A randomized controlled trial of the efficacy and safety of varenicline for smoking cessation after acute coronary syndrome: Design and methods of the Evaluation of Varenicline in Smoking Cessation for Patients Post-Acute Coronary Syndrome trial

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Background Patients who continue to smoke after an acute coronary syndrome (ACS) have a significantly increased risk of reinfarction and death compared with those who quit. Varenicline is a first-line smoking cessation therapy with proven efficacy in the general population. However, its efficacy and safety immediately after an ACS are unknown.

Methods The EVITA trial is a multicenter, double-blind, randomized, placebo-controlled trial (NCT00794573). The primary objective is to evaluate the efficacy of varenicline after ACS in achieving biochemically validated smoking abstinence at 24 weeks. The secondary objectives are to examine the efficacy of varenicline for smoking abstinence and reduction in daily cigarette consumption at 52 weeks and to describe the occurrence of adverse events. Three hundred and two patients motivated to quit smoking were enrolled in the United States and Canada from November 2009 to December 2014 while hospitalized with an ACS. These participants were randomized (1:1) to either varenicline (1.0 mg twice daily) or placebo for 12 weeks. The trial includes follow-ups by telephone at weeks 1, 2, and 8 and clinic visits at weeks 4, 12, 24, and 52. Data collected include demographic and clinical characteristics, self-reported smoking, exhaled carbon monoxide (an indicator of current smoking), and adverse events.

Conclusion The EVITA trial will provide novel information concerning the efficacy and safety of varenicline immediately after ACS. If varenicline is efficacious in this population, it will have a major impact on secondary prevention of recurrent clinical events in patients post-ACS. (Am Heart J 2015;170:635-640.e1.)

An acute coronary syndrome (ACS), including myocardial infarction and unstable angina, is a significant medical event, which prompts many individuals to consider lifestyle changes such as smoking cessation.[1] Through using this "teachable moment" immediately after an ACS, it may be possible to increase smoking abstinence in this high-risk population. If these patients continue to smoke, they have a 35% increased risk of reinfarction and death compared with patients who successfully quit.[2] However, quitting is difficult, and two-thirds of patients will return to smoking within 1 year of their ACS.[3]

Varenicline (Chantix/Champix; Pfizer) is a selective $\alpha4\beta2$ nicotinic acetylcholine receptor partial agonist, specifically designed for smoking cessation.[4] Its efficacy is attributed to partial activation of the $\alpha4\beta2$ nicotine receptor, which reduces cravings and withdrawal symptoms during abstinence while also decreasing the reinforcing effects of nicotine.[4] Varenicline is efficacious as a smoking cessation therapy in the general population, including when compared with nicotine replacement therapies (NRTs) and bupropion (Zyban, GlaxoSmithKline).[5-7]

Although NRTs, bupropion, and varenicline have demonstrated efficacy compared with placebo in the general population, patients with cardiovascular disease

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Randomized controlled trial no. NCT00794573.

Funding source: EVITA is an investigator-initiated trial, which received funding and study drug/placebo from Pfizer Canada Inc (Kirkland, Quebec, Canada). Pfizer Canada Inc has no role in the design, conduct, analysis, interpretation of data, or reporting of the EVITA trial.

Submitted March 25, 2015; accepted July 11, 2015.

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0002-8703

http://dx.doi.org/10.1016/j.ahj.2015.07.010

differ in important ways, including age, duration of addiction, and strength of addiction.[3] Nicotine replacement therapies are commonly used in acute cardiovascular patients; however, the hemodynamic effects of nicotine may make NRTs less than ideal in these patients.[8] Safety and efficacy data from randomized controlled trials of NRTs in patients with either acute or stable cardiovascular disease are extremely limited.[9] Trials of bupropion have not shown a significant increase in long-term smoking abstinence compared with placebo in patients with acute cardiovascular disease.[3,10,11] Varenicline has not been evaluated in ACS patients during the initial hospitalization period. The EVITA trial will assess the efficacy and safety of varenicline in these patients. If efficacious, varenicline will have a major impact on secondary prevention of recurrent clinical events in ACS patients.

Objectives

The primary objective of the EVITA trial (clinicaltrials.gov registration NCT00794573) is to evaluate the efficacy of varenicline after ACS in achieving biochemically validated smoking abstinence at 24 weeks. The secondary objectives are to examine the efficacy of varenicline for smoking abstinence and reduction in daily cigarette consumption at 52 weeks and to describe the occurrence of adverse events during study treatment and follow-up.

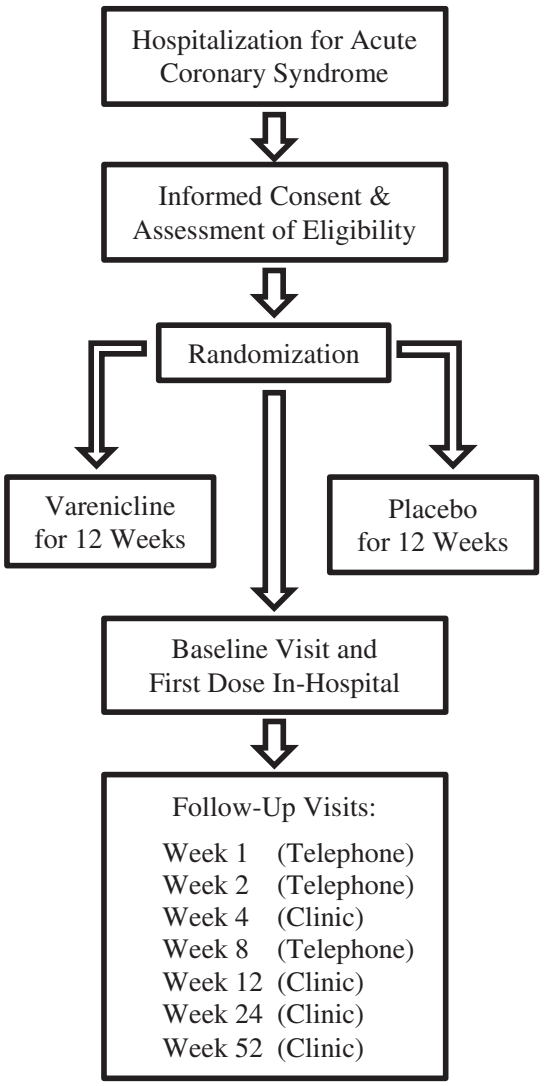
End points

The primary end points are 7-day point prevalence abstinence at week 24, defined as self-reported abstinence in the past week and exhaled carbon monoxide ≤10 ppm, and continuous, abstinence, defined as self-reported abstinence since baseline and exhaled carbon monoxide ≤10 ppm at all follow-up visits up to and including week 24. Secondary end points include 7-day point prevalence and continuous abstinence at week 52, reduction in self-reported daily cigarette consumption by ≥50% at week 52, and the incidence of adverse events throughout the treatment and follow-up periods.

Study design

The EVITA trial is a multicenter, double-blind, randomized, placebo-controlled trial (Figure). Forty centers across the United States and Canada enrolled participants from November 2009 to December 2014. A total of 302 participants motivated to quit smoking were randomized (1:1) to either varenicline or placebo for 12 weeks. Participants randomized to varenicline receive a titrated dose of 0.5 mg once daily for 3 days, followed by 0.5 mg twice daily for 4 days and 1.0 mg twice daily for the remainder of the 12-week treatment period. All participants receive ≥5 minutes of smoking cessation or relapse prevention counseling at each follow-up. Participants and study personnel are blinded to participant treatment allocation. Computer-generated permutated block randomization was used to produce comparable groups and conceal treatment allocation. Treatment is initiated in hospital, with ≥1 dose taken before or at the time of discharge from hospital. Adherence is monitored through self-report and the return of unused study medication. Concomitant use of other smoking cessation pharmacotherapies is not permitted during the treatment period. However, participants who are still smoking at the end of the treatment period are permitted to use other smoking cessation therapies during follow-up, and this use is reported to study personnel at each follow-up visit. Participants are encouraged to use additional behavioral counseling outside the trial (including during the treatment period), which is also recorded at each visit.

Figure



Trial flow chart.