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Research Article

Cardiovascular Effect of Alternative Smoking; Is There an "Innocent" Substitute?

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Abstract

Background: Recently, in order to achieve smoking cessation, the use of either varenicline substitute either electronic cigarette (e-cigarette) or heat-not-burn tobacco products (HnBP) has been encouraged. The aim of this study was to investigate the effect of smoking cessation on cardiovascular outcome comparing among e-cigarette, HnBP and varenicline substitution.

Methods: 374 consecutive patients were followed up for 1 year and divided in 4 groups; a) patients who stopped smoking overall, b) patients who changed smoking with e-cigarette, c) patients who changed smoking with an HnBP, d) patients who stopped smoking and followed varenicline administration. Patient surveillance process included 4 visits per year.

Results: There was a significant association between cardiovascular event and type of smoking cessation (without substitute vs. all types of substitutes). Those who experienced smoking cessation without substitute reduced the odds of having an event by 47.6% (Odds Ratio: .524, p:0.012, 95% Confidence Interval: .316, .868) compared with those using current types of cessation agents (varenicline, IQOS, e-cigarette). A statistically significant association was found between cardiovascular disease (CVD) history and event in the whole sample ($p<0.001$), since the events were far more frequent in those with CVD history (88.6%) than in those without CVD history (28.9%).

Conclusions: The incidence of cardiovascular events in humans during 1-year follow-up of smoking cessation using varenicline or e-cigarette or HnBP, is significant higher compared with smoking discontinuation without any substitute. This finding is particularly profound in people with pre-existing coronary artery disease, highlighting a serious advisory notice for smoking cessation substitutes.

Keywords: Smoking cessation; E-cigarette; IQOS; Varenicline; Cardiovascular event; Smoking substitute

Introduction

Cardiovascular Disease (CVD) is the major cause of death in smokers since more smokers die from heart adverse effects than respiratory disease including cancer of all types [1]. Tobacco smoking has been demonstrated to be the most common cause of reversible mortality in modern world accounting for one of every five deaths in the United States each year [2]. During last decades, in order to enable smoking cessation, varenicline substitute, electronic cigarette (e-cigarette) and heat-not-burn tobacco products (HnBP) use have been adopted. There are very few studies investigated their potential effect on myocardial function, and most of these studies are cell culture-based or animal clinical studies. Since the establishment of their patent, all these cigarette substitutes have been extensively promoted especially in the West estimating to become a billion dollar/euro industry [3]. Especially the marketing of e-cigarette, as well as of HnBP, as healthy alternative to smoking, has led to astonishing increase of their use among younger adolescents and current smokers who believe that e-cigarette and HnBP are not harmful [4-8].

At experimental level, several early studies demonstrated that e-cigarette seems to be less toxic comparing to HnBP in cultured cardiac myocytes and endothelial cells [9-12]. Moreover, Goniewicz et al found that changing HnBP to e-cigarette led to reduced levels of several carcinogens and toxicants [13]. On the other hand, Wang et al suggested possible similar toxicity for e-cigarette and HnBP as well [14]. Furthermore, e-cigarette seems to damage stem cells and gingival fibroblasts by aldehydes/carbonyls generation, leading to protein carbonylation and DNA impairment, as well as cellular ageing [15]. It seems that the use of e-cigarette favors sympathetic predominance over parasympathetic system, enhancing oxidative stress which is correlated with increased Cardiovascular (CV) risk [16]. These findings cast doubt as far as it concerns the safety of e-cigarette use and its distinction as a substitute for HnBP.

Varenicline as pharmacotherapy for smoking cessation has proven its effectiveness in quitting smoking and sustaining abstinence [17]. Varenicline binds with high affinity and selectivity to α4β2 nicotinic acetylcholine receptors of neurons, leading to lightened symptoms of nicotine withdrawal [18]. However, several small clinical trials with varenicline including several meta-analyses have demonstrated controversial effects with regard to CV event risk (myocardial infracts and strokes) especially in smokers with established CVD [19-22]. Recently, EAGLES clinical trial showed that varenicline does not increase the risk of serious CV events only in general population [23] excluding smokers with acute or unstable CVD.

The aim of our study was to investigate the effect of smoking cessation on cardiac function comparing e-cigarette, HnBP and varenicline substitution. Specifically, the primary end point was the recording of the major adverse CV event such as CV death, myocardial infraction or stroke during the one year of surveillance. The secondary purpose was the comparison of events incidence among smoking cessation substitute especially in people with known coronary artery disease.

Materials and Methods

Study population

Power analysis showed that in order to evaluate differences in the incidence of cardiovascular events higher than 20% among study groups, a sample size of 86 participants in each group was adequate to achieve statistical power of 75% at a type I error of 0.05. Therefore, a total of 374 consecutive patients from smoking cessation and preventive cardiology offices were included and followed up for 1 year. The present study was approved by Ethical Committees of participated Hospitals. Baseline characteristics are shown on Table 1. At the beginning of the study 70% of patients presented with history of stable coronary disease of one vessel diagnosed by coronary angiography and preserved ejection fraction since they had not experienced myocardial infraction. All patients followed the appropriate medical therapy (e.g. statins). During their visits they were advised and planned for smoking cessation with or without substitute. The following substitutes were used; e-cigarette, IQOS or varenicline. All patients were mostly divided according to each patient will, 1x1x1x1 in 4 groups; a) patients who stopped smoking without using any substitute (N=86), b) patients who changed smoking with e-cigarette (N=86), c) patients who changed smoking with an HnBP (N=91), d) patients who stopped smoking and followed varenicline administration (N=111) - but in a such a way that every group, finally, had included 70% of patients with coronary artery disease of 1 vessel. As far as it concerns e-cigarette the liquid used in the device contained 11mg/ml nicotine, propylene glycol, linalool, tobacco essence and methyl vanillin. HNPB group used the same IQOS product after quit smoking with similar level of nicotine with e-cigarette group (»0.30 mg of nicotine). All patients were considered as "heavy smokers" since they used to smoke more than 1 pack-year.

Exclusion Criteria

Candidates with atrial fibrillation, thyroid disorders, valvular heart disease, acute coronary syndromes, acute myocarditis, pulmonary embolism, recent heart surgery, prosthetic valves, pericarditis, pericardial effusion, chronic obstructive lung disease, congenital heart disease, sick sinus syndrome, unstable psychiatric illness and active substance abuse, were excluded from the study. Study protocol was approved by institutional ethic committee and informed written consent was obtained from each patient.

Monitoring

Patient surveillance process included 4 visits per year (1 visit/3 months). Day one was the first day of smoking cessation and its displacement by e-cigarette or I-QOS or varenicline or no substitute at all. The aim of the following 4 visits was identification of any CV event, check of lasting smoking cessation, physical examination with estimation of blood pressure and heart rate and appropriate regulation of all CV risk factors. Echocardiography study with treadmill exercise and laboratory tests were performed at day one and at the last visit while electrocardiogram was executed in every visit. If a participant of the study reported possible CV event at any time of 1-year monitoring, a study investigator was collecting all appropriate medical records-laboratory and imaging tests-and essential information in order to affirm and register the event.

Statistical analysis

All continuous variables were tested for normal distribution using Shapiro-Wilk statistic. Since all variables deviated from normality, non-parametric tests were used for the analysis (Mann-Whitney U and Wilcoxon sign-rank). Categorical variables are shown as absolute (N) and relative (%) frequencies while continuous variables are described as medians and interquartile ranges (IQRs, 75^{th}-25^{th} percentile). Pearson's χ^2 and Fisher's exact statistics were used for testing for associations between categorical variables. Univariate logistic regression was used for evaluating the effect of types of smoking cessation on CV event. All tests were two-sided. Due to multiple comparisons, Bonferroni adjustment was used in order to adjust for inflation of type I error, setting the significance of p-value<.003. STATA® v.16.0 (StataCorp, College Station, Texas 77845 USA) statistical software was used for the analysis.

Results

From the whole of 359 patients, 96% stopped smoking while 31.9% of study participants substituted smoking with varenicline administration, 26.1% with IQOS, 17.2% with e-cigarette and 24.7% quitted smoking without using any substitute. Of these participants, 268 (74.7%) were men and the median age was 60 (12.0) years old. All groups of patients presented with preserved ejection fraction and similar baseline characteristics as no significant difference was recorded concerning the main characteristics of our sample (gender, body mass index category, family history, hypertension, diabetes mellitus and high levels of cholesterol) according to smoking cessation type. The descriptive baseline characteristics of all patients randomized in our study are presented in Table 1.

		Smoking cessation type								
		Cessation without substitute		Cessation with Varenicline		Cessation with IQOS		Cessation with e-cigarette		
		N=86	%	N=111	%	N=91	%	N=86	%	Overall p
Gender	Men	61	70.9	81	73	73	80.2	65	70	0.42
	Women	25	29.1	30	27	18	19.8	21	30	
BMI categories	Normal (18.5-24.9 kg/m^2)	16	18.6	22	19.8	15	16.5	18	17	0.11
	Overweight (25-29.9 kg/m^2)	36	41.9	45	40.5	51	56	45	60	
	Obese (>30 kg/m^2)	34	39.5	44	39.6	25	27.5	23	23	
Family History	No	33	38.4	41	36.9	28	30.8	26	22	0.13

	Yes	53	61.6	70	63.1	63	69.2	60	78	
Hypertension (SAP>135 or/and DAP>85mmHg)	No	33	38.4	40	36	44	48.4	32	32	0.16
	Yes	53	61.6	71	64	47	51.6	54	68	
DM	No	41	47.7	50	45	45	49.5	40	45	0.92
	Yes	45	52.3	61	55	46	50.5	46	55	
Cholesterol (LDL>130mg/dl)	No	15	17.4	22	19.8	26	28.6	21	13	0.11
	Yes	71	82.6	89	80.2	65	71.4	65	87	
		Median	IQR	Median	IQR	Median	IQR	Median	IQR	
Age(ys)		60	11	62	14	62	12	59	9.5	0.18
BMI(kg/m^2)		28.5	4.4	28.5	7.1	28.1	4.4	28	4	0.47
EF (%)		64	10	64	11	64	9	64	9	0.74
BMI: Body Mass Index, DM: Diabetes Mellitus, EF: Ejection Fraction										

Table 1: Baseline characteristics of 4 groups.

Study individuals were in generally good health while many of them presented with coronary artery disease (70%) and baseline CV risk factors beyond smoking; hypertension (60.4%), dyslipidemia (79.7%), diabetes mellitus (53.5%), obesity (82.2%). Minor changes from baseline values were marked in body weight, blood pressure and heart rate during this one year of close patient monitoring.

There was a significant association between CV event (myocardial infract and/or need for revascularization) and type of smoking cessation (without substitute vs. all types of substitute) (Table 2, Figure 1). This association is better described after univariate logistic modeling; Those who experienced smoking cessation without substitute reduced the odds of having an event by 47.6% (Odds Ratio: .524, p:0.012, 95% Confidence Interval: .316, .868) compared with those using specific types of cessation agents (varenicline, IQOS, e-cigarette). A statistically significant association was found between CVD history and event in the whole sample ($p<0.001$), since the events were far more frequent in those with CVD history (88.6%) than in those without CVD history (28.9%) (Table 3). Significant associations were found between CVD history and event among every cessation type category (even without substitute), since the events were more frequent in those with CVD history than in those without CVD history in every category. On the other hand, no significant association was found between CVD history and event in those who did not quit smoking (p:0.055). However, the latter result should be read with caution given the relatively low number of observations (Table 3).

		Cardiovascular Event					
		No		Yes			
		Count	%	Count	N %	Pairwise comparison p-value	Overall p-value
Smoking cessation type	Cessation without substitute	37	33.30%	49	20.80%	<.001[2], .013[3], .007[4]	0.068
	Cessation with Varenicline	34	30.60%	76	32.20%	.378[3], .726[4]	
	Cessation with IQOS	23	20.70%	68	28.80%	0.6774	
	Cessation with e-cigarette	17	15.30%	43	18.20%		
Smoking cessation overall	Cessation without substitute	37	32.70%	49	20.00%		0.087
	Cessation with Varenicline	34	30.10%	76	31.00%		
	Cessation with IQOS	23	20.40%	68	27.80%		
	Cessation with e-cigarette	17	15.00%	43	17.60%		
	No cessation	2	1.80%	9	3.70%	.191[1], .503[2], .999[3], .715[4]	
Smoking cessation	Varenicline, IQOS, e-cigarette	74	66.70%	187	79.20%		0.011
	Without substitute	37	33.30%	49	20.80%		
Smoking cessation	IQOS, e-cigarette	40	54.10%	111	59.40%		0.434
	Varenicline	34	45.90%	76	40.60%		
Smoking cessation	Varenicline, e-cigarette	51	68.90%	119	63.60%		0.42
	IQOS	23	31.10%	68	36.40%		
Smoking cessation	Varenicine, IQOS	57	77.00%	144	77.00%		0.997
	E-cigarette	17	23.00%	43	23.00%		

[1]: Pairwise comparison with cessation without substitute, [2]: Pairwise comparison with cessation with Varenicline, [3]: Pairwise comparison with cessation with IQOS, [4]: Pairwise comparison with cessation with e-cigarette

Table 2: Cardiovascular event according to type of smoking cessation.

		Cardiovascular history				
		No		Yes		
	Cardiovascular event	Count	%	Count	%	p
Cessation without substitute	No	27	73.00%	10	20.40%	<0.001
	Yes	10	27.00%	39	79.60%	

Cessation with Varenicline	No	31	72.10%	3	4.50%	<0.001
	Yes	12	27.90%	64	95.50%	
Cessation with IQOS	No	16	64.00%	7	10.60%	<0.001
	Yes	9	36.00%	59	89.40%	
Cessation with e-cigarette	No	10	76.90%	7	14.90%	<0.001
	Yes	3	23.10%	40	85.10%	
No cessation	No	2	66.70%	0	0.00%	0.055
	Yes	1	33.30%	8	100.00%	
All patients	No	86	71.10%	27	11.40%	<0.001
	Yes	35	28.90%	210	88.60%	

Table 3: Association between cardiovascular history and cardiovascular event (according to type of smoking cessation).

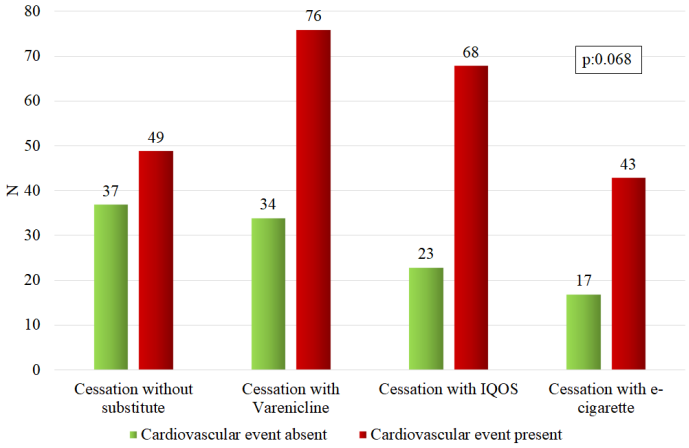

Figure 1: Number of cardiovascular events following the type of smoking alternative.

As far as it concerns stroke events, a total of 9 events was described, equally divided among 4 groups. Eventually, this low number of vascular events does not allow us to use them, due to the lack of statistical power.

Discussion

The main point of the present study is that smoking cessation in humans either with varenicline or e-cigarette or HnBP, after 1-year of follow-up, demonstrated higher incidence of CV adverse events comparing with those individuals that quitted smoking completely. Furthermore, the significant association between preexisted coronary artery disease and new onset of CV event observed in all groups with smoking alternative indicate that we must be particularly skeptic about their use at least in people with known coronary disease.

CV impairment by smoking substitutes

To the best of our knowledge this the first study to examine and compare in humans the CV effect- during 1-year monitoring- of vaping (e-cigarette), heat-not-burn tobacco products (IQOS) and varenicline administration, head-to-head, using fully smoking cessation as control-comparator. Long research over the last decades has established tobacco use worsening of approximately all classical CVD risk factors leading to major CV adverse effects. The key-case is whether the new smoking alternative strategies (i.e IQOS, e-cigarette), which are surprisingly popular especially in young people, are adequately safe as far as it concerns their CV profile particularly in people with known coronary artery disease.

The fact that the distribution of the main attributes (descriptive characteristics of our population) which might act as confounding factors did not differ among the smoking cessation categories supports the reliability of the results of present study. We found no evidence of impairment of any cessation substitute on heart rate or blood pressure. However, higher incidence of CV events was marked in all groups with smoking alternatives compared with the group of fully smoking discontinuation despite the optimal medical therapy. This is in accordance with previous studies highlighting minimal CV toxic effects of smoking cessation substitutes [19, 24-25]. Shi H et al reported [26] that e-cigarette exposure may increase tissue angiogenesis in rats which could be beneficial in case of myocardial infraction but also it may promote tumor growth and atherogenesis. Furthermore, vaping with nicotine can lead to increase of arterial stiffness and oxidative stress, impairing micro- and macro-vascular function [27]. A small study demonstrated that conventional and e-cigarette equally impaired endothelial function and induced decreased nitric oxide bioavailability [28] while Antoniewicz et al. showed augmented levels of circulating endothelial progenitor cells and soluble E-selectin after smoking of e-cigarette [29]. In accordance with our findings, Alzahrani et al reported, using the National Health Interview Surveys, increased risk for plaque rupture and acute coronary syndromes associated with e-cigarette use [30]. To the same direction, IQOS aerosol may cause endothelial dysfunction, a well-established pathophysiological index of CV risk, to similar level as cigarette smoking in rats [31], emphasizing that adverse CV effects of cigarette smoking probably are not avoided with the use of IQOS. The mechanism of this endothelial dysfunction seems to be the impaired flow-mediated dilation by IQOS which was apparent even in lower level to IQOS exposure. Additionally, concerning varenicline that in our study increased CV events compared to overall smoking cessation, this is in contrast with previous findings where no significant treatment differences were observed in CV events between varenicline and placebo [24] and also, varenicline administration restored vascular endothelial function associating with decreased oxidative stress [32]. However, varenicline binds to a7 homomeric nAChR and some data indicate potential impact on nonneuronal endothelial a7nAChRs, leading to endothelial function impairment and/or angiogenesis that could explain its contribution to CV adverse effects [33-34]. Furthermore, the population of our study suffered from stable coronary disease with 70% prevalence, explaining possibly, the difference of CV events incidence in previous studies with varenicline, which did not include patients with known coronary disease.

CV risk monitoring of smoking alternative strategies

The present study underlines the truth that atherosclerosis- the main cause of coronary artery disease- is an active and sometimes genetically defined process which does not always stop with a stent or the optimal medical therapy. Our results highlight the need for overall smoking cessation in order to stabilize possibly the atheromatic plaque and intercept atherosclerosis evolution.

Looking to the widespread use of these new smoking substitutes and the need for determine their real CVD risk, it may be helpful not only examine 'hard' end points, such as CV manifestations or their impact on classical CVD risk factors (eg. blood pressure) but also their effect on cardiac and vascular function as well as their associated biomarkers. To this direction, the evaluation of arterial stiffness, coronary artery calcification, flow-mediated dilation, endothelial progenitor cells and endothelial microparticles could be very instructive about short- and long-term changes after smoking substitutes use. Additionally, biomarkers of inflammation (eg. C-reactive protein), thrombosis (Intercellular Adhesion Molecule-1) and oxidative stress (eg. Monocyte Chemoattractant Protein-1) known to be affected by classical cigarette use, could be used for monitoring potential CV injury triggered by smoking alternative strategies [35].

Limitations

The results should be seen in the light of some limitations. For both HnBP and the e-cigarettes, we used just one specific type. Whereas the offer of different heated tobacco products is limited, a variety of e-cigarette types and e-liquids flavors, with various nicotine concentrations exists, which may differ with respect to the impact on cardiac function studied in this paper. Therefore, we should be very cautious generalizing these results to all types of vaping and HnBP. Furthermore, even though all patients including in this study could be characterized as "heavy" smokers, there was certainly variation as far as it concerns frequency and duration of using IQOS or e-cigarette during the day.

Clinical implication and future direction

The findings of our study have great importance since HnBP and e-cigarette use which is characterized by better controlling cigarette craving, seem to have the potential of a promising offering in the area of smoking cigarette cessation. Looking to this prospective, it is important to further independently investigate the effects of HnBP and e-cigarette in the long-term, not only with respect to health impact, but also with respect to be an alternative, safer and more compelling for the substitution of smoking cigarettes. Until this moment, smoking cessation alternatives should not be considered as safe CV products.

Conclusions

The results of this study concerning a relatively large number of patients, indicate that in humans during 1-year of smoking cessation with varenicline or e-cigarette or HnBP, the incidence of CV events is significant higher compared with smoking discontinuation without any substitute. The latter finding

is particularly profound in people with pre-existing coronary artery disease, demonstrating a serious warning sound for smoking cessation substitutes which should be further confirmed in future studies.

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