KARDIOLOGIA POLSKA

Polish Heart Journal
The Official Peer-reviewed Journal of the Polish Cardiac Society since 1957

Online first
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ISSN 0022–9032 e-ISSN 1897–4279

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Article type: Original article

Received: March 25, 2021

Accepted: May 30, 2021

Published online: May 31, 2021

Is cytisine contraindicated in smoking patients with coronary artery disease after percutaneous coronary intervention?

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Short title: Cytisine in smoking patients with CAD after PCI

Conflict of interest: AB acquired consulting fees from Sanofi-Aventis, AstraZeneca, Bristol-Myers Squibb/Pfizer, GlaxoSmithKline, Bayer, and Novartis; investigator fees from Sanofi-Aventis, AstraZeneca, GlaxoSmithKline, Novartis, Bristol-Myers Squibb/Pfizer, and Eisai; and honoraria for lectures from Sanofi-Aventis, AstraZeneca, Bristol-Myers Squibb/Pfizer, and Novartis. BR received honoraria for lectures from Werfen, Boehringer-Ingelheim, GE Healthcare.

Funding: This work was supported by the Centre of Postgraduate Medical Education, Warsaw, Poland (grant number 501-1-10-14-16/17). The sponsor was not involved in study design; data collection, analysis, and interpretation; manuscript writing; or manuscript publication decision.

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WHAT'S NEW?

Cytisine increases the success rates of smoking cessation in general population. Due to lack of relevant data the drug was contraindicated in patients early after acute coronary syndromes (ACS) or unstable coronary artery disease, with special warnings to patients with coronary artery disease (CAD). This is the first prospective study to assess the safety and short-term effectiveness of cytisine on smoking cessation in active smokers with CAD, who have undergone percutaneous coronary intervention (PCI). Our findings suggest that cytisine may be introduced in wider group of patients with CAD.

ABSTRACT

Background: Cytisine is contraindicated and its effects have not been evaluated in patients with coronary artery disease (CAD).

Aim: The safety, feasibility and short-term efficacy of cytisine for smoking cessation were evaluated in active smokers with CAD after percutaneous coronary interventions (PCI).

Methods: Patients with stable CAD and acute coronary syndromes (ACS), who smoked at least 10 cigarettes per day, were included 30 days post PCI and offered cytisine therapy. Adverse events, smoking activity and drug adherence were assessed after 30 days.

Results: 117 patients participated (mean standard deviation [SD] age, 60.8 [7.7] years; men, 73.6%, mean [SD] number of pack-years 39.1 [13.9]). Overall, 79 patients consented (study group) and 38 declined (control group) to use cytisine. At follow-up visit the incidence of adverse events did not differ between groups (17.7% vs 21%; $P = 0.67$). The groups had similar success rate of smoking cessation in the intention-to-treat analysis (41.8% vs 36.8%; $P = 0.61$). In as treated analysis, patients who completed the therapy achieved a higher success rate than patients who declined (69.7% vs 36.9%; $P = 0.006$) or did not complete therapy (69.7% vs 34.8%; $P = 0.01$). In the multivariable analysis, complete cytisine therapy and ACS at admission were associated with an increased and male sex with decreased chance of smoking cessation.

Conclusion: Cytisine therapy is not associated with an increase in adverse events in patients with CAD after PCI. Cytisine is tolerable but effective in short-term follow-up only when the treatment is completed.

Key words: coronary artery disease, cytisine, Fagerström index, NicAlert test, smoking cessation

INTRODUCTION

Cardiovascular diseases are the most common cause of death among cigarette smokers [1]; thus, smoking cessation, an effective lifestyle intervention [2], is crucial for primary and secondary prevention of coronary artery disease (CAD). Pharmacotherapy for smoking cessation significantly increases the rate of smoking cessation, but it is rarely implemented in clinical settings [3, 4]. First-line pharmacotherapies with nicotine replacement therapy (NRT), varenicline or bupropion, are the recommended course of action for smoking cessation [5]. NRTs (gum, transdermal patch, nasal spray, inhaler, and sublingual tablets/lozenges) increase the probability of smoking cessation, with a risk ratio of 1.6, compared with placebo [6]. The hemodynamic effects of NRT, due to nicotine release, causes adverse effects such as hypertension; thereby, NRT is less preferred among patients with CAD. Varenicline, a partial agonist of the α4-ß2 nicotinic acetylcholine receptor (nAChR), increases the success rate of effective smoking cessation by two-fold [7]. Moreover, patients with acute coronary syndromes (ACS) treated with varenicline show a 10% increase in smoking abstinence compared with placebo, without an increase in major adverse cardiovascular events [8]. Another partial agonist of the α4-ß2 nAChR, with a similar mechanism of action as varenicline, is cytisine, which is naturally derived from *Cytisus laburnum* and affects the reward pathway [9]. The treatment duration with cytisine (25 days) is substantially shorter than that with varenicline (12 weeks). In addition, cytisine is inexpensive, as effective as varenicline, and outperforms NRTs (odds ratio [OR] 1.5; 95% confidence interval [CI] 1.2–1.9; $P = 0.003$) for smoking cessation [7, 10]. Despite large randomized trials cytisine is registered only in Europe and still not approved in the United States. Due to low cost and high accessibility cytisine might be an option as smoking cessation aid in secondary prevention in patients with CAD. However, to the best of our knowledge, there are no studies regarding cytisine use in patients with CAD after PCI. Cytisine was registered for the approved indications, except for early ACS or unstable coronary disease, with special warning to patients with CAD, owing to the lack of relevant data at the time of approval [11]. Furthermore, the registration was based on unpublished data from the 1960s; the data did not include patients who underwent PCI. This data have not been updated ever since, despite a substantial progress in the interventional treatment of CAD. Furthermore, contraindications of cytisine in these groups of patients are not well documented and are based on a mild elevation in blood pressure, transient tachycardia, and blood glucose levels [9, 12, 13, 14]. These effects are driven by adrenergic stimulation and by neuronal and adrenal nAChR activation. Both cytisine and nicotine have a high affinity to the α4-β2 subtype, which is involved in the mechanism of action of nicotine [9, 12].

In the present study, we sought to evaluate the safety, feasibility and efficacy of cytisine for smoking cessation in active smokers with CAD, 30 days post PCI. We hypothesized that cytisine use will increase the rate of successful smoking cessation without increased rate of adverse events.

METHODS

Study population

This was a nonrandomized prospective investigation of active smokers, following PCI. Patients with stable CAD and ACS admitted to the catheterization laboratory in the Department of Cardiology, Grochowski Hospital, Warsaw, Poland between 2015 and 2018 were screened for active smoking. The inclusion criteria for patients were as follows: 28–32 days after PCI, aged 18 years or older, smoking at least 10 cigarettes a day, urine cotinine level of 6 based on the NicAlert test [15], and planning to quit smoking. The exclusion criteria for patients were as follows: hypersensitivity to cytisine, clinically relevant rhythm disorder, uncontrolled hypertension, class III CAD according to Canadian Cardiovascular Society, under alternate treatment for smoking cessation, and pregnancy. Medical history, nicotine dependence, and readiness for smoking cessation were determined at baseline. Patients were included based on the self-declaration to quit smoking; the readiness to quit smoking score was assessed. Adverse events, smoking activity based on the NicAlert test, and drug adherence were assessed at the follow-up visit 28–32 days after baseline visit. Patients who did not attend the follow-up visit were contacted by telephone.

Ethical considerations

This study complied with the Declaration of Helsinki and was approved by the ethics committee of the Centre of Postgraduate Medical Education (approval number 16/PB/2014 and 10/PB-A/2015). The study was registered at ClinicalTrials.gov and the identifier NCT040784702 was assigned. All patients provided written informed consent for participation in the study. Patients were recruited in the Department of Cardiology of the Centre of Postgraduate Medical Education, Warsaw, Poland.

Smoking status

Fagerström test and readiness to quit score were used to assess nicotine dependence and motivation to quit smoking, respectively; these were performed at baseline. The Fagerström test is the most commonly used test to assess nicotine dependence. Levels 6 and above predict a

high level of nicotine dependence and indicate the need for high level of behavioral support and pharmacological aid [16, 17]. The readiness to quit score, which assesses the motivation to quit smoking, consists of 12 questions, and it was locally developed for Polish patients. Levels 7 and above indicate a high motivation for smoking cessation [18]. Self-declaration of smoking status was verified by evaluating urine cotinine level at baseline and follow-up visits (30 days) using the Accutest NicAlert (Jant Pharmacal Corporation, Encino, CA, USA); a level of 0, 1, or 2 indicated a urine cotinine level of ≤100 ng/ml, and confirmed smoking cessation [15].

Interventions

All patients declared to willingly attempt to quit smoking. All patients were advised to stop smoking and received low-intensity counseling focused on the benefits of quitting, such as the reduced risk of CAD. Additionally, behavioral therapy was offered, which consisted of brief medical advice, psychological advice (<30 minutes), and being contacted twice during follow-up. Standard cytisine therapy (Desmoxan®; 1.5 mg tablet, a 25-day course) was offered to all patients, and cytisine therapy was started at the discretion of the patients. The study group consisted of patients who consented to start cytisine therapy. Patients who denied cytisine therapy formed the control group.

Endpoints

The primary endpoint was the differences in adverse events between the study and control group. The observed adverse events were as follows: gastrointestinal symptoms, including dry mouth, nausea, and abdominal pain; psychiatric symptoms, including anxiety, insomnia, and suicidal thoughts; cardiovascular symptoms, including chest pain, increased blood pressure (mean self-measured blood pressure ≥140/90, or single measurement ≥180/110 either self-measured or measured at clinical visit), and arrhythmia. Major adverse events observed were myocardial infarction, stroke, hospitalization, and death from any cause.

The secondary endpoint was confirmed smoking cessation using the NicAlert test at the follow-up visit.

Statistical methods

It was estimated to enroll 117 patients powered to have a 80% chance of detecting a between-group difference of 25% in smoking cessation using a *P* value of 0.05 with 10% drop-out rate. Baseline characteristics were presented as mean and SD or median and interquartile range (Q1–Q3) for continuous data normally and non-normally distributed, respectively and frequency for

categorical data. A Shapiro-Wilk test was applied to assess for data normality. A t-test or Wilcoxon rank-sum test was used for between-group comparisons of continuous data. A Chi-squared or Fisher exact test was used for between-group comparisons of categorical data. A multivariable logistic regression model was used to investigate the covariates associated with higher odds of smoking cessation. The following variables were included in the model: age, sex, body mass index, education, marital status, number of pack-years of smoking, previous attempts to stop smoking, passive smoking, Fagerström index, readiness to quit score, reason for PCI (CAD or ACS), and medical history. Relevant medical histories included: myocardial infarction, stroke, coronary artery by-pass grafting, PCI, hypertension, hyperlipidemia, chronic obstructive pulmonary disease, peripheral artery disease, diabetes mellitus, renal failure, and rheumatoid arthritis. Backward selection at level of 0.1 was implemented to fit the model to identify factors at the 5% level of significance. ORs with 95% CI were calculated. All analyses were performed using the Stata 14.1 software (StataCorp LP, College Station, Texas, USA).

RESULTS

One hundred and seventeen active smokers with a level of 6 (NicAlert) were included in this study, 28–32 days post-PCI. Seventy nine (67.5%) patients consented to use cytisine (study group) at the first visit (baseline) (Figure 1). The remaining 38 (32.5%) patients declined cytisine treatment (control group). Among patients who declined to use cytisine 6 (15.8%) declared strong will to withdraw smoking which according to patient did not require pharmaceutical help, 4 (10.5%) clearly declared that they would not use cytisine due to cardiovascular contraindications mentioned in product information, 28 (73.7%) refused but did not provide particular reason. Of the patients who consented to use cytisine at the first visit, only 64 started cytisine treatment; 15 patients did not start the treatment despite consenting. Of the 64 patients who started cytisine treatment, 32 completed the 25-day course. Ninety one patients (64 from the study group and 27 from the control group) completed the 30-day follow-up visit. Of these, 47 patients quit smoking; confirmed using the NicAlert test (levels from 0–2), and 44 patients did not quit smoking (levels ≥3). All patients from the study group who attended the follow-up visit, had started cytisine therapy. Patients who did not attend the follow-up visit were contacted via telephone and requested to complete a questionnaire regarding smoking cessation, cytisine use, and adverse events. All patients who failed to attend the follow-up visit did not stop smoking and declared lack of motivation as the reason for not attending the follow-up visit.

The clinical characteristics of the patients enrolled in the trial are presented in table 1. The mean (SD) age of patients was 60.8 (7.7) years; 67 (73.6%) patients were men, and 42 (46.15%) patients underwent PCI for ACS. The median and interquartile range (Q1–Q3) of number of cigarettes smoked was 14.5 (10–20), and average pack-years was 39.1 (13.9). The mean and SD of Fagerström and readiness to quit index indices were 4.8 (1.7) and 9.0 (1.6), respectively. The clinical characteristics of the patients in the study group did not differ from the control group (Table 1). Neither the criterion for high nicotine addiction (Fagerström index ≥6) nor increased motivation for smoking cessation (readiness to quit score ≥7) differed between the groups at baseline.

The frequency of all the adverse events were similar between the groups (14 [17.7%] vs 8 [21%]; P = 0.67). Additionally, the prevalence of particular adverse events did not differ between the groups (Table 2). Among all of the adverse events the most common were gastrointestinal symptoms (10 [45%]; nausea, 5 [23%]; abdominal pain, 3 [14%]; and dry mouth, 2 [9%]). Other reported adverse events were increased anxiety, 5 (23%); insomnia, 2 (9%); atypical chest pain, 3 (14%); and increased blood pressure, 2 (9%). No major cardiovascular adverse events were reported at follow-up. Thirty-two patients (40.5%) discontinued cytisine therapy. The most common reason for cytisine discontinuation was a perceived lack of effectiveness (19 [59.3%]). Thirteen patients (20.3%) who started cytisine therapy discontinued treatment due to adverse events.

The study and control groups had similar success rates of smoking cessation in an intention-to-treat analysis (33 [41.8%] vs 14 [36.8%]; P = 0.61). An analysis of patients who completed cytisine therapy revealed that, only the patients who completed cytisine therapy significantly succeeded in smoking cessation compared with those not treated with cytisine, or those who did not complete cytisine therapy (Table 3) (complete therapy: 69.7%; not treated: 36.8%; incomplete therapy, 25%; P <0.001). According to the multivariable logistic regression analysis, completion of cytisine therapy (OR: 5.79; 95 % CI: 1.99–16.86) and ACS at admission (OR: 3.2; 95% CI: 1.05–9.78) were associated with an increased success rate of smoking cessation, whereas decreased smoking cessation was observed with male sex (OR: 0.21; 95% CI: 0.06–0.68) (Table 4).

DISCUSSION

To the best of our knowledge this is the first prospective study to assess the safety and effect of cytisine on smoking cessation in active smokers with CAD previously treated with PCI. Our results revealed that cytisine use in this group of patients was not associated with increased

number of adverse events. However, a substantial proportion of patients did not start cytisine therapy despite obtaining the drug and a substantial proportion of patients did not complete the therapy. Noteworthy, only complete course of cytisine was associated with a higher rate of smoking cessation.

As mentioned before, there are no previous reports on cytisine treatment in patients with CAD and the safety of this drug in the early period post-PCI; especially in patients with ACS. A meta-analysis on NRT proved higher incidence of symptoms related to sympathomimetic effects of nicotine such as tachycardia and arrhythmia, without an increase in major adverse cardiovascular events [19]. Cytisine is a partial nicotine agonist; therefore, may cause similar symptoms [9, 12, 13, 14]. In this trial, only a small number of patients reported atypical chest pain or elevated blood pressure, which might be attributable to nAChR activation; we did not observe any events of tachycardia or arrythmia. In patients with stable CAD treated with varenicline, the event rate of cardiovascular events was comparable to placebo [20]. Among these patients, the most commonly reported symptoms were nausea, vomiting, insomnia, and abnormal dreams [20]. Most common adverse events in our study were gastrointestinal symptoms such as nausea, and this is consistent with the findings of previous studies with cytisine [21]. We did not record any major adverse events such as serious cardiovascular events. In our trial, patients were recruited 30 days after PCI. Due to lack of published data on cytisine use, a 30-day waiting period following PCI was chosen to avoid the period of the highest risk of cardiovascular adverse events and major fluctuations in platelet reactivity [22, 23].

In the largest randomized study on cytisine published to date, West et al. [24] reported a smoking cessation rate of 8.4% (vs 2.4%) during 12 months of observation, and abstinence was verified by assessing the concentration of carbon monoxide. However, patients with a previous diagnosis of severe atherosclerotic disease and had undergone PCI, were excluded in the latter study. In our study, we found relatively high rates of smoking cessation (69.7% in the complete cytisine therapy group, 36.8% in the no therapy group, and 25% in the incomplete therapy group). The high rate of cessation may be owing to the preselection of patients with established CAD treated with PCI, short observation period, or the high level of counseling. On the other hand the rate of cytisine discontinuation in our trial was 40.5%, whereas the previously reported rate of varenicline discontinuation is 9.6% [20]. The most common reason for discontinuation in our trial was perceived lack of effectiveness. Increased attendance of follow-up and more frequent contact with patients scheduled to undergo cytisine therapy might be requested to reduce the risk of discontinuation.

In this study, we excluded patients treated with NRT because their smoking status could not be confirmed with the urine cotinine test. Moreover, cytisine was found to be superior to NRT therapy in a large randomized trial [10].

Although West et al. [24] verified smoking cessation by evaluating the concentrations of carbon monoxide, we assessed urine cotinine levels; it is considered to be a stronger indicator of smoking cessation over 48–72 h [25].

The pharmacodynamics of cytisine is a matter of concern because it does not cross the blood-brain barrier. Additionally, there is no information on serious adverse events in patients with mood disorders and other addictions. Varenicline is a synthetic drug that binds to the same α4-β2 nAChR as cytisine, and crosses the blood-brain barrier with a marked effect on the receptors [26]. Furthermore, in 2009, the Food and Drug Administration released a black box warning against varenicline, associating the drug to mental health disorders [27], although further studies did not support its detrimental effect on mood disorders [28, 29]. Nevertheless, varenicline use was related to higher risk of sleep disorders or anxiety syndromes [20]. In our study, patients treated with cytisine rarely reported increased anxiety or insomnia in both the groups.

Our study has a few limitations. First, the study was not randomized and did not include a placebo control group. Second, cytisine intake was at the discretion of the patients, and this may have led to an entry of bias. Third, some patients were lost to follow-up visit, especially from the control group (29%). However, such patients were contacted via phone, and none of them declared smoking cessation. Fourth, patients were followed-up only for a short term of 30 days, nevertheless the follow-up did include cotinine assessment as an objective biomarker. Finally, the small sample size limits our findings. Despite these limitations, our study provides important data regarding cytisine use in smoking patients with CAD. Our findings suggest that cytisine use may not be contraindicated in CAD patients including ACS group 30 days after PCI. To increase compliance, patients undergoing cytisine therapy should be regularly contacted and supported.

CONCLUSION

Cytisine is a safe and promising drug for the treatment of patients with CAD initiated 30 days after PCI. However, the compliance of the patients is low including patients who do not start and do not complete the treatment. Owing to the low cost, cytisine therapy may be beneficial for smoking cessation in a wide group of patients with CAD. Further research is required to confirm its efficacy and safety.

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Figure 1. Flow chart of the study

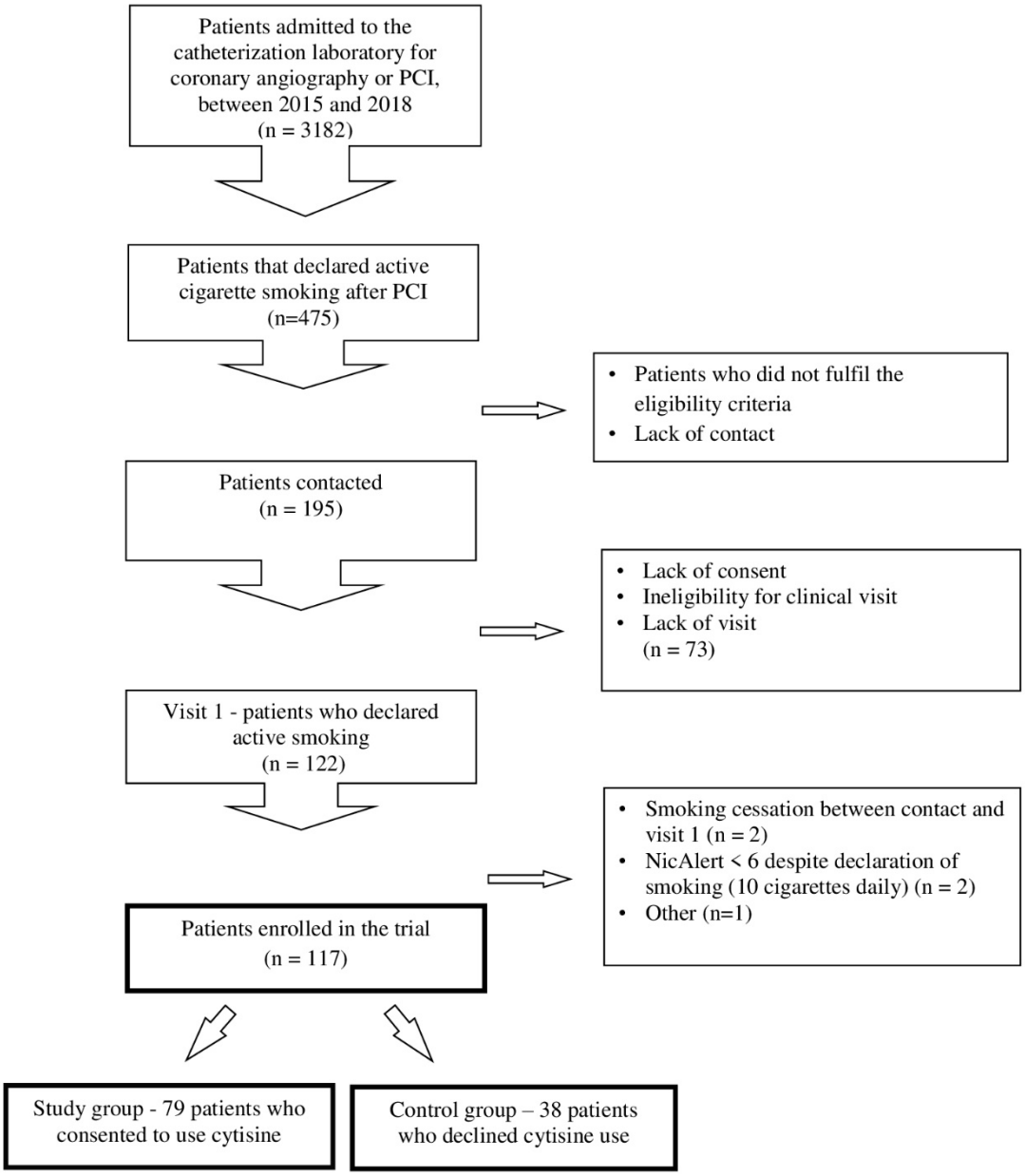

Table 1. Patient demographics and clinical characteristics

Variables	**Baseline visit (n = 117)**	**Study group (n = 79)**	**Control group (n = 38)**	***P*** **(study vs control group)**
Age (mean [SD]), years Range, years	60.8 (7.7) (56–65)	59.9 (7.8) (58–62)	59.8 (7.8) (57–62)	0.951
Males, n (%)	67 (57.2)	61 (77.2)	25 (66)	0.19
BMI (mean (SD]), kg/m^2	27.9 (4.4)	28 (4.2)	28.1 (4.9)	0.91
Indications for PCI ACS, n (%)	55 (47)	33 (41.8)	22 (57.9)	0.102
Diabetes, n (%)	29 (24.8)	19 (24)	10 (26.3)	0.79
Hypertension, n (%)	94 (80.3)	63 (79.75)	30 (78.95)	0.92
History of MI, n (%)	30 (25.6)	20 (25.3)	10 (26.3)	0.908
Hyperlipidemia, n (%)	84 (71.8)	53 (67)	31 (81.6)	0.103
History of renal failure, n (%)	7 (5.9)	5 (6.3)	2 (5.2)	1.0
COPD, n (%)	8 (6.8)	6 (7.6)	2 (5.2)	1.0
Data on smoking number of cigarettes smoked, median (IQR)	14.5 (10–20)	12 (10–20)	15 (10–20)	0.54
Habit of smoking, years, median (IQR)	40 (32.5–45)	40 (33–45)	40 (30–43)	0.32
Pack-years, median (IQR)	40 (30–46.5)	40 (30–47)	39 (27–36)	0.46
Fagerström questionnaire, mean (SD), [a]index ≥6; n (%)	4.8 (1.7)	4.8 (1.8) 34 (43)[a]	4.9 (1.6) 15 (39.5)[a]	0.607 0.714
Readiness to quit test, mean (SD), [b]index ≥7; n (%)	9 ± 1.6	9.1 (1.5) 76 (96.2)[b]	8.8 (1.7) 35 (92)[b]	0.377 0.347

Abbreviations: ACS, acute coronary syndrome; BMI, body mass index; COPD, chronic obstructive pulmonary disease; MI, myocardial infarction; PCI, percutaneous coronary intervention; SD, standard deviation

Table 2. Frequency of adverse events

Adverse events	**Study group**	**Control group**	***P***
Nausea, n (%)	4 (5)	1 (2.6)	1.0
Abdominal pain, n (%)	1 (1.3)	0 (0)	1.0
Dry mouth, n (%)	2 (2.5)	0 (0)	1.0
Anxiety, n (%)	2 (2.5)	3 (7.9)	0.327
Insomnia, n (%)	2 (2.5)	0 (0)	1.0
Atypical chest pain [n (%)]	3 (3.8)	2 (5.3)	0.639
Increase in blood pressure, n (%)	1 (1.3)	1 (2.6)	0.546

Table 3. Success rates in smoking cessation with regard to complete cytisine therapy

Groups	**Frequency**	***P***
Complete cytisine therapy vs incomplete therapy, n (%)	23 (69.7) vs 24 (34.8)	0.001
Complete cytisine therapy vs no therapy, n (%)	23 (69.7) vs 14 (36.8)	0.006
Incomplete cytisine therapy vs no therapy, n (%)	10 (25) vs 14 (36.8)	0.257

Table 4. Factors influencing the success of smoking cessation at follow-up visit – multivariable regression analysis

Variables	**OR (95 % CI)**	***P***
Complete cytisine therapy (complete vs others)	5.79 (1.99–16.86)	0.001
ACS at admission (yes vs no)	3.2 (1.05–9.78)	0.041
Male sex (male vs female)	0.21 (0.06–0.68)	0.01

Abbreviations: ACS, acute coronary syndrome; CI, confidence interval; OR, odds ratio