Cardiovascular Toxicity of Nicotine: Implications for Nicotine Replacement Therapy

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This review discusses the known cardiovascular effects of smoking and the effects of nicotine without tobacco smoke and interprets the available data on cardiovascular risk during nicotine replacement therapy (NRT). Nicotine gum and patches are now approved for over the counter sale in the United States. Smokers with cardiovascular disease are advised to seek physician counseling before using nicotine products, but information regarding the safety of these products in such patients is not readily available to most physicians. Nicotine may contribute to cardiovascular disease, presumably by hemodynamic consequences of sympathetic neural stimulation and systemic catecholamine release. However, there are many potential cardiovascular toxins in cigarette smoke other than nicotine. The doses of nicotine obtained by regular cigarette smoking generally exceed those delivered by NRTs, and the cardiovascular effects of nicotine are, in general, more intense when delivered rapidly by cigarette smoking than the slower delivery by transdermal nicotine or nicotine gum. Because the dose–cardiovascular response relation for nicotine is flat, the effects of cigarette smoking in conjunction with NRT are similar to those of cigarette smoking alone. Cigarette smoking increases blood coagulability, a major risk factor for acute cardiovascular events, whereas transdermal nicotine does not appear to do so. Clinical trials of NRT in patients with underlying, stable coronary disease suggest that nicotine does not increase cardiovascular risk. At worst, the risks of NRT are no more than those of cigarette smoking. The risks of NRT for smokers, even for those with underlying cardiovascular disease, are small and are substantially outweighed by the potential benefits of smoking cessation.

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Nicotine gum and patches are now approved for over the counter sale in the United States. The package inserts advise smokers with cardiovascular disease to seek physician counseling before using the products, but information on the safety of nicotine in the setting of cardiovascular disease is not readily available to most physicians.

Cigarette smoking is well known to increase the risk of cardiovascular disease. Nicotine affects cardiovascular function and could contribute to cardiovascular disease. Of concern is whether nicotine medications pose a cardiovascular risk, and, if so, how does this risk compare to that of cigarette smoking? The risk–benefit analysis for nicotine medication in patients with active or silent heart disease is important both in helping to make decisions on rational therapy for smoking cessation and for other potential indications for nicotine therapy, such as ulcerative colitis.

Cigarette smoking accelerates atherosclerosis, producing premature atherosclerosis at epicardial coronary arteries, the aorta, the carotid and cerebral arteries and large arteries in the peripheral circulation (1,2). Smoking is also associated with an increased risk of acute cardiovascular events, including acute myocardial infarction, sudden death and stroke. Other effects include aggravation of stable angina pectoris, intermittent claudication and vasospastic angina, rethrombosis after thrombolysis and restenosis after angioplasty (3–7).

The acute cardiovascular effects of nicotine are of primary concern with respect to clinically relevant risks of nicotine replacement therapy (NRT) because of their potentially serious nature. There have been anecdotal reports of acute myocardial infarction and stroke in patients taking NRT, with or without simultaneous cigarette smoking (Table 1). The possible contribution of nicotine to acute cardiovascular events is the major focus of this review.

Smoking-related atherosclerosis is not necessarily an effect of nicotine (1,2). It is important to recognize that cigarette smoke is a complex mixture of chemicals that includes not only nicotine but also potentially cardiotoxic substances, such as carbon monoxide, oxidant gases and polycyclic aromatic hydrocarbons. The role of nicotine, if any, in causing acute or chronic cardiovascular disease has not been definitely demon-

Abbreviations and Acronyms

CGRP = calcitonin growth-related peptide
ECG = electrocardiographic
HDL = high density lipoprotein
LDL = low density lipoprotein
NO = nitric oxide
NRT = nicotine replacement therapy
VLDL = very low density lipoprotein

strated. If nicotine contributes to smoking-related atherosclerosis, it is unlikely to be of clinical importance during the relatively brief duration of NRT for smoking cessation.

Mechanisms by Which Cigarette Smoking Contributes to Acute Vascular Events

Mechanisms by which cigarette smoking is likely to contribute to acute vascular events include 1) induction of a hypercoagulable state; 2) increased myocardial work; 3) carbon monoxide–mediated reduced oxygen-carrying capacity of the blood; 4) coronary vasoconstriction; and 5) catecholamine release.

Hypercoagulable state. Several lines of evidence suggest that cigarette smoking–mediated thrombosis is a major factor in acute vascular events. Epidemiologic studies (2) indicate that cigarette smoking increases the risk of acute myocardial infarction and sudden death much more than it increases the

risk of angina pectoris. The former are believed to be mediated by thrombosis, the latter primarily by hemodynamic factors. Recent research with thrombolysis supports this concept. The prognosis in patients with myocardial infarction after treatment with thrombolysis is better in smokers than in nonsmokers (8). Smokers, at the time of myocardial infarction, were younger, had fewer cardiac risk factors and had less severe underlying coronary disease than did nonsmokers. Enhanced thrombosis superimposed on less severely stenotic arteries best explains these observations. Observations that smokers who continue to smoke after thrombolysis or angioplasty have substantially increased risk of reinfarction or reocclusion support the idea that thrombosis is a major mechanism of smoking-related events (5,7).

Increased myocardial work. Although surveys of outpatient blood pressure measurement report that smokers have a lower blood pressure than matched nonsmokers (9), more recent studies of ambulatory blood pressure monitoring show that long-term cigarette smoking increases average heart rate and blood pressure throughout the day (10,11). In addition, each cigarette transiently increases heart rate and blood pressure (12). Cigarette smoking causes an acute increase in the stiffness of large peripheral arteries (13,14). Cigarette smoking also increases myocardial contractility (15,16). Thus, myocardial work is increased. When myocardial blood flow increases, coronary blood flow must increase to provide necessary oxygen and nutrients. Where coronary blood flow is limited, the blood flow requirements of the heart may not be able to be met, resulting in ischemia.

Table 1. Summary of Published Adverse Cardiovascular Events in People Using Nicotine Replacement Therapy

Age (yr)/Gender	Underlying Cardiovascular Disease	Type and Dose of Nicotine Product	Time of Onset of Event	Concurrent Cigarette Smoking
AF (109–111)				
52/M	Coronary disease, Hx and paroxysmal AF	2-mg gum	5 min after 1st piece of gum, day 3 of use	Unknown
35/M	None known	2-mg gum, 30 pieces/day	At night during sleep, after 2-mo use	Unknown
55/F	None known	21-mg patch	5 h after applying patch	Yes
MI (112–114)				
34/M	Normal CAs, except for thrombosed LAD	21-mg patch	Angina began several hours after 1st patch; MI 10 AM, day 14	Yes
47/M	Recent MI with 50% LAD stenosis	21-mg patch	While smoking 1st cigarette and wearing patch, day 7	Yes
39/M	Normal coronary angiogram	21-mg patch	Several hours after application of patch, day 20	No
69/F	Unknown	44-mg patch	Day 25	Unknown
Cerebral isch (114–116)				
40/M	Internal carotid aneurysm clipped, persistent cerebral artery spasm	One 10-mg patch	4 h after 1st patch application, postoperative day 8	Yes
43/F	Unknown	44-mg patch	Day 3	Unknown
70/F	Unknown	22-mg patch	Day 11 of 22-mg patch, after 4 wk of 44-mg patch	Unknown
62/F	None known	21-mg patch	Day 21	Unknown

Numbers in parentheses are reference numbers. AF = atrial fibrillation; CAs = coronary arteries; F = female; Hx = hypertension; isch = ischemia; LAD = left anterior descending coronary artery; M = male; MI = myocardial infarction.

Carbon monoxide effects on oxygen delivery. Smokers inhale carbon monoxide in cigarette smoke, and carboxyhemoglobin levels average ~5%, but may be ≥10%. This compares to levels of 0.5% to 2% in nonsmokers, depending on their exposure to automobile exhaust. Carbon monoxide binds to hemoglobin, reducing both the amount of hemoglobin available to carry oxygen and also impeding oxygen release by hemoglobin that is not directly binding carbon monoxide (17). In experimental studies, inhalation of carbon monoxide at levels comparable to those found in cigarette smokers has been shown (18–20) to reduce exercise tolerance in patients with angina pectoris, intermittent claudication and chronic obstructive lung disease. Carbon monoxide exposure in people with obstructive coronary disease also results in a greater degree of exercise-induced ventricular dysfunction, as well as an increased number and complexity of ventricular arrhythmias during exercise (21,22). Carbon monoxide inhalation reduces the ventricular fibrillation threshold in animals and may contribute to atherogenesis (23,24).

Coronary vasoconstriction. Coronary vasoconstriction reduces myocardial blood supply and could produce ischemia or arrhythmias. Cigarette smoking increases coronary blood flow, associated with a small decrease in coronary vascular resistance, in people with normal coronary arteries, presumably a response to increased myocardial work and the need for additional blood supply (25). However, in people with obstructive coronary disease, cigarette smoking results in a lesser increase, no change or even a decrease in coronary blood flow, depending on the severity of the underlying coronary disease (25,26). In these patients, cigarette smoking increases coronary vascular resistance, consistent with coronary vasoconstriction. Cigarette smoking is associated with increased risk of vasospastic angina and a poor response to medications in patients who have vasospastic angina (27,28). Cigarette smoking has been observed to acutely produce vasospasm during angiography (6).

Pretreatment with calcium channel blocking agents or nitroglycerin results in an increase in coronary blood flow after cigarette smoking in patients with coronary artery disease who had no increase after cigarette smoking alone, further supporting the idea that cigarette smoking normally results in coronary vasoconstriction (29). Recently, intracoronary Doppler measurements have demonstrated (30) that cigarette smoking constricts epicardial arteries as well as increases total coronary vascular resistance. Thus, the impairment of coronary blood flow by cigarette smoking appears to result from constriction of both epicardial and resistance blood vessels.

Catecholamine release. Cigarette smoking acutely increases plasma levels of norepinephrine and epinephrine and increases 24-h urinary excretion of these catecholamines (31,32). The effects of cigarette smoking on coronary blood flow appear to be catecholamine mediated because the increase in coronary vascular resistance is blocked by alpha-adrenoceptor blocking agents (33). In addition to mediating the hemodynamic effects of cigarette smoking, catecholamines could contribute to arrhythmogenesis. For example, acute ischemia combined with smoking-related catecholamine release could result in a greater risk of sustained and potentially fatal tachyarrhythmias. Cigarette smoking has been shown (34) to accelerate atrioventricular node conduction, which could contribute to supraventricular arrhythmias. Catecholamine release has been speculated to account for the greater risk of sudden death in smokers than in nonsmokers (35).

Mechanisms by Which Cigarette Smoking May Promote Atherosclerosis

Cigarette smoking could accelerate atherosclerosis by a variety of mechanisms. Some of those more prominently mentioned include 1) adverse effects on lipids; 2) producing endothelial damage or dysfunction, or both; 3) hemodynamic stress; 4) oxidant injury; 5) neutrophil activation; 6) enhanced thrombosis; and 7) increased fibrinogen and blood viscosity.

Effects of cigarette smoking on lipids. Smokers on average have a higher risk lipid profile than do nonsmokers. Levels of very low density lipoprotein (VLDL) are higher; high density lipoprotein (HDL) cholesterol levels (primarily HDL-2) are lower; triglycerides are higher; and apoprotein A1 levels are perhaps lower in smokers than in nonsmokers (36,37). There is also some evidence (38) that smokers have higher levels of oxidized low density lipoprotein (LDL), which is believed to promote atherogenesis. Oxidized LDL is taken up preferentially by macrophages, which become the foam cells that are an integral part of the atherosclerotic plaque. These abnormalities in the blood lipid profile appear to reverse, at least in part, within 2 weeks of smoking cessation (39).

Endothelial toxicity. Endothelial damage is thought to be an initiating event in atherosclerosis. There is evidence that cigarette smoking produces endothelial damage (40). For example, endothelial changes have been described in the umbilical artery of babies of smoking mothers (41). Endothelial changes included swelling, blebbing and contraction, with resultant opening of endothelial junctions and formation of subendothelial edema.

Cigarette smoking is associated with impaired flow-mediated, endothelium-dependent peripheral arterial vasodilation, an effect that is at least partly reversible after smoking cessation (42). Smokers without atherosclerosis have coronary vasoconstrictor responses to acetylcholine, which in the presence of endothelial cell function normally produces vasodilation (43). Impaired arterial vasodilation in smokers appears to be a consequence of impaired release of endothelium-derived relaxing factor (believed to be nitric oxide [NO]) (44,45). Normal NO release has potentially beneficial cardiovascular effects in mediating acetylcholine-induced coronary vasodilation and inhibiting platelet aggregation, smooth muscle cell proliferation and adhesion of monocytes to the endothelium. Impaired release of NO in cigarette smokers could contribute to acute cardiovascular events and to accelerated atherogenesis.

Hemodynamic stress may contribute to endothelial dam-

age, as occurs in chronic hypertension. As discussed, regular smoking increases daytime blood pressure, blood pressure variability and heart rate. Persistent heart rate elevation has been shown (46) in primates on an atherogenic diet to accelerate atherosclerosis. Thus, hemodynamic effects of cigarette smoking would be expected to result in more turbulent blood flow and could contribute to endothelial damage.

Oxidant injury. Cigarette smoke contains many oxidant gases. Reduced plasma levels of the antioxidant glutathione and increased levels of lipid peroxidation products have been measured in the plasma of smokers, reflecting the oxidant stress of cigarette smoke (47,48). As noted previously, cigarette smoking is believed to be associated with oxidation of LDL, which may promote atherosclerosis (38). Oxidant substances in cigarette smoke appear to be responsible for endothelial dysfunction. Antioxidants such as vitamin C reverse the impairment in endothelium-mediated vasodilation in smokers (49).

Neutrophil activation. Cigarette smoking is consistently associated with increased circulating neutrophil counts (50). Neutrophil counts decline rapidly after cessation of cigarette smoking (51). An elevated neutrophil count is a risk factor for coronary events (52). Neutrophils may contribute to ischemic heart disease through release of oxygen-derived free radicals, proteases and leukotrienes (53). These mediators can result in endothelial cell injury and aggregation and activation of platelets, which in turn can aggravate coronary ischemia.

Enhanced thrombosis. Cigarette smoking produces a hypercoagulable state, associated with platelet activation and possibly other changes in clotting factors (54). Enhanced viscosity is contributed to by increased fibrinogen levels and increased red cell mass in cigarette smokers (55). Hypercoagulability may contribute to atherosclerosis, presumably by release of platelet factors that promote smooth muscle cell migration and other effects that promote atherosclerosis (56).

Fibrinogen and blood viscosity. Increased fibrinogen is one of the strongest predictors of coronary events (57). Cigarette smoking increases fibrinogen levels, although the mechanism is unclear. Smokers also have elevated red blood cell mass, as a response to long-term carbon monoxide exposure (58). Carbon monoxide reduces oxygen-carrying capacity, resulting in a state of relative hypoxia. In response, red blood cell masses increase, allowing more oxygen to be carried to body organs. Both increased fibrinogen and increased red blood cell mass increase blood viscosity, which is believed to contribute to platelet activation, which, as discussed, promotes atherogenesis. Fibrinogen may also contribute to atherosclerosis through direct activation of platelets, acting on specific platelet receptors (57).

Cardiovascular Pharmacology of Nicotine

Thus far, the discussion has focused on the cardiovascular effects of cigarette smoking. At this point, the focus will be the known effects of nicotine itself.

Nicotine binds to nicotinic cholinergic receptors, which are located in the brain, autonomic ganglia, the adrenals and neuromuscular junction (59). The main cardiovascular effect of nicotine is sympathetic neural stimulation. Sympathomimetic effects are mediated by several mechanisms. Central nervous system–mediated sympathetic stimulation can occur through activation of peripheral chemoreceptors, direct effects on the brain stem and effects on more caudal portions of the spinal cord. Intrapulmonary chemoreceptors may also contribute to brain-mediated sympathetic arousal. The site that appears to be most sensitive to low levels of nicotine is the carotid chemoreceptor. Peripheral mechanisms include catecholamine release from the adrenals and direct release or enhancement of release of catecholamines from vascular nerve endings.

Nicotine works primarily by enhancing the release of various neurotransmitters, including epinephrine, norepinephrine, dopamine, acetylcholine, serotonin, vasopressin, glutamate, NO (60), calcitonin growth-related peptide (CGRP) (60) and beta-endorphin. Thus, in addition to catecholamine-mediated actions, some other of these effects, such as acetylcholine, serotonin, NO, CGRP or vasopressin release, may contribute to effects of nicotine on blood vessels.

Salient observations on the pharmacokinetics and pharmacodynamics of nicotine most relevant to cardiovascular safety are summarized in Table 2. More detail is available in comprehensive reviews of the pharmacology of nicotine (59,61).

Acute Cardiovascular Effects of Nicotine

Hemodynamic actions of nicotine. The hemodynamic effects of cigarette smoking appear to be mediated by nicotine. Intravenous nicotine, nicotine nasal spray and nicotine chewing gum all acutely increase heart rate up to 10 to 15 beats/min and increase blood pressure up to 5 to 10 mm Hg, responses similar to the effects of cigarette smoking (62–64). Transdermal nicotine appears to cause lesser acute hemodynamic changes than smoking (32).

Nicotine increases cardiac output by increasing both heart rate and myocardial contractility. Nicotine gum chewing has been shown to aggravate regional myocardial hypoperfusion in patients with known coronary artery disease (65). Nicotine constricts some vascular beds, such as the skin. Cutaneous vasoconstriction explains the reduction in fingertip skin temperature that is seen with administration of nicotine (63). There is evidence that cutaneous vasoconstriction is modulated at least in part by release of vasopressin because the effect was inhibited by administration of a vasopressin antagonist (66). Nicotine appears to dilate other vascular beds, such as skeletal muscle (67,68). Skeletal muscle vasodilation may in part be a result of the increase in cardiac output, although animal studies suggest that release of epinephrine from nerve terminals may also contribute (13).

In anesthetized dogs, coronary blood flow has a biphasic response to nicotine. Initially, blood flow increases, in the large coronary vessels as well as in the smaller resistance vessels, believed to be a result of increased myocardial metabolic demand. Secondarily, there is a decrease in blood flow that

Table 2. Pharmacokinetic and Pharmacodynamic Considerations Concerning Cardiovascular Safety of Nicotine

Nicotine from cigarette smoke is absorbed rapidly and results in arterial plasma concentrations in body organs 6–10 times higher than venous plasma concentrations (117). Slower delivery systems, such as nicotine gum or patch, will produce much lower peak arterial concentrations

When smokers involved in most treatment trials are considered, the level of nicotine produced and the daily dose of nicotine delivered by standard doses of NRT are less than that typically taken in from cigarette smoking (118–122)

When people using NRT to quit smoking continue to smoke, the resulting plasma nicotine concentrations are not likely to be much greater than those observed before attempting to quit. Only modest increases in plasma nicotine concentration are observed when transdermal nicotine is combined with usual smoking (108)

Because of rapid delivery of high concentrations of nicotine, with minimal time for development of tolerance, cigarette smoking results in more intense acute cardiovascular effects than the same dose of nicotine absorbed from NRT (123)

Cigarette smoking and transdermal nicotine appear to have similar overall hemodynamic effects; however, cigarette smoking activates coagulation and increases 24-h epinephrine excretion, whereas transdermal nicotine does not (32)

The cardiovascular dose–response relation for nicotine is relatively flat; that is, after a threshold effect, nicotine produces little more effect despite higher blood levels (106)

Combining cigarette smoking with nicotine administered by other routes appears to have cardiovascular effects similar to cigarette smoking alone (107); thus, smoking while using nicotine-reduced therapy would not be expected to have additional effects but would produce the same effects as smoking alone

Numbers in parentheses are reference numbers. NRT = nicotine replacement therapy.

appears to be mediated by alpha-adrenergic vasoconstriction of coronary resistance vessels (69,70). As described previously, cigarette smoking may constrict coronary arteries, presumed due to nicotine-mediated catecholamine release. Of note, the chewing of 4 mg of nicotine gum by healthy nonsmokers has also been shown (70) to blunt the increase in coronary blood flow that occurs with an increase in heart rate, produced either by nicotine or cardiac pacing. This finding confirms that nicotine is capable of constricting coronary arteries even at low doses in humans.

Nicotine has been shown (71) to worsen myocardial dysfunction in regionally "stunned," ischemic myocardium of anesthetized dogs. In a placebo-controlled experiment, transient ischemia was induced in dogs by 15 min of left anterior descending coronary artery clamping. Segmental shortening recovered to only 29% of the preischemic baseline in nicotine-pretreated animals (80 μg/kg body weight intravenously over 15 min) compared with 54% for saline-treated control dogs (p < 0.01). The dose of nicotine did not alter heart rate, blood pressure or blood flow or cause myocyte necrosis.

Nicotine and platelet function. There has been considerable research into the effects of nicotine on platelet function. Nicotine appears not to have a significant direct effect on platelets in vitro, at least at concentrations relevant to human smoking (72). Studies of long-term nicotine administration in rodents do not show increased platelet activity; rather, they show reduced platelet aggregability (73). However, in a study in dogs with partially occluded coronary arteries (74), intravenous nicotine increased the frequency and severity of phasic reductions in blood flow, an effect that indicates platelet aggregation. The effects of nicotine on phasic blood flow were blocked by phentolamine, an alpha-adrenergic blocker, consistent with the idea that catecholamine release mediates the effects. Unfortunately, the study is not readily generalizable to human smoking because the dogs were naive (nontolerant) to nicotine, and the dose (80 μg/kg over 3 to 5 min) was large

(equivalent to a human smoking approximately five cigarettes in 5 min).

Platelet studies in human smokers yield conflicting results and are difficult to interpret because cigarette smoke contains many other factors besides nicotine that could promote platelet aggregation. Studies of nicotine gum and transdermal nicotine do not show evidence of platelet activation (32,75).

Also of potential importance in assessing the role of nicotine in platelet activation are studies of urinary thromboxane A_2 metabolite excretion in tobacco snuff users (76). Thromboxane A_2 is released from platelets when they aggregate, and excretion of thromboxane A_2 metabolites reflects in vivo platelet activation. Snuff users have long-term exposure to levels of nicotine comparable to those experienced by cigarette smokers but are not exposed to tobacco combustion products. Snuff users had no evidence of platelet activation. Thromboxane A_2 metabolite excretion rates in snuff users were similar to those who did not use tobacco and lower than those of cigarette smokers (who are known to have activated platelets), suggesting that nicotine itself is not responsible for platelet activation.

Nicotine and prostaglandins. Nicotine can inhibit the in vitro synthesis of prostacyclin in isolated blood vessels and isolated hearts (77,78). Prostacyclin is thought to be important in vascular homeostasis in that it is a local vasodilator and has antiplatelet aggregation effects. It has been speculated that nicotine could produce an imbalance between the vasodilating antiplatelet prostacyclin and the vasoconstricting platelet-aggregating thromboxane A_2, the latter of which is released from platelets. One early study (79) in smokers using radioimmunoassay of urinary eicosanoid metabolites supported the idea that nicotine might inhibit prostacyclin synthesis. However, more recent studies (80–82) using gas chromatographic–mass spectrometric specific assays for urinary prostacyclin metabolites have found no evidence that cigarette smoking is associated with reduced release of prostacyclin. In contrast,

prostacyclin metabolite excretion increased, suggesting stimulation of endothelial activity. Smokeless tobacco users, who have high systemic levels of nicotine, do not have increased prostacyclin metabolite excretion compared with people who use no tobacco. Thus, there is no convincing evidence that nicotine affects prostacyclin synthesis or release in people.

Chronic Cardiovascular Effects of Nicotine

Long-term atherosclerosis experiments. An increased rate of development of aortic (83) and carotid (84) atherosclerosis during nicotine treatment of cholesterol-fed rabbits has been observed. Although these two studies suggest that nicotine may be atherogenic in the presence of hypercholesterolemia, the rabbit atherosclerosis models used are not readily generalizable to humans: 1) The plasma concentrations of cholesterol produced were severalfold greater than those usually seen in hypercholesterolemic humans, and there may be a threshold below which a synergistic effect of nicotine and hypercholesterolemia is no longer clinically relevant. 2) High per-kilogram doses of nicotine were used in one study (11 mg/kg per day) (84), and plasma concentrations were not measured in either study. Another study (85) used a lower dose of nicotine (1 mg/kg per day) and a 2% cholesterol diet and failed to demonstrate increased atherosclerosis.

Nicotine and endothelial cell injury. Nicotine at concentrations similar to those of cigarette smokers modulates the structural and functional characteristics of cultured vascular smooth muscle and endothelial cells (86,87). Animal studies (88–90) support the idea that nicotine can produce endothelial cell injury, although the mechanism is not clear. Oral nicotine administered to rats to achieve blood levels comparable to those in human smokers produced greater myointimal thickening of the aorta after experimental injury (denudation of the endothelium with a balloon catheter) than that in control animals (91). The excessive myointimal thickening in nicotine-treated animals is consistent with a response to persistent injury to endothelial cells. In support of the relevance of animal or in vitro studies to the effects of nicotine in humans, Davis et al. (92) reported an increase in the number of endothelial cells found in venous blood (reflecting endothelial injury) and a decrease in platelet aggregate ratios (reflecting platelet aggregation) in nonsmokers who smoked tobacco but not nontobacco cigarettes.

Nicotine and lipids. Nicotine, by release of catecholamines, induces lipolysis and releases plasma free fatty acids. There is evidence that these free fatty acids are primarily taken up by the liver, which might be expected to increase the synthesis of VLDL, consistent with changes described in cigarette smokers (93).

Results of studies of the effects of nicotine on lipids in animals are conflicting. Injection of nicotine or feeding of nicotine has been reported (83,84,88) to increase total cholesterol in rabbits and monkeys receiving a high cholesterol diet. Nicotine feeding in squirrel monkeys for 2 years has been shown (94) to increase plasma levels of LDL. The mechanism

in monkeys included both accelerated synthesis of LDL through lipolysis of HDL and VLDL and impaired clearance of LDL. Of importance in interpreting these animal studies is that high doses of nicotine have been administered, often by an oral route, and without measurement of blood levels of nicotine to determine exposure adequately.

Most studies in humans given nicotine preparations suggest that nicotine delivered in these forms does not have an adverse effect on lipid profiles. In one study (95), nicotine chewing gum (2 mg eight times a day) was given to healthy nonsmokers for 2 weeks. No changes in plasma concentrations of triglycerides; total, HDL or LDL cholesterol; or apolipoprotein A1 or B were noted. In another study (96), 20 nonsmokers with ulcerative colitis received transdermal nicotine (15 mg/day) for 12 weeks. No changes in plasma lipids were found. Also, there were no changes in white cell count or platelet activation (assessed by platelet volume and expression of P-selectin), and no evidence of endothelial damage (assessed by plasma Von Willebrand factor antigen levels) was detected. Data from smokers who stop smoking and use transdermal nicotine indicate that lipids change toward normal while taking nicotine (97).

Nicotine Replacement in Patients With Cardiovascular Disease

In this section, evidence from cardiovascular adverse event reports and from clinical trials of NRT is examined.

Case reports of adverse cardiovascular events. In view of the known adverse effects of cigarette smoking and the current understanding of the pharmacology of nicotine, as reviewed previously, it is to be expected that acute cardiovascular events occurring in people using nicotine medications would raise concern. Accordingly, there are scattered published reports linking nicotine replacement therapies to acute cardiovascular events. Acute myocardial infarction in five patients who were smoking cigarettes while using nicotine patches has been reported in the press (98). Full details of these cases have not been published, but they were carefully reviewed by a Food and Drug Administration (FDA) advisory committee and judged not to be causally related to nicotine (99). Published case reports of adverse cardiovascular events are summarized in Table 1. Postmarketing surveillance data (New Drug Application Supplement) have shown only isolated and sporadic cardiovascular events, with no consistent relationship to the NRT.*

Establishing whether the relation between NRT and cardiovascular events is causal is difficult. Acute cardiovascular events are common in cigarette smokers, and the increased risk for such events persists beyond the time when they stop smoking. Therefore, it is impossible to ascertain from retro-

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spective reports whether acute cardiovascular events reflect the risk of underlying disease, cigarette smoking, concurrent cigarette smoking or nicotine medications, alone or in combination. Smokers and ex-smokers are at increased risk for acute myocardial infarction, and a higher than average number of infarctions would be expected in the general population of people trying to quit smoking, with or without the use of NRT to aid smoking cessation.

Because of the relative infrequency of the cardiovascular events of concern, the number of subjects in a formal study needs to be quite large. One large source of observational data is the Lung Health Study cohort, in which 5,887 middle-aged smokers with chronic obstructive pulmonary disease were followed up for 5 years. During that study (100), two-thirds of the subjects were provided with smoking cessation therapy, including nicotine gum. Many of these subjects used nicotine gum heavily for several years. A comparison of smokers versus quitters with nicotine gum versus quitters without nicotine gum showed no increase in hospital admissions for cardiovascular events with nicotine gum treatment (101). In fact, the opposite was observed. Study participants who quit smoking and used nicotine gum had a lower hospital admission rate for cardiovascular disease than participants who quit smoking and did not use gum. Hospital admission rates were similar among subjects who failed to quit smoking, with or without nicotine gum use. In considering these results, it should be remembered that nicotine treatment was not randomly assigned, and therefore the usual caveats regarding sources of bias from comparisons of subgroups must be applied. For example, some participants motivated to use nicotine gum may have had a lower cardiovascular risk to begin with. Nevertheless, the data strongly suggest that nicotine gum use did not increase the rate of hospital admissions for cardiovascular disease.

Clinical trials of NRT in patients with cardiovascular disease. The results of two controlled trials of NRT in patients with cardiovascular disease have been published (102,103). The first study was a 5-week, placebo-controlled trial of 14 to 21 mg/day of transdermal nicotine in 156 patients with stable coronary artery disease (102). Cardiac symptoms were recorded, and in a subgroup, 24-h ambulatory electrocardiographic (ECG) monitoring was performed before and during the first and last weeks of treatment. Of note, the quit rates were low, so there was much concomitant smoking and patch use in each group. Frequency of angina declined both in nicotine and placebo groups, with no difference between treatments. Ambulatory ECG monitoring revealed no differences in arrhythmias or ST segment depression changes in nicotine- versus placebo-treated patients. Plasma nicotine concentrations averaged 14.1 ng/ml with transdermal nicotine in those who did and 21.1 ng/ml in those who did not quit smoking. Joseph et al. (103) recently reported the results of a large Veterans Affairs cooperative study of 584 smokers with cardiovascular disease. Patients received a 10-week course of transdermal nicotine (beginning at 21 mg/day and tapering to 7 mg/day) or placebo. Many participants continued to smoke cigarettes. The incidence of primary end points (death, myo-

cardial infarction, cardiac arrest and admission to the hospital for increased severity of angina, arrhythmias or congestive heart failure) was similar in both groups (nicotine group: 5.4%; placebo group: 7.9%). These two studies (102,103) found no evidence of aggravation of coronary artery disease by NRT.

A recent experimental study (104) further supports the safety of transdermal nicotine, even in the setting of concomitant cigarette smoking, in patients with severe coronary artery disease. Thirty-six male smokers with a baseline ≥5% reversible perfusion defect by quantitative thallium-201 single-photon emission computed tomography were treated with 14- and 21-mg nicotine patches sequentially. Despite instructions to stop, most continued smoking, although they smoked fewer cigarettes per day. In the setting of increasing plasma nicotine levels (average: 15.8 ng/ml at baseline, 24.2 ng/ml for 14-mg nicotine patches, 30.4 ng/ml for 21-mg nicotine patches), there was a highly significant reduction in total exercise-induced perfusion defect size (average: 17.5% at baseline, 12.6% for 14-mg nicotine patches, 11.8% for 21-mg nicotine patches). No patient had a significant increase in myocardial ischemia while using nicotine patches. The progressive reduction in defect size was most closely related to the reduction in the blood carboxyhemoglobin concentration, which had decreased as a consequence of smoking fewer cigarettes. This study (104) suggests that carbon monoxide or some other component of tobacco smoke rather than nicotine is most important in limiting myocardial nutrient supply in patients with coronary heart disease. In that the perfusion defect size is known to have predictive implications for future myocardial infarction or death, or both (105), this study (104) suggests that treatment with transdermal nicotine is not hazardous in patients with coronary heart disease and may even reduce cardiovascular risk in continuing smokers if the smoking rate is reduced.

Risk Versus Benefit Considerations: Cigarette Smoking Versus NRT

In summary, cigarette smoking appears to precipitate acute cardiac events by at least three mechanisms. One mechanism, and perhaps the most important, is by producing a hypercoagulable state and promoting thrombosis. Studies with high doses of nicotine in animals suggest that this effect could be due to significantly increased levels of circulating epinephrine released by bolus dose nicotine. Importantly, such effects do not appear to be present during NRT with transdermal nicotine or nicotine gum. A second mechanism is the delivery of carbon monoxide, which limits oxygen delivery to the heart. This is a problem with cigarette smoking but not NRT. A third mechanism is through hemodynamic effects of nicotine. These include an increase in heart rate and blood pressure, which in turn increase myocardial work and oxygen demand, as well as constriction of coronary arteries, which would impair blood flow and oxygen supply to the heart.

The data presented in this review indicate that nicotine delivered by nicotine polacrilex gum or transdermal nicotine

has similar or lesser effects than cigarette smoking with respect to increasing myocardial work. No data are available on the effects of transdermal nicotine on coronary blood flow. However, because the vasoconstricting effects of nicotine appear to be mediated by sympathetic nervous system activation, and we have found that transdermal nicotine produces less sympathetic activation than does cigarette smoking, it is likely that transdermal nicotine would have no greater, and probably less, an effect than cigarette smoking on coronary vascular resistance.

The risk of smoking while using nicotine replacement products appears not to be greater than the risk of smoking alone. The explanation presumably lies in the flat dose–response relation for nicotine (106,107) and the fact that even when people smoke ad libitum during NRT, the total intake of nicotine is no more than modestly increased compared with that during usual smoking (108). Because smoking is usually substantially reduced during NRT compared with that before quitting, it is likely that the risk of cardiovascular events will be less, even with concurrent smoking, because it is smoking that carries with it the greatest burden of cardiovascular risk.

The risks of NRT in patients with cardiovascular disease have not been fully elucidated, but available data on patients with cardiovascular disease as well as experimental studies of the pharmacokinetics and pharmacodynamics of nicotine in healthy smokers, suggest that the risk is not great. In contrast, cigarette smoking remains the greatest cause of morbidity and mortality from cardiovascular disease in middle-aged people. NRT has been shown to substantially increase the likelihood of smoking cessation. The available information suggests that the benefit of NRT to aid smoking cessation in patients with coronary heart disease who cannot stop smoking without such therapy outweighs the risks of continued smoking or of NRT itself.

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