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Smoking reduction fails to improve clinical and biological markers of cardiac disease: A randomized controlled trial

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Abstract

Cigarette reduction has been proposed as a treatment goal for smokers who are not interested in stopping completely. This randomized controlled trial was designed to determine the effect of a smoking reduction intervention on smoking behavior, symptoms of heart disease, and biomarkers of tobacco exposure. It included 152 patients with heart disease who did not intend to stop smoking in the next 30 days. Participants were randomly assigned to smoking reduction (SR) or usual care (UC). SR subjects received counseling and nicotine replacement therapy to encourage 50% reduction in cigarettes per day (CPD). They were followed at 1, 3, 6, 12 and 18 months to assess smoking, heart disease symptoms, quality of life and nicotine, cotinine, carbon monoxide

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(CO), white blood cell (WBC) count, fibrinogen, hs-C-reactive protein (hs-CRP), F₂-isoprostane, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol and its glucuronides (total NNAL), and 1-hydroxypyrene (1-HOP). At 6 months SR participants reduced by 10.9 CPD, compared with 7.4 CPD in UC (difference NS). At 18 months, 9/78 SR vs. 9/74 UC participants quit smoking. There were no significant differences between treatment groups in angina, quality of life or adverse events, nicotine, cotinine, CO, WBC count, fibrinogen, hs-CRP, F₂-isoprostane, total NNAL or 1-HOP levels at any time point. To determine if smoking reduction, regardless of treatment condition, was associated with improved outcomes, we compared all subjects at 6 months to baseline (mean reduction in CPD from 27.4 to 18.1, $p < .01$). There were no significant changes in outcome variables except CO, which decreased by 5.5 ppm ($p < .01$). There were also no significant improvements considering only subjects who reduced by 50%, or those who had no history of reduction prior to enrollment in the study. The SR intervention did not significantly reduce CPD or toxin exposure, or improve smoking cessation or clinical outcomes compared to UC. These results emphasize the importance of abstinence for smokers with heart disease to minimize health risks from tobacco.

Introduction

Cigarette smoking promotes atherosclerosis and is associated with an increased risk of sudden death, myocardial infarction, angina, peripheral vascular disease and stroke (U.S. Department of Health and Human Services [USDHHS], 1983). In patients with cardiac disease who stop smoking, there is a rapid decline in the recurrence of acute cardiovascular events and the symptoms of atherosclerotic disease (U.S. Surgeon General's Report, 1990).

Current efforts to reduce harm from cigarette smoking stress total abstinence as the target outcome. Intervention in patients hospitalized for acute coronary syndromes results in higher than average cessation rates but treatment in ambulatory care settings results in only modest rates (Thomson & Rigotti, 2003). Therefore, alternative strategies that might reduce exposure to cigarette smoke are of interest. Epidemiological and clinical studies demonstrate a dose-response curve between the amount smoked and cardiovascular risk (USDHHS, 1983); this relationship supports investigation of methods to reduce smoking as an alternative to abstinence.

Harm reduction strategies have been controversial because of: (a) concern that this goal will detract from efforts to completely stop smoking, (b) data that suggest smokers will compensate by smoking fewer cigarettes more intensively or revert to other means to attain the nicotine levels to which they are accustomed (Hatsukami et al., 2002), and (c) lack of demonstrated health benefits. A recent qualitative review, however, examined 19 studies and found no evidence that reduction undermined future cessation, and 16 studies found a positive association between reduction and future cessation (Hughes & Carpenter, 2006).

The safety and widespread availability of nicotine replacement products raise the possibility that reduced smoking accomplished with their aid may improve cardiovascular health when compared to the attendant morbidity and mortality associated with continued smoking. These facts suggest that for patients with atherosclerotic cardiovascular disease (ASCVD)

who cannot stop smoking, alternative treatment to reduce smoking might be preferable to no intervention at all.

We conducted a randomized controlled trial to examine the effects of an intervention to reduce cigarette smoking in people who were not interested in quitting. We selected a population of patients with ASCVD in order to maximize the opportunity to observe changes in clinical disease outcomes. We also examined the effect of the intervention on a set of biological measures of tobacco toxin exposure, chosen to reflect pathophysiological pathways for both heart disease and cancer. Secondary data analyses permitted assessment of the association between successful smoking reduction and biomarker measures.

Method

Study Design

The study design was a randomized controlled trial. The protocol was approved by the University of Minnesota and Minneapolis Veterans Affairs Medical Center (VAMC) Human Subjects Committees, and all participants provided informed consent.

Setting

The protocol was conducted at the University of Minnesota and Minneapolis VAMC.

Participants

Inclusion criteria were cigarette smokers aged 18–80 who smoked at least 15 cigarettes per day (CPD) and had one of eleven cardiovascular disorders: history of myocardial infarction, coronary artery bypass surgery, angioplasty, stent placement, thrombolytic therapy, angina, arrhythmia, cardiac arrest, greater than 50% coronary artery stenosis by angiography, ischemia on exercise tolerance testing or congestive heart failure. Medical record review was used to confirm diagnoses using standard definitions. Participants were required to confirm that they were unwilling or uninterested in setting a stop smoking date in the next 30 days. Exclusion criteria were (a) unstable angina within the past 2 weeks, (b) unstable psychiatric or substance use disorders, or (c) contra-indications to nicotine replacement therapy (including pregnancy or intention to become pregnant).

Participants were recruited by advertising in newspapers, on the radio and on posters at the two medical centers. Cardiology clinicians were invited to refer patients. At the VAMC a list of patients with heart disease who were also documented to be smokers was developed from the electronic medical record and patients were invited to participate in the study with providers' permission.

Intervention

Smoking reduction (SR)—Three experienced tobacco cessation counselors were trained in the intervention protocol. We attempted to maintain a consistent counselor assignment throughout the course of treatment. Visits were scheduled at 1 and 2 weeks and at 1, 2, 3, 4, 6, 12 and 18 months. The initial in-person visit was followed by a combination of in-person (weeks 1 and 2, months 1 and 3) and telephone care (all others). During the 4, 6, 12 or 18

month calls, if a subject expressed interest in reinitiating reduction treatment additional intervention visits could be scheduled. Thus, support for reduction was available for 18 months.

The SR intervention included behavioral and pharmacological components (nicotine replacement therapy, NRT). The goal of treatment was to reduce smoking by at least 50% of the baseline level, but also by as much as possible. The counseling protocol provided specific information about the relationship between smoking and heart disease. Counselors described specific smoking reduction strategy options, such as eliminating cigarettes at work, in the home, or least favorite or most favorite cigarettes of the day. Since there was inadequate evidence that any one of these strategies was more effective than another, participants were encouraged to choose those that were most appealing. At each visit counselors reminded participants that abstinence from smoking was the optimal goal.

Participants were encouraged to substitute a piece of 4 mg nicotine gum for each cigarette they eliminated in order to reduce nicotine withdrawal symptoms. If a participant used more than six pieces of gum per day we suggested that he or she switch to nicotine patches to provide more adequate replacement. If participants did not accomplish reduction with nicotine gum alone they were invited to try nicotine patches alone. Flexibility of dosing with NRT was incorporated because NRT was considered an adjunctive therapy and not the sole method of intervention.

Usual care (UC)—The UC group had an initial, brief in-person visit. The counselor reiterated the importance of abstinence from cigarette smoking for patients with heart disease. Participants were encouraged to seek smoking cessation assistance from their health care provider(s), but no additional counseling or pharmacological treatments were delivered.

Data collection

Study personnel who provided the intervention also performed data collection for participants in both treatment groups. The decision to vary from an independent approach to data collection was based on inability to blind data collectors to treatment condition, and the repetition of information needed by both counselors and data collectors.

Demographic data and medical histories were obtained at baseline. We collected detailed information on past smoking and attitudes toward stopping smoking compared to reducing smoking. Subjects reported heart disease symptoms and severity and completed the Ferrans and Powers Quality of Life Index for cardiac patients (Ferrans & Powers, 1984).

Participants underwent a 6-minute walk test to assess exercise tolerance (Bittner, 1997; Montgomery et al., 1996; O’Keeffe, Lye, Donnellan, & Carmichael, 1998). The standard outcome of distance walked was measured and the proportion of subjects who completed the test was also calculated, because many subjects had a high degree of impairment. Expired carbon monoxide (CO) testing was performed and total cotinine (cotinine plus cotinine-glucuronide) and total nicotine (nicotine plus nicotine-glucuronide) in urine were quantified by GC/MS (Hecht, Carmella, Chen et al., 1999; Hecht, Carmella, & Murphy, 1999). Subjects submitted blood specimens for measurement of white blood cell count and

fibrinogen, and urine specimens for measurement of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) and its glucuronides (total NNAL), metabolites and biomarkers of uptake of the tobacco-specific lung carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) in urine (Carmella, Akerkar, Richie, & Hecht, 1995; Hecht, Carmella, Chen et al., 1999). We measured 1-hydroxypyrene (1-HOP) in urine, a widely accepted biomarker of polycyclic aromatic hydro-carbon (PAH) uptake (Carmella, Le, & Hecht, 2004). High sensitivity C-reactive protein (hs-CRP) and F₂-isoprostane (a circulating product of lipid peroxidation) were measured in blood samples at baseline and 6 months.

Follow-up visits were conducted at 1, 3, 6, 12 and 18 months. Subjects described smoking behaviors, symptoms and severity of heart disease, quality of life and adverse events. They performed a 6-minute walk test, and provided specimens to measure biomarkers of tobacco exposure.

Sample Size

Power analysis was based on a 2-sided 2-sample *t*-test to compare the percentage reduction of smoking from baseline at an alpha level of 0.05, assuming equal sample sizes of 75 per group, a standard deviation of 0.4, allowing for a 10% reduction in the UC group and targeting a 30% reduction in the SR group. Given these specifications, power was calculated to be 86%.

The observed standard deviation was larger than anticipated. Given sample sizes of 119, 106 and 99 at 6, 12 and 18 month follow up, respectively, we had 80% power to detect an absolute increase in cigarette reduction of 20% at 6 months, and 70% at 12 and 18 months.

Randomization

Participants were randomly assigned to receive SR treatment or UC by a computer-generated scheme, blocked in groups of 10 by site. After enrollment, treatment assignment was revealed by opening a sealed envelope that noted the assigned treatment condition.

Statistical methods

Baseline sample characteristics, past smoking behaviors and attitudes toward smoking reduction were compared between the UC and SR treatments using *t*-tests or chi-squared tests. Study retention rates were compared between the UC and SR treatments using Fisher's exact test.

The amount of smoking reduction for each visit was defined as the difference between number of cigarettes smoked at baseline and the number smoked at that visit. Student's *t*-tests were conducted on the differences to compare treatments. Reduction amounts and percent reduction for a given visit were calculated for a participant if data for both the given visit and baseline were obtained. For participants who ceased smoking during the study, or where any variable amount was 0 at the follow-up visit, the percent reduction (for that variable) for that visit was set to 100.

Clinical outcomes were compared between the UC and SR treatments using *t*-tests or chi-squared tests. Biomarker outcomes were compared between UC and SR treatments using *t*-

tests on the rate of change per month from baseline to the last follow-up visit. The proportion of participants experiencing any severe adverse event or cardiac event was compared between the UC and SR treatments using Fisher's exact test.

Results

Participant flow

There were 1042 respondents and referrals in response to advertising and invitations that were pre-screened to confirm that they currently smoked at least 15 CDP. Of the resulting 254 patients who were fully screened, 181 were eligible and 152 were enrolled. Reasons for exclusion were no documented heart disease ($n=34$), plans to quit smoking in the next month ($n=25$), and smoking below the cut-off level ($n=5$).

Baseline characteristics—The baseline characteristics of the study population are shown in Table 1. The mean age was 58 years and 88% of the population was male. The baseline level of smoking was obtained at the time of screening and at the time of enrollment with the concern that participants might reduce prior to randomization, since they were recruited because of interest in smoking reduction rather than smoking abstinence. The mean number of CPD was 27 at both time points. The average Fagerström Test for Nicotine Dependence (FTND) score was 6, indicating a relatively high level of dependence. Past peak smoking was 42 CPD, but many participants had reduced prior to enrollment. This observation is described in detail in a prior publication (Joseph, Bliss, Zhao, & Lando, 2005). Nearly all participants had made prior attempts to stop smoking; on average six times. Approximately three-quarters of subjects had experience with NRT, about half had tried bupropion, but only a minority had tried behavioral counseling. Baseline characteristics were not significantly different between groups.

The most common cardiac diagnoses in the study population were a history of myocardial infarction, angina, greater than 50% stenosis by angiography, or a history of angioplasty. Approximately half had a history of depressive disorder and one third had experienced problems with substance abuse.

Attitudes toward smoking reduction—Ninety percent of participants had tried to cut down on smoking in the past and most had switched to low tar/low nicotine cigarettes. In order to evaluate the reasons for interest in a smoking reduction study, we asked participants about their beliefs about smoking reduction and abstinence. The primary reason smoking reduction was appealing was that it would be healthier; more than 80% endorsed health improvement as a reason for reduction. Nearly 90% of participants believed reduction would improve health "some" or "a great deal." About half thought that NRT was "a great deal safer" than cigarettes, but most did not believe it was safe to smoke and use NRT at the same time.

Numbers analyzed

Follow-up response rates were 82.4%–88.5% at one month, 79.7%–82.1% at 3 months, 75.7%–82.1% at 6 months, 69.2%–70.3% at 12 months, and 64.1%–68.5% at 18 months.

There were no significant differences in response rates between treatment groups. We compared baseline characteristics of respondents to non-respondents at 6 and 18 months and found no differences in sex, number of CPD, FTND, self-rating of overall health, number of heart disease diagnoses or number of other medical diagnoses. Non-respondents to the 6 month follow-up were significantly younger than respondents (mean age of respondents 59.23 years, non-respondents 53.24 years, $p=.0007$); this was not true at the 18 month follow-up.

Intervention characteristics—Of 78 participants in the SR group, 77 reported receipt of smoking intervention, compared to 2 of 74 UC participants. SR participants received an average of 7.49 visits ($SD=2.20$, range 2–11). One of the 2 UC group participants who received intervention received NRT. Among smoking reduction group subjects 57% used nicotine gum, 62% used nicotine patch and 88% used some form of NRT.

Smoking reduction and smoking cessation—The amount of cigarette reduction in the two treatment groups is shown in Table 3. Comparisons of the amount of reduction were significantly different at 1 and 3 months but did not persist at 6, 12 or 18 months. Results show that in the SR group most of the reduction occurred in the first month following initiation of treatment and in the UC group in the first 3 months after study enrollment. Smokers in the SR group decreased consumption from 27.7 CPD at baseline to 17.9 CPD at 18 months, compared to 27.0 CPD at baseline to 18.2 CPD in the UC group (difference not significant). Of note, there was considerable variability in the amount of change of smoking from baseline, including some participants who increased the number of CPD.

At 6, 12 and 18 month follow-up approximately the same number of participants in the SR and UC groups reported abstinence from smoking (7 vs. 5, 6 vs. 4, and 9 vs. 9; respectively).

Clinical outcomes—We compared clinical markers of heart disease between groups at 1, 3, 6, 12 and 18 months (see Table 4). There were no significant differences at any time point in the prevalence of angina, frequency of angina or distributions of CCSC classification (data not shown). There were no differences between groups in the Quality of Life Index at any follow-up point during the course of the study. At 18 months there was a greater decline in distance walked in UC subjects (535 feet vs. 224 feet in SR, $p=.01$), but a significant increase in the proportion of subjects completing the 6-minute walk (SR 30% vs. UC 52%, $p=.039$).

Adverse events—We compared need for urgent cardiac care and serious adverse events (cardiac and total events) between groups (see Table 4). There were no differences in need for urgent cardiac care other than at 6 months ($n=0$ in the SR group vs. $n=5$ in UC, $p=.02$). Serious cardiac events (including myocardial infarction, unstable angina, coronary angiography, stent placement, cardiac bypass surgery, hospital admission for congestive heart failure, arrhythmia and syncope) and other serious adverse events (including hospitalization for noncardiac chest pain, depression, psychosis, pulmonary problems, rash, elective surgery, infection including pneumonia, cerebrovascular disease, bowel obstruction, cancer and renal failure) were roughly equally distributed between treatment groups.

Biomarker data—Changes in biomarker data in the two treatment groups are shown in Table 5. There were no significant differences at any time point between treatment groups in nicotine and cotinine measures, in spite of the fact that the SR group was encouraged to use NRT to reduce smoking. Expired CO levels decreased to a similar degree in both treatment groups. Markers of inflammation and oxidation including WBC count, fibrinogen, hs-CRP and F₂-isoprostanes showed minimal change. Total NNAL and 1-HOP decreased slightly but to a similar extent in both treatment groups (see Table 5).

Secondary analyses—We performed three secondary analyses to examine the association between smoking reduction, regardless of treatment condition, and biomarker measurements. First, because of the observation that smoking reduction occurred in both treatment groups, we compared data from all participants between 6 months and baseline (see Table 6). The 6-month time point was chosen because there was minimal incremental smoking reduction after this time point and data from the full complement of biomarkers was available.

There was a significant reduction in CPD (27.4 to 18.1, $p<.01$). There was a significant decrease in the distance completed in the six-minute walk test (990 feet to 828 feet, $p<.01$) and the proportion completing the test (70% at baseline compared to 50% at 6 months, $p<.01$), and a significant decrease in expired CO (24.5 ppm at baseline to 18.9 ppm at 6 months, $p<.01$). In spite of an average reduction of 9.6 CPD, there were no significant changes in the frequency of angina or the biomarkers nicotine, cotinine, WBC count, fibrinogen, hs-CRP, F₂-isoprostane, total NNAL or 1-HOP.

Second, we examined data from the subgroup of participants who reduced their cigarette smoking by at least 50% between baseline and 6 months ($n=43$; $n=25$ from the SR group and $n=18$ from the UC group). On average they reduced from 26.7 CPD to 6.7 CPD ($p<.01$). The clinical indicators and bio-markers that improved significantly in this subset of participants were expired CO (from 22.2 ppm at baseline to 13.4 ppm at 6 months, $p=0.02$), WBC count (from 7.8 at baseline to 7.2 at 6 months, $p=0.01$) and total NNAL (from 2.3 pmol/mg creatinine at baseline to 1.4 pmol/mg creatinine at 6 months, $p<0.01$). Reductions between baseline and 6 months in nicotine (1599 to 1452 nmol/mg creat) and cotinine (3910 to 3570 nmol/mg creat) were not significant, but may have been influenced by use of nicotine replacement therapy. Fibrinogen, hs-CRP, F₂-isoprostane and 1-HOP were not significantly changed.

Finally, since a prior analysis of baseline data from this study population showed that a large proportion of participants (107/152, 70%) had spontaneously reduced during the natural history of their smoking (prior to enrollment in the study) (Joseph et al., 2005), we compared treatment outcomes in those who had no prior reduction ($n=45$) to those who had reduced on their own in the past ($n=107$) to test the hypothesis that the intervention might be more effective in smokers who had not reduced on their own in the past. Cigarette reduction was similar in past reducers and non-reducers and there was no significant interaction with treatment condition at any time point. Nicotine, cotinine, expired CO, WBC and fibrinogen did not decline significantly in the subgroup of participants who had no history of prior reduction.

Discussion

This study did not find differences between treatment groups with regard to smoking behavior, clinical outcomes of heart disease such as severity of angina and exercise tolerance, or measures of quality of life. This study contributes information about clinical outcomes in patients with heart disease that are of considerable interest because surrogate endpoints, such as biomarkers, are not consistently associated with health outcomes. There were no significant differences in biomarkers of inflammation and oxidation that are considered to be risk factors for cardiac disease, or biomarkers of carcinogenesis. Reduction treatment did not have a positive or negative impact on smoking cessation and although the study size was small, there were no reported complications of concomitant smoking and use of NRT. In general, secondary analyses that give the best potential advantage to smoking reduction (e.g. analyzing only participants who accomplished at least 50% reduction, or only participants who had no experience with smoking reduction prior to enrollment in the study) also failed to demonstrate positive effects.

One explanation for the lack of intervention effect in this study is that participants in both groups were selected on the basis of interest in smoking reduction, and perhaps the behavioral and pharmacological intervention was not more potent than the self-reported interest in reduction. Another explanation may be considerable experience with spontaneous smoking reduction in the past in the study population, indicated by past peak smoking levels of nearly 43 CPD (compared to 27 CPD at the time of enrollment); however, the intervention was equally ineffective in those who had accomplished prior smoking reduction on their own. We have reported additional analyses of reduction prior to enrollment in this study population (Joseph et al., 2005), and this may be an important methodological concern in smoking reduction studies.

The lack of effect of smoking reduction, even by at least 50%, on clinical or biomarker parameters may be explained by compensatory smoking, which was indicated by expired CO measurements in this cohort. In addition, the amount of cigarette reduction may have been insufficient to achieve improvements. There is ongoing debate regarding a possible threshold for harmful health effects of tobacco and potential benefits of smoking reduction being nonlinear (Hughes & Carpenter, 2006). Very low levels of exposure such as a few cigarettes per day (Burns, 2003), occasional smoking (Luoto, Uutela, & Puska, 2000) or environmental tobacco smoke exposure (Law & Wald, 2003) are sufficient to significantly increase the risk of heart disease. Epidemiological evidence suggests even small exposures to tobacco smoke significantly increase the relative risk of an ischemic cardiac event (Pechacek & Babb, 2004). Increased thrombosis, endothelial dysfunction and inflammation occur at low levels of exposure to secondhand smoke (Pechacek & Babb, 2004). It is also possible that smoking reduction must be maintained for a certain duration of time before biochemical or clinical benefits occur (Hughes & Carpenter, 2005).

These results are consistent with other published data that suggest reduction in toxin exposure is not proportional to reduction in CPD. Eliasson et al. (2001) showed that smoking reduction by 50% resulted in 17% CO and 20% plasma thiocyanate reductions. In spite of an average cigarette reduction from 40 CPD to 10 CPD, Hurt et al. (2000) found no

significant decrease in expired CO. Hatsukami et al. (2005) examined the effect of smoking reduction on cardiovascular risk factors using nicotine patches and gum. Among those who reported 40% or more reduction in self-reported CPD ($n=61$), WBC count, HDL-cholesterol, HDL/LDL ratios and ApoB improved, but triglycerides, total cholesterol and ApoA1 did not change and LDL cholesterol increased. There were modest and sometimes transient reductions in tobacco-specific carcinogens that were not proportional to the reduction in cigarettes per day (Hecht et al., 2004).

Our results also are consistent with a population-based study by Godtfredsen et al. (2003) that compared 643 individuals who reported unassisted reduced tobacco consumption by at least 50% to 1379 smokers who reported total abstinence. Smoking cessation was associated with a hazard ratio of 0.71 (95% $CI=0.59-0.85$) but smoking reduction was not associated with a significant reduction in risk of myocardial infarction (hazard ratio 1.15, 95% $CI=0.94-1.40$). A follow-up of 51,210 men and women in Norway showed reducers, compared to continuing heavy smokers, had an adjusted relative risk for dying from (a) any cause, 1.02 (95% $CI=0.84-1.22$); (b) cardiovascular disease, 1.02 (95% $CI=0.75-1.39$); (c) ischemic heart disease, 0.96 (95% $CI=0.65-1.41$); and (d) smoking-related cancer, 0.86 (95% $CI=0.57-1.29$) (Tverdal & Bjartveit, 2006).

A limitation of this study was suboptimal power to exclude some important differences in clinical outcomes, namely cardiac events. The biomarker data confirm considerable variability of toxin exposure for similar smoking levels, and therefore group differences may mask benefits for individual smokers. The study population also included mostly men who were heavily dependent smokers with a high prevalence of co-morbid mental health disorders which limited the generalizability of results. For ethical reasons, in order to be enrolled in the study, patients with heart disease had to report no interest in quitting smoking in the next month. Participants, therefore, reflected a select population since many smokers with heart disease expressed a desire to stop. We considered only subjects not lost to follow-up, and we combined smokers who reduced with abstinent smokers, which might offer an advantage to smoking reduction, but no benefit was observed in spite of this analytic method.

Our results, in conjunction with the available epidemiological, observational and clinical trial data suggest that smoking reduction has limited promise to significantly reduce risk in patients with heart disease (Hughes & Carpenter, 2006). This is not consistent with patients' beliefs about the benefits of smoking reduction. The data suggest that the amount of reduction that is feasible to achieve clinically is associated with neither an improvement in clinical outcomes nor promising changes in measures of tobacco toxin exposure. Smoking cessation for patients with heart disease, rather than smoking reduction, has an established beneficial effect on future risk, and should therefore be emphasized as the goal of tobacco intervention.

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Table 1

Baseline characteristics

	<u>Smoking reduction</u>	<u>Usual care</u>	
	<u>n=78</u>	<u>n=74</u>	
	<u>n (%) or mean (SD)</u>		<u>p value</u>
Demographics			
Age (years)	57.49 (8.59)	58.39 (9.55)	.540
Male	70 (89.74%)	65 (87.84%)	.709
Income less than \$30,000/year	44 (65.67%)	45 (70.31%)	.569
White	73 (96.05%)	62 (87.32%)	.053
Married			
Currently	39 (50.65%)	34 (46.58%)	.609
Previously	33 (42.86%)	31 (42.47%)	
Education			
High school graduate	55 (71.43%)	52 (72.22%)	.992
College graduate	13 (16.88%)	12 (16.67%)	
Currently employed (full-time or part-time)	32 (41.03%)	27 (36.49%)	.566
Smoking History			
Cigarettes/day at the time of enrollment	27.69 (12.53)	27.04 (10.98)	.735
Made at least one prior attempt to quit smoking lasting 24 hours	75 (96.15%)	69 (94.52%)	.633
How many times have you tried to quit smoking?	6.57 (9.84)	5.77 (6.53)	.561
Past use of quit smoking methods			
NRT (patch, gum, nasal spray or inhaler)	58 (74.36%)	64 (86.49%)	.060
Bupropion SR	35 (44.87%)	40 (54.05%)	.258
Behavioral counseling	10 (12.82%)	14 (18.92%)	.303
Do you think you are physically addicted to nicotine? (Yes)	71 (91.03%)	61 (88.41%)	.601
FTND score (0–11)*	6.03 (2.17)	5.95 (1.84)	.808
Contemplation Ladder (0–10)	7.01 (2.25)	7.5 (2.23)	.187
Medical History			
Overall health (range 0 (poor) – 10 (excellent))	5.63 (2.12)	5.37 (1.57)	.394
Heart disease; history of:			
Myocardial infarction	47 (60.26%)	48 (65.75%)	.518
Bypass surgery	24 (30.77%)	21 (28.77%)	.788
Angioplasty	26 (33.33%)	32 (43.84%)	.408
Stent placement	22 (28.21%)	24 (32.88%)	.820
Thrombolytic therapy	12 (15.38%)	11 (15.07%)	.995
Angina	43 (56.58%)	45 (61.64%)	.530
Angiogram: 50% Stenosis	36 (46.75%)	42 (57.53%)	.265
Ischemia on exercise tolerance testing	29 (39.73%)	23 (32.86%)	.265
Arrhythmia	18 (23.38%)	19 (26.39%)	.908
Cardiac arrest	12 (15.38%)	6 (8.45%)	.385

	<u>Smoking reduction</u>	<u>Usual care</u>	
	<u><i>n</i>=78</u>	<u><i>n</i>=74</u>	
	<i>n</i> (%) or mean (<i>SD</i>)		<i>p</i> value
Congestive heart failure	11 (14.10%)	13 (18.06%)	.491
Hypertension	41 (52.56%)	37 (51.39%)	.612
COPD **	11 (14.10%)	18 (25.35%)	.150
Peptic ulcer disease	22 (28.21%)	19 (26.76%)	.381
Diabetes	16 (20.51%)	15 (20.83%)	.573
Peripheral arterial disease	22 (28.21%)	19 (26.39%)	.159
Cerebrovascular disease	6 (7.79%)	10 (14.29%)	.334
Cancer	7 (8.97%)	2 (2.74%)	.228
Substance abuse treatment	24 (30.77%)	20 (27.40%)	.549
Alcohol problems	28 (37.84%)	21 (30.88%)	.384
Depression or other psychiatric disorders ***	46 (61.33%)	39 (54.93%)	.433

* Fagerström Test for Nicotine Dependence.

** Chronic obstructive pulmonary disease.

*** History of alcohol problems and/or depression self-reported at baseline interview.

Table 2

Smoking reduction: Past behaviors and attitudes.

	<u>Smoking reduction</u>	<u>Usual care</u>	
	<u>n=78</u>	<u>n=74</u>	
	<u>n (%) or mean (SD)</u>		<u>p value</u>
Past peak cigarettes/day	42.83 (18.19)	41.82 (15.34)	.713
Attempted to cut down on smoking in the past	69 (88.46%)	68 (91.89%)	.479
Switched to low tar/low nicotine cigarettes in the past	53 (70.67%)	61 (82.43%)	.090
Believe smoking reduction will improve health outcomes (some or a great deal)	68 (84.62%)	61 (82.43%)	.717
Primary reason that reduced smoking is appealing?			
Not interested in quitting	0 (0.00%)	1 (1.45%)	.608
Step toward quitting	4 (5.41%)	7 (10.14%)	
Healthier for me	65 (87.84%)	57 (82.61%)	
Would be satisfied reducing	1 (1.35%)	0 (0.00%)	
To save money	2 (2.70%)	2 (2.90%)	
How much will reducing the number of cigarettes you smoke improve your health?			
None	3 (3.95%)	4 (5.41%)	.855
Some	33 (43.42%)	33 (44.59%)	
A great deal	33 (43.42%)	28 (37.84%)	
Don't know	7 (9.21%)	9 (12.16%)	
"NRT is safer than cigarettes."			
Not safer	2 (2.56%)	2 (2.70%)	.076
Somewhat safer	14 (17.95%)	27 (36.49%)	
A great deal safer	45 (57.69%)	31 (41.89%)	
Don't know	17 (21.79%)	14 (18.92%)	
"It is safe to smoke and use NRT at the same time."			
Strongly agree	4 (5.19%)	1 (1.39%)	.499
Agree	18 (23.38%)	18 (25.00%)	
Neutral	4 (5.19%)	3 (4.17%)	
Disagree	27 (35.06%)	25 (34.72%)	
Strongly disagree	15 (19.48%)	10 (13.89%)	
Don't know	9 (11.69%)	15 (20.83%)	

Table 3

Smoking reduction.

	Smoking reduction		Usual care		<i>p</i> value
	At baseline <i>n</i> =78		At baseline <i>n</i> =74		
	Number of cigarettes per day (<i>SD</i>)	Change in cigarettes per day** (range)	Number of cigarettes per day (<i>SD</i>)	Change in cigarettes per day (range)	
Baseline	27.7 (12.5)	N/A	27.0 (11.0)	N/A	.745
1 month	19.3 (13.1)	−8.2 (−49, 15)	21.6 (11.4)	−4.6 (−29, 33)	.042
3 months	17.8 (12.9)	−10.6 (−37, 10)	19.8 (11.4)	−5.8 (−44, 27)	.016
6 months	16.8 (12.3)	−11.2 (−45, 30)	19.6 (15.3)	−7.8 (−40, 68)	.202
12 months	17.6 (12.1)	−9.5 (−50, 10)	20.5 (12.3)	−5.3 (−47, 35)	.088
18 months	17.9 (13.5)	−9.7 (−55, 20)	18.2 (13.4)	−8.6 (−40, 32)	.694

* For each visit, the difference between the number of cigarettes smoked at baseline and the number of cigarettes smoked at that visit was calculated. A Student's *t*-test was then conducted on the difference to compare the treatments. Probability values in the table correspond to the observed *p* values from these tests.

** The number of cigarettes per day at each follow-up point may be slightly different from the change in cigarettes per day subtracted from the baseline due to small differences in the numbers of participants included in each comparison.

Table 4

Clinical markers of heart/vascular disease

	<u>Smoking reduction</u>	<u>Usual care</u>	
	<u>Baseline <i>n</i>=78</u>	<u>Baseline <i>n</i>=74</u>	
	Mean (<i>SD</i>) or <i>n</i> (%)		<i>p</i> value
Distance completed – 6 minute walk (feet)			
Baseline	1017.87 (490.80)	1009.15 (514.95)	.915
1 month	877.82 (560.60)	899.53 (536.60)	.826
3 months	683.59 (618.88)	826.87 (594.68)	.202
6 months	888.21 (624.67)	760.45 (623.53)	.291
12 months	785.59 (711.00)	566.84 (602.15)	.101
18 months	793.72 (628.36)	474.49 (564.06)	.011
Proportion completing 6 minute walk			
Baseline	56 (71.79%)	51 (69.86%)	.859
1 month	38 (56.72%)	35 (58.33%)	.860
3 months	29 (46.03%)	29 (52.73%)	.580
6 months	32 (51.61%)	26 (49.06%)	.852
12 months	26 (49.06%)	21 (41.18%)	.438
18 months	15 (30.00%)	25 (52.08%)	.039
Do you have angina?			
Baseline	18 (23.08%)	13 (17.81%)	.546
1 month	12 (17.39%)	14 (22.95%)	.512
3 months	8 (12.70%)	9 (15.25%)	.796
6 months	11 (17.19%)	9 (16.07%)	.191
12 months	11 (20.37%)	6 (11.54%)	.291
18 months	9 (18.37%)	8 (16.67%)	1.000
Frequency of angina (number episodes last week)*			
Baseline	2.1 (2.5)	2.1 (3.9)	.372
1 month	1.8 (1.6)	5.0 (12.9)	.629
3 months	4.7 (5.7)	6.0 (6.3)	.943
6 months	1.8 (2.6)	2.2 (2.0)	.419
12 months	1.7 (1.6)	4.2 (6.3)	.570
18 months	2.3 (2.2)	2.5 (2.6)	.981
Quality of Life Index**			
Baseline	16.93 (1.69)	16.83 (1.82)	.728
1 month	17.15 (1.74)	16.92 (1.42)	.405
3 months	17.13 (1.85)	17.18 (1.78)	.873
6 months	17.26 (1.87)	16.91 (2.15)	.348
12 months	17.32 (1.72)	16.64 (1.83)	.056
18 months	16.77 (1.89)	16.74 (2.03)	.934
Needed urgent cardiac care			
1 month	1 (1.47%)	3 (4.92%)	.344

	<u>Smoking reduction</u>	<u>Usual care</u>	<i>p</i> value
	<u>Baseline <i>n</i>=78</u>	<u>Baseline <i>n</i>=74</u>	
	Mean (<i>SD</i>) or <i>n</i> (%)		
3 months	4 (6.35%)	3 (5.08%)	1.000
6 months	0 (0.00%)	5 (8.93%)	.021
12 months	3 (5.56%)	5 (9.62%)	.484
18 months	8 (16.33%)	6 (12.00%)	.577
Severe adverse events (all events)	15 (19.23%)	13 (17.81%)	.837
Severe adverse events (cardiac events ^{***})	2 (2.74%)	6 (7.69%)	.278

* Of those with angina last week.

** Ferrans and Powers Quality of Life Index, range 0 (very dissatisfied) to 30 (very satisfied).

*** Severe cardiac events include myocardial infarction, arrhythmia, acute coronary syndrome.

Table 5

Biomarkers

	<u>Smoking reduction</u>	<u>Usual care</u>	
	<u>n=78</u>	<u>n=74</u>	
	Level (SD)		p value
Nicotine (nmol/mg creat)			
Baseline	1740 (1467)	2077 (2568)	
1 month	1882 (2187)	1985 (2259)	
3 months	1486 (1387)	1917 (2582)	
6 months	2557 (6064)	1899 (3483)	
12 months	1087 (842)	1133 (1583)	
18 months	1701 (1664)	1701 (1664)	
Slope(SD)	−83.1 (365.6)	−83.0 (700.4)	1.000
Cotinine (nmol/mg creat)			
Baseline	4233 (2621)	4499 (3259)	
1 month	3870 (2647)	3870 (2647)	
3 months	3460 (2611)	4692 (4166)	
6 months	4223 (2859)	4121 (3370)	
12 months	3382 (2182)	2809 (2071)	
18 months	2523 (1858)	5548 (4283)	
Slope(SD)	−104.4 (430.8)	19.9 (653.3)	.155
Expired CO (ppm)			
Baseline	24 (16)	25 (12)	
1 month	21 (10)	21 (11)	
3 months	18 (10)	22 (14)	
6 months	19 (12)	19 (13)	
12 months	18 (12)	21 (14)	
18 months	16(11)	18 (13)	
Slope(SD)	−0.21 (1.5)	− 0.47 (2.3)	.425
WBC count (× 10 ⁹ /L)			
Baseline	8.18 (2.10)	8.11 (1.85)	
1 month	7.82 (2.13)	8.22 (2.14)	
3 months	7.84 (2.30)	8.26 (2.31)	
6 months	8.09 (2.02)	7.87 (2.16)	
12 months	8.17 (2.11)	8.33 (2.39)	
18 months	7.76 (1.81)	8.40 (1.81)	
Slope(SD)	0.00 (0.4)	−0.05 (0.3)	
Fibrinogen (mg/dL)			
Baseline	383 (79)	384 (69)	
1 month	381 (80)	387 (71)	
3 months	385 (91)	377 (78)	
6 months	391 (80)	388 (67)	

	Smoking reduction	Usual care	
	<i>n</i>=78	<i>n</i>=74	
	Level (SD)		<i>p</i> value
12 months	391 (87)	380 (95)	
18 months	367 (79)	352 (97)	
Slope(SD)	2.5 (18.9)	-3.1 (6.6)	.019
Hs-CRP (mg/L)			
Baseline	0.516 (0.705)	0.452 (0.503)	
6 months	0.502 (0.831)	0.558 (0.853)	N/A
F ₂ -isoprostanes (pmol/L)			
Baseline	98.587 (66.838)	81.908 (30.117)	
6 months	93.517 (64.070)	86.314 (39.129)	N/A
Total NNAL (pmol/mg creat)			
Baseline	2.60 (1.58)	2.66 (2.40)	
1 month	2.16 (1.50)	2.44 (1.98)	
3 months	1.92 (1.51)	2.43 (2.12)	
6 months	3.11 (6.15)	1.96 (1.55)	
12 months	2.02 (1.68)	1.52 (1.11)	
18 months	1.89 (1.43)	2.24 (2.03)	
Slope(SD)	-0.1 (0.3)	-0.4 (2.7)	.353
1-HOP (pmol/mg creat)			
Baseline	1.71 (1.38)	2.01 (2.45)	
1 month	1.45 (1.19)	1.69 (2.19)	
3 months	1.54 (1.79)	1.95 (2.12)	
6 months	1.67 (1.60)	1.63 (1.58)	
12 months	1.84 (2.52)	1.49 (1.16)	
18 months	1.49 (2.51)	1.48 (1.63)	
Slope(SD)	-0.1 (1.1)	0.1 (0.6)	.136

The slope is an estimate of change in value of each biomarker per month.

Table 6

All subjects: comparison between baseline and 6 months

		<u>Mean (SD) baseline</u>	<u>Mean (SD) 6 months</u>	<u>Mean (SD) of difference (6 months –baseline)</u>	
	<i>n</i> (at baseline and 6 months)		Mean (SD) or <i>n</i> (%)		<i>p</i> value
Smoking Outcomes					
Cigarettes per day	119	27.7 (12.0)	18.1 (13.8)	–9.6 (13.8)	<0.01
Clinical Outcomes					
Six-minute walk, distance completed (feet)	108	989.5 (513.9)	827.9 (624.5)	–161.6 (524.8)	<0.01
Six-minute walk, test completed	115	81 (70%)	58 (50%)	N/A	<0.01
Presence of angina	120	22 (18%)	20 (17%)	N/A	0.85
Frequency of angina* (number of episodes in past week)	9	1.9 (1.6)	2.7 (2.8)	0.8 (2.5)	0.38
Biomarker Outcomes					
Nicotine (nmol/mg creat)	81	2000.6 (2390.4)	2265.0 (5092.5)	264.4 (5222.3)	0.65
Cotinine (nmol/mg creat)	81	4306.8 (3017.9)	4117.3 (3013.8)	–189.5 (3154.2)	0.59
Expired Co (ppm)	113	24.5 (15.5)	18.9 (12.5)	–5.5 (17.0)	<0.01
WBC count ($\times 10^9/L$)	106	8.3 (1.9)	8.0 (2.1)	–0.3 (1.7)	0.13
Fibrinogen (mg/dL)	105	389.4 (76.5)	389.8 (74.9)	0.3 (63.6)	0.96
hs-CRP (mg/L)	115	0.5 (0.6)	0.5 (0.8)	0.1 (0.6)	0.28
F ₂ -Isoprostanes (pmol/L)	116	92.4 (56.0)	90.2 (54.8)	–2.2 (41.9)	0.58
Total NNAL (pmol/mg creat)	89	2.5 (1.5)	2.6 (3.8)	0.1 (3.8)	0.72
1-HOP (pmol/mg creat)	94	2.4 (5.8)	2.0 (2.1)	–0.4 (5.3)	0.41

* Of those with angina previous week.