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Nicotine Patch Therapy in Smoking Cessation Reduces the Extent of Exercise-Induced Myocardial Ischemia

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Objectives. **We sought to determine the effects of nicotine patch therapy, when used to promote smoking cessation, on myocardial ischemia in patients with coronary artery disease.**

Background. **Nicotine patches substantially increase quit rates among cigarette smokers, but their safety in patients with myocardial ischemia who are attempting to quit smoking is unknown.**

Methods. **This is a prospective study using exercise thallium-201 single-photon emission computed tomography (SPECT) to assess serial changes in the total and ischemic myocardial perfusion defect size at baseline while patients were smoking and during treatment with 14- and 21-mg nicotine patches. Entry criteria required that patients 1) smoked ≥1 pack of cigarettes per day; 2) had known coronary artery disease; and 3) had myocardial ischemia (i.e., ≥5% reversible perfusion defect) on SPECT. All patients performed symptom-limited treadmill exercise, and the baseline SPECT study served as its own control. We interpreted and computer quantified the SPECT images with no knowledge of the testing sequence.**

Results. **Thirty-six of the 40 enrolled patients had exercise SPECT at baseline and during treatment with at least 14-mg nicotine patches. These patients had an initial perfusion defect size of 17.5 ± 10.6% while smoking an average of 31 ± 11 cigarettes per day for 40 ± 12 years. A significant reduction in the total perfusion defect size ($p < 0.001$) was observed from baseline (17.5 ± 10.6%) to treatment with 14-mg (12.6 ± 10.1%) and 21-mg (11.8 ± 9.9%) nicotine patches. This reduction occurred despite an increase in treadmill exercise duration ($p < 0.05$) and higher serum nicotine levels ($p < 0.001$). There was a significant correlation between the reduction in defect size and exhaled carbon monoxide levels ($p < 0.001$) because patients reduced their smoking by ~74% during the trial.**

Conclusions. **Nicotine patches, when used to promote smoking cessation, significantly reduce the extent of exercise-induced myocardial ischemia as assessed by exercise thallium-201 SPECT.**

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The long-term cardiovascular health risks associated with cigarette smoking are well established, particularly with regard to the development of coronary artery disease and myocardial infarction (1). For this reason, smoking cessation is clearly desirable but often difficult to achieve owing to nicotine addiction (2). Although patients who use nicotine patches have over twice the long-term success rate for stopping smoking compared with those who receive placebo (3), there is still much concern by physicians regarding nicotine treatment in patients with coronary artery disease. Much of the concern stems from a few case reports in 1992 of acute myocardial infarction in men who were using nicotine patches while continuing to smoke cigarettes (4). In 1992, a Food and Drug Administration Advisory Committee reviewed these cases and concluded that the occurrence rate of myocardial infarction was no greater than that expected for a population of middle-aged smokers (5). However, many physicians and patients remain skeptical, because the safety of nicotine patches in smokers who have coronary artery disease and ischemia is not yet known. Of particular concern is that patients may continue to smoke while using nicotine patches, which can result in higher plasma levels of nicotine than smoking alone. Nicotine activates the sympathetic nervous system, which generally increases heart rate and blood pressure, and may also induce coronary vasoconstriction (6). This interplay of effects may lead to diminished myocardial blood flow at times of heightened demand. Thus, patients with occult coronary artery disease could potentially develop worsening manifestations of myocardial ischemia when given nicotine patches.

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Abbreviations and Acronyms

ECG = electrocardiogram, electrocardiographic
PDS = perfusion defect size
SPECT = single-photon emission computed tomography (tomographic)

The purpose of this pilot investigation was to determine whether nicotine patch therapy, when used to promote smoking cessation, could affect the extent of exercise-induced myocardial ischemia in patients with coronary artery disease. Exercise thallium-201 single-photon emission computed tomography (SPECT) was used to assess sequential changes in myocardial ischemia within the same patients before and after initiation of nicotine therapy. We chose SPECT for this study because it affords an accurate quantitative assessment of left ventricular ischemia (7,8), which is directly related to the risk of subsequent cardiac events (9–11).

Methods

Patients. The study group consisted of 40 patients (35 men and 5 women, mean [± SD] age 55 ± 10 years) who 1) had coronary artery disease on angiography; 2) smoked ≥1 pack of cigarettes per day but had a strong desire to quit; and 3) had a qualifying abnormal SPECT (≥5% exercise-induced reversible perfusion defect). Patients were excluded if they had unstable angina, recent (<3 months) coronary angioplasty or bypass surgery, significant valvular heart disease or intolerance to nicotine preparations.

Study design. This was a single-center, longitudinal pilot study evaluating the effects of nicotine patch therapy in smoking cessation on exercise-induced myocardial ischemia. The study protocol was approved by the institutional review boards of both The Methodist Hospital and Baylor College of Medicine, and all patients gave written informed consent.

Patients meeting the entry criteria were evaluated in the outpatient clinic and were weaned off antianginal medications, including nitrates, beta-blockers and calcium antagonists. In hypertensive patients, angiotensin-converting enzyme inhibitors were substituted for beta-blockers and calcium antagonists for blood pressure control. Patients were allowed to take sublingual nitroglycerin if needed for chest pain. After initial evaluation, a baseline symptom-limited treadmill exercise test was performed using the Bruce or modified Bruce protocol, followed by thallium-201 SPECT.

Patients who had a reversible perfusion defect ≥5% were started on 14-mg nicotine patches (Nicoderm) and encouraged to stop smoking. The patches were applied at the same time each morning and maintained for a 24-h period. After a minimum of 3 days (mean 8.6 ± 4.3), exercise SPECT was repeated. Patients were then given 21-mg nicotine patches to be worn for 24 h for a minimum of 3 days (mean 7.6 ± 2.5), followed by a third exercise SPECT. Patients performed symptom-limited exercise using the same treadmill protocol on the second and third exercise tests as on the baseline study.

Before each exercise test, exhaled carbon monoxide levels were determined and serum nicotine and cotinine levels were drawn for subsequent analysis. Expired carbon monoxide levels were determined using the Bedfont Micro Smokelyzer and expressed in ppm. The frozen plasma samples were sent to Wisconsin Analytical and Research Services, where they were analyzed for nicotine and cotinine using gas liquid chromatography (12).

Treadmill exercise test and stress electrocardiogram. Rest heart rate, blood pressure and a 12-lead electrocardiogram (ECG) were recorded before treadmill exercise and at 1-min intervals during exercise with constant monitoring of leads II, V_5 and V_6. The patients were queried as to the presence of chest pain throughout the exercise test. Electrocardiographic ischemia was defined as ≥1 mm ST segment depression during exercise.

Single-photon emission computed tomography. Thallium-201 SPECT was performed by the method previously reported from our laboratory (7,9,13,14). At peak exercise, 3 mCi of thallium-201 was injected intravenously and flushed with saline solution. Images were acquired using a large field-of-view, single-crystal, rotating gamma camera (ADAC ARC 3000/3300) equipped with a high resolution, parallel-hole collimator. Image acquisition was performed over a 180° anterior arc at 6° intervals and for 40 s per image. Imaging commenced 5 min after completion of the exercise test and was repeated 4 h later.

Computer quantification of tomographic images. Our method of SPECT quantification has been previously described in great detail (7,9). The stress and redistribution SPECT images were computer quantified and displayed as polar maps by one experienced investigator (J.J.M.) who had no knowledge of the time sequence of the three SPECT studies per patient or the carbon monoxide, nicotine and cotinine results. The raw data polar maps for each patient were statistically compared with those in an exercise normal data bank consisting of 150 patients with a low (<5%) likelihood of coronary artery disease to determine the total left ventricular perfusion defect size (PDS) and the extent of scintigraphic scar and ischemia. The intraobserver and interobserver reproducibility of our method for quantifying perfusion defects is excellent, with correlation coefficients of 0.98 and 0.97, respectively (15). Furthermore, based on a previous study evaluating the reproducibility of sequential SPECT imaging, a ≥9% absolute change in PDS defines the 95% confidence limit for a reliable change beyond the variability of the technique (14).

Statistical analysis. The primary end point of this study was the group mean absolute percent change in the total PDS from baseline compared with during treatment with 14- and 21-mg nicotine patches. Based on our previous study describing the reproducibility of exercise SPECT (14), a sample size of 40 patients had 80% power to detect a 4% absolute percent change in PDS from baseline. Secondary analysis included the effects of smoking cessation and nicotine patches on ischemic PDS, the duration of treadmill exercise and rest/exercise hemodynamic variables.

Differences in mean scintigraphic, treadmill, carbon monoxide, nicotine and cotinine values from baseline to 14- and 21-mg patch therapy were assessed by repeated measures analysis of variance. This was used to avoid the multiple comparisons issue that arises when pairwise comparisons are made across time points. In this regard, one hypothesis test (and one p value) was generated for each dependent variable. However, because alpha error accumulates across each dependent variable, a multiple comparison adjustment was executed using the Bonferroni approach. A *t* test was used to compare nicotine, cotinine and carbon monoxide levels between patients who either did or did not have a ≥9% decrease in their total PDS. Multiple linear regression analysis determined the relation between changes in PDS and observed changes in carbon monoxide, nicotine and cotinine levels, as well as specific exercise variables. All data are presented as mean value ± SD. A p value <0.05 was considered significant.

Results

A total of 40 patients signed informed consent and entered the trial. Of these, 36 completed at least two SPECT studies (baseline and 14-mg nicotine patch), and so were considered evaluable for the primary end point. The reasons for the remaining dropouts will be described later.

The baseline characteristics of the study group are shown in Table 1. Most patients were male, had significant risk factors for coronary artery disease and were taking anti-ischemic medications before enrollment. Virtually all patients had a history of exertional angina. The patients enrolled smoked for 40 ± 12 years, and the mean number of cigarettes currently smoked per day was 31 ± 11.

Table 1. Baseline Characteristics

Age (yr)	55 ± 10
Male	32 (89%)
Female	4 (11%)
Race/ethnicity	
Black	7 (19.4%)
White	26 (72.2%)
Hispanic	3 (8.4%)
Risk factors for CAD	
Positive family history	29 (80.6%)
Hyperlipidemia	11 (30.6%)
Diabetes mellitus	3 (8.3%)
Hypertension	20 (55.6%)
Claudication	5 (13.9%)
History of angina	35 (97.2%)
Cardiac history	
Angina (yr)	4.0 ± 4.9
Prior MI (non-Q wave)	7 (19.4%)
Prior CABG	7 (19.4%)
Prior PTCA	8 (22.2%)
CCS class (angina)	
I	23 (63.9%)
II	13 (36.1%)
Antianginal therapy before enrollment	
Calcium antagonists	19 (52.8%)
Beta-blockers	15 (41.7%)
Nitrates	21 (58.3%)
ASA	35 (97.2%)
Smoking history	
Years smoked	40 ± 12
Cigarettes smoked/day	31 ± 11

Data presented are mean value ± SD or number (%) of patients. ASA = aspirin; CABG = coronary artery bypass graft surgery; CAD = coronary artery disease; CCS = Canadian Cardiovascular Society; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty.

Treadmill exercise test results (Table 2). The rest heart rate and blood pressure were similar at baseline and during treatment with nicotine patches. Patients also had no significant change in any of their treadmill exercise hemodynamic variables from baseline to 14- and 21-mg patch therapy. Fourteen patients had exercise-induced ST segment depression during the baseline exercise test. In these patients, the time to 1 mm ST segment depression significantly increased from 352 ± 132 s at baseline to 436 ± 121 s on 14-mg and 417 ± 133 s on 21-mg patches ($p < 0.01$). Four patients (29%) had resolution of their ST segment depression after the baseline study. Exercise duration evaluated in all patients significantly increased from baseline values (Table 2).

Group scintigraphic variables (Table 3). A significant reduction in the total exercise-induced PDS ($p < 0.001$) was observed from baseline (17.5 ± 10.6%) to treatment with 14-mg (12.6 ± 10.1%) and 21-mg (11.8 ± 9.9%) nicotine patches. The reduction in PDS was associated with a significant reduction in the number of cigarettes smoked per day ($p < 0.001$) and exhaled carbon monoxide levels ($p < 0.001$). This improvement in myocardial perfusion occurred despite significant increases in treadmill exercise duration (Table 2) and nicotine and cotinine blood levels from baseline to 14- and 21-mg nicotine patches (Table 3). The benefits of smoking cessation on myocardial perfusion were largely observed within the first week of patch therapy (baseline to 14-mg patch) with a minimal further reduction in the PDS while the subjects were on 21-mg nicotine patches.

Individual scintigraphic results (Fig. 1). Based on our previous results with sequential exercise SPECT (14), a ≥9% temporal change in total PDS occurs in only 5% of patients by chance alone. This is the threshold for describing a significant change in PDS in an individual patient. Thus, only one or two of the 36 patients in the present study should have had this magnitude of change. Yet, 11 (31%) of the 36 patients had a ≥9% decrease in their total PDS from baseline to 14-mg patch therapy and 10 (29%) of 34 patients from baseline to 21-mg patch therapy (Fig. 1). No patient had a ≥9% increase in PDS from baseline values. Patients whose defects decreased by ≥9% had a significantly greater reduction in carbon monoxide levels (−13.7 ± 8.3 vs. −7.6 ± 7.1 ppm, $p = 0.031$) and a lesser increase in serum nicotine levels (3.1 ± 10.8 vs. 11.2 ± 11.8 ng/ml, $p = 0.06$) compared with those who did not show an improvement. This result is not unexpected, because changes in nicotine levels after patch application were predominantly determined by reductions in cigarette smoking (i.e., exhaled carbon monoxide levels). In fact, a significant and direct

Table 2. Treadmill Exercise Variables

	Baseline (n = 36)	Nicotine Patch 14 mg (n = 36)	Nicotine Patch 21 mg (n = 34)	p Value
Rest				
HR (beats/min)	79 ± 15	79 ± 14	79 ± 15	NS
SBP (mm Hg)	137 ± 19	136 ± 18	140 ± 18	NS
DBP (mm Hg)	81 ± 11	83 ± 12	85 ± 9	NS
RPP (HR·SBP)	10,782 ± 2,145	10,580 ± 1,971	10,998 ± 2,106	NS
Exercise				
HR (beats/min)	141 ± 16	141 ± 17	142 ± 18	NS
% target HR	86 ± 8	86 ± 9	86 ± 10	NS
SBP (mm Hg)	187 ± 25	184 ± 24	184 ± 19	NS
DBP (mm Hg)	86 ± 14	87 ± 22	89 ± 22	NS
RPP (HR·SBP)	26,462 ± 5,243	25,929 ± 4,787	26,282 ± 5,025	NS
Exercise duration (s)	452 ± 123	472 ± 116	493 ± 108	0.014
Time to 1-mm ST segment depression (s) (n = 14)	352 ± 132	436 ± 121	417 ± 133	<0.01

Data presented are mean value ± SD. DBP = diastolic blood pressure; HR = heart rate; RPP = rate–pressure product; SBP = systolic blood pressure.

relation was observed between changes in nicotine and carbon monoxide levels over the course of the study ($r = 0.63$, $p < 0.001$).

Multivariate linear regression analysis (Table 4). Multivariate linear regression determined which variables most influenced a change in total PDS over the time course of this study. Numerous independent variables were assessed, including baseline scintigraphic results, medical history information, nicotine and cotinine levels and the number of cigarettes smoked per day. The baseline PDS and the final carbon monoxide level were the only two variables that significantly influenced the final defect size. Patients with initially large perfusion defects had the greatest opportunity for change, and this occurred predominantly in patients who had the largest reductions in carbon monoxide levels. Based on regression analysis, 76% of the observed changes in PDS could be explained by the initial defect size and the serial change in carbon monoxide level ($r = 0.87$, $p = 0.0013$). Nicotine and cotinine plasma levels did not appear to temporally alter PDS.

Table 3. Scintigraphic and Smoking Variables

	Baseline (n = 36)	Nicotine Patch 14 mg (n = 36)	Nicotine Patch 21 mg (n = 34)	p Value
Perfusion defect size (%LV)				
Total	17.5 ± 10.6	12.6 ± 10.1	11.8 ± 9.9	<0.001
Ischemia	10.1 ± 8.5	7.2 ± 6.7	6.7 ± 6.3	0.036
Carbon monoxide (ppm)	23.3 ± 10.5	13.8 ± 9.6	12.4 ± 8.8	<0.001
Nicotine (ng/ml)	15.8 ± 8.3	24.2 ± 12.0	30.4 ± 10.8	<0.001
Cotinine (ng/ml)	290 ± 137	338 ± 186	422 ± 224	<0.002
Cigarettes smoked/day	31 ± 11	11 ± 10	8 ± 7	<0.001

Data presented are mean value ± SD. LV = left ventricle.

Clinical outcome. Four of the 40 enrolled patients withdrew from the study after the baseline exercise test. Two more patients completed only the 14-mg nicotine patch phase but were included in the analysis. The four patients who withdrew did so for a variety of reasons: one patient discontinued for job-related personal reasons; another had a back injury the day after enrollment and was unable to ambulate; a third patient had angina before and after nicotine patch therapy and was referred for elective coronary artery bypass graft surgery; and the last patient had an acute myocardial infarction the morning after his baseline exercise test before starting nicotine patch therapy.

The two patients who did not complete the study protocol had nausea and vomiting on nicotine patches. In one patient, symptoms quickly resolved after stopping 21-mg patches. The other patient had nausea on the 14-mg patch, which was

Figure 1. Mean and individual patient changes in exercise-induced left ventricular (LV) perfusion defects from baseline to 14- and 21-mg nicotine patch therapy. **Bold lines** = patients whose perfusion defect size changed by ≥9% (beyond technique variability).

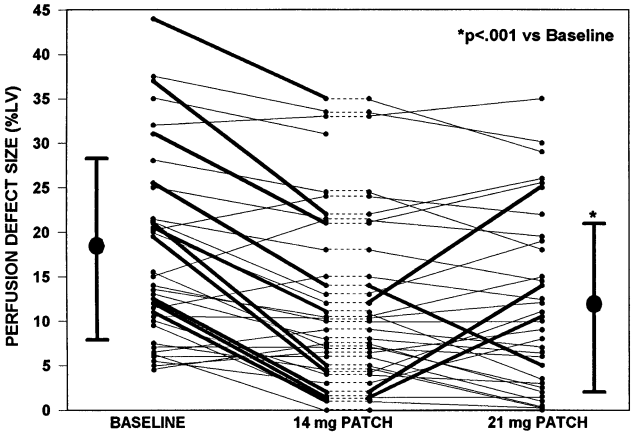

Table 4. Multivariate Analysis: Determinants of Perfusion Defect Size Reduction From Baseline to 21-mg Nicotine Patch Therapy

Variable	p Value
Baseline perfusion defect size	0.0001
Baseline carbon monoxide level	0.91
Final carbon monoxide level	0.005
Baseline nicotine level	0.51
Baseline cotinine level	0.81
History of hypertension	0.55
History of diabetes mellitus	0.26
History of hyperlipidemia	0.17
Family history of CAD	0.11
History of COPD	0.88
History of angina	0.60
Prior MI	0.86
Cigarettes smoked/day	0.16

COPD = chronic obstructive pulmonary disease; other abbreviations as in Table 1.

exacerbated by excessive alcohol consumption. His symptoms resolved while he was maintained on patch therapy. Both patients later developed worsening angina and were referred for bypass surgery. The latter patient continued on 21-mg patches until the day of the operation. Of note, both patients had large ischemic perfusion defects on their baseline exercise SPECT (35% and 37%, respectively).

The most common side effects with nicotine patches were skin irritation at the patch site (n = 12), nervousness and insomnia (n = 5) and altered taste (n = 5). Ten (28%) of the 36 patients had no side effects on either the 14- or 21-mg patches. Sixteen (44%) of the 36 patients smoked ≤5 cigarettes per day by the end of the study and 19% stopped smoking entirely.

Discussion

Nicotine patch therapy significantly improves quit rates among motivated patients who want to stop smoking (2,3). However, legitimate concerns exist regarding the potential adverse cardiovascular effects of nicotine substitute therapy, particularly in patients with coronary artery disease (2,6). This study demonstrates that nicotine patches, when used to promote smoking cessation, significantly reduce the extent of exercise-induced myocardial ischemia despite higher plasma nicotine levels. These scintigraphic findings are strengthened by the concomitant increased time to exercise-induced ECG ischemia after patch application and smoking cessation. In this regard, nicotine does not appear to pose significant safety concerns for patients who are attempting to quit smoking. The long-term adverse cardiovascular effects of cigarette smoking are well described (1). This study further suggests that carbon monoxide and possibly other components of cigarette smoke, rather than nicotine, may actually be more critical for the development of myocardial ischemia.

The number of patients who had a significant reduction in myocardial ischemia during nicotine patch therapy was particularly striking and far exceeded the known variability attributable to exercise SPECT (14). Thirty-one percent of the patients in the current study had a significant reduction in PDS—a result similar to that previously reported by our group after anti-ischemic drug therapy in patients with stable coronary artery disease (13). Furthermore, the patients with the largest PDS at baseline had the most dramatic improvement. Because cardiac risk is known to be directly related to the extent of the exercise-induced PDS (9–11), the significant reduction in defect size observed in this study would imply that nicotine patches are safe when used for the purpose of smoking cessation.

Possible mechanisms for observed reduction in myocardial ischemia. This study was designed to allow examination of several potential mechanisms for the observed changes in exercise-induced myocardial ischemia. We prospectively collected hemodynamic information on each treadmill test and measured serial carbon monoxide, nicotine and cotinine levels. The reduction in PDS was associated with a significant reduction in exhaled carbon monoxide, as demonstrated by multiple linear regression analysis. The results of this investigation, focusing on the quantitative aspects of myocardial ischemia, are consistent with earlier studies demonstrating that increasing levels of carboxyhemoglobin exacerbate treadmill exercise-induced ST segment changes in patients with coronary artery disease (16,17). Although our results implicate carbon monoxide, other components of cigarette smoke might also induce myocardial ischemia due to effects on the coronary vasculature or at the cellular level.

The effects of nicotine on coronary microvascular resistance were not directly measured in this study, but rest and exercise hemodynamic data did not significantly change from baseline after the use of nicotine patches, despite significant increases in serum nicotine and cotinine levels. The lack of any distinct hemodynamic effect from higher nicotine levels is most likely due to nicotine tolerance (18) and may explain why myocardial ischemia did not worsen, even in patients who continued to smoke. Although the overall results of this study are compelling, the lack of a placebo control group limits conclusions regarding the interplay between nicotine and carbon monoxide, and their individual effects on myocardial ischemia. A conservative interpretation of our results is that carbon monoxide from smoking worsens myocardial ischemia to a greater extent than nicotine.

Study limitations. This pilot study did not have the power to detect potential adverse clinical events associated with nicotine patch therapy. Rather, we chose to examine serial changes in myocardial perfusion as a surrogate end point to assess safety. The observed reduction in scintigraphic ischemia with nicotine patches supports their safety in smoking cessation, compared with the alternative of continuing to smoke. The scintigraphic results are strengthened by the observed increased time to exercise-induced ST segment depression after smoking cessation with the aid of nicotine patches. Our results may help explain one of the findings from the Lung

Health Study, which showed a lower cardiac event rate among patients using nicotine gum (Nicorette) who quit or decreased smoking, compared with those who continued to smoke (19). In other studies, smoking has been shown to be an important trigger of myocardial ischemia during normal life activities (20) and can acutely reduce rest regional myocardial blood flow in patients with coronary artery disease who have exercise-induced ischemia (21). All of these studies support our observation that a higher nicotine level from patch administration is a safe tradeoff if it encourages patients to quit smoking.

The lack of a placebo control group might raise concern about the validity of our results. However, the patients we studied were clinically and scintigraphically very similar to those who had sequential exercise SPECT in a previous placebo-controlled trial from our laboratory (13). Based on our data establishing the reproducibility (95% confidence limits) of computer-derived assessments of myocardial perfusion by SPECT (14), one would expect only one or two patients in the present study to have a significant decrease in PDS, and yet this occurred in 11 (31%) of 36 patients. Furthermore, the 5.7% absolute mean reduction in PDS from baseline to treatment with 21-mg patches is a statistical result that has >95% power. Therefore, although a placebo group was not incorporated into the study design, the observed changes we report exceed the known variability associated with sequential thallium-201 SPECT.

Clinical implications. The present study demonstrates that the extent of exercise-induced left ventricular ischemia is significantly reduced in patients with coronary artery disease who attempt to quit smoking while using nicotine patches. The use of nicotine substitutes could have important health implications for the 3 to 5 million smokers with coronary artery disease in the United States today who would derive both an immediate and long-term health benefit if they were to stop smoking.

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