

COPD smokers who switched to e-cigarettes: health outcomes at 5-year follow up

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Abstract

Background and Aims: The long-term health effects of the use of electronic cigarettes (ECs) in patients with chronic obstructive pulmonary disease (COPD) are largely unexplored. We present findings from a 5-year prospective assessment of respiratory parameters in a cohort of COPD patients who substantially reduced conventional smoking or achieved abstinence by switching to ECs.

Methods: Patients were evaluated prospectively for their measurements of respiratory exacerbations, spirometric indices, quality of life using the COPD assessment tool (CAT), 6-min walk distance (6MWD), as well as conventional cigarette consumption. Baseline measurements prior to switching to EC use were compared with follow-up visits at 12-, 24-, 48- and 60-months. Age- and sex-matched COPD patients reporting to be regular smokers (not using ECs) were the reference group for the analysis.

Results: Complete data were available from 39 patients. Those in the EC user group achieved a marked decline in cigarette smoking or abstinence. COPD EC users had a significant diminution in COPD exacerbations; with the mean (\pm SD) exacerbation rate falling from 2.3 (\pm 0.9) at baseline to 1.1 (\pm 1.0) at 5 years ($p < 0.001$), whereas no significant changes were observed in the control group.

Significant and constant improvements in lung function, CAT scores and 6MWD were reported in the EC user group over the 5-year observation period compared with the reference group ($p < 0.05$).

Conclusion: The present study suggests that EC use may ameliorate objective and subjective COPD outcomes, and that the benefits gained appear to persist long term. EC use for abstinence and smoking reduction may ameliorate some of the harm resulting from tobacco smoking in COPD patients.

Keywords: COPD, electronic cigarette, smoking cessation, tobacco harm reduction

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Introduction

Tobacco smoking is a major cause of preventable premature mortality worldwide, caused primarily by lung cancer, cardiovascular disease and chronic obstructive pulmonary disease (COPD).^{1,2}

COPD is a condition epitomised by ongoing inflammation and remodelling of the airways, culminating in respiratory symptoms, progressive lung function deterioration, respiratory failure and death.³⁻⁵ Long-term exposure to a variety of smoke intoxicants is assumed to be the cause of

this distinct airway inflammatory response.^{6,7} Abstinence from conventional tobacco use is the only reported evidence-based strategy that improves the prognosis for COPD.^{8,9} Besides, quitting has been shown to attenuate the decline in lung function and to enhance overall health status.¹⁰⁻¹² In addition, smoking cessation attenuates the risk of developing other tobacco-related illnesses.²

While addressing smoking cessation is a priority for smokers with COPD, these patients experience

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high failure rates in their quit attempts.^{13,14} Licensed quitting therapies [i.e. nicotine replacement therapy (NRT), bupropion and varenicline] appear to have only fairly small or variable effects on sustained cessation in patients with COPD who smoke.^{15–17} Patients experience difficulty in completely ceasing nicotine use, and may require prolonged treatment and/or sustained nicotine use to attain continued abstinence from smoking. Obviously, a better understanding of predictors of quitting attempts and quitting success in smoking cessation could help routine clinical consultation and may improve outcomes,^{18,19} though this knowledge is lacking for COPD patients who smoke. An alternative for patients with COPD who are having difficulty quitting is one of the pragmatic strategies of tobacco harm reduction (THR), substituting combustion-free nicotine delivery strategies [i.e. electronic cigarettes (ECs)] for cigarette smoking to achieve significant health gains. The harm reduction potential mechanism is to reduce combustible tobacco chemicals that are responsible for the devastating aetiology of tobacco-related morbidity and mortality. As pulmonologists, we must be cognisant of the damage caused by tobacco smoke, and be aware of the limited negative health effects of nicotine when consumed at low concentrations.²⁰ Of course, the use of electronic cigarettes is a strategy for treating patients who smoke, and not an endorsement of its use by those who do not smoke and youth, who should be discouraged from consuming nicotine in any form.

ECs have been gaining acceptance by smokers for decreasing their cigarette consumption, saving money compared with cigarettes, and seeking a much less harmful alternative to smoking that allows them to have a 'smoking encounter without smoking'.^{21–24} The advantage of ECs is that they do not contain tobacco, nor do they operate with the combustion temperatures that generate smoke toxicants. However, they are not completely safe, though in routine conditions of use, laboratory testing has demonstrated that the amount of chemical constituents in emissions from EC aerosols is considerably lower than smoking conventional cigarettes.^{23,25,26} The significant reductions in toxic exposures from substituting EC for conventional cigarette consumption is expected to bring about substantial health gains. ECs as a THR strategy may save more lives more swiftly than possible previously. However, the odds of completely abstaining from conventional cigarettes for EC users are

variable.^{27–29} Most studies suggesting low quit rates for ECs have investigated earlier poor quality vaping products with inadequate nicotine delivery profile.^{30,31} On the contrary, more recent (and better designed) randomised controlled trials (RCTs) using high-quality vaping products are now showing remarkable quit rates – even compared with NRTs.^{32,33} Nevertheless, data on the risk–benefit ratio of EC use in COPD smokers is limited.

United States (US) surveys from 2014 and 2015 indicate that former smokers with COPD may be using ECs to avoid relapse.³⁴ A large cross-sectional survey of 1190 COPD EC users found that 75.7% stated that they had benefits in respiratory symptoms after switching, and only 0.8% reported a worsening of symptoms.²⁴

In a retrospective analyses of smokers with COPD who had been 'vaping' (the acting of inhaling from ECs) routinely for at least 24 months reported no negative effects.³⁵ Furthermore, the same study found a marked reduction in yearly exacerbations of COPD and overall health status improvements assessed with the COPD assessment tool (CAT) and physical activity assessed using the 6-min walk distance test (6MWT). A subsequent prospective follow up at 3 years of the same cohort of COPD patients using ECs regularly, by the same group of researchers, confirmed that these objective and subjective benefits persist long term.³⁶

Nonetheless, more knowledge on the long-term health impacts of routine 'vaping' in this patient population is essential in order to provide sound advice to COPD patients who cannot quit or who are not interested in quitting.

The aim of the current study was to validate and expand these initial findings by reporting objective and subjective health parameters of subsequent follow ups in the same cohort of COPD patients who continued to vape daily for up to 5 years. Findings were compared with age- and sex-matched COPD patients who smoked regularly.

Methods

Patient population

A review of medical records of COPD patients followed up routinely in outpatient clinics of four Italian hospitals was conducted. A diagnosis of

COPD was made in accordance to the criteria set out by the Global initiative for Chronic Obstructive Lung Disease (GOLD).³⁷ Regarding pharmacological treatment, patients were taking various combinations of inhaled corticosteroids with bronchodilators (including long-acting β_2 agonists and long-acting anti-cholinergics, individually or in combination) as recommended by GOLD guidelines.

Over a period of approximately 6 years (September 2013–October 2019), data were extracted from patients' medical records from baseline and follow-up visits. Details of these patients' population have been described previously.^{35,36} In brief, eligible COPD patients reported regular daily EC use at their scheduled outpatients appointments. They were using their own vaping product as part of their choice in embracing a new tobacco-smoke-free lifestyle. Those who reported daily ECs use on at least two successive outpatients appointments (no less than 12 months apart) were included in the study (EC users group). The baseline visit was considered as the clinic visit prior to the first of the two consecutive follow-up visits when the patients were not using ECs. EC devices and corresponding nicotine e-liquid strengths were noted. Datasets from age- and sex-matched COPD patients who regularly smoked conventional cigarettes (and not using ECs) over the same observation period and attending the same clinics were included as a reference group (cigarette smokers group). Outpatients in this study group were not keen to stop smoking, in spite of brief cessation advice routinely offered at every contact. The study objectives and design were not known to the hospital staff; data extraction was carried out from patients' medical record.

In the current study, data analyses was conducted for follow-up visits that were timed at approximately 12, 24, 48 and 60 months from baseline. Approval for the study was acquired by the coordinating centre's ethics review board at 'Policlinico-Vittorio Emanuele Hospitals' (approval number 647 on 14 May 2013) and each patient provided written informed consent.

Study design and study assessments

Study design and assessments of the study have been detailed previously.^{35,36} In brief, a review of patients' clinical notes at baseline (when COPD

patients in the EC group first reported EC use), at 12 ± 1.5 (follow-up visit 1; F/up1) and at 24 ± 2.5 (follow-up visit 2; F/up2) months to obtain data about (i) their respiratory symptoms, (ii) smoking status [biochemically confirmed by exhaled breath carbon monoxide (eCO)], cigarette consumption per day (cig/day), as well as EC use, (iii) the annual number of severe COPD exacerbations, (iv) lung function parameters post-bronchodilator [forced expiratory flow in 1 s (FEV1); forced vital capacity (FVC); expiratory ratio (FEV1/FVC)]; (v) CAT scores and (vi) 6MWD.

In the current study, COPD EC user and COPD control groups were evaluated prospectively for changes in the same objective and subjective parameters at follow-up visits at 48 ± 3 months (follow-up visit 3; F/up3) and 60 ± 3 months (follow-up visit 4; F/up4).

Additionally, we also assessed variations in the relative proportion of COPD GOLD stages over the 5-year study period.

For the purposes of the study severe exacerbations were defined as changes in the patients' pulmonary symptoms necessitating antibiotics and/or oral corticosteroids *via* the primary care physician, emergency department attendance and/or admission to hospital. Nebulised therapy may have been administered to attain improvements in the patients' condition for the latter two instances.

The CAT is a health status validated questionnaire used in COPD patients. A two unit difference is considered a minimal clinical important difference in patients' symptomatology.^{38,39}

The 6MWD is an assessment of patients' overall ability to conduct everyday activities. This test was offered only to patients who were agreeable and physically able to complete the test.⁴⁰

Smoking/vaping status

Abstinence from smoking was defined as a complete self-reported termination of conventional smoking (not even a puff) from the prior study visit; which was confirmed biochemically at F/up3 and 4 by eCO levels of ≤ 7 ppm.

COPD EC users who completely ceased conventional tobacco smoking were defined as quitters

(single users), and patients who reported using ECs in combination with conventional tobacco smoking were defined as dual users.

Data management and statistical analyses

Demographic and clinical data for all patients recruited onto the study were recorded in their case notes at the time of the outpatient visit. Patient data were extracted for the current study from case records onto an electronic spreadsheet before statistical computation. Of note, the investigators engaged in the study analyses were not involved in the medical management of the study participants or in the extraction of the data from the case records.

In the current analyses patient parameters are presented as means [\pm standard deviation (SD)] and medians [interquartile range (IQR)] for parametric and non-parametric data, respectively. Data from single and dual users were also extracted for secondary analyses. Statistical analyses using the student's *t*-test and Wilcoxon-signed rank test were conducted for parametric or non-parametric data, respectively. Within-group dual and single users had similar statistical analyses conducted from baseline, and these analyses

were excluded in the overall analyses. Analysis of repeated measures with Bonferroni correction between the two study groups was conducted for repeated parameter measurements over the 5-year period. A two-tailed *p* value of less than 0.05 was considered to signify statistical significance. All statistical evaluations were performed with the Statistical Package for Social Science (SPSS for Windows, version 20.0, Chicago, IL, USA).

Results

Patient characteristics

At 60 months, complete datasets were available for 39 COPD patients (33 male, 6 female) of the 48 individuals enrolled at baseline, 19 in the COPD smokers group and 20 in the COPD EC user group. Datasets from four patients (16.7%) were excluded in the EC user group due to relapse to cigarette smoking or quitting vaping. In the COPD smokers group, dataset from five patients were excluded or unavailable because two quit smoking (8.3%), one moved to another city, one developed a malignancy and was transferred to another clinic and one died. The baseline demographics, parameters assessed and COPD GOLD staging are outlined in Table 1. There were no statistical

Table 1. Baseline demographics of participants who completed 60-months of evaluation (before switching to ECs).

	COPD controls (<i>n</i> = 19)	COPD EC users (<i>n</i> = 20)	Baseline <i>p</i> -value between groups
Age [‡]	65 (\pm 5.7)	66.9 (\pm 5.8)	0.338
Sex	16M, 3F	17M, 3F	–
COPD GOLD Staging			
Stage 1	2	2	–
Stage 2	5	6	–
Stage 3	8	9	–
Stage 4	4	3	–
post-BD FEV1* (l)	1.46 (1.19, 1.67)	1.25 (0.98, 1.78)	0.508
post-BD FVC* (l)	2.31 (2.10, 2.54)	2.49 (2.08, 2.65)	0.785
%FEV1/FVC [‡]	60.9 (\pm 6.8)	55.8 (\pm 10.8)	0.088
Pack years of smoking [‡]	49.7 (\pm 6.8)	52.8 (\pm 11.0)	0.304

(Continued)

Table 1. (Continued)

	COPD controls (n = 19)	COPD EC users (n = 20)	Baseline p-value between groups
Cig/day [‡]	20.2 (±2.9)	22.1 (±4.7)	0.140
FTND	5.8 (±3.1)	5.9 (±3.3)	0.355
CAT score*	20 (17, 24.5)	21 (17, 25.3)	0.714
COPD exacerbations [‡]	2 (±1.1)	2.3 (±0.9)	0.350
6MWD* (m)	285 (219.3, 361.8)	278 (186, 313)	0.463
Co-morbidities			
Respiratory failure	4 (21%)	5 (25%)	–
Chronic heart failure	4 (21%)	4 (20%)	–
Coronary heart disease	2 (10.5%)	3 (15%)	–
Hypertension	9 (47.4%)	8 (40%)	–
Diabetes	4 (21%)	5 (25%)	–
Obstructive sleep apnoea	6 (31.6%)	6 (30%)	–
Chronic kidney failure	1 (5.3%)	0	–
Liver cirrhosis	1 (5.3%)	0	–
Lung cancer	0	1 (5%)	–
Pulmonary hypertension	0	1 (5%)	–
Gastroesophageal reflux	5 (26.3%)	4 (20%)	–
Degenerative joint disease	4 (21%)	5 (25%)	–
Osteoporosis	3 (15.8%)	3 (15%)	–
Depression/anxiety	4 (21%)	5 (25%)	–
Others	3 (15.8%)	3 (15%)	–
6MWD, 6-min walk distance; BD, bronchodilator; CAT, COPD assessment tool; Cig, conventional cigarettes; COPD, chronic obstructive pulmonary disease; EC, electronic cigarettes; F, Female; FEV1, forced expiratory volume in 1 s; FTND, Fagerstrom test nicotine dependence; FVC, forced vital capacity; GOLD, global initiative for chronic obstructive lung disease; IQR, interquartile range; M, Male; SD, standard deviation. *Median (IQR). [‡] Mean (±SD).			

differences between the two study groups for any of the parameters. Patients had mild-to-severe airway obstruction as per the COPD GOLD guidelines, and were managed accordingly.³⁷

Smoking consumption and EC use

In the COPD EC users, a significant reduction in conventional cigarette use was noted with a mean

(±SD) cigarettes/day of 22.1 (±4.7) at baseline, falling to 2.2 (±2.2), 1.8 (±2), 1.4 (±1.6) and 1.4 (±1.6) at F/up1, F/up 2, F/up 3 and F/up 4, respectively ($p < 0.001$ for all four visits) (Table 2; Figure 1). No significant changes were observed in the COPD controls in the number of cigarettes smoked per day. In the COPD EC user group, complete abstinence (quitters; exclusive EC users or single users) in cigarettes smoked per day was

Table 2. Changes in study parameters from baseline at 12-, 24-, 36-, 48- and 60-month follow-up visits in COPD controls and COPD EC users.

	Baseline	12-month follow-up	Within group p value versus baseline	24-month follow-up	Within group p value versus baseline	48-month follow-up	Within group p value versus baseline	60-month follow-up	Within group p value versus baseline	Overall between group p value from baseline
COPD Controls (n= 19)										
post-BD FEV1* (l)	1.46 (1.19, 1.67)	1.41 (1.17, 1.61)	0.532	1.36 (1.18, 1.61)	0.747	1.34 (1.17, 1.61)	0.732	1.33 (1.13, 1.53)	0.387	0.004
post-BD FVC* (l)	2.31 (2.10, 2.54)	2.27 (2.20, 2.57)	0.135	2.31 (2.18, 2.66)	0.268	2.33 (2.11, 2.45)	0.286	2.34 (2.20, 2.58)	0.840	0.016
%FEV1/FVC	60.9 (±6.8)	59.7 (±6.9)	0.008	59.6 (±6.9)	0.026	60.2 (±8.7)	0.637	57.9 (±9.1)	0.074	0.038
Cig/day [‡]	20.2 (±2.9)	20.5 (±3.6)	0.618	19.9 (±5.0)	0.810	17.9 (±3.9)	0.061	18.3 (±3.4)	0.091	< 0.001
CAT score*	20 (17, 24.5)	20 (17.5, 23)	0.294	20 (15, 24)	0.367	20 (18, 23)	0.618	20 (17.5, 23.5)	0.962	0.158
COPD Exacerbations*	2 (±1.1)	2.2 (±1)	0.494	2 (±1.1)	1.000	1.8 (±1.0)	0.385	1.7 (±1.1)	0.331	0.046
6MWD* [‡] (m)	285 (219.3, 361.8)	270 (227, 372.5)	0.286	277.5 (243, 374.8)	0.213	306 (245.3, 355.5)	0.328	305 (243, 342.5)	0.722	0.012
COPD EC users (n= 20)										
post-BD FEV1* (l)	1.25 (0.98, 1.78)	1.23 (0.96, 1.73)	0.038	1.29 (0.95, 1.69)	0.093	1.40 (1.10, 1.80)	0.008	1.42 (1.22, 1.95)	0.001	
post-BD FVC* (l)	2.49 (2.08, 2.65)	2.51 (2.15, 2.73)	0.046	2.46 (2.07, 2.86)	0.156	2.54 (2.14, 3.00)	0.008	2.70 (2.17, 3.03)	0.002	
%FEV1/FVC [‡]	55.8 (±10.8)	55.6 (±10.8)	0.806	56.1 (±10.7)	0.558	57.5 (±9.0)	0.147	58.2 (±9.2)	0.054	
Cig/day [‡]	22.1 (±4.7)	2.2 (±2.2)	< 0.001	1.8 (±2)	< 0.001	1.4 (±1.6)	< 0.001	1.4 (±1.6)	< 0.001	
CAT score*	21.0 (17, 25.3)	18 (16, 20.5)	< 0.001	18 (14.8, 20)	0.002	17.5 (14.8, 22.5)	0.033	17 (14.8, 20.8)	0.020	
COPD exacerbations [‡]	2.3 (±0.9)	1.8 (±1)	0.004	1.4 (±0.9)	< 0.001	1.2 (±1.0)	< 0.001	1.1 (±1.0)	< 0.001	
6MWD* [‡] (m)	278 (186, 313)	305 (217.6, 337.8)	0.007	319.3 (225.6, 355.5)	0.007	347.5 (232.5, 404.5)	0.005	344.5 (239, 394.8)	0.005	

6MWD, 6 min walk distance; BD, bronchodilator; CAT, COPD assessment tool; Cig, conventional cigarettes; COPD, chronic obstructive pulmonary disease; EC, electronic cigarettes; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; IQR, interquartile range; SD, standard deviation.
^{*}Median (IQR).
[‡]Mean (±SD).
[‡]10 subjects in the COPD EC user group and 11 in the COPD control group at all time points.

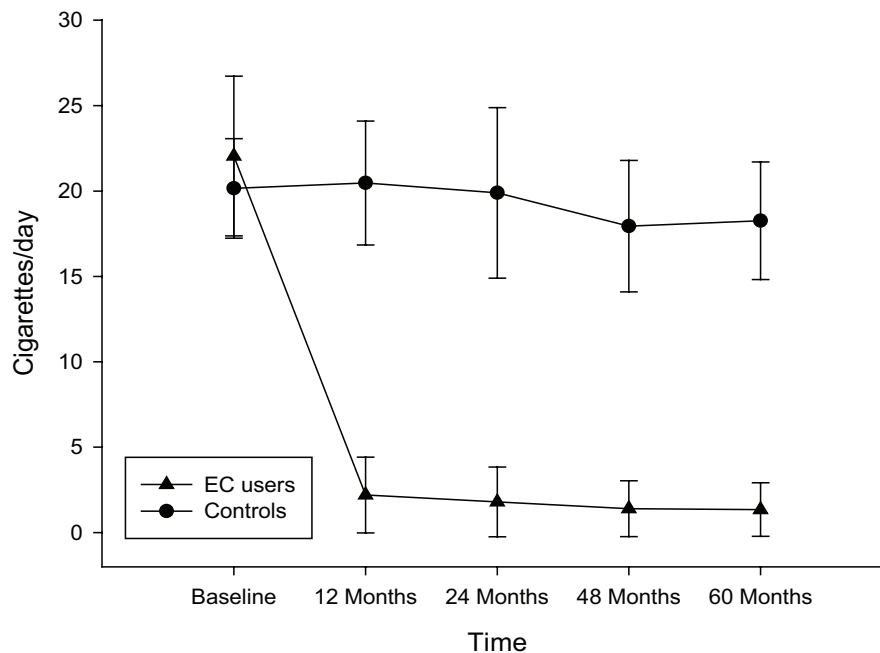


Figure 1. Number of cigarettes smoker per day at baseline, follow-up visit 1 (12 ± 1.5 months), visit 2 (24 ± 2.5 months), visit 3 (48 ± 3 months) and visit 4 (60 ± 3 months) separately for COPD electronic cigarettes users (closed triangles) and COPD controls (closed circles). All data expressed as mean and error bars are standard deviation of the mean. COPD, chronic obstructive pulmonary disease; EC, electronic cigarette.

reported in 9/20 (45%) at F/up 4; and in those continuing to smoke (dual users) in 11/20 (55%) (Table 3). There was a considerable decline in conventional cigarette consumption in dual users with the mean (±SD) cigarettes/day at baseline decreasing from 23.7 (±5.4) to 4 (±1.2), 3.6 (±1.3), 3.1 (±0.6) and to 3.0 (±0.5) at F/up 1, F/up 2, F/up 3 and F/up 4, respectively ($p < 0.001$ for all four visits) (Table 3). Of note, all the dual users consistently reduced their daily smoking by at least 80% of their baseline consumption throughout the whole duration of the study. Overall, there was a significant reduction in conventional cigarettes smoked per day between the study groups over the 60-month observation period ($p < 0.001$).

A mix of different vaping products were used by COPD patients in the COPD EC users group over the 5-year duration of the study. Devices and/or e-liquids were changed quite frequently over time. An increasing percentage of users switched from standard refillable e-cigs to more advanced devices during the study (from 9% at baseline to 18% at first wave). Further details were not recorded in subsequent waves. However, nicotine strength was more accurately tracked.

Most users started with 12–18 mg/ml (medium/high) nicotine strength at baseline and then gradually reduced their nicotine strength over time; by 5-year follow up, only 2 out of 20 users were still using medium/high nicotine strength e-liquids, whereas the others were consuming 3–9 mg/ml (low) nicotine strength.

COPD exacerbations

COPD EC users had a marked reduction in COPD exacerbations; with the mean (±SD) annual exacerbation rate declining from 2.3 (±0.9) at baseline to 1.8 (±1) at F/up1 ($p = 0.004$), 1.4 (±0.9) at F/up2 ($p < 0.001$), 1.2 (±1.0) at F/up3 ($p < 0.001$) and 1.1 (±1.0) at F/up 4 ($p < 0.001$), respectively (Table 2). Conversely there were no significant changes from baseline in the annual COPD exacerbation rates in the control group over the 5 years. An overall significant ($p = 0.046$) between group reduction in COPD exacerbations was noted over the 5-year observation period (Table 2; Figure 2). Consistent decline in COPD exacerbations were noted in the dual users from baseline; with the mean (±SD) annual exacerbation rate of 2.6 (±0.8) at baseline significantly reducing to 1.5 (±0.9) at F/up2

Table 3. Changes in study parameters from baseline at 12-, 24-, 36-, 48- and 60-month follow-up visits in single and dual users.

Parameter	Baseline (n = 11)	12-month follow-up (n = 11)	Within group p value versus baseline	24-month follow-up (n = 10)	Within group p value versus baseline	48-month follow-up	Within group p value versus baseline	60-month follow-up (n = 9)	Within group p value versus baseline
COPD EC users reducing cig use (dual users)									
Sex	10M, 1F	10M, 1F	-	10M	-	9M	-	9M	-
% Smoking reduction compared with baseline	-	82.7 (±4.8)	-	84.7 (±4.7)	-	88.4 (±4.2)	-	91.0 (±6.9)	-
post-BD FEV1* (l)	1.23 (0.94, 1.6)	1.2 (0.91, 1.7)	0.026	1.18 (0.91, 2.01)	0.108	1.18 (1.0, 1.8)	0.086	1.29 (1.0, 1.9)	0.055
post-BD FVC* (l)	2.34 (2.04, 2.86)	2.35 (2.07, 2.89)	0.074	2.52 (2.2, 2.93)	0.274	2.41 (2.2, 3.04)	0.105	2.50 (2.3, 3.1)	0.075
%FEV/FVC*	53.8 (±9.5)	53.8 (±9.9)	1.000	54.0 (±12.1)	0.940	52.7 (±8)	0.759	53.6 (±7.9)	0.461
Cig/day [‡]	23.7 (±5.4)	4 (±1.2)	< 0.001	3.6 (±1.3)	< 0.001	3.1 (±0.6)	< 0.001	3.0 (±0.5)	< 0.001
CAT score*	25 (19.5, 26.5)	20 (18, 22)	< 0.001	19 (15.8, 22)	0.011	20 (16, 25)	0.156	20 (15, 24)	0.176
COPD exacerbations [‡]	2.6 (±0.8)	2.3 (±0.8)	0.104	1.5 (±0.9)	0.004	1.4 (±0.9)	0.010	1.6 (±1.0)	0.021
COPD EC users ceasing cig use (single users)									
Sex	7M, 2F	7M, 2F	-	7M, 3F	-	8M, 3F	-	8M, 3F	-
Smoking reduction compared with baseline	-	-	-	-	-	-	-	-	-
post-BD FEV1* (l)	1.32 (1.05, 1.76)	1.26 (1.09, 1.72)	0.632	1.34 (1.22, 1.57)	0.388	1.45 (1.2, 1.77)	0.026	1.5 (1.32, 1.93)	0.003
post-BD FVC* (l)	2.57 (2.27, 2.65)	2.6 (2.22, 2.72)	0.444	2.44 (1.92, 2.81)	0.384	2.57 (2.08, 2.91)	0.034	2.7 (2.11, 2.93)	0.003
%FEV/FVC*	58.2 (±12.4)	57.9 (±12.1)	0.351	58.2 (±9.2)	0.338	61.4 (±8.1)	0.110	62.0 (±8.7)	0.063
Cig/day [‡]	20 (±2.7)	-	-	-	-	-	-	-	-
CAT score*	18 (17, 22)	16 (14, 18)	0.009	16 (14.3, 19.5)	0.014	16 (14.5, 19.5)	0.073	16 (14.5, 18.5)	0.065
COPD exacerbations [‡]	1.9 (±0.9)	1.1 (±0.8)	< 0.001	1.2 (±0.9)	0.019	1.0 (±1)	0.019	0.7 (±0.9)	0.008

BD, bronchodilator; CAT, COPD assessment tool; cig, conventional cigarettes; COPD, Chronic obstructive pulmonary disease; EC, electronic cigarettes; F, female; FEV1, forced expiratory volume in 1 sec; FVC, forced vital capacity; M, male; IQR, interquartile range; SD, standard deviation.
^{*}Median (IQR).
[‡]Mean (±SD).

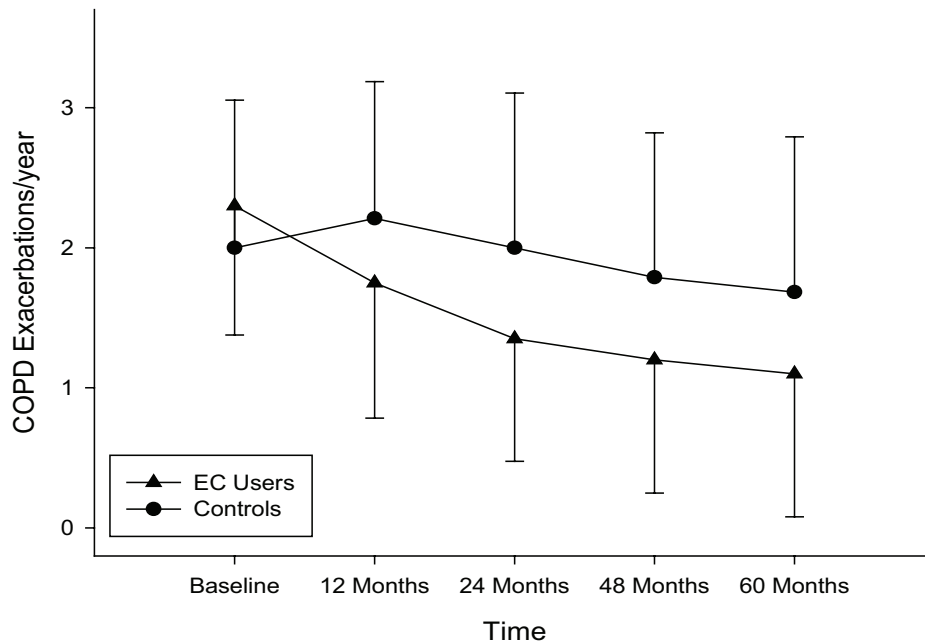


Figure 2. Changes in the number of COPD exacerbations per year from baseline, at follow-up visit 1 (12 ± 1.5 months), visit 2 (24 ± 2.5 months), visit 3 (48 ± 3 months) and visit 4 (60 ± 3 months) separately for COPD electronic cigarettes users (closed triangles) and COPD controls (closed circles). Data expressed as mean and error bars are standard deviation of the mean. COPD, chronic obstructive pulmonary disease; EC, electronic cigarette.

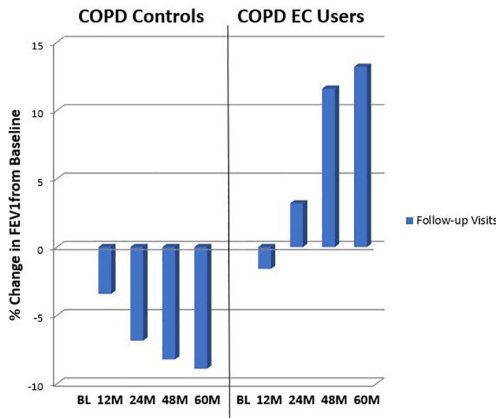


Figure 3. Percentage change in median FEV1 (a) and FVC (b) from baseline, at follow-up visit 1 (12 ± 1.5 months), visit 2 (24 ± 2.5 months), visit 3 (48 ± 3 months) and visit 4 (60 ± 3 months) separately for COPD EC users and COPD controls. BL, baseline; COPD, chronic obstructive pulmonary disease; EC, electronic cigarette; FEV1, forced expiratory volume in 1 second; FVC, Forced vital capacity; L, litres; M, months.

($p=0.004$), $1.4 (\pm 0.9)$ at F/up 3 ($p=0.010$) and $1.6 (\pm 1.0)$ at F/up4 ($p=0.021$), respectively (Table 3). Significant reductions in the annual

COPD exacerbations were noted at all the follow-up visits compared with baseline in the exclusive EC users (single users) (Table 3).

Lung function assessments and COPD staging

There were substantial improvements in post-bronchodilator FEV1 and FVC in the EC users compared with baseline at all follow-up visits except for F/up 2 (Table 2; Figure 3a–b). Reductions in spirometric indices compared with baseline at all follow-up visits in the control group were noted, though this was not significant (Table 2; Figure 3a–b). There were overall marked differences between the two study groups in the spirometric assessments were observed in favour of the EC users (Table 2).

GOLD COPD staging changes throughout the study are illustrated in Figure 4. Over the 60-month observation period, a number of patients in the EC group down-staged (i.e. improved) from GOLD COPD Stages 4 and 3 to Stages 3 and 2, respectively. In contrast, minimal changes in COPD GOLD stages were observed in the control group.

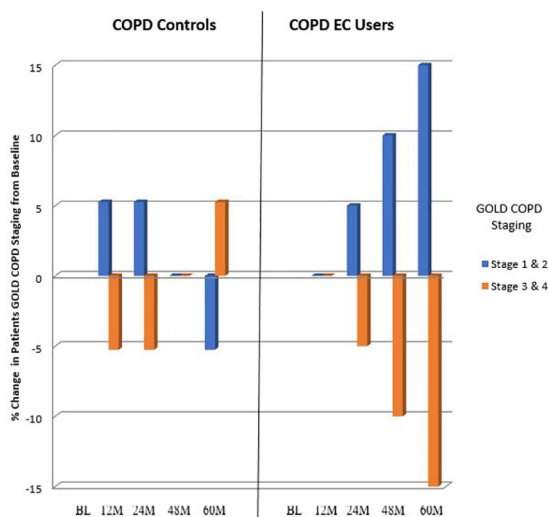


Figure 4. Percentage change in patients COPD GOLD stage over the study period. BL, baseline; COPD, chronic obstructive pulmonary disease; GOLD, global initiative for chronic obstructive lung disease; EC, electronic cigarette; M, months.

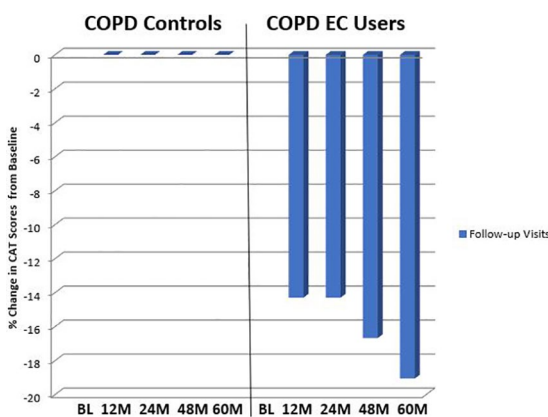


Figure 5. Percentage change in the median CAT scores from baseline, at follow-up visit 1 (12 ± 1.5 months), visit 2 (24 ± 2.5 months), visit 3 (48 ± 3 months) and visit 4 (60 ± 3 months) separately for COPD EC users and COPD. BL, baseline; CAT, COPD assessment tool; COPD, chronic obstructive pulmonary disease; EC, electronic cigarette; M, Months.

CAT scores and 6MWD

CAT scores, which is a subjective COPD assessment, significantly improved in the EC COPD group at all four follow-up time points compared with baseline ($p < 0.05$ at all follow-up visits) (Table 2). Similarly, throughout the study relevant clinical improvements in median CAT scores were observed from baseline (Table 2). In the

control group, no significant or clinically relevant improvements were noted at any of the follow-up visits from baseline. There was no overall significant improvement in CAT scores between groups over the 5-year study period ($p = 0.158$) (Table 2; Figure 5).

Results of 6MWD at all four follow-up visits were available for 10 patients in the COPD EC group, whilst those from the COPD control group were available for 11 subjects. In the EC user group, significant improvements from baseline in 6MWD was observed all time points ($p < 0.01$); there were no notable improvements in 6MWD in the control group (Table 2). At 5 years from baseline the 6MWD improved by a median of 66.5m ($p = 0.005$) in the COPD EC user group, whereas it increased by a median of 20m ($p = 0.722$) in the COPD control group (Table 2). A significant ($p = 0.012$) improvement in 6MWD was observed between the study groups over the 5-year period of follow-up (Table 2).

Discussion

In our study, offering the longest clinical follow up ever reported in this field, patients with COPD who abstained from smoking or substantially reduced their cigarette consumption by swapping to vaping experienced improvements in objective and subjective health outcomes. These positive health effects persisted long term, for up to 5 years. Switching from smoking to vaping leads to improved COPD outcomes, which is expected because quitting smoking is known to slow COPD progression and to improve patients' respiratory health.^{8,10-12}

A major finding of the study is that COPD exacerbations were reduced by approximately 50% in patients who stopped or considerably reduced their smoking consumption after switching to vaping. The magnitude of the number of COPD exacerbations prevented in these patients is of clinical significance and similar to that observed with pharmacological interventions.⁴¹ Prolonged exposure to cigarette smoke has been demonstrated to increase susceptibility to airway infection and respiratory exacerbations so that quitting smoking may reduce these conditions and related symptoms.⁴²⁻⁴⁴ Former smokers in one study reported a 43% lower risk for COPD-related hospitalizations compared with active smokers.⁴⁵ Another study found a 22% risk reduction of

COPD exacerbation in former smokers compared with active smokers; this was confirmed after adjusting for co-morbidity, COPD severity indices, and socioeconomic status.⁴⁶ Studies that have not found differences in hospital admissions between smokers and former smokers with COPD failed to account for critical confounders for COPD exacerbation risk, such as duration of smoking abstinence duration, disease severity, presence of co-morbidities, and age.^{47,48} Therefore, switching from smoking to vaping would be expected to result in the marked attenuation of respiratory infections and COPD exacerbations.

In agreement with our previous observations,^{35,36} lung function, respiratory health (i.e. CAT) and physical activity (i.e. 6MWD) improved consistently in COPD patients who quit or reduced substantially cigarette consumption after switching to vaping products. These results are similar to those of COPD patients undergoing intensive rehabilitation programs.^{39,49}

Small improvements in post-bronchodilator FEV1 were noted over the 5-year observation period in COPD EC users, but the differential impact of medication usage between the two study groups cannot be excluded. Alternatively, due to the prolonged absence/reduction of exposure to cigarette smoke in the COPD EC users, we might speculate that the airways could have improved their responsiveness to salbutamol. In further support of this hypothesis, a *post hoc* analysis of pre- versus post-bronchodilator difference in FEV1 values between the two groups indicated that post-bronchodilator values at F/up 3 and 4 were higher than pre-bronchodilator values in the COPD EC user group. Nonetheless, the benefits of EC use in determining improvements of lung function have been disputed in some studies. The association of EC use and self-reported chronic respiratory conditions have been reported in cross-sectional surveys of adults in the US,^{34,50} but these cross-sectional studies cannot demonstrate causation, and are not adjusted for smoking history, an obvious critical confounder. A recent paper analysing data from two large prospective cohorts concluded that e-cigarette users had more rapid decline in lung function,⁵¹ but this trend did not persist after adjustment for conventional cigarette smoking – which is of course the key factor driving the accelerated decline in lung function – and the study did not measure frequency of EC use. Also, e-cigarette users had heavier conventional

cigarette smoking history, thus explaining why they also had poorer respiratory health, and were more likely to report chronic bronchitis and exacerbations as clarified in a detailed critique of this study.⁵²

Down staging from GOLD COPD classes 3/4–1/2 in the COPD EC user group over the 5-year duration of the study was not a surprising observation given the above-mentioned improvements in exacerbation rates, overall health status and lung function.

Another important finding of the study is that only 8.3% patients from the COPD EC user group relapsed to cigarette smoking over the 5-year duration of the study, thus suggesting that relapse prevention may be an important mechanism by which vaping contributes to long-term smoking abstinence. Vaping mimics the experience of smoking and related rituals and provides powerful compensatory physical and behavioural effects, possibly serving as an effective relapse prevention method contributing to the low relapse rates observed in this study. Similar lower relapse rates with vaping have also been observed in studies of smokers with schizophrenia, asthma and hypertension.^{53–55} The reduction in relapse rates is vital because smokers with COPD do not respond very successfully to smoking cessation programs.^{15,56,57}

The decline in carbon monoxide exposure and in carboxyhaemoglobin levels following smoking abstinence and the associated time-dependent improvement in exercise tolerance that occurs after quitting smoking may account for the reported improved health outcomes.^{44,58}

Our study has a number of limitations. First, our findings are based on a small cohort of COPD patients must be interpreted with care. Notwithstanding, beneficial effects in several COPD health indicators were consistently observed over the entire 5-year duration of the study. Second, patients in the index study may represent a self-selected sample, and as such may not be indicative of the archetypical COPD smoker. Finally, the 6MWD test was not performed in approximately half of the study participants.

The present study confirms our previous research that switching from smoking to vaping ameliorates respiratory health in COPD patients and that these

positive health effects may persist long term.^{35,36} By substantially reducing cigarette smoking or achieving abstinence with EC use, thereby curtailing exposure to several toxic chemicals, may have resulted in the ameliorated respiratory outcomes and bestowed an overall health advantage

The findings of this study are valuable because many COPD patients show little interest in quitting or reducing cigarettes in spite of their symptoms. Switching to much less harmful substitutes may limit the suffering of many patients by reducing some of the otherwise unavoidable burden of respiratory morbidity and mortality caused by cigarette smoking. Physicians in charge of the smoking patient with COPD should consider all the options available and opt for the ones that provide the greatest probability of stopping exposure to tobacco smoke, including ECs.⁵⁹

Larger studies will be required to clarify the role of the e-vapour category for smoking cessation and/or harm reversal in smokers with COPD. Although these findings are preliminary, the evidence presented in our study about the long-term health impacts of vaping on COPD can be considered by health professionals when providing specific advice to their COPD patients who cannot or do not want to quit smoking.^{59,60}

Author contributions

RP – study design, data interpretation, drafting and manuscript drafting and revision.

JBM – data analyses, data interpretation and manuscript drafting and revision.

UP - review of medical records and data collection.

BB - review of medical records and data collection.

AP – review of medical records, data collection, data interpretation and manuscript revision.

M Malerba - data interpretation and manuscript revision.

M Maglia - review of medical records and data collection.

PC – study design, data interpretation and manuscript revision.

All authors have read and approved the final manuscript.

Conflict of interest statement

In relation to his work in the area of tobacco control and respiratory diseases, RP has received lecture fees and research funding from Pfizer, GlaxoSmithKline, CV Therapeutics, NeuroSearch A/S, Sandoz, MSD, Boehringer Ingelheim,

Novartis, Duska Therapeutics and Forest Laboratories. He has also served as a consultant for Pfizer, Global Health Alliance for treatment of tobacco dependence, CV Therapeutics, Boehringer Ingelheim, Novartis, Duska Therapeutics, ECITA (Electronic Cigarette Industry Trade Association, in the UK), Arbi Group Srl. and Health Diplomats. RP has been the Director of the Center of Excellence for the acceleration of Harm Reduction at the University of Catania (CoEHAR), which has received a grant from Foundation for a Smoke Free World to develop and carry out eight research projects. RP is also currently involved in the following pro bono activities: scientific advisor for LIAF (Lega Italiana Anti Fumo – Italian acronym for Italian Anti-Smoking League), the Consumer Advocates for Smoke-free Alternatives (CASAA) and the International Network of Nicotine Consumers Organizations (INNCO); Chair of the European Technical Committee for standardization on ‘Requirements and test methods for emissions of electronic cigarettes’ (CEN/TC 437; WG4). All other authors have no relevant conflict of interest to declare in relation to this study. The Associate Editor of *Therapeutic Advances in Chronic Disease* is an author of this paper, therefore, the peer review process was managed by alternative members of the Board and the submitting Editor had no involvement in the decision-making process


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