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Original Investigation | Diabetes and Endocrinology

Efficacy and Safety of Varenicline for Smoking Cessation in Patients With Type 2 Diabetes

A Randomized Clinical Trial

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Abstract

IMPORTANCE Evidence of effective smoking cessation interventions in patients with diabetes is limited. The unique behavioral and metabolic characteristics of smokers with type 2 diabetes warrants a randomized clinical trial of the smoking cessation drug varenicline.

OBJECTIVE To evaluate the efficacy and safety of varenicline in patients with type 2 diabetes with an intention to quit smoking.

DESIGN, SETTING, AND PARTICIPANTS This multicenter, double-blind, placebo-controlled randomized clinical trial recruited patients from 6 outpatient clinics in 5 hospitals in Catania, Italy. Patients with type 2 diabetes, who were smoking at least 10 cigarettes a day, and who intended to quit smoking were screened for eligibility. Eligible patients were randomized to either varenicline or placebo treatment. The trial consisted of a 12-week treatment phase followed by a 40-week follow-up, nontreatment phase. Intention-to-treat data analysis was performed from December 2020 to April 2021.

INTERVENTIONS Varenicline, 1 mg, twice daily or matched placebo administered for 12 weeks. Patients in both treatment groups also received smoking cessation counseling.

MAIN OUTCOMES AND MEASURES The primary efficacy end point of the study was the continuous abstinence rate (CAR) at weeks 9 to 24. Secondary efficacy end points were the CAR at weeks 9 to 12 and weeks 9 to 52 as well as 7-day point prevalence of abstinence at weeks 12, 24, and 52.

RESULTS A total of 300 patients (mean [SD] age, 57.4 [0.8] years; 117 men [78.0%] in varenicline group and 119 men [79.3%] in placebo group) were randomized to receive varenicline (n = 150) or placebo (n = 150). The CAR at weeks 9 to 24 was significantly higher for the varenicline than placebo group (24.0% vs 6.0%; odds ratio [OR], 4.95; 95% CI, 2.29-10.70; $P < .001$). The CARs at weeks 9 to 12 (31.3% vs 7.3%; OR, 5.77; 95% CI, 2.85-11.66; $P < .001$) and weeks 9 to 52 (18.7% vs 5.3%; OR, 4.07; 95% CI, 1.79-9.27; $P < .001$) as well as the 7-day point prevalence of abstinence at weeks 12, 24, and 52 were also significantly higher for the varenicline vs placebo group. The most frequent adverse events occurring in the varenicline group compared with the placebo group were nausea (41 [27.3%] vs 17 [11.4%]), insomnia (29 [19.4%] vs 19 [12.7%]), abnormal dreams (19 [12.7%] vs 5 [3.4%]), anxiety (17 [11.4%] vs 11 [7.3%]), and irritability (14 [9.4%] vs 8 [5.4%]). Serious adverse events were infrequent in both groups and not treatment-related.

(continued)

Key Points

Question Is varenicline efficacious and safe in achieving long-term abstinence in patients with type 2 diabetes who are willing to quit smoking?

Findings In this randomized clinical trial involving 300 patients with type 2 diabetes who smoked, varenicline was efficacious at weeks 12, 24, and 52 of the trial compared with placebo. Nausea, insomnia, abnormal dreams, anxiety, and irritability were reported at higher frequency among patients in the varenicline vs placebo group. No treatment-related serious adverse events were noted.

Meaning Findings of this study suggest that varenicline should be included in diabetes education programs to help patients with type 2 diabetes quit smoking.

+ Visual Abstract

+ Multimedia

+ Supplemental content

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Abstract (continued)

CONCLUSIONS AND RELEVANCE Results of this trial showed that inclusion of varenicline in a smoking cessation program is efficacious in achieving long-term abstinence without serious adverse events. Varenicline should be routinely used in diabetes education programs to help patients with type 2 diabetes stop smoking.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT01387425

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Introduction

Cigarette smoking is a major risk factor for cardiovascular disease[1] and is highly prevalent among patients with type 2 diabetes.[2] It is not surprising that smoking exacerbates the combined harmful effects of hyperglycemia and other risk factors, accelerating vascular damage in patients with diabetes.[3] Increased risk of total mortality, coronary heart disease, stroke, and peripheral arterial disease has been observed in smokers with diabetes compared with nonsmokers with diabetes.[3,4] Consistent with these observations is that stopping smoking has been associated with reduced mortality risk in patients with type 2 diabetes.[5,6] Moreover, patients with type 2 diabetes who participated in smoking cessation programs were found to have better glycemic control and lower cardiometabolic risk factors.[7] Therefore, counseling on quitting smoking and treatment of tobacco addiction should be components of routine diabetes care.[8,9]

Behavioral counseling and smoking cessation medications are generally combined in efforts to help people quit smoking. Consideration of smoking cessation methods should include the individual circumstances and underlying diseases of the smoker. High-quality evidence supports the benefits of individually delivered smoking cessation counseling,[10] and combining smoking cessation medications with counseling can substantially reduce smoking rates.[11-13] Nonetheless, the evidence for efficacious smoking cessation interventions in patients with diabetes is limited.[9,14]

Randomized clinical trials (RCTs) have indicated that varenicline is more efficacious for smoking cessation than placebo, bupropion,[15,16] or nicotine replacement therapy.[17] Varenicline has been shown to be efficacious also in smokers with cardiovascular disease,[18] chronic obstructive pulmonary disease,[19] or depressive disorders.[20] The efficacy and safety of varenicline in smokers with diabetes have not been extensively studied, however. A retrospective pooled analysis of 15 RCTs including 323 smokers with type 2 diabetes found that varenicline was efficacious for these patients and had a safety profile that was similar to that for smokers without diabetes.[21]

Smokers with diabetes may differ from other smokers regarding not only risks but also reasons for smoking and motivations to quit. Evidence suggests that they are less motivated to quit than other smokers, possibly because they fear weight gain.[22,23] When assisting patients with diabetes in quitting smoking, health care professionals should closely monitor metabolic parameters and not assume that these parameters will improve.[9] In particular, prevention of weight gain after smoking cessation must be considered a top priority because of its detrimental implications for several metabolic parameters and diabetic control. For example, Lycett et al[24] found among 3131 adult smokers with type 2 diabetes who quit smoking, an increase in hemoglobin A_{1c} (HbA_{1c}) level within the first year after quitting.

However, to our knowledge, there has been no randomized, prospective study conducted of varenicline use in patients with type 2 diabetes. Rigorous research is required to guide the decisions of health authorities and clinicians. The aim of this multicenter, double-blind, placebo-controlled RCT was to evaluate the efficacy and safety of varenicline in patients with type 2 diabetes with an intention to quit smoking.

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Methods

The ethical review board of the leading site, Azienda Ospedaliero Universitaria Policlinico-Vittorio Emanuele, Università di Catania, reviewed and approved this RCT (Supplement 1). All enrolled patients provided written informed consent before participation in the trial. We followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline.

Participants

Patients with type 2 diabetes who were receiving regular treatment in an outpatient diabetic clinic, smoking at least 10 cigarettes a day, and intending to quit were screened for eligibility. The first 300 consecutive patients who were eligible were recruited from 6 outpatient clinics located in 5 hospitals in Catania, Italy (Ambulatorio di Diabetologia, Unità Operativa Complessa [UOC]; Medicina Interna E D'Urgenza, Policlinico Universitario; Centro Diabetologico-UOC Andrologia Ed Endocrinologia, Policlinico Universitario; Centro per il Diabete e l'Obesità-UOC Endocrinologia, Ospedale Garibaldi Nesima; and Centro per il Diabete, Ospedale Cannizzaro).

Inclusion criteria were as follows: (1) aged 75 years or younger; (2) met the American Diabetes Association diagnostic criteria for type 2 diabetes[25]; (3) type 2 diabetes diagnosis for more than 12 months; (4) HbA_{1c} level between 7.0% and 12.0% (to convert to proportion of total hemoglobin, multiply by 0.01); (5) smoked 10 or more cigarettes per day for the past year; and (6) willingness to quit smoking as confirmed by a yes answer to both of these questions, Do you plan to quit smoking within the next 30 days? and Do you wish to participate in a smoking cessation program?

Exclusion criteria were as follows: (1) mental illness, including major depression, panic disorder, psychosis, or bipolar disorder that was diagnosed and treated by psychiatrists or clinical psychologists; (2) history of alcoholism or substance use disorder within 12 months before screening; (3) use of medications that could interfere with the efficacy of the study drug (eg, nicotine replacement therapy); (4) body mass index (BMI; calculated as weight in kilograms divided by height in meters squared) of less than 18.5 or greater than 34.9; (5) known clinically significant medical condition, including any recent (within the past 4 weeks) acute decompensation of type 2 diabetes that required hospital treatment and any history of neurological, gastrointestinal, kidney, hepatic, cardiovascular, psychiatric, respiratory, metabolic, endocrine, hematologic, or other major disorder that, in our opinion, would compromise the safety or participation of the patient; and (6) current pregnancy or breast feeding or intention to become pregnant during the trial.

Eligible patients were randomized to receive the active drug or placebo. The flow diagram of patients is shown in **Figure 1**. Recruitment started in June 2011 and concluded in December 2014. Most screening failures were associated with patients' unwillingness to quit and the presence of clinically significant comorbidities. Last follow-up visit was completed in December 2015.

Trial Design and Study Visits

This RCT compared the efficacy and safety of varenicline, 1 mg, administered twice daily for 12 weeks vs placebo (1 mg, administered twice daily, for 12 weeks) for smoking cessation in patients with type 2 diabetes. The total duration of the study was 52 weeks. The 12-week treatment phase was followed by a 40-week nontreatment phase (**Figure 2**). Details of the trial design and protocol were described in a previous publication.[26]

After screening, eligible patients were invited to attend the baseline visit (visit 1), during which the eligibility criteria were reviewed and patients were randomized 1:1 to either varenicline or placebo. The list for treatment randomization was generated using SAS software (SAS Institute). The size of the blocks was a variable of 3, and the sequence of blocks was randomized and blinded.

Sociodemographic characteristics, medical history, drug prescriptions, smoking history, and motivation for quitting were self-reported at baseline. Race and ethnicity were investigator observed and included White individuals.

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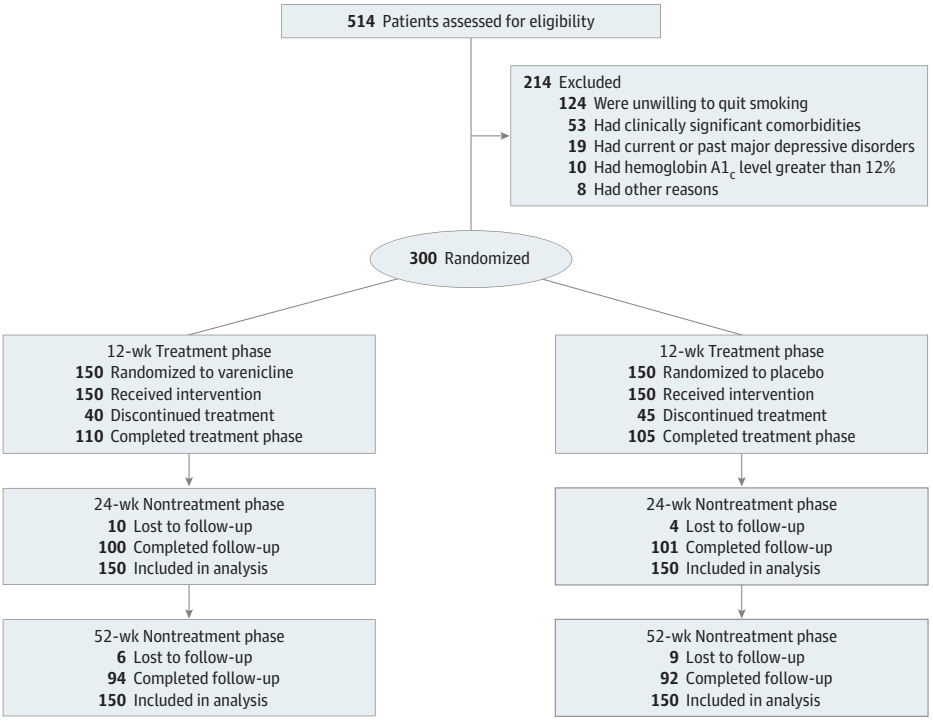
The following baseline measures were recorded: number of cigarettes smoked per day, exhaled carbon monoxide (eCO) levels, blood pressure, heart rate, BMI, waist circumference, scores on various questionnaires, and adverse events (AEs). Blood and urine samples were collected for laboratory tests (chemistry profile, including fasting blood glucose, HbA_{1c} level, fasting insulin level, and lipid profile; microalbuminuria; and proteinuria). Patients received smoking cessation counseling and were instructed to set a target quit date within the next 5 to 8 days. Before checkout, patients were given a full week's supply of the study drug, either varenicline or placebo, depending on the treatment group to which they were randomized. Study drugs were dispensed in accordance with the plan (eTable 1 in Supplement 2)

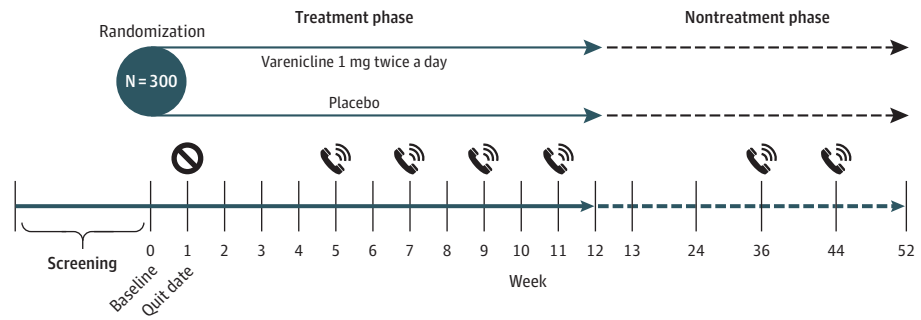
After visit 1, patients were invited to return to their respective outpatient clinic on a weekly basis for the next 12 weeks (visits 2-13), except for visits 6, 8, 10, and 12, which were conducted by telephone contact. Patients attending visit 2 for their target quit date must have abstained from smoking or substantially reduced cigarette consumption. Regardless of their level of cigarette consumption, all patients were followed up. At each visit, patients were reminded of the importance

Figure 1. Study Flow Diagram of Study Participants



To convert hemoglobin A_{1C} to proportion of total hemoglobin, multiply by 0.01.

Figure 2. Schematic Diagram of the Study Design



Smokers with type 2 diabetes who intended to quit in the next 30 days were randomized to receive either varenicline, 1 mg, twice daily for 12 weeks or matched placebo for 12 weeks. Participants were prospectively reviewed for up to 52 weeks during which smoking habits, exhaled carbon monoxide levels, questionnaire answers, adverse events, vital signs, waist circumference, body mass index, and laboratory test results were assessed at each visit. Dashed lines indicate follow-up phase; telephone symbol, telephone contact.

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of quitting smoking and were offered professional counseling to help with relapse prevention. Number of cigarettes smoked per day, eCO levels, blood pressure, heart rate, and any AEs were recorded in the case report form at each study visit; BMI and waist circumference were recorded only at the week-12 visit. At week 2 (visit 3) and week 12 (visit 13), blood and urine samples were collected for laboratory tests. Study drugs were dispensed before checkout in accordance with the plan (eTable 1 in Supplement 2)

Completion of the treatment phase (visits 2-13) was followed by the nontreatment phase (visits 14-18). Only patients who completed their treatment schedule were invited to the nontreatment follow-up phase. Except for visits 16 and 17 (telephone contact), patients were invited to return to the clinic for week 13 (visit 14), week 24 (visit 15), and week 52 (visit 18). Number of cigarettes smoked per day, eCO levels, blood pressure, and heart rate were recorded in the case report form at each study visit; BMI and waist circumference were recorded only at the week-24 and week-52 visits. At week 24 (visit 15) and week 52 (visit 18), blood and urine samples were collected for laboratory tests.

All randomized patients received study treatments and were included in the efficacy and safety analyses. We attempted to continue to follow-up participants who stopped treatment during the 12-week treatment phase, and all of those who stopped treatment were considered to be smokers in the analysis.

Outcome Measures

In keeping with previous varenicline RCTs[14,15,27] and recommendations by the Society for Research on Nicotine and Tobacco,[28] we established the primary efficacy end point as the continuous abstinence rate (CAR) at weeks 9 to 24. Abstinence from smoking was defined as eCO level–verified (<10 ppm) self-reported abstinence from cigarette smoking. Secondary efficacy end points were the CAR at weeks 9 to 12 and weeks 9 to 52 as well as 7-day point prevalence of abstinence at weeks 12, 24, and 52.

Safety reporting details were described in a previous study.[23] In brief, safety end points included information on the number of AEs and serious AEs occurring between treatment randomization (visit 1) and 1 week after treatment discontinuation (visit 14). Secondary analyses of metabolic and cardiovascular parameters by smoking phenotype classification (continuous quitters vs reducers vs failures) are planned.

Interventions

Varenicline, 0.5 mg, tablets and matched placebo tablets were supplied by Pfizer and packaged by Depo Pack. Secondary packaging of these tablets was sent to the hospital pharmacy for double-blinding preparation. Labels from the containers of the secondary packaging were removed, and the unlabeled study drugs were repackaged in coded containers. Blinding was ensured by the identical appearance of the tablets and containers.

Patients who were randomized to varenicline were titrated to full dose by the time of their target quit date (0.5 mg daily for 2-3 days, 0.5 mg twice daily for 4 to 5 days, and then 1 mg twice daily for 11 weeks). All patients in both treatment groups received the same smoking cessation counseling throughout the duration of the trial. One-on-one counseling was provided at each visit for a total of 10 minutes by psychologists who were trained in motivational interviewing.

Assessments

Assessments were carried out during the study visits and included the following laboratory tests: complete blood count, chem-20 panel, urinalysis, lipid profile, fasting blood glucose, HbA_{1c} level, and insulin level. Other measurements taken and questionnaires completed included (1) resting heart rate; (2) systolic and diastolic blood pressure; (3) BMI; (4) waist circumference; (5) eCO levels; (6) Fagerström Test for Cigarette Dependence, a 6-item questionnaire for classifying cigarette dependence into 3 levels with a score range of 0 to 3 points indicating mild, 4 to 6 points indicating moderate, and 7 to 10 points indicating severe dependence[29]; (7) Beck Depression Inventory II, a

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21-item self-rating of characteristics, attitudes, and symptoms of depression[30] with a score range of 0 to 9 points indicating no or minimal, 10 to 18 points indicating mild to moderate, and 19 to 29 points indicating moderate to severe depression; (8) Beck Anxiety Inventory, a 21-item self-rating of physiological and cognitive symptoms of anxiety[31] with a score range of 0 to 7 points indicating minimal, 8 to 15 points indicating mild, 16 to 25 points indicating moderate, and 26 to 63 points indicating severe level of anxiety; (9) Glover-Nilsson Smoking Behavioral Questionnaire (GN-SBQ), a self-rating of behaviors or thoughts about smoking[32] with a score less than 12 points indicating mild, 12 to 22 points indicating moderate, 23 to 33 points indicating strong, and higher than 33 points indicating very strong dependence; and (10) visual analog scale (VAS) for self-efficacy and motivation, with a score range of 0 points indicating low to 10 points indicating high self-efficacy or motivation. eTable 1 in Supplement 2 has a full list of the assessments performed and the instruments used.

Statistical Analysis

The sample size calculation for this RCT was based on quit rates from previous smoking cessation studies.[17,33,34] We computed that 174 patients (87 per study group) were required to have 90% power with a 2-sided α error rate of .05 to detect a difference of at least 18.7% between treatment groups in CAR at weeks 9 to 24. Allowing for a conservative attrition rate of approximately 40%, the target number of participants was increased to a total of 300 (150 per each study group).

Baseline and demographic data were listed for all treatment groups. Summary statistics were provided for each treatment group. At baseline, differences in primary end point (CAR at weeks 9-24) between varenicline and placebo groups were evaluated by means of 1-way analysis of variance for normally distributed continuous variables and by Mann-Whitney test for not normally distributed continuous variables. The χ^2 test was used for categorical variables, and differences in primary end point were evaluated by means of χ^2 test. Secondary end points were analyzed using procedures similar to those for the primary end point. Intention-to-treat analysis was adopted for efficacy evaluation, on the assumption that patients who were lost to follow-up continued smoking.

Safety data were summarized for both treatment groups, and summary statistics were provided. Any events that were documented from the point of treatment initiation until 1 week after discontinuation of randomized treatment (visit 14) were considered to be relevant to the safety analysis.

Additional analyses of interest included baseline clinical and demographic variables that could influence smoking cessation rate at weeks 12, 24, and 52. Aiming to identify these variables, we built a multiple logistic regression model in which the CAR at weeks 9 to 24 (but also the CAR at weeks 9-12 and weeks 9-52 in separate models) was the outcome variable and the possible independent variables were introduced along with all the available confounders or effect modifiers. Independent variables were selected by an a priori evaluation of the variables that were able to act as determinants, effect modifiers, or confounders of success in quitting sessions.

Despite the analysis of clinical and demographic features that could influence the outcome, this is not the main point of the study. We believe such analysis provides information on when varenicline can be routinely included in diabetes education programs to help patients quit smoking. We performed an a priori selection of variables that were able to act as determinants, effect modifiers, or confounders of success in quitting sessions. Number of cigarettes smoked per day was excluded from the multiple logistic analysis because of its strong association with pack-years.

Intention-to-treat data analyses were carried out from December 2020 to April 2021, using Statistical Package for Social Sciences for Windows, version 20 (SPSS Inc). All tests were 2-sided, and $P < .05$ was considered to be significant.

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Results

Trial Participants

Three hundred patients were randomized to either varenicline (n = 150) or placebo (n = 150) treatment. These patients had a mean (SD) age of 57.4 (0.8) years and included 117 men (78.0%) and 33 women (22.0%) in the varenicline group and 119 men (79.3%) and 31 women (20.7%) in the placebo group). A total of 215 participants completed the treatment phase, of whom 73.3% (n = 110 of 150) were in the varenicline group and 70.0% (n = 105 of 150) were in the placebo group. For the nontreatment phase, 201 participants completed the 24-week study visits, of whom 66.6% (n = 100 of 150) were in the varenicline group and 67.3% (n = 101 of 150) were in the placebo group; 195 patients completed the 52-week study visits, of whom 66.6% (n = 100 of 150) were in the varenicline group and 63.3% (n = 95 of 150) were in the placebo group.

Baseline characteristics of the patients are comparable between groups (**Table 1**). Despite our best efforts to keep and support all randomized participants, treatment discontinuation was frequent (approximately 30%). In general, most participants were White, middle-aged (approximately 57 years), and male (approximately 78%) individuals who had smoked about 25 cigarettes daily for at least 40 years. They had a Fagerström Test for Cigarette Dependence score of 6, indicating moderate to marked nicotine dependence; a VAS motivation score of 9, indicating high motivation to quit; and a VAS self-efficacy score of 5, indicating a low perception of their ability to quit smoking. A similar proportion of patients in both treatment groups (56% [n = 84] for the

Table 1. Baseline Characteristics of Patients by Treatment Group

Characteristic	No. (%)	
	Varenicline group (n = 150)	Placebo group (n = 150)
Sex		
Female	33 (22.0)	31 (20.7)
Male	117 (78.0)	119 (79.3)
Age, mean (SE), y	57.3 (0.8)	57.4 (0.8)
Educational level		
Primary	21 (14.0)	26 (17.3)
Secondary, first degree	59 (39.3)	63 (42.0)
Secondary, second degree	54 (36.0)	51 (34.0)
Doctoral degree	16 (10.7)	10 (6.7)
No. of cigarettes smoked per d, median (IQR)	25 (20-35)	25 (20-40)
Duration of smoking, median (IQR), y	42 (35-48)	41 (35-47)
No. of packs smoked per y, median (IQR)	50.8 (36.4-70.8)	53.4 (35.0-70.0)
Proportion with quitting attempts	84 (56.0)	75 (50.0)
Self-efficacy score by VAS	5 (5-7)	5 (4-8)
Motivation to quit score by VAS	9 (6-10)	9 (7-10)
FTCD score, median (IQR)	6 (4-8)	6 (5-8)
BAI score, median (IQR)	6 (3-12)	8 (2-16)
BDI-II score, median (IQR)	7 (3-13)	8 (3-14)
GN-SBQ score, median (IQR)	18 (11-23)	19 (12-22)
Hemoglobin A_{1c} level, mean (SE), %	7.68 (0.12)	7.63 (0.13)
Type 2 diabetes medications		
Metformin	124 (82.7)	129 (86.0)
Insulin or insulin analogs	74 (49.3)	77 (51.3)
Statins	65 (43.3)	62 (41.3)
GLP-1 receptor agonist	44 (29.3)	45 (30.0)
Sulphonylureas (includes repaglinide)	35 (23.3)	38 (25.3)
DPP-4 inhibitors	28 (18.7)	23 (15.3)
α-Glucosidase inhibitors (acarbose)	18 (12.0)	14 (9.3)
Glitazones	3 (2.0)	5 (3.4)

Abbreviations: BAI, Beck Anxiety Inventory; BDI-II, Beck Depression Inventory II; DPP-4, dipeptidyl peptidase-4; FTCD, Fagerström Test for Cigarette Dependence; GLP-1, glucagon-like peptide-1; GN-SBQ, Glover-Nilsson Smoking Behavioral Questionnaire; VAS, visual analog scale.

SI conversion: To convert to proportion of total hemoglobin, multiply by 0.01.

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varenicline group and 50% [n = 75] for the placebo group) had made at least 1 serious quit attempt (defined as complete abstinence for at least 24 hours) in the past. The mean (SE) HbA_{1c} level was 7.68% (0.12%) for the varenicline group and 7.63% (0.13%) for the placebo group, indicating a suboptimal level of control.

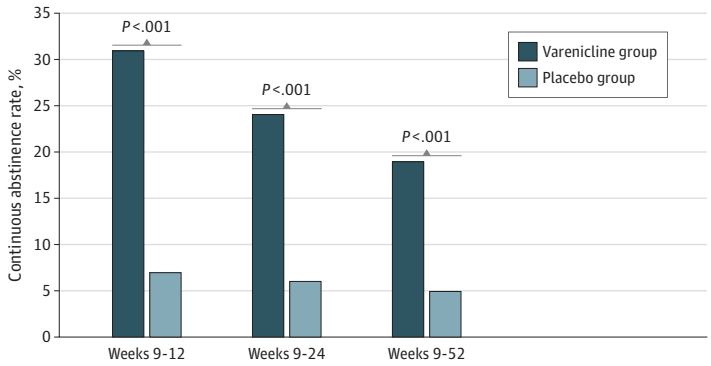
Smoking Abstinence Rates

The eCO level–verified (<10 ppm) CARs at weeks 9 to 12, 9 to 24, and 9 to 52 are shown in **Figure 3** and **Table 2**. We found that the CARs were significantly higher for the varenicline group vs the placebo group at each interval: 31.3% vs 7.3% (odds ratio [OR], 5.77; 95% CI, 2.85-11.66; *P* < .001) at weeks 9 to 12; 24.0% vs 6.0% (OR, 4.95; 95% CI, 2.29-10.70; *P* < .001) at weeks 9 to 24; and 18.7% vs 5.3% (OR, 4.07; 95% CI, 1.79-9.27; *P* < .001) at weeks 9 to 52. The 7-day point prevalence of smoking abstinence was also significantly higher for the varenicline group than the placebo group at each time point: 40.0% vs 11.0% (OR, 7.67; 95% CI, 3.91-15.05; *P* < .001) at week 12; 29.0% vs 8.3% (OR, 4.44; 95% CI, 2.17-9.07; *P* < .001) at week 24; 23.7% vs 9.5% (OR, 3.27; 95% CI, 1.57-6.78; *P* < .001) at week 52.

Clinical and Demographic Features Influencing Smoking Abstinence

In a multiple logistic regression model, including baseline characteristics (sex, age, educational level, cohabiting smoker, previous quitting attempt, VAS self-efficacy, VAS motivation, Beck Anxiety Inventory score, Beck Depression Inventory II score, GN-SBQ score, number of cigarette pack-years, and study group) as independent variables, we found that the varenicline group vs the placebo group had an OR of 4.80 (95% CI, 2.06-11.16; *P* < .001) for the CAR at weeks 9 to 24. Those in the varenicline group with strong behavioral cigarette dependence (GN-SBQ score >22 points) had reduced odds for CAR at weeks 9 to 24 (OR, 0.27; 95% CI, 0.11-0.65; *P* < .01), indicating that strong behavioral cigarette dependence impairs the success of continuous abstinence with varenicline. A

Figure 3. Continuous Abstinence Rates for Weeks 9 to 12, 9 to 24, and 9 to 52



Proportion of participants who reported abstinence from smoking was defined by exhaled carbon monoxide level–verified (<10 ppm) self-reported abstinence. Primary efficacy end point was the continuous abstinence rate at weeks 9 to 24.

Table 2. Primary and Secondary Efficacy Outcomes

Outcome	Varenicline group, No. (%)	Placebo group, No. (%)	OR (95% CI)	*P* value
CAR at weeks				
9-12	47 (31.3)	11 (7.3)	5.77 (2.85-11.66)	<.001
9-24	36 (24.0)	9 (6.0)	4.95 (2.29-10.70)	<.001
9-52	28 (18.7)	9 (5.3)	4.07 (1.79-9.27)	<.001
7-d point prevalence, wk				
12	60 (40.0)	16 (11.0)	7.67 (3.91-15.05)	<.001
24	43 (29.0)	13 (8.3)	4.44 (2.17-9.07)	<.001
52	35 (23.7)	14 (9.5)	3.27 (1.57-6.78)	<.001

Abbreviations: CAR, continuous abstinence rate; OR, odds ratio.

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higher number of pack-years reduced the odds of the CAR at weeks 9 to 24 (OR, 0.21; 95% CI, 0.09-0.50; $P < .001$) (eTable 2 in Supplement 2). Similar findings were observed for the CAR at weeks 9 to 12 (OR, 0.28; 95% CI, 0.13-0.60; $P < .001$) and weeks 9 to 52 (OR, 0.38; 95% CI, 0.16-0.92; $P = .03$) (eTable 4 and eTable 5 in Supplement 2).

Adverse Events

A total of 105 patients (70.0%) who received varenicline and 96 patients (64.0%) who received placebo reported AEs. Most AEs were rated as mild or moderate and rarely led to treatment discontinuations in either group (6 [4.0%] in the varenicline group; 5 [3.3%] in the placebo group). The most common AEs that resulted in treatment discontinuation were anxiety and depression. The AEs that occurred more frequently in the varenicline group than in the placebo group were nausea (41 [27.3%] vs 17 [11.4%]), insomnia (29 [19.4%] vs 19 [12.7%]), abnormal dreams (19 [12.7%] vs 5 [3.4%]), anxiety (17 [11.4%] vs 11 [7.3%]), and irritability (14 [9.4%] vs 8 [5.4%]) (eTable 3 in Supplement 2).

There were few AEs reported (n = 380), and only a few withdrawals from the study occurred as a result (n = 11). Patients did not report suicidal ideation, worsening of depressive symptoms, or serious AEs (with the exception of 1 intervertebral disc protrusion in the varenicline arm at visit 11 as well as 1 severe hypoglycemia and 1 hypertensive crisis in the placebo group at visit 6 and visit 8).

No significant changes in mean (SE) resting heart rate and systolic and diastolic blood pressure during treatment were observed between and within treatment groups (eTable 6 in Supplement 2). Similarly, no significant differences in BMI, waist circumference, fasting blood glucose, HbA_{1c} level, insulin level, and creatinine level were observed between and within treatment groups (eTable 6 in Supplement 2).

Discussion

To our knowledge, this RCT was the first to investigate the efficacy and safety of varenicline, 1 mg, twice daily for smoking cessation among patients with type 2 diabetes. The findings suggest that substantial changes in smoking habits may occur among patients with type 2 diabetes who intend to stop smoking, leading to prolonged abstinence from smoking. These findings were not associated with differences in AEs between treatment groups, suggesting a good safety profile for varenicline in smokers with type 2 diabetes. Moreover, the findings confirmed the results of a previous meta-analysis of Pfizer-sponsored varenicline trials.[22]

Throughout the trial, patients in the varenicline group were at least 3 times more likely to quit smoking compared with patients in the placebo group; eCO level–verified CAR in the varenicline group was 31.3% at weeks 9 to 12, 24.0% at weeks 9 to 24, and 18.7% at weeks 9 to 52. The ORs for the varenicline group in the present trial were higher than the ORs in previous RCTs,[17-19] which resulted from lower abstinence rates in the placebo group. These findings support the notion that patients with type 2 diabetes who smoke have greater difficulty quitting when provided with only cessation counseling.

When investigating clinical and demographic features that influenced the CARs, we found that lifetime cumulative smoking history and stronger cigarette dependence, as assessed by GN-SBQ, resulted in less probability of smoking abstinence over time. Smokers with high cigarette dependence were found to have a difficult time quitting,[35] and lifetime cumulative smoking history was shown to have a significant effect on varenicline efficacy.[24] A smoking cessation program alone was significantly less likely to be successful in patients with or affected by smoking rituals (ie, high GN-SBQ scores >23 points). This finding was not surprising given that smoking cessation medications may only alleviate nicotine withdrawal symptoms and reduce reinforcement from smoking but cannot replace the need for smoking-related rituals. A study that examined the effect of adding a nicotine-free cigarette-like plastic stick to a smoking cessation program found that participants who were assigned to use the plastic stick had quit rates that were more than 3-fold higher if their GN-SBQ

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scores were high, whereas those with low GN-SBQ scores showed no advantage from using the plastic stick.[36]

Although it is highly unlikely that varenicline would be less effective in smokers with diabetes, there may be potential concern about the safety of varenicline in patients with type 2 diabetes. Given that varenicline is exclusively excreted in the urine through glomerular filtration and active tubular secretion,[37] patients with type 2 diabetes may have some concerns about oral antidiabetic drugs (such as metformin, glucagon-like peptide-1 agonists, and most dipeptidyl peptidase-4 inhibitors),[38] which are also eliminated via the kidneys by glomerular filtration and tubular secretion and can accelerate kidney failure. The safety profile of varenicline in these patients was similar to that observed in previous varenicline trials involving smokers in the general population,[16,17] which reported nausea, insomnia, abnormal dreams, anxiety, and irritability as the most common AEs.

There were no differences in metabolic and cardiovascular parameters between or within treatment groups. No weight gain was observed, which was somewhat surprising given that smoking cessation is typically associated with increase in body weight.[39,40] Similarly, lack of post–smoking cessation weight gain was reported in a retrospective pooled analysis of 15 RCTs of varenicline use among smokers with type 2 diabetes.[22] Most patients in the present trial were receiving metformin, which might have contributed to preventing weight gain after smoking cessation.

Limitations

This study has several limitations. First, findings in an ambulatory population of asymptomatic patients with type 2 diabetes cannot be extended to those with untreated or uncontrolled diabetes or with clinically significant comorbidities. Therefore, the potential efficacy and safety of varenicline in these subpopulations could not be assessed. Second, we excluded patients who were being treated for major depression, panic disorder, psychosis, bipolar disorder, or other conditions frequently associated with major depressive disorders, thus limiting the generalizability of the results. Third, treatment discontinuation was frequent (approximately 30%) and occurred across both treatment groups, but it was unrelated to the occurrence of AEs. Discontinuation could have affected safety outcomes by reducing the statistical power to detect small changes. Fourth, findings were restricted to a selected population of patients who were highly motivated and ready to quit in the next 30 days, further limiting the generalizability of the results.

Conclusions

Smoking cessation in diabetes is largely neglected, and the efficacy and safety of the antismoking medication varenicline have not been investigated in patients with type 2 diabetes. The findings of the present RCT indicate that inclusion of varenicline in a smoking cessation program for patients with type 2 diabetes with the intention to quit may result in prolonged abstinence without serious AEs. This evidence supports the use of varenicline in diabetes education programs to help patients with type 2 diabetes stop smoking.

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Garibaldi Nesima, assisted with patient recruitment. G. Di Vincenzo's (MD) team at MD, Vittorio Emanuele Hospital assisted with laboratory analyses. R. Vigneri, MD; S. Squatrito, MD; and F. Purrello, MD, Centro per il Diabete e l'Obesità-UOC Endocrinologia, Ospedale Garibaldi Nesima, provided scientific advice. These individuals received no additional compensation, outside of their usual salary, for their contributions. Mike Coughlan edited the manuscript with funding from ECLAT Srl. Staff at Università degli Studi di Catania provided Open Access support under the CRUI-CARE Agreement.

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SUPPLEMENT 1.
Trial Protocol

SUPPLEMENT 2.
eTable 1. Study Schedule and Assessments
eTable 2. Multiple Logistic Regression Model for CAR 9-24 Week
eTable 3. Summary of Adverse Events Occurring in ≥5% of Either Treatment Group
eTable 4. Multiple Logistic Regression Model for CAR 9-12 Week
eTable 5. Multiple Logistic Regression Model for CAR 9-52 Week
eTable 6. Metabolic and Cardiovascular Parameters Measured at Baseline and Week 12

SUPPLEMENT 3.
Data Sharing Statement

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