular medication (evidence of the presence of cardiovascular diseases). However, they are not discussing the use of antihistamines. Patients in cluster 1 are receiving antihistamines in a higher percentage compared with clusters 2 and 3 and this difference is statistically significant. (p=0.0062). Usually, antihistamines are used for allergic diseases such as allergic rhinitis or hay fever which are very often related with asthma. Although it is mentioned in the methods section that the presence of asthma was excluded from the study participants, I believe that the authors should discuss the use of such medication by the study subjects and its probable relation to the benefit of the use of ICS. They should also discuss this as a potential limitation in this study.

Thank you for your comments, particularly on the antihistamines and asthma. While allergic rhinitis is

a co-morbidity frequent in asthma (and therefore subsequent antihistamine use could be expected), at least some literature suggests that allergic rhinitis is more frequent in COPD than those with normal lung function. For example, Lindberg A, Larsson LG, Rönmark E, Lundbäck B. Co-morbidity in mild-to-moderate COPD: comparison to normal and restrictive lung function. COPD. 2011 Dec;8(6):421-8.

We have added information about the potential for overlap in asthma and COPD in the discussion.

VERSION 2 – REVIEW

REVIEWER	Leonardo M. Fabbri, MD Professor of Respiratory Medicine and Director Department of Oncology Haematology and Respiratory Diseases University of Modena & Reggio Emilia Via del Pozzo 71, I-41124 MODENA
REVIEW RETURNED	11-Mar-2013

- The reviewer completed the checklist but made no further comments.

REVIEWER	Stelios Loukides Ass Professor University of Athens Medical School No competing interests
REVIEW RETURNED	16-Mar-2013

THE STUDY	I still have some concerns in regard to what we call overlap syndrome. However the authors clearly comment on this in the discussion section