

Impact of Smokeless Tobacco Products on Cardiovascular Disease: Implications for Policy, Prevention, and Treatment

A Policy Statement From the American Heart Association

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Various forms of smokeless tobacco (ST) products (snuff, chewing tobacco) are used by individuals of all ages. Over the past several years, US tobacco companies have expanded marketing and promotion of ST products. A major aim of this statement is to review and summarize the scientific evidence regarding ST product use and the potential cardiovascular risks associated with ST product use that can be used to inform policy related to tobacco control and strategies related to tobacco harm reduction. A specific policy question is whether ST products should be recommended to smokers instead of cigarettes to reduce the morbidity and mortality associated with smoking and/or as an approach to enhance smoking cessation. Although evidence is consistent with the suggestion that the cardiovascular risks are lower with ST products compared with cigarette smoking, ST products are not without harm. As reviewed in this statement, there is evidence that long-term ST product use may be associated with a modest risk of fatal myocardial infarction (MI) and fatal stroke, suggesting that ST product use may complicate or reduce the chance for survival after a MI or stroke. In addition, there is inadequate evidence to support the use of ST products as a smoking cessation strategy. Based on the findings reviewed in this statement, clinicians should continue to discourage use of all tobacco products and emphasize prevention of smoking initiation and smoking cessation as primary goals for tobacco control.

In the United States, various forms of ST products (snuff, chewing tobacco) are used by individuals of all ages, including adolescents and young adults.¹ Over the past several years, US cigarette companies have been purchasing companies that only previously sold ST products.² Consequently, there has been a proliferation of ST products such as moist snuff and snus that are sold under cigarette brand names such as Marlboro and Camel.² The latter has been accompanied by expanded promotion of ST products.² In 2009, the US Congress passed the Family Smoking Prevention and Tobacco Control Act (Tobacco Control Act) authorizing the regulation of tobacco products, including ST products.³ Recently, the US Food and Drug Administration (FDA) issued a final regulation related to the Tobacco Control Act that became effective June 22, 2010, which prohibits the sale of cigarettes and ST products to individuals younger than 18 years of age. This federal regulation also specifies new requirements related to tobacco marketing (labeling, advertising, and promotion) (Table 1).³ As smoke-free air laws proliferate across the country, ST products have been marketed as a situational substitute (“pleasure for whenever”) for cigarette smoking when smoking is prohibited in public places.⁴

A major aim of this statement is to review and summarize the scientific evidence regarding ST product use and the

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Table 1. New FDA Rules Effective on June 22, 2010

The rules prohibit:

1. Sales of cigarettes or smokeless tobacco to individuals <18 years of age; sales of cigarette packages with <20 cigarettes*;
2. Sales of cigarettes and smokeless tobacco in vending machines, self-service displays, or other impersonal modes of sale, except in very limited situations;
3. Free samples of cigarettes; tobacco brand name sponsorship of any athletic, musical, or other social or cultural event, or any team or entry in those events;
4. Gifts or other items in exchange for buying cigarettes or smokeless tobacco products; and sale or distribution of items, such as hats and tee shirts, with tobacco brands or logos;
5. The new regulations also limit distribution of smokeless tobacco products and require that audio advertisements use only words with no music or sound effects.

*The sale of cigarettes and ST products to minors (<18 years of age) has been prohibited by state laws for many years; however, this will be the first time these sales are prohibited by federal law. The Family Smoking and Prevention and Tobacco Control Act also establishes new federal enforcement efforts, including compliance checks.

potential cardiovascular effects and risks associated with ST product use. The evidence can be used to inform policy related to tobacco control and strategies related to tobacco harm reduction. A specific policy question is whether ST products should be recommended to smokers instead of cigarettes to reduce the morbidity and mortality associated with smoking and/or as an approach to enhance smoking cessation.

This article reviews the different types of ST products and prevalence of ST product use in the United States. Scientific evidence is presented on the potential adverse cardiovascular (CV) effects of ST product use, along with likely biological mechanisms for ST-associated CV risk and the potential role for ST product use as a potentially reduced exposure product (PREP) in reducing smoking-associated CV risk.

Smokeless Tobacco Products

Many forms of ST products exist worldwide. In the United States, the predominant forms of ST products are snuff (moist and dry) and chewing tobacco. Smokeless tobacco products have also been collectively referred to as spit tobacco, because moist snuff or chewing tobacco may require spitting.⁵ In the United States, however, the types of ST products have been evolving, such that tobacco companies are manufacturing spitless ST products (pouched moist snuff) and compressed tobacco lozenges.⁵

ST products are manufactured through a wide variety of processes (finely ground/shredded tobacco or powdered tobacco). ST products contain many additives, some of which are added for flavor (sugar, nuts, spices, and oils), and some, such as ammonium carbonate and sodium carbonate (alkaline buffers), of which are applied to increase the pH and therefore the level of unprotonated nicotine. Unprotonated or free base nicotine is more readily absorbed than protonated or ionized nicotine. There are different formulations of chewing tobacco (loose leaf, plug, and twist formulations) and snuff (loose tobacco particles [packaged in tin or plastic cans] or sachets

[packaged similar to tiny tea bags in tin or plastic cans]). Most ST products are held in the mouth, cheek, or lip or chewed to allow absorption of nicotine across the buccal mucosa.⁶ The act of using the ST product (placing it in the mouth or chewing) has sometimes been referred to as “dipping.” Dry fine powder formulations of snuff can be sniffed into the nose.⁵

Chewing tobacco is held in the cheek between the gum and tooth area. The nicotine is released by chewing. Snuff is also held in the mouth, but typically is not chewed.⁶ Most snuff formulations sold in the United States are classified as moist snuff (loose particles and sachets/pouches) with users placing a “wad or pinch” or a sachet between cheek and gum. Other ST products used in the United States include ST products mixed with other substances.⁵ For example, Iq’mik is a ST product prepared from fire-cured tobacco leaves mixed with punk ash (ash generated by burning woody fungus off of the bark of birch trees). Iq’mik is predominantly used by Alaska Natives, including men, women, and teething children.⁷ Also available are compressed tobacco lozenges (Ariva and Stonewall), and tobacco pellets, such as Camel Orbs.⁸ Manufactured by Star Scientific, Ariva and Stonewall are compressed tobacco, mint, and eucalyptus products that are held in the mouth and sucked as a lozenge until dissolved.⁹ With nicotine contents ranging from 0.6 mg to 3.1 mg and dissolving in 3 to 15 minutes, 2 other Camel ST products are Camel Sticks (resembling a toothpick) and Camel Strips (resembling mouthwash strips).⁹ R. J. Reynolds Tobacco, the nation’s second-largest cigarette maker behind Philip Morris, is test marketing the product, Camel Orbs, a dissolvable ST product that resembles the candy Tic-Tac. Camel Orbs are small pellets made of finely ground tobacco with mint or cinnamon flavoring.

With the exception of Sweden and Norway, the sale and distribution of ST products such as moist snuff or snus is banned in most of the European Union. Snus is the most common ST product used in Sweden. Originating in Sweden, snus is a drier form of moist snuff, packaged as sachets in plastic or tin cans. However, snus is also available in a loose form. Typically formulated with high pH levels and a 50% moisture concentration, snus differs from American snuff in placement (upper lip versus lower lip), method of manufacture (steam cured versus fire cured), and disposal (marketed as spitless). In Sweden, the average user keeps snus in the mouth for 11 to 14 hours per day.¹⁰ Snus production and use are increasing in the United States.⁴ Snus products sold in the United States include Exalt (by Swedish Match). However, other multinational tobacco companies are either test marketing or marketing their own snus brands at a rapid pace (ie, Marlboro snus, Camel snus, Lucky Strike snus, Grand Prix snus, and Triumph snus).^{9,11}

ST products are also used in other parts of the world and come in a wide variety of forms (Table 2).^{6,12} ST products can range from ground tobacco mixed with spices and sugars (Chimo in Venezuela) to sodium bicarbonate (Toombak in Sudan) to areca and betel nuts (mawa or gutkha in India).⁶ The popularity and prevalence of specific ST products varies among World Health Organization (WHO) regions: gutkha in the Eastern Mediterranean Region; betel quid, gutkha, and

Table 2. Overview of Global ST Products

Americas	
North America	Chewing tobacco (spit tobacco): Loose leaf, Plug, Twist (ie, Red Man, Beechnut, Levi Garrett); Iq'mik (predominantly in Alaska; tobacco and punk ash) Snuff (spit tobacco): Moist (ie, Copenhagen, Bandit, Kodak; loose particles or sachets); Dry (ie, Al Capone, Wawith, Tube Rose) Oral Compressed: Ariva and Stonewall (compressed tobacco lozenges) Snus (ie, Exalt, Revel, Marlboro, Camel)
South America	Chimo (predominantly in Venezuela; tobacco with sodium bicarbonate, brown sugar, and vanilla)
Europe	
Sweden	Snus (finely ground moist tobacco)
United Kingdom	Gutkha (betel quid with tobacco, betel nut, and slaked lime); Snuff (dry)
Asia	
Central Asia	Gul (tobacco powder and molasses); Nass or <i>Naswar</i> , <i>Niswar</i> (tobacco, ash, lime and cotton or sesame oil); Pan Masala or <i>Betel quid</i> (betel leaf with or without tobacco, areca nuts, and slaked lime); Zarda (tobacco, slaked lime, spices, and areca nut)
East/Southeast Asia	Gutkha (betel quid with tobacco, betel nut, and lime); Pan Masala or <i>Betel quid</i> (betel leaf with or without tobacco, areca nuts, and slaked lime)
South Asia	Snuff (creamy); Gul (tobacco powder and molasses); Gutkha (betel quid with tobacco, betel nut, and lime); Khaini (tobacco, slaked lime, and areca nut); Mawa (tobacco, slaked lime, and areca nut); Mishri or <i>Masheri</i> , <i>Misheri</i> (partially burnt tobacco used on gums and teeth as a powder); Qiwan or <i>Kima</i> (tobacco and spices); Red Tooth Powder; Snus or snuff
Middle East	
Iran, Saudi Arabia, Arab countries	Nass or <i>Naswar</i> , <i>Niswar</i> (tobacco, ash, slaked lime, and cotton or sesame oil); Shammah (tobacco and minerals); Zarda (tobacco, slaked lime, spices, and areca nut)
Africa	
Sudan	Toombak (fermented ground powdered tobacco and sodium bicarbonate)

creamy snuff in South-East Asia Region; tobacco mixed with betel nut in the Western Pacific Region; and snuff in the African Region.^{6,12}

Chemical Composition of ST Products

ST products contain a large array of chemicals, including nicotine, nitrosamines, nitrosamine acids, polycyclic aromatic hydrocarbons (PAHs), aldehydes, and metals.¹³ As noted above, there are many different types of ST products. Because of the different manufacturing/preparation techniques, ST products vary widely in nicotine and chemical composition. This section examines in brief the chemical composition of ST products.

Similar to cigarettes, nicotine is the principal alkaloid found in ST products. Other minor alkaloids include nornicotine, anatabine, and anabasine.¹⁴ The amount of total and free (unprotonated, base) nicotine varies substantially among ST products (Table 2). Nicotine concentration is determined by manufacturing/blending strategies, types of tobacco (eg, Maryland versus Turkish), product design features (dry versus moist), and the type and amount of additives. In general, the concentrations of nicotine (milligrams per gram of tobacco) are similar in oral snuff and cigarette tobacco, whereas they are somewhat lower in chewing tobacco (Table 2). Stepanov et al¹³ reported that the average amount of free-base nicotine in several popular traditional ST brands, including Copenhagen snuff, Skoal, and Kodiak Wintergreen, was greater (mean=7.57 mg/g tobacco for traditional brands) compared with new ST products, such as Taboka, Marlboro

snus, and Camel snus (mean=2.57 mg/g tobacco for all the newer ST products). Other new ST products such as Camel orbs (size of a tic tac) contain 1 mg of nicotine per orb, and Camel sticks (size of a toothpick) contain 3.1 mg per stick.

There are numerous carcinogens in ST products.⁵ Combustion-derived benzo[a]pyrene and other polycyclic aromatic carcinogens are present in lower concentration in ST compared with cigarette smoke (CS). In contrast, nitrosamines, such as 4-(methylnitrosamino)-1-(3-pyridyl)-1-butane (NNK) and *N'*-nitrosornicotine (NNN) are present in relatively high concentrations in ST products.¹⁵ In fact, the highest known nonoccupational exposure to nitrosamines occurs with ST use. Every gram of ST contains approximately 1 to 5 μ g of tobacco-specific nitrosamines such as NNN and NNK, two established carcinogens.¹⁵ Other tobacco-specific carcinogens in ST products include *N'*-nitrosoanabasine (NAB), *N'*-nitrosoanatabine (NAT), and nitrosamine acids (eg, 3-[methylnitrosamino] propionic acid).¹⁵ Even though certain manufacturing techniques are used to reduce the level of these compounds in some products, they remain present in substantial concentrations in ST products, including Swedish snus.¹⁶

Recently, Stepanov and colleagues¹³ compared the levels of total tobacco-specific nitrosamines (TSNA) (Total TSNA=NNN+NNK+NAB+NAT) among traditional ST brands (eg, Swedish Snus General, Copenhagen Snuff, Copenhagen Long Cut, Skoal Long Cut, and Kodiak Wintergreen) and new ST products (eg, Taboka, Marlboro Snus, Camel Snus and Skoal Dry). Total TSNA averaged

Table 3. Range of Nicotine Concentrations in ST Products Sold in Massachusetts (USA) in 2003 and Cigarettes Sold in the United States

	Chewing Tobacco* (Mean Range)	Dry Snuff* (Mean Range)	Moist Snuff* (Mean Range)	Cigarettes Sold in USA†		
				High	Moderate	Low
Nicotine	9.9 (3.41–39.7)	16.8 (10.48–24.84)	12.6 (4.7–24.29)	9.5–13.4	8.9–11.4	7.2–11.5

*mg/g product.

†Different nicotine yields (mg/g tobacco) among cigarettes marketed as low, moderate and high nicotine yield.

Adapted and used with permission from Djordjevic and Doran, 2009.¹⁴

1.97 $\mu\text{g/g}$ dry weight in new tobacco brands such as Taboka, Marlboro Snus, and Camel Snus, whereas higher amounts (total TSNA 4.54 $\mu\text{g/g}$ dry weight tobacco) were found in Skoal Dry. Even greater amounts (7.42 $\mu\text{g/g}$ dry weight tobacco) were found in traditional brands, such as Copenhagen snuff and Skoal Long Cut.¹³ Levels of minor tobacco alkaloids, such as nornicotine, anatabine, and anabasine, were higher in the newer ST products (Taboka, Marlboro Snus, and Skoal Dry), compared with traditional products such as Copenhagen Snuff, Skoal Long Cut, and Kodiak Wintergreen. Mean levels of nitrite and nitrate were 0.003 mg/g and 1.96 mg/g dry weight, respectively, for the new ST products and 0.030 mg/g and 6.82 mg/g dry weight, respectively, for the traditional ST products. Other anions found in both newer and traditional ST products included formate, chloride, sulfate, and phosphate. Stepanov and colleagues¹³ also found large variation in PAHs and aldehyde levels among all the brands evaluated.

Prevalence of ST Use in the United States and Worldwide

Various forms of ST have been used for thousands of years.¹⁷ Worldwide, approximately 1.3 billion individuals smoke cigarettes or use other tobacco products (which includes ST products).^{7,18} In the United States there are an estimated 8.1 million (3.2%) ST product users.¹ Among adults ≥ 18 years of age in the United States, ST product use is more prevalent in men than women and, overall, individuals between 18 and 25 years of age are most likely to be users of ST products.^{19,20} Nationally, American Indian/Alaska natives have the highest prevalence (7%), followed by whites (4.3%), Hispanics (1.3%), African Americans (0.7%), and Asian Americans (0.6%).²⁰ High prevalence of use is also noted for individuals living in southern states and rural areas and those employed as blue-collar workers or service or labor workers, or those who are unemployed.^{19,20} Individuals who graduated from high school but did not go to college have a high prevalence of use as well.¹

ST product utilization trends among past-month tobacco users (>12 years of age) have not changed significantly from 2002 through 2007. When examining distinct age groups, specifically those between 12 and 17 years of age, there was a slight increase in past-month use of ST from 2.0% in 2002 to 2.2% in 2008.¹ Similar to adult trends, the Centers for Disease Control and Prevention (CDC) Youth Risk Behavior Survey reveals that ST product use among boys is higher (6.3%) than among girls (0.4%), with the largest prevalence of use noted among high school students (8%); white youth use ST products significantly more (10.2%) than Hispanic

(5.1%) or African American youth (1.7%).²¹ State prevalence estimates for ST use among youth range from 4.2% (Maryland) to 15.8% (Kentucky), with similar patterns among adults, with highest prevalence in southern states and rural areas.^{21,22}

Initiation of ST product use within the past year among persons ≥ 12 years of age was 1.4 million in 2008, which was not significantly different from 1.3 million in 2006. “However, the estimated number of past year initiates of ST product use in 2008 was 47% higher than the 2002 estimate of 951 000.”²¹ In addition, and of concern, less than half of the new initiates of ST product use were <18 years of age at first use and adolescent males.¹

With regard to the use of different types of ST products, in the United States the prevalence of chewing tobacco (loose leaf, plug, and twist) use has been declining since the mid-1980s.²³ In contrast, snuff consumption and production has been on the rise.²³ In contrast to the United States, various types of ST products are used globally that include, Toombak, Nass, and Pan Masala (Table 2). Similarly to the United States, men use ST products at a much higher rate than women, but the overall prevalence rate of ST product usage is much higher among both men and women in some countries, compared with the United States. For example, in India 22% of men and 17% of women use ST,^{24,25} in Sudan 40% of men and 10% of women use Toombak,²⁶ and in Sweden, among those ≥ 16 years of age, 21% of men and 3.9% of women use snus.²⁷

In looking to the future, it will be critical to develop standardized global surveillance methods for all forms of tobacco use among adolescents and adults. To this end, the Global Youth Tobacco Survey, an international surveillance program developed by WHO and the CDC, is underway to examine tobacco use among youth.²⁸ Another initiative underway is the Global Adult Tobacco Survey, an initiative to provide global surveillance of adult ST use.

CV Risk and Outcomes Associated With ST Use

The main aim of this section is to summarize evidence regarding CV risk and ST product use, specifically focusing on comparisons between ST users who have never smoked cigarettes and a reference/control group members who also have never smoked or used any form of tobacco. It should be noted that one of the concerns about expanded and increased use of ST products in the general population is the dual use of cigarettes and ST products; however, the risks of combined ST product use and cigarettes are not reviewed in this statement. Limiting the comparisons between these groups

Table 4. ST Product Use and Hypertension

Reference and Health Outcome	Country/Design/Population/Subjects	ST Product Use	Sample Size and Cases of Events	Adjusted Confounding Variables	Results/Comment
Siegel et al, 1992 ³⁴ BP	<ul style="list-style-type: none"> Case control United States, members of American professional league baseball teams Collected data on subjects between March 1988 and 1989 BP was measured in the sitting position after a 5-min rest period 	<ul style="list-style-type: none"> Self-report Nonusers were defined as those who never used ST (but never more frequently than once a month) ST users were defined as those who used ST within the past week 75% of ST users used primarily oral snuff, the remaining subjects used chewing tobacco 	<ul style="list-style-type: none"> Nonusers (n=176) and ST users (n=127) (between 20 and 29 y of age) 	<ul style="list-style-type: none"> Age, race, alcohol use, and serum caffeine level 	<p>Results:</p> <ul style="list-style-type: none"> No significant difference was found in SBP and DBP (mm Hg) between nonusers (117/72) and ST users (117/71) (95% CI for SBP difference -2.48 to 2.53 and for DBP -1.62 to 2.79). <p>Comment:</p> <ul style="list-style-type: none"> Duration of ST use was not noted.
Eliasson et al, 1995 ³⁵ BP	<ul style="list-style-type: none"> Case control Northern Sweden, International, WHO MONICA Project. Men >25 years of age Collected data on subjects between January and April 1990 BP was measured in the sitting position after a 5-min rest 	<ul style="list-style-type: none"> Current snuff use was defined as use of one can of moist snuff (50 g tobacco/d) 	<ul style="list-style-type: none"> Current moist snuff dippers (n=104) (mean age, 42 y) versus nontobacco users (n=581) (mean age, 45 y) 	<ul style="list-style-type: none"> Age, BMI 	<p>Results:</p> <ul style="list-style-type: none"> No significant difference was found in SBP and DBP (mm Hg) between nontobacco users (SBP=130 [range, 127-132], DBP=82.4 [range, 80.9-83.8]) and snuff dippers (SBP=129 [range, 126-133], DBP=82.9 [range, 80.6-85.2]). <p>Comment:</p> <ul style="list-style-type: none"> Neither the duration or amount of snuff use was noted.
Johansson et al, 2005 ³⁸ Hypertension (based on subjects self-report)	<ul style="list-style-type: none"> Cohort/12-y follow-up Northern Sweden, data obtained from Swedish national survey (Swedish Annual Level-of-Living Survey) Men surveyed between 1988 and 1989 (age, 30-74 y) 	<ul style="list-style-type: none"> Daily snuff users (assessed on entry into study by trained interviewers) no information on amount of snuff use or duration 	<ul style="list-style-type: none"> Never smoker (n=1036) (mean age, 47.0 y) Daily snuff users (n=107) (mean age, 41 y) 	<ul style="list-style-type: none"> Age, BMI 	<p>Results:</p> <ul style="list-style-type: none"> Age-adjusted incidence rates (per 10 000 person years) for hypertension was 180 for nonsmokers and 207 for snuff users. <p>Comment:</p> <ul style="list-style-type: none"> The presence of hypertension was based on self-report, specifically answers to questions such as "Do you suffer from diabetes/hypertension?" The primary aim of the study was to determine the risk of fatal and nonfatal CHD events.
Hergens et al, 2008 ³⁶ <ul style="list-style-type: none"> The term "high BP" was used to describe BP actually measured in subjects, whereas the term "hypertension" was used to describe hypertension identified by specific ICD codes noted in the Swedish Inpatient Registry High BP and hypertension were defined as SBP >160 and DBP >100 (mm Hg) 	<ul style="list-style-type: none"> Cohort/baseline+15-y follow-up Sweden (national sample), Swedish male construction workers who were eligible for health checkups between 1969 and 1993 BP measured at study baseline and then at follow-up in some subjects; however, BP data were also obtained from the Swedish Inpatient Registry ST use assessed at baseline health checkup 	<ul style="list-style-type: none"> Regular snuff use was defined as consumption of at least 1 g/d for at least 1 y (consumption ranged from 12.5 g/d to >50 g/d) 	<ul style="list-style-type: none"> Never snuff users (n=4815) and current snuff users (n=1010) At the 15-y follow-up, the RR for hypertension was determined in snuff users who were normotensive at baseline and who were available for follow-up BP (n=42 005) 	<ul style="list-style-type: none"> Age, BMI, and region of residence 	<p>Results:</p> <ul style="list-style-type: none"> Prevalence of "high" BP at baseline: Never snuff users, 5.6% and 3.07% in current snuff users. At the 15-y follow-up, there was an increased RR of hypertension (RR 1.43; 95% CI: 1.1.2-1.83) and "high BP" (RR 1.34; 95% CI: 1.03-1.74) in current snuff users. Only the latter increase was significant (P=0.02). <p>Comment:</p> <ul style="list-style-type: none"> Did not control for potential confounders such as alcohol use, or other lifestyle factors such as physical activity.

SBP indicates systolic blood pressure; DBP, diastolic blood pressure; BP, blood pressure; CI, confidence interval; BMI, body mass index; HR, hazard ratio; CHD, coronary heart disease; MONICA, Monitoring of Trends and Determinants in cardiovascular Diseases; RR, relative risk; ICD, International Classification of Disease.

Table 5. Findings Related to ST Product Use and Myocardial Infarction and Ischemic Heart Disease Mortality

Reference and Health Outcome	Country/Design/Population/Subjects	ST Product Use	Sample Size and Cases of Events	Adjusted Confounding Variables	Results/Comment
Huhtasaari et al, 1992 ⁴⁶ WHO criteria for acute MI	<ul style="list-style-type: none"> ● Case control ● Northern Sweden, MONICA ● Cases of acute MI between 1989 and 1991 ● Men (35–64 y) ● Snuff use obtained via questionnaire by trained nurses at time of MI 	<ul style="list-style-type: none"> ● Daily snuff users 	<ul style="list-style-type: none"> ● Never used tobacco (n=295, cases of MI=118) ● Regular snuff users (n=146, cases of MI=59) 	<ul style="list-style-type: none"> ● Age, region of residence 	<p>Results:</p> <ul style="list-style-type: none"> ● Snuff use was not associated with the occurrence of more MIs (snuff users who did not have an MI=15% versus snuff users who did have a MI=10%). ● No difference was found in age-adjusted odds ratio for MI between nontobacco and snuff dippers (OR 0.89, 95% CI: 0.62–1.29). ● OR for MI in low (<2 cans weekly) and high (≥2 cans weekly) compared with nontobacco users were as follows: low OR 0.63, 95% CI: 0.41–0.98 and high OR 0.93 CI 95%: 0.61–1.41. <p>Comment:</p> <ul style="list-style-type: none"> ● No information on the duration of snuff use or consideration of other potential CV confounding variables (eg, alcohol use, physical activity, hypertension).
Bolinder et al, 1994 ⁴⁶ CV-related mortality (ICD-8 390–458)	<ul style="list-style-type: none"> ● Cohort/12-y follow-up ● Sweden (national sample), Swedish construction worker study (enrolled between 1971 and 1974) ● Information about ST use was obtained via questionnaire at voluntary medical examination 	<ul style="list-style-type: none"> ● Referred to as “ST” users (collected information about duration and categorized as duration<or>15 y) 	<ul style="list-style-type: none"> ● Nonusers (n=13 784), CV-related mortality cases (n=154) for 35–45 and 55–65 year olds (n=480) ● Current ST users 35–54 y (n=1672, CV-related mortality cases=44) 55–65 y (n=1734, CV-related mortality cases=174) 	<ul style="list-style-type: none"> ● Age, region of origin 	<p>Results:</p> <ul style="list-style-type: none"> ● For ST users compared with nonusers the RR for CV-related mortality among 35–54 year olds was 2.1 (95% CI:1.5–2.9) or and 1.1 (95% CI 1.0–1.4) for 55–65 year olds. <p>Comment:</p> <ul style="list-style-type: none"> ● Authors state that in addition to age and region of origin, when BMI, diabetes, history of heart symptoms or BP medications at study entry were considered, the RR from CV disease remained unchanged (revised RR and CIs not reported). Subjects in this study were snus users before 1985, after which the manufacturing process of snus was changed to reduce nitrosamine content (Critchley and Unal, 2004⁴⁸).
Huhtasaari et al, 1999 ⁴⁵ Nonfatal and fatal MI (ICD 410–414, version not indicated)	<ul style="list-style-type: none"> ● Case control ● Northern Sweden, MONICA ● All cases of acute MI (fatal and nonfatal) and sudden death between 1991 and 1993 ● Men (25–64 y, mean age 55.6 y) ● Snuff use (assessed at time of MI by MONICA team nurses) 	<ul style="list-style-type: none"> ● Current snuff users ● Median consumption: 2 boxes/d ● Median age at onset of snuff use 31.5 y 	<ul style="list-style-type: none"> ● Never used tobacco (n=366, MI cases=149) ● Current snuff users (n=149, MI cases=59, fatal MI=15) 	<ul style="list-style-type: none"> ● Hypertension, diabetes, high cholesterol, family history of early cardiac death, low educational status, and not being married 	<p>Results:</p> <ul style="list-style-type: none"> ● Among never used tobacco users, 21.7% had a MI compared with 8.6% of current snuff users ● Snuff dipping was not found to be a significant predictor of nonfatal MI (OR 0.58, 95% CI: 0.35–0.94) or fatal MI (OR 1.50; 95% CI: 0.45–5.03). <p>Comments:</p> <ul style="list-style-type: none"> ● Authors note that information on the duration of snuff use was not reliable and no information was collected on alcohol use.

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Table 5. Continued

Reference and Health Outcome	Country/Design/Population/Subjects	ST Product Use	Sample Size and Cases of Events	Adjusted Confounding Variables	Results/Comment
Accortt et al, 2002 ⁵⁰ Ischemic heart disease mortality (<i>ICD-9</i> 410–414)	<ul style="list-style-type: none"> ● Cohort ● United States, First NHANES I (1971–1975) and the NHANES I Epidemiological Follow-up Study (NHEFS) (surveys conducted between 1982 and 1984), 1986, 1987, 1992 providing 10, 15, and 20 y of follow-up ● Information about ST use was collected via direct interview of subjects by use of a questionnaire 	<ul style="list-style-type: none"> ● Exclusive ST users 	<ul style="list-style-type: none"> ● No tobacco users (n=5192) (mean age, 54 y) ● Exclusive ST users (n=414) (mean age, 64.9 y) ● Total ischemic heart disease mortality cases not reported 	<ul style="list-style-type: none"> ● Age, race, sex, region of residence, poverty index ratio, alcohol consumption, recreational activity, BMI, BP, serum cholesterol, and family history of cancer 	<p>Results:</p> <ul style="list-style-type: none"> ● Among males, no significant increase in death due to IHD (HR 0.6, 95% CI: 0.3–1.2) was found in male ST users compared with nontobacco users. <p>Comment:</p> <ul style="list-style-type: none"> ● In NHANES I, cigarette smoking information was only gathered on only a “sample” of subjects (ie, not the entire No. of subjects participating), leading to the possibility that some ST users could have been previous cigarette smokers. Nontobacco users could have been pipe or cigar users. However, considering the direction of the results, confounding due to the above is unlikely. ● Total No. of mortality cases related to IHD were not reported for either ST users or nonusers.
Johansson et al, 2005 ³⁸ First nonfatal or fatal coronary heart disease (CHD) event (<i>ICD-9</i> (410–414) and <i>ICD-10</i> (120–125))	<ul style="list-style-type: none"> ● Cohort/12-y follow-up ● Northern Sweden, data obtained from Swedish national survey (Swedish Annual Level-of-Living Survey) ● Men surveyed between 1988 and 1989 (age, 30–74 years) 	<ul style="list-style-type: none"> ● Daily snuff users (assessed on entry into study by trained interviewers) no information on amount of snuff use or duration 	<ul style="list-style-type: none"> ● Never smoker (n=1036) (mean age, 47.0 y) ● Daily snuff users (n=107) (mean age, 41 y) ● Total nonfatal and fatal CHD cases not reported 	<ul style="list-style-type: none"> ● Age, BMI, physical activity, diabetes, and hypertension (the latter 2 measures were based on self-report) 	<p>Results:</p> <ul style="list-style-type: none"> ● Found an increased (nonsignificant) HR of 1.41 (95% CI: 0.61–3.28) for first hospitalization for fatal or nonfatal CHD event. <p>Comment:</p> <ul style="list-style-type: none"> ● ST use determined at baseline and not reassessed during the 12-y follow-up. Former snuff users could have been categorized as “never smokers” ● Total No. of nonfatal and fatal cases related to CHD were not reported for either ST users or nonusers.
Hergens et al, 2005 ³⁷ First acute MI (nonfatal and fatal) were identified from hospital databases in Stockholm	<ul style="list-style-type: none"> ● Case control ● Northern Sweden, 45- to 70-year-old males ● Data obtained from 2 identical questionnaires (Stockholm Heart Epidemiology Program [1992–1993]) and the Vasternorrland Heart Epidemiology Program [1993–1994]) ● Mailed questionnaire to determine ST use 	<ul style="list-style-type: none"> ● Never smokers and snuff users (history of using snuff within past 2 y of study entry) users 	<ul style="list-style-type: none"> ● Total nonfatal MI cases among never, former and current snuff users (n=1173) and total fatal cases among never, former, and current snuff users (n=259) ● Controls (n=1810) 	<ul style="list-style-type: none"> ● Age, hospital catchment area, and smoking 	<p>Results:</p> <ul style="list-style-type: none"> ● No increase in risk for nonfatal MI (OR 1.0; 95% CI: 0.8–1.3) or fatal MI (OR 1.0; 95% CI: 0.7–1.6) among current snuff users. <p>Comment:</p> <ul style="list-style-type: none"> ● Duration of snuff use not indicated and information about fatal cases was obtained from relatives.

(Continued)

Table 5. Continued

Reference and Health Outcome	Country/Design/Population/Subjects	ST Product Use	Sample Size and Cases of Events	Adjusted Confounding Variables	Results/Comment
Henley et al, 2005 ⁵¹ Mortality related to CHD (CPS-I ICD-7 code 420; CPS-II ICD-9 410–414)	<ul style="list-style-type: none"> ● Cohort ● United States, Cancer Prevention Study (CPS-I) (12-y follow-up, 1959–1972) and CPS-II (18-y follow-up, 1982–2000). ● Information about spit tobacco use was obtained at enrollment 	<ul style="list-style-type: none"> ● Current spit tobacco users were defined as those using snuff or chewing tobacco 	<ul style="list-style-type: none"> ● Nontobacco users (CPS-I n=69 662, CHD-related mortality cases=4035.; CPS-II (N=111 482, CHD-related mortality cases=8315) ● Current spit tobacco users CPS-I (n=7745, CHD-related mortality cases=799; CPS-II (n=2488, CHD-related mortality cases= 172) 	<ul style="list-style-type: none"> ● Age, race, education, current alcohol consumption, exercise, aspirin use, BMI, quartiles of vegetable and fruit consumption, quartiles of dietary fat consumption, and in CPS-II occupation 	<p>Results:</p> <ul style="list-style-type: none"> ● In CPS-I, current use of spit tobacco was associated with a significantly greater HR for mortality related to coronary heart disease (HR 1.12; 95% CI: 1.03–1.21). ● In CPS-II, current use of spit tobacco was associated with a significantly greater HR for mortality related to CHD (HR 1.25; 95% CI: 1.08–1.47). <p>Comment:</p> <ul style="list-style-type: none"> ● In both CPS-I and -II, information about spit tobacco use was only collected at baseline. ● The use of earlier less specific ICD (eg, ICD-7) may have resulted in misclassification of CHD mortality statistics. ● As others have highlighted (Lee, 2007²⁹), even though there was adjustment of multiple confounders, ST users in general had poorer lifestyle characteristics (eg, tended to be older, had less education, and consumed more dietary fat and fewer vegetables than nonusers).
Hergens et al, 2007 ⁴⁹ Nonfatal and fatal MI (ICD-7 420 before 1969 and ICD-8 410 from 1969 to 1986, ICD-9 410 (1987–1997), and ICD-10 121–122 (from 1997 onward)	<ul style="list-style-type: none"> ● Cohort/19-y follow-up ● Sweden, Swedish male construction workers who were eligible for health checkups between 1969 and 1993 (however, analysis based on those in which tobacco use information was available between 1978 and 1993) (mean age on entry, 31.5 y) ● ST use assessed at baseline health checkup 	<ul style="list-style-type: none"> ● Regular snuff use defined as 1 g/d for at least 1 y (mean consumption 22.5 g/d). ● Snuff consumption ranged from 12.5 g/d to >50 g/d 	<ul style="list-style-type: none"> ● N=118 395 never smoking men (sample size of snuff users and nontobacco users not indicated) ● Cases of nonfatal MI in never use tobacco group=2485 and fatal MI cases=713 ● Cases of nonfatal MI in ever snuff users (past snuff users+current users)=325 and fatal MI cases=128 	<ul style="list-style-type: none"> ● Age, BMI 	<p>Results:</p> <ul style="list-style-type: none"> ● Among ever snuff users (past snuff users+current users), no increase was found in RR for nonfatal MI (RR 0.91; 95% CI: 0.81–1.02), however there was an increase in RR for fatal MI amongst ever snuff users (RR 1.28; 95% CI: 1.06–1.55). When risk was evaluated in only current snuff users, no significant increase in RR for nonfatal MI (RR 0.94; 95% CI: 0.83–1.06, 121 cases) or fatal MI (RR 1.32; 95% CI: 1.08–1.61, 118 cases) was found. <p>Comment:</p> <ul style="list-style-type: none"> ● The finding that RR was only significantly elevated in “ever snuff users” and not current snuff users, suggests that perhaps other factors, duration or amount of ST use or other confounding factors (comorbid conditions, diet, alcohol use) were not adequately controlled for in the past snuff users.

(Continued)

Table 5. Continued

Reference and Health Outcome	Country/Design/Population/Subjects	ST Product Use	Sample Size and Cases of Events	Adjusted Confounding Variables	Results/Comment
Wennberg et al, 2007 ⁴⁴ Nonfatal and fatal MI (ICD-9 codes 410–414, ICD-10 120–125)	<ul style="list-style-type: none"> Prospective incident case-referent study Northern Sweden, design nested in the Vasterbotten Intervention Program and MONICA Male snuff users (mean age, 53 y) surveyed in 1986, 1990, 1994, 1999 Completed health survey at local primary health care center 	<ul style="list-style-type: none"> Snuff users defined as daily use of snuff 	<ul style="list-style-type: none"> Never used tobacco group (n=654; cases of MI=130, total fatal cases=77) Snuff users (n=117; cases of MI=21, fatal cases=18) 	<ul style="list-style-type: none"> Matched for age and sex BMI, leisure time physical activity, educational level, and cholesterol level SCD was defined 2 ways: SCD survival time <24 hours and SCD with survival <1 h. 	<p>Results:</p> <ul style="list-style-type: none"> No increased OR for first MI (0.82 95% CI: 0.80–1.43) in current snuff users compared with nontobacco users. No increased risk of fatal MI (OR 1.12; 95% CI: 0.38–3.29), SCD survival time <24 h or SCD survival <1 h (OR 1.18; 95% CI: 0.38–3.70, OR 0.38; 95% CI: 0.08–1.80, respectively). <p>Comment:</p> <ul style="list-style-type: none"> The total No. of fatal MI was low (n=18), when categorizing according to SCD survival time <24 h or SCD survival <1 h and all SCD cases were 7 and 4, respectively, limiting the conclusions about snuff use and fatal MI. No information on type or duration of snuff use.
Haglund et al, 2007 ⁵³ Nonfatal and fatal MI (ICD-9 codes 410–414, ICD-10 120–125)	<ul style="list-style-type: none"> Cohort/14- to 16-y follow-up Northern Sweden, Swedish Survey of Living Conditions (1988–1989) (face-to-face interviews) 	<ul style="list-style-type: none"> Snuff users defined as daily use of snuff 	<ul style="list-style-type: none"> No tobacco users (n=2579, IHD cases=227, stroke cases=126) and snuff users (n=721, IHD cases=28, stroke cases=19) 	<ul style="list-style-type: none"> Age at event, socioeconomic status, residential status, self-reported health, No. of longstanding illnesses and physical activity 	<p>Results:</p> <ul style="list-style-type: none"> No increase in IHD incidence (IRR for IHD [IRR 0.77; 95% CI:0.51–1.15]) in snuff users. <p>Comment:</p> <ul style="list-style-type: none"> Mortality risk ratio was also determined for both IHD and stroke; however, the No. of stroke cases (n=8 and n=4, respectively) was low.

NHANES indicates National Health and Nutrition Examination Survey; OR, odds ratio; CV, cardiovascular; SCD, sudden cardiac death; IHD, ischemic heart disease; IRR, incidence rate ratio.

will shed light on the CV risks associated with ST product use alone, which is important to know in determining whether ST product use could potentially serve as a safe smoking cessation strategy.

For this section, the search and review methods were thorough and comprehensive but not systematic. Several systematic reviews and meta-analyses related to this topic had been previously published.^{29–31} We conducted a series of searches using PubMed and the Cochrane Library. We also reviewed the references lists of published meta-analyses and systematic reviews.^{29–31} We used the following search terms: smokeless tobacco, snus or snuff, cardiovascular disease, cardiovascular risk factors, hypertension, myocardial infarction, and stroke. We limited the search to English-language studies of adult humans (age >18 years). The initial search yielded over 138 citations. The included studies (Tables 3 to 5) were limited to randomized clinical trials, cohort or case control, as well as those that included comparisons between ST product users who had never smoked cigarettes and a reference/control group that had never smoked or used any form of tobacco. Similar to others, epidemiological studies had to have an adequate sample size (case control >100 cases and controls, cohort studies >20 cases) and used appropriate statistical analysis.^{29–31} Based on the latter, the included studies were primarily conducted in Sweden and the United States.

Hypertension

Hypertension is a strong predictor of future CV events such as MI and stroke and, therefore, determination of the impact of ST product use on the development of hypertension is important.^{32,33} We found several studies that evaluated the relationship between ST product use and the risk of developing hypertension or the presence of hypertension (Table 3). In a nested case control study of 20- to 29-year-old American baseball players, no differences were found in measured systolic or diastolic blood pressure (BP) between ST users and non-ST users.³⁴ Similarly, in a nested case control study, Eliasson et al³⁵ found no differences in measured systolic or diastolic BP between current snuff dippers and nontobacco users. It is noteworthy that in both studies, BP was directly measured, allowing for the analysis of the actual BP values. However, neither study accounted for the duration of ST product use and subjects from northern Sweden and American baseball players are not representative of the general population, therefore limiting the generalizability of these findings.

In a cohort study of male Swedish snuff users, the prevalence of hypertension (defined as systolic BP \geq 160 mm Hg and diastolic BP \geq 100 mm Hg) at study enrollment was not different between nontobacco users and current snuff users (mean snuff use, 22.5 g/day >1

year) (Table 4).³⁶ In the same study at the 15-year follow-up time point, and after adjustment for age and body mass index only, there was a modest increase in the relative risk for developing hypertension in current snuff users.³⁶ In another study (case control) by these same investigators, the prevalence of hypertension (systolic BP >170/diastolic BP >95 mm Hg) was 26% in never snuff users, 23% in former, and 35% in current snuff users.³⁶ Because the latter study was designed to examine moist snuff use and risk of MI, statistical analysis was not performed using the hypertension prevalence data. In another cohort study, using data from the Swedish Annual Level-of-Living Survey, Johansson et al³⁸ found no difference in the age-adjusted incidence rates of hypertension between Swedish daily snuff users and nontobacco users. In the latter study, hypertension was not defined; instead, it was based on subject self-report.³⁸

In summary, data from the majority of studies in this section do not support an increase in the incidence or prevalence of hypertension in ST product users. The exception is the findings from Hergens et al³⁶ which suggest that current snuff use is associated with a small, but significant increase in the relative risk for developing hypertension (designated as “high BP” in the study, indicating BP measured at the end follow-up health visit). In Hergens et al,³⁶ hypertension was defined as a systolic BP >160 mm Hg and diastolic BP >90 mm Hg (stage II hypertension),³⁹ and this study only controlled for age and body mass index and did not consider other lifestyle factors, such as alcohol use or lack of physical activity.³⁶ It is important to note that some ST products, such as loose snuff and chewing tobacco, contain large amounts of sodium as part of the sodium bicarbonate alkaline buffer that is necessary to facilitate nicotine absorption; the sodium load (30 to 40 excess mEq sodium per day) could aggravate hypertension, as well as cardiac failure.⁴⁰ Furthermore, some ST products contain as a flavorant a large amount of licorice, which contains glycyrrhizic acid that has mineralocorticoid activity, which can also aggravate hypertension and produce potassium wasting.⁴¹

These studies were primarily designed to examine the long-term effects of ST product use. Others have shown that “one-time” use of snuff or chewing tobacco results in acute, transient (30 to 60 minutes) increases in BP and heart rate.⁴² One crossover study examined circadian BP and heart rate in people smoking cigarettes, using oral snuff or chewing tobacco, and using no tobacco.⁴³ CS and both forms of ST were associated with a significant increase in heart rate throughout the day and no change in BP. Both of the aforementioned studies were conducted in subjects with a history of tobacco use. Based on data from the latter studies, the acute effects of ST product use include an increase in heart rate and no change or transient increases in BP.

Myocardial Infarction

A number of population-based studies have evaluated the risk for nonfatal and fatal coronary heart disease events, such as MI and sudden death in ST users (Table 5). The

majority of these studies have been conducted in Sweden. Wennberg et al⁴⁴ examined risk of first MI and sudden cardiac death among male snuff users who were part of the Vasterbotten Intervention Program and the WHO Monitoring of Trends and Determinants Cardiovascular Disease (MONICA) study in northern Sweden. Multivariate analyses revealed no increased risk of first MI or sudden death for current snuff users compared with nontobacco users.⁴⁴ Similarly, Hergens et al³⁷ found no increase in risk for nonfatal MI or fatal MI among current snuff users living in northern Sweden. Two other case-control studies in Sweden have confirmed these latter findings.^{45,46} Two separate Swedish long-term follow-up cohort studies have reported a nonsignificant increase in relative risk for CV-related mortality and hazard ratio for nonfatal and fatal coronary heart disease events (Table 5).^{38,47} Subjects in the Bolinder et al⁴⁷ study were snus users before 1985, after which the manufacturing process of snus was changed to reduce its nitrosamine content, therefore challenging the relevance of these findings to present-day ST users.⁴⁸

Some recent studies conducted in Sweden, evaluating long-term (19-year) CV outcomes suggest that snus use is associated with an increased risk of fatal MI.⁴⁹ During a 19-year follow-up of Swedish construction workers, Hergens et al⁴⁹ found no increase in the multivariate-adjusted relative risk of nonfatal MI (relative risk [RR] 0.91, 95% CI: 0.81 to 1.02) in ever snuff users (past snuff users + current users); however, there was an increased risk of fatal MI among ever snuff users (RR 1.28, 95% CI: 1.06 to 1.55) (Table 4). When risk was evaluated in only current snuff users, relative risk for nonfatal MI was 0.94 (95% CI: 0.83 to 1.06) and for fatal MI the relative risk was 1.32 (95% CI: 1.08 to 1.61).⁴⁹ However, as noted in Table 5, the only potential confounding variables controlled for were age and body mass index. Other lifestyle factors such as alcohol use and physical activity were not considered and snuff use was only measured at study enrollment.

To date, 3 studies have been conducted in the United States. Using data from the first National Health and Nutrition Examination Survey (NHANES) Epidemiological Follow-up Study, Accortt et al⁵⁰ found no association between ST product use and all-cause CV mortality (Table 5). The other US studies include two American Cancer Society prospective cohort studies: the Cancer Prevention Study I (CPS-I, 12-year follow-up) that enrolled subjects in 1959 (follow-up 12 years, 1972) and the Cancer Prevention Study II (CPS-II) that enrolled subjects in 1982 (follow-up 18 years, 2000).⁵¹ In both CPS-I and CPS-II, current ST use was associated with an increased hazard ratio for mortality related to coronary heart disease and cerebrovascular disease (Table 5).⁵¹ In all of the aforementioned US studies information on spit tobacco use was collected only at baseline and not updated during or at follow-up. In CPS-II, the frequency and duration of spit tobacco use were examined, but no statistically significant relationships between frequency or duration of use and CV disease (CVD) risk were found. Some experts have minimized findings related to CPS-I because the data were collected many years ago (1959–1972) when there was a

Table 6. Findings Related to ST Product Use and Stroke

Reference and Health Outcome	Country/Design/Population/Subjects Studied	ST Product Use	Sample Size and Cases of Events	Adjusted Confounding Variables	Results/Comment
Bolinder et al, 1994 ⁴⁷ Stroke Mortality (ICD-9 430–438)	<ul style="list-style-type: none"> ● Cohort/12-y follow-up ● Sweden (national sample), Swedish construction worker study (enrolled between 1971 and 1974) ● Information about ST use was obtained via questionnaire at voluntary medical examination 	<ul style="list-style-type: none"> ● Referred to as “ST” users (collected information about duration and categorized as duration < or > 15 y). 	<ul style="list-style-type: none"> ● Nonusers (n=13 784, stroke mortality cases=16) ● Current ST users <ul style="list-style-type: none"> – 35–54 y (n=1672, stroke mortality cases=4) – 55–65 y (n=1734, stroke mortality cases=26) 	Age, region of origin	<p>Results:</p> <ul style="list-style-type: none"> ● No significant increase in relative risk for stroke mortality among 35–54 year olds (RR 1.9; 95% CI: 0.6–5.7) or among 55–65 year olds (RR 1.2; 95% CI: 0.7–1.8). <p>Comment:</p> <ul style="list-style-type: none"> ● No. of stroke cases among 35–54 year olds was very low (n=4). Authors state that in addition to age and region of origin, when BMI, diabetes, history of heart symptoms, or BP medications at study entry were considered, the RR from CV disease remained unchanged (revised RR and CIs not reported). Subjects in this study were snus users before 1985, after which the manufacturing process of snus was changed to reduce nitrosamine content (Critchley and Unal, 2004⁴⁸).
Accortt et al, 2002 ⁵⁰ Stroke mortality (ICD-9 430–438)	<ul style="list-style-type: none"> ● Cohort ● United States, First NHANES I (1971–1975) and the NHANES I Epidemiological Follow-up Study (NHEFS). Surveys conducted between 1982 and 1984, 1986, 1987, 1992 providing 10, 15, and 20 y of follow-up ● Information about ST use was collected via direct interview of subjects using a questionnaire 	<ul style="list-style-type: none"> ● Exclusive ST users 	<ul style="list-style-type: none"> ● No tobacco users (n=5192) (mean age, 54 y) ● Exclusive ST users (n=414) (mean age, 64.9 y) ● Total stroke cases not reported 	Age, race, sex, region of residence, poverty index ratio, alcohol consumption, recreational activity, BMI, BP, serum cholesterol, and family history of cancer	<p>Results:</p> <ul style="list-style-type: none"> ● Among males, no significant increase in death due to stroke (HR 0.7, 95% CI: 0.2–2.0) was found in male ST users compared with nontobacco users. <p>Comment:</p> <ul style="list-style-type: none"> ● In NHANES I, cigarette smoking information was gathered only on a “sample” of subjects (ie, not the entire No. of subjects participating), leading to the possibility that some ST users could have been previous cigarette smokers. Nontobacco users could have been pipe or cigar users. However, considering the direction of the results, confounding due to the above is unlikely.

(Continued)

Table 6. Continued

Reference and Health Outcome	Country/Design/Population/ Subjects Studied	ST Product Use	Sample Size and Cases of Events	Adjusted Confounding Variables	Results/Comment
Henley et al, 2005 ⁵¹ Cerebrovascular mortality CPS-I (ICD-7 codes: 330–334) CPS-II (ICD-9 codes 430–438)	<ul style="list-style-type: none"> ● Cohort ● US Cancer Prevention Study (CPS-I) (12-y follow-up, 1959–1972) and CPS-II (18-y follow-up, 1982–2000) ● Information about spit tobacco use was obtained at enrollment only (1959 for CPS-I and 1982 for CPS-II) 	<ul style="list-style-type: none"> ● Current spit tobacco users were defined as those using snuff or chewing tobacco 	<ul style="list-style-type: none"> ● Nontobacco users (CPS-I n=69 662, cerebrovascular-related mortality cases=1451; CPS-II (n=111 482, cerebrovascular-related mortality cases=1451) ● Current spit tobacco users CPS-I (n=7745, cerebrovascular cases=460); CPS-II (n=2488, cerebrovascular cases=71) 	<ul style="list-style-type: none"> ● Age, race, education, current alcohol consumption, exercise, aspirin use, BMI, quartiles of vegetable and fruit consumption, quartiles of dietary fat consumption, and in CPS-II occupation 	<p>Results:</p> <ul style="list-style-type: none"> ● In CPS-I, current use of spit tobacco was associated with a significantly greater HR for mortality related to cerebrovascular disease (HR 1.46; 95% CI: 1.31–1.64). ● In CPS-II, current use of spit tobacco was associated with a significantly greater HR ratio for mortality related to cerebrovascular disease (HR 1.40; 95% CI: 1.10–1.79). <p>Comment:</p> <ul style="list-style-type: none"> ● In both CPS I and II information about spit tobacco use was only collected at baseline. ● In CPS-II data analysis included examination of mortality related to ST subtype (snuff or chewing tobacco), frequency, and duration; however, the No. of cases was low, therefore limiting interpretation related to dose and duration. ● Similar to other large epidemiological registers, the use of earlier less specific ICD codes (eg, ICD-7) may have resulted in misclassification of CHD mortality statistics. ● As others have highlighted (Lee, 2007²⁹), even though there was adjustment of multiple confounders, ST users in general had poorer lifestyle characteristics (eg, tended to be older, had less education, and consumed more dietary fat and fewer vegetables than nonusers).
Haglund et al, 2007 ⁵³ Nonfatal and fatal stroke incidence and mortality (ICD-9 430–438, ICD-10 160–169).	<ul style="list-style-type: none"> ● Cohort/14- to 16-y follow-up ● Sweden (national sample), Swedish Survey of Living Conditions (1988–1989) (face-to-face interviews) ● Tobacco use determined at entry and not thereafter 	<ul style="list-style-type: none"> ● Snuff users defined as daily use of snuff 	<ul style="list-style-type: none"> ● Nontobacco users (n=2579 nonfatal stroke cases=126) and snuff users (n=721, nonfatal stroke cases=19) 	<ul style="list-style-type: none"> ● Age at event, socioeconomic status, residential status, self-reported health, No. of longstanding illnesses, and physical activity 	<p>Results:</p> <ul style="list-style-type: none"> ● No increase in stroke incidence (IRR 1.07; 95% CI: 0.65–1.77) in snuff users. <p>Comment:</p> <ul style="list-style-type: none"> ● Mortality risk ratio was also determined for fatal stroke; however, the No. of cases (n=4) was low. ● To account for the possibility that tobacco habits changed, investigator reanalyzed estimates of incidence at a 5-y follow-up time point and stated that the results were not different (data not shown). ● This study also did not subdivide current snuff users into those that never smoked or those that quit smoking; therefore, there could have been residual mortality risk for ex-smokers in the snuff group.

(Continued)

Table 6. Continued

Reference and Health Outcome	Country/Design/Population/Subjects Studied	ST Product Use	Sample Size and Cases of Events	Adjusted Confounding Variables	Results/Comment
Hergens et al, 2008 ⁵⁴ Risk for nonfatal and fatal stroke (ICD 7-10), different ICD codes for different follow-up years)	<ul style="list-style-type: none"> ● Cohort/18-y follow-up ● Sweden (national sample), Swedish male construction workers who were eligible for health checkups between 1971 and 1993 (however, analysis based on those who had tobacco use information between 1978 and 1993) ● Identified cases and subjects dying of ischemic, hemorrhagic, and unspecified stroke (because investigators collected data that spanned many years, different ICD revisions were used) ● Snuff use obtained from the first registered visit and not reevaluated 	<ul style="list-style-type: none"> ● Regular snuff use was defined as consumption of at least 1 g/d for at least 1 y (mean consumption 23 g/d) ● Snuff use divided into <12.5 g/d, 12.5–24.9 g/d, 25–49.9 g/d, and ≥50 g/d 	<ul style="list-style-type: none"> ● Never users (n=84 110, cases of stroke=2805) ● All snuff users (ever+current) n=34 354, cases for all types of stroke=412) 	<ul style="list-style-type: none"> ● Age, BMI, region of residence 	<p>Results:</p> <ul style="list-style-type: none"> ● Among “current users,” no increase in RR for nonfatal stroke was found (RR 1.02; 95% CI: 0.91–1.14); however, there was an increase in RR for fatal stroke (RR 1.38; 95% CI: 0.99–1.91). (Cases of nonfatal stroke=368; cases of fatal stroke=44) ● Similarly among, “ever users” no increase in RR for nonfatal stroke was found (RR 1.00; 95% CI: 0.89–1.11); however, there was an increase in RR for fatal stroke (RR 1.27; 95% CI: 0.92–1.76). (Cases of nonfatal stroke=398, cases of fatal stroke=45) <p>Comment:</p> <ul style="list-style-type: none"> ● In this study, the associations between snuff use (amount) and risk of different types of stroke were also reported; however, for example, when examining current snuff users by amount of snuff use and type of stroke, case numbers were low (eg, for ischemic stroke by amount of snuff use varied from n=1–13). ● Did not account for other important lifestyle confounders

greater prevalence of cardiovascular disease.⁴⁸ However, the percent of nontobacco users who had coronary heart disease-related mortality (5.7%) in the CPS-I cohort was lower than in nontobacco users in the CPS-II cohort (7%).⁵¹ The latter finding could also be due to the use of less specific International Classification Codes (ICD) (eg, ICD-7) which could result in misclassification or underestimation of coronary heart disease mortality events. The results of CPS-I and CPS-II may also differ from those conducted in Sweden because of the type of ST product. In the United States there is a wide variety of ST products, whereas in Sweden, Swedish snus is the primary ST product. Swedish snus is manufactured using the Gothia Tek process that limits the content of some tobacco toxicants and specifies the standards for manufacturing and provides consumer information about the product.⁵

The idea that the manufacturing process and type of ST product is important to consider when evaluating any type of health risk is supported by the results of the large international INTERHEART study. The INTERHEART study was a case-control study of 15 152 cases of first MI, conducted in 52 countries (Asia, Europe, Africa, Middle East Crescent, Africa, Australia, and North and South America).⁵² Subjects included were those that used a

variety of ST products such as chewing tobacco, snuff, and paan. A subanalysis was performed examining risk of MI associated with the type of ST product. Subjects who only chewed tobacco had a significantly increased risk of first MI (odds ratio [OR] 2.23; 95% CI: 1.41 to 3.52) compared with those who never used tobacco.⁵² The authors, however, did not note the number of MI cases among subjects who used chewing tobacco or the sample size of the subjects who used chewing tobacco included in the subanalysis.

The risk of CVD in ST users has been estimated in 2 meta-analyses.^{29,30} In both meta-analyses, several of the aforementioned studies were included. Lee²⁹ found that ST use was associated with an increased risk of heart disease (RR 1.12, 95% CI: 0.99 to 1.27, n=8 studies). The increase in risk was primarily attributable to the inclusion of both CPS-I and CPS-II, since analysis of the Swedish studies alone revealed a RR of 1.06 (95% CI: 0.83 to 1.37, n=5) for heart disease.²⁹ Boffetta and Strai³⁰ analyzed 11 studies (United States+Europe). Ever use of ST products was associated with a RR of 1.13 (95% CI: 1.06 to 1.21) for fatal MI.³⁰

In summary, data derived from the majority of studies conducted in Sweden, whereby snuff/snus is the major ST

product used, have not demonstrated a significant increase risk of nonfatal or fatal MI.^{37,38,44–46} However, findings from one meta-analysis³⁰ and the more recent findings from a long-term follow-up study indicate a modest increased risk of fatal MI among ST users and ever Swedish snuff users, respectively.⁴⁹ Data derived from predominately US populations are equivocal. Data from the international INTERHEART study, which included a variety of ST products, indicate that ST product use is associated with an increased risk of acute MI.⁵² It is likely that differences in the risk of MI in ST users reported in different studies are due to use of different types of ST products and/or different patterns of ST use in the various study groups as well as different research designs and methods. More research is needed in the United States with currently marketed ST products to assess the potential relationship between ST product use and MI risk in the US population.

Stroke

Stroke is a leading cause of adult disability.³³ Several studies have examined the relationship between ST use and the risk of nonfatal and fatal stroke, and findings are equivocal (Table 6). In the US CPS-I and CPS-II, male subjects qualified as spit tobacco users (snuff or chewing tobacco) were monitored for 12 and 18 years, respectively.⁵¹ After adjustment for multiple potential confounders, such as race, education, current alcohol consumption, exercise, aspirin use, body mass index, and dietary fat consumption, Henley and colleagues⁵¹ found spit tobacco use in CPS-I and CPS-II was associated with an increased hazard ratio for mortality due to cerebrovascular disease (Table 6). In CPS-II the frequency and duration of spit tobacco use was examined, but no dose or frequency relationship was found. The latter finding should be interpreted with caution, because the number of stroke cases in both the frequency and duration categories was small (eg, n=7 stroke cases in the ST duration category of 1 to 10 years).⁵¹ In contrast, using data from the US NHANES follow-up study and after adjustment for multiple confounders, Accortt et al⁵⁰ found no association between ST use and death due to stroke among ST users (Table 6). Similarly, among Swedish snuff users (Swedish Survey of Living Conditions), Haglund et al⁵³ also found no increase in stroke incidence or mortality; however, the number of mortality cases was low (n=4) (Table 6). Bolinder et al⁴⁷ also found no increase in death from stroke among Swedish construction workers (Table 6). In a prospective 15-year follow-up of a cohort of Swedish construction workers, the age-adjusted RR for nonfatal stroke was not increased in “ever” or “current” snuff users; however, the RR for fatal stroke was increased in both “ever” or “current” snuff users (Table 6).⁵⁴

In summary, data from 2 studies (1 from the United States and 1 from Sweden) suggest that ST product use is associated with a slight increase in the risk of stroke mortality.^{51,54} The latter findings have been confirmed by 2 meta-analyses. Lee²⁹ and Boffetta and Straif³⁰ found that ST use was associated with an increased risk of fatal stroke

(RR 1.42, 95% CI: 1.29 to 1.57, n=5 studies and RR 1.40, 95% CI 1.28 to 1.54, n=5 studies, respectively). Both meta-analyses included studies presented in Table 6. The meta-analysis performed by Lee was weighted heavily by the CPS-I and CPS-II results, because this study had the largest sample size.^{29,31} The Boffetta and Straif³⁰ analysis included CPS-I and CPS II as well as data reported by Hergens et al.⁵⁴ As noted above findings related to CPS-I have been minimized because the data were collected many years ago (1959–1972). In addition, even though there was adjustment for multiple confounders in both CPS-I and CPS-II, ST users in general had poorer lifestyle characteristics (eg, tended to be older, less educated, and consumed more dietary fat and fewer vegetables than nonusers) suggesting the potential for other unidentified confounding factors.³⁰ The only potential confounders considered in the Hergens et al study were age, body mass index, and region of residence.⁵⁴ More research is needed in the United States regarding currently marketed ST products to assess the potential relationship between ST use and stroke risk in the US population.

Metabolic Syndrome and Diabetes Mellitus

To date only a few studies have examined the relationship between ST product use and metabolic syndrome (MetSy) and/or diabetes mellitus (DM). According to the National Cholesterol Education Program Adult Treatment Panel III (NCEP/ATP III), individuals in whom MetSy is diagnosed must have 3 of the following 5 criteria: fasting plasma glucose >5.6 mmol/L (≥ 100 mg/dL), blood pressure >130/85 mm Hg, triglycerides >1.7 mmol/L (<150 mg/dL) (or specific drug treatment), high-density lipoprotein (HDL) cholesterol <1.0 mmol/L (<40 mg/dL) in men and <1.3 mmol/L (<50 mg/dL) in women (or specific drug treatment) and waist circumference >102 cm (40.15 inches) in men and >88 cm (34.6 inches) in women.⁵⁵ The presence of MetSy increases the risk of heart disease, stroke, and diabetes. Using the International Diabetes Federation criteria for MetSy, Norberg and colleagues⁵⁶ prospectively examined the contribution of snuff use to the development of MetSy in individuals participating in the longitudinal Västerbotten Intervention Programme in Northern Sweden (10-year follow-up). The International Diabetes Federation criteria are similar to NCEP/ATP III, with the exception that, instead of an increased waist circumference, a body mass index >30 kg/m² is used as a criterion.⁵⁷ Multivariate analyses revealed an increased OR of developing MetSy (OR=1.5, 95% CI: 1.13 to 2.10) for those using 5 to 6 cans per week of moist snuff and a greater risk for those using 7 cans per week (OR 2.0, 95% CI: 1.20 to 1.39).⁵⁶ Those consuming <2 cans of snus per week or 2 to 4 cans per week did not have an elevated OR for developing MetSy.⁵⁶ In another cohort study (MONICA), the prevalence of type 2 diabetes or impaired glucose tolerance was determined among ST users and nontobacco users.⁵⁸ In both “ever snus users” and “current snus users,” there was not a significant increase in the OR (after adjustment of age and waist circumference) in both groups for development of type 2 diabetes (OR 1.21; 95%

CI: 0.59 to 2.49, OR 1.06; 95% CI: 0.43 to 2.64).⁵⁸ Ever or current snus use was not associated with impaired glucose tolerance (fasting glucose <7 mmol/L).⁵⁸ In a cross-sectional study, after adjustment for age, body mass index, diabetic family history, physical activity, and alcohol consumption, Persson et al⁵⁸ found heavy snuff use (>3 boxes per week) was associated with a significantly greater OR (2.7; 95% CI: 1.3 to 5.5) for prevalence of type 2 diabetes. No increased prevalence of impaired glucose tolerance (defined as 2-hour plasma glucose levels between 7.8 mmol/L and 11.0 mmol/L) was found in snuff users.⁵⁹ Impaired glucose tolerance is sometimes referred to as a prediabetic state; therefore, the latter negative findings related to impaired glucose intolerance may seem contradictory. However, prediabetic states can also include an elevated fasting glucose level. Future studies should include both measures to determine whether ST use increases the development of a prediabetic state. Based on data from two of the above studies conducted solely in Swedish populations, heavy use of moist snuff appears to increase the odds of developing MetSy⁵⁶ and type 2 diabetes.⁵⁹

Additional Risk Factors for CVD

There are limited data evaluating the relationship between ST product use and other risk factors for CVD. The following have been examined in relationship to ST product use: C reactive protein (CRP), total cholesterol, HDL cholesterol, low-density lipoprotein cholesterol, triglycerides, fibrinogen, fibrinolytic biomarkers, white blood cells, and thromboxane A₂ and prostacyclin production.

CRP, a marker of inflammation, has been shown in prospective epidemiological studies to be correlated with an increased risk of MI, stroke, peripheral arterial disease, and sudden cardiac death.⁶⁰ One population-based study found no significant differences in CRP levels among healthy controls, snuff dippers, and those who had never used tobacco.⁶¹

Several studies have evaluated the effect of ST product use on serum lipids. No significant differences in total or HDL cholesterol levels were found between ST (snuff and chewing tobacco) product users and nonusers observed among professional baseball players.³³ Similarly, data from the northern Sweden MONICA Study also found no differences in total cholesterol, HDL cholesterol, or serum triglycerides between snuff dippers and nontobacco users.⁶² Wallenfeldt et al⁶¹ found no association between snuff use and total cholesterol, HDL cholesterol, or low-density lipoprotein cholesterol. However, snuff use was associated with elevated serum triglycerides. In contrast, data from another large population-based study found that subjects who regularly used ST products had 2.5 times the prevalence of hypercholesterolemia (>6.2 mmol/L) compared with nonusers of tobacco.⁶³ Khurana et al⁶⁴ also found a relationship between chewing tobacco use and dyslipidemia. Tobacco chewers showed significantly decreased levels of HDL cholesterol and significantly in-

creased levels of very low-density lipoprotein cholesterol and triglycerides.⁶⁴

Thromboxane A₂ and prostacyclin have been implicated in both acute and chronic CV disorders.⁶⁵ Thromboxane A₂ is released when platelets are activated and has prothrombotic effects; prostacyclin is released by endothelial cells and has antithrombotic effects.⁶⁵ Wennmalm et al⁶⁶ measured urinary excretion of these eicosanoid metabolites in healthy 18- and 19-year-old men who used snuff compared with a group of nontobacco users. The snuff-only group displayed no increase in thromboxane A₂ or prostacyclin compared with the nontobacco users.⁶⁶

Increased fibrinogen level, another risk factor for CVD, has been examined in individuals using ST.⁶⁰ In a large population-based study, Eliasson et al⁵⁸ found that snuff dipping had no effect on fibrinogen levels. In addition, they examined components of the fibrinolytic system, tissue plasminogen activator and plasminogen activator inhibitor type 1 and found no differences in activity of either variable between the groups.⁵⁸ They concluded that snuff dipping had no detrimental effects on the fibrinolytic system.

In summary, although equivocal, available data suggest that ST product use may be associated with dyslipidemia. Although the data are limited, most studies have found no relationship between ST use and other biochemical risk factors for CVD. More research is needed in the United States to evaluate the effect of use of currently marketed ST products on biochemical markers.

Biological Mechanisms for ST Product and Cigarette Smoking and CVD

If ST causes CVD it is likely to do so by mechanisms related to those by which CS causes CVD. Therefore, to understand potential mechanisms and biological plausibility that ST might cause or contribute to CVD, it is informative to briefly describe mechanisms by which CS causes CVD. Cigarette smoking is well established to cause acute CV events and chronically produces endothelial dysfunction, hypercoagulability, and inflammation, resulting in acceleration of atherosclerosis.⁶⁷ Acute CV events caused by smoking include acute MI, stroke, and sudden death.⁶⁸ Accelerated atherogenesis affects coronary, carotid, cerebral, and peripheral vessels, including the aorta, causing aortic aneurysm.

The acute clinical CV manifestations of CS result, to a substantial degree, from thrombotic events. In people with sudden death, thrombosis of coronary arteries, probably resulting in ischemic dysrhythmias, is much more common in smokers than nonsmokers.⁶⁹ Smokers with MI are reported to have, on average, less severe underlying atherosclerosis than nonsmokers, with a greater amount of thrombus.⁷⁰ CS can cause a variety of mechanistic disruptions—platelet activation and thrombogenesis, endothelial dysfunction, accelerated atherogenesis, inflammation, sympathoadrenal activation, arrhythmogenesis, insulin resistance, and hyperlipidemia—all of which can contribute to CVD.⁶⁷

Constituents of CS That Contribute to CVD

CS is a complex mixture of combustion products, nicotine, and related alkaloids. Several CS constituents have been identified as potential contributors to CVD. These include oxidizing chemicals, carbon monoxide, nicotine, acrolein, 1,3-butadiene, particulates, PAHs, and metals such as cadmium. ST products do not deliver gaseous combustion products, but depending on the ST product, some ST products deliver as much nicotine as CS.^{42,66,71} We briefly review how combustion products might contribute to CVD in smokers below. Later, we discuss what role nicotine might play, comparing effects of smoking and the effects of nicotine per se, including nicotine medications and ST products.

CS delivers high concentrations of oxidants, including oxides of nitrogen and free radicals.^{71,72} Oxidants cause peroxidation and injury to lipid membranes, contribute to inflammation and atherogenesis, and promote platelet activation and thrombosis.^{73,74} Oxidant chemicals contribute to endothelial dysfunction both owing to proinflammatory effects and to oxidative destruction of endothelial nitric oxide, the latter of which serves important local vasodilator and antiplatelet functions. Endothelial dysfunction in smokers, assessed by flow-mediated vasodilation techniques, is reversed, at least in part, by some types of antioxidants.⁷⁵

Carbon monoxide binds tightly to hemoglobin and reduces the oxygen-carrying capacity and release of oxygen from erythrocytes. The consequence of reduced oxygen delivery is a state of relative hypoxemia, which aggravates preexisting ischemic vascular disease. To compensate for relative hypoxemia, smokers develop polycythemia, which increases blood viscosity and contributes to the hypercoagulable state. Carbon monoxide also increases the number and complexity of ventricular arrhythmias during exercise and reduces the threshold for ventricular fibrillation in animals.^{76,77}

Acrolein is a reactive aldehyde that is found in high concentrations in CS. It can form protein adducts and can oxidize thioredoxins in endothelial cells—effects that promote atherogenesis in model systems.⁷⁸ Acrolein can also promote thrombosis, lead to lipoprotein alterations, induce endothelial dysfunction, and destabilize arterial plaque, all of which could contribute to CV risk. Butadiene and PAHs have been shown to accelerate atherosclerosis in some animal studies.^{79,80} Metals such as cadmium accumulate in the walls of blood vessels and may damage endothelial cells and promote atherogenesis.⁸¹ Exposure to particulate matter reduces heart rate variability, increases thrombosis, induces endothelial dysfunction and promotes atherosclerosis in experimental studies in animals.⁸² Ambient air pollution has been associated with increased CV mortality in relation to the particulate concentration.

All of the chemicals discussed above are products of the combustion of tobacco. Only PAHs are present in significant amounts in ST.¹³ However, the role of PAHs in causing CVD is unknown and more than likely minor. The one chemical that is found both in CS and in ST, and

about which there is concern for adverse CV effects, is nicotine.

Nicotine Exposure From ST Products Compared With Cigarette Smoking

Regular users of ST products take in as much nicotine per day as do regular smokers.^{42,43,66} There are, however, important pharmacokinetic differences that could affect CV toxicity. Nicotine that is inhaled in CS is absorbed quickly in the lungs, from which it moves into the arterial circulation in high concentrations, and then to the heart, brain, and other organs. Nicotine from ST is absorbed much more slowly than from cigarettes, with absorption continuing for ≥ 30 minutes.⁷¹ This is relevant because the speed of absorption and maximum arterial blood levels achieved are determinants of the acute CV effects of nicotine. For example, more rapid absorption of nicotine is associated with greater heart rate acceleration.⁸³ Rapid absorption of nicotine might be expected to cause more intense vasoconstriction, although this has not been demonstrated. Thus, if nicotine does contribute to acute adverse CV events, it is likely that the same daily dose of nicotine from CS would cause more injury than from ST.

Hemodynamic Effects of Nicotine

Nicotine acts on nicotinic cholinergic receptors in the brain and adrenal gland to activate the sympathetic nervous system, including the release of epinephrine. Nicotine acts as a sympathomimetic drug to increase heart rate, BP, and cardiac contractility and to constrict some blood vessels.⁶⁷ The heart rate and BP effects of smoking and ST use are similar (Figure).⁴³ Heart rate is increased throughout most of the day while using tobacco, either CS or ST, compared with when not using tobacco.⁴³ Daily smoking of cigarettes or use of ST is also associated with increased urinary catecholamine excretion, compared with not using tobacco.⁴³

Although nicotine from CS acutely increases BP, CS is not associated with hypertension in epidemiological studies.⁸⁴ This is probably because BP is measured a considerable time after the last cigarette is smoked. Ambulatory BP studies show that CS does influence the circadian pattern of BP.⁴³ As discussed in an earlier section of this report, the majority of studies reported in Table 3 do not support an association between ST use and hypertension. Nicotine from ST use can precipitate a hypertensive crisis in patients with pheochromocytoma.⁸⁵ As discussed previously, ST product use can also increase BP owing to additives such as licorice (mineralocorticoid hypertension) and sodium (in the basic buffer needed to facilitate buccal absorption of nicotine).⁴⁰

Nicotine constricts coronary arteries via an α -adrenergic mechanism.⁸⁶ Coronary vasoconstriction after cigarette smoking is greater in diseased compared with healthy coronary arteries.⁸⁷ In healthy smokers, CS or nicotine increases coronary blood flow in response to increased myocardial work, although the increase is less than would be seen in response to the same increase in myocardial

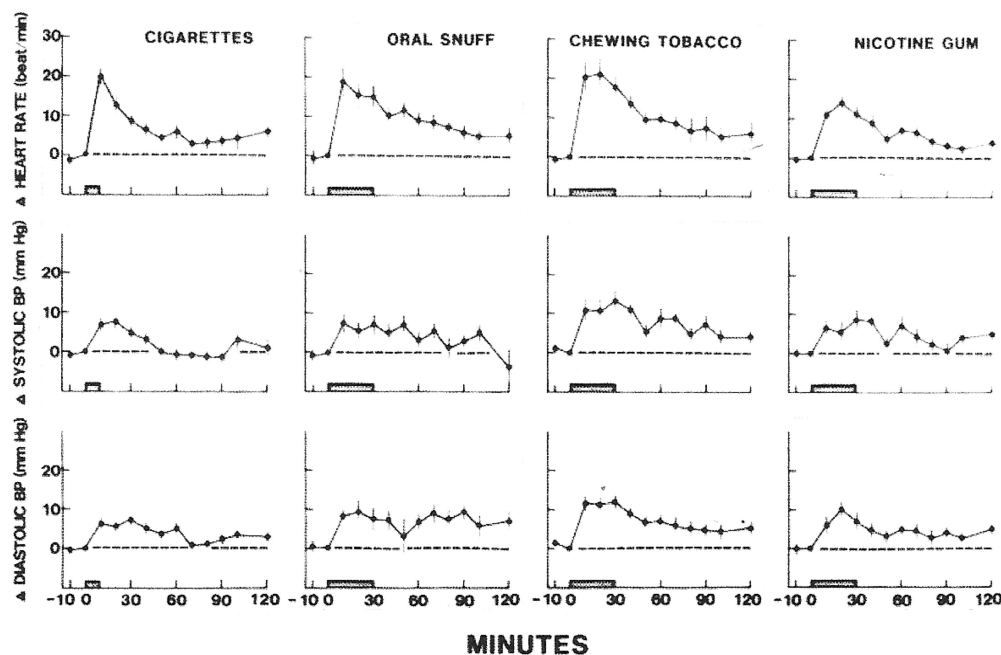


Figure. Heart rate, systolic and diastolic BP (mm Hg) changes measured in healthy male subjects ($n=10$) after smoking 1 cigarette (1 puff every 45 seconds for a total of 12 puffs over 9 minutes), using oral snuff (2.5 g placed between lip and gum held in place for 30 minutes), using chewing tobacco (average 7.9 g and chewed for 30 minutes), and chewing nicotine gum (2 pieces chewed slowly over 30 minutes). Studies were performed over 5 days in the morning after abstinence from tobacco and food.⁴²

work in the absence of nicotine.⁸⁷ In people with coronary artery disease, nicotine and CS can decrease coronary blood flow. CS is a strong risk factor for coronary vasospasm and may attenuate the vasodilator effects of certain vasodilator medications.⁸⁸

Nicotine and Endothelial Dysfunction

In addition to hemodynamic effects mediated by sympathetic effects, nicotine may also contribute to endothelial dysfunction. Nicotine has been reported to injure endothelial cells *in vitro* and in animal studies.^{89,90} Nicotine has been found to release growth factors and to promote angiogenesis, which could contribute to atherogenesis.⁹¹ In animals with hyperlipidemia, nicotine promotes neovascularization of vascular plaque.⁹¹ Intravenous nicotine acutely impairs endothelial function in human smokers.⁹³ The relevance of the *in vitro*, animal, and acute experimental studies to human users of ST is not clear. In addition to differences in doses, routes, and patterns of nicotine exposure that could influence these responses, many of the experimental studies on nicotine involve short-term effects of nicotine, whereas substantial tolerance to the CV effects of nicotine is known to develop with long-term use.

Nicotine and Thrombogenesis

As mentioned earlier, CS-induced thrombogenic effects are thought to be an important pathophysiologic mechanism underlying the acute adverse CV events. Data from some animal studies demonstrate that nicotine, in high doses, activates platelets.⁹⁴ Nicotine added to platelet-rich plasma of nonsmokers has been reported to increase

platelet-dependent formation of thrombin.⁹⁵ In humans, platelet activation has been studied by measuring urinary excretion of dinor and 11-dehydro metabolites of thromboxane (TxM), which is released when platelets aggregate *in vivo*. TxM is a platelet agonist and, importantly, is released by aggregating platelets and serves to amplify the process of platelet activation.⁹⁶ The cardioprotection from low-dose aspirin observed in secondary prevention trials is explicable solely in terms of inhibition of platelet thromboxane production. Smokers have higher levels of TxM compared with nonsmokers.⁹⁷ One study found that the decline in TxM after stopping cigarette smoking was not found when smokers used nicotine patches, but was seen in those who did not use patches.⁹⁸ However, another experimental study switching smokers to a nicotine patch or no nicotine found similar decreases in TxM excretion.⁹⁹ Furthermore, studies comparing ST users versus nontobacco users found no difference in TxM excretion, whereas (as expected) smokers had higher levels.⁶⁶ Overall, these findings do not support a significant effect of nicotine on platelet activation. Of note is a recent report suggesting that nicotine may have antiplatelet effects.¹⁰⁰

Nicotine and Inflammation

Cigarette smoking produces a systemic inflammatory effect, and inflammatory biomarkers are strong predictors of future CV events.¹⁰¹ Smoking is associated with higher polymorphonuclear leukocyte counts, fibrinogen, CRP, and other inflammatory markers. Data from some *in vitro* and animal studies found that nicotine is a chemoattractant, enhances leukocyte adhesion, and increases release of

some proinflammatory cytokines.^{102,103} However, studies of smokers switching to nicotine medications found that inflammatory biomarkers declined as would be seen in those not taking nicotine.¹⁰¹ As reviewed previously in this report, there is no evidence that ST use is associated with the biomarkers of inflammation. These clinical observations suggest that nicotine is not a primary determinant of the inflammatory state found in smokers.

Metabolic Effects of Nicotine

Cigarette smoking is associated with an increased risk of developing type 2 diabetes, which in turn is an important CV risk factor.^{104,105} As noted previously, data from Swedish snus users suggest that heavy ST use is a risk factor for the development of type 2 diabetes but (for unclear reasons) is not associated with the impairment of glucose tolerance among ST users.^{59,105}

Cigarette smoking is associated with changes in blood lipids, resulting in an atherogenic risk profile—primarily low HDL cholesterol.¹⁰⁶ Smoking is believed to exert effect on lipids, at least in part, by the sympathomimetic effects of nicotine. Nicotine increases lipolysis and increases free fatty acid concentrations.¹⁰⁷ Increased fatty acid turnover is associated with overproduction of very low-density lipoprotein-total triglycerides, increased low-density lipoprotein cholesterol, and lowered HDL cholesterol. One study reported that nicotine patch administration prevented the expected normalization of HDL cholesterol after smoking cessation.¹⁰⁸ As reviewed earlier, data are equivocal regarding ST product use and the development of dyslipidemia.

In summary, multiple mechanisms are likely to contribute to CS-induced CVD, and multiple chemicals in CS activate these mechanisms. The direct oxidants are believed to be the class of chemicals that contribute most to CS-induced CVD, which is not an issue in ST users. A number of *in vitro* and animal studies and a few experimental studies in humans suggest that nicotine may contribute to CVD by a variety of mechanisms. Human studies involving administration of medicinal nicotine indicate that nicotine is not a major factor.

Cardiovascular Effects of Medicinal Nicotine in Clinical Trials

Several clinical trials of nicotine patches in patients with known CVD found no evidence that transdermal nicotine increased CV risk.^{109–111} The Lung Health Study involved treating >3000 middle-aged smokers with chronic obstructive lung disease with nicotine gum for up to 5 years, with no evidence of increased CV risk compared with those who quit smoking without using nicotine gum.¹¹² A case-control study of 653 cases of acute MI and 2990 controls found no increased risk associated with the use of nicotine patches for smoking cessation at the time of or just before the event (OR=0.46; 95% CI: 0.09 to 1.47).¹¹³ A recent study of patients with acute coronary syndrome treated with nicotine patches in the hospital found no adverse impact on future CV events.¹¹⁴ Finally, an experimental study showed that patients

with severe coronary artery disease treated with transdermal nicotine, which suppressed but did not eliminate smoking, showed a substantial reduction in exercise-induced myocardial perfusion defect size, as measured by quantitative thallium-201 single-photon emission-computed tomography.¹¹⁵ Improved perfusion was noted despite a 2-fold increase in nicotine levels while using patches and smoking at the same time, compared with baseline smoking alone. It is likely that the improved perfusion was due to reduced exposure to carbon monoxide and other combustion products.

We conclude from this review of the biochemical mechanism of smoking, nicotine, and CVD that nicotine might contribute to smoking-induced CVD, but that other chemicals in CS appear to be much more important contributors. Biomarker studies with medicinal nicotine and ST, as well as clinical studies of medicinal nicotine for smoking cessation in smokers with CVD, provide only modest evidence that nicotine causes or aggravates CVD in humans. Based on this evidence, one would anticipate that the CV risks of ST, if any, would be much lower than those of cigarette smoking.

Reducing Smoking Prevalence

In the United States, developing interventions to help cigarette smokers quit and reduce total tobacco-related mortality remains a major health concern.¹¹⁶ One objective of the Healthy People 2010 report was to reduce adult smoking prevalence to no more than 12% by the year 2010.¹¹⁶ Smoking initiation and smoking cessation rates have been impacted, in part, by social norms, tobacco control policy, mass media/education initiatives, and a variety of tobacco treatment strategies. Reviewed in brief below is how social norms and PREPs have influenced societal use of tobacco products. The use of PREPs has also been suggested as a harm reduction strategy. Among the suggested tobacco harm reduction strategies is the use of ST products for cigarette smokers who are unable or unwilling to quit.¹¹⁷ Reviewed below is the potential role for ST product use in reducing smoking-associated CV risk.

The Role of Social Norms and PREPs for Cigarette Smoking Cessation

Changing social norms or the unacceptability of cigarette smoking has been an important strategy for reducing the prevalence of smoking. Social norms have been strongly influenced by governmental legislation and national policies: for example, those that have resulted in smoke-free workplaces, even in places with a protobacco tradition.^{118–120} Not only is there overwhelming public support for smoke-free legislation, but there is also evidence that these policies have changed social norms such that adults find cigarette smoking less acceptable and are more likely to perceive secondhand smoke as a serious health risk.¹¹⁹ The social norms regarding ST product use, however, vary by region and culture, and (as noted above) there are geographical pockets within the United States where ST use is high. For example, one third of males in rural Appalachia use ST.¹²¹

In recent years, ST product use has been marketed as a means of nicotine delivery in smoke-free environments, a way for smokers to ease their cravings when they are in smoke-free public places especially for prolonged periods of time. The new ST products on the market are also aimed at smokers who are unable or unwilling to quit.¹²² Product changes have made ST more acceptable to consumers (eg, discreet, spitless, tea bag-like pouch, dissolvable pellet, or flavorful sticks). Consumers need to be aware that nicotine levels, moisture, texture, and nitrosamine content of ST products are ever changing as new products are introduced.¹³ Marlboro snus, for example, is a very different product than the original Swedish snus in that it has lower moisture, pH, and nicotine content and it is flavored.¹¹ The use of the term “snus” to refer to both the original product and the newer and significantly different product creates public confusion about snus. Given the variation in contents of ST products and the newer PREPs, tobacco manufacturers cannot make blanket health claims about all ST products.¹²³

Nicotine replacement therapies (NRTs) are considered the least hazardous PREP alternative to cigarette smoking, and they have an impressive safety record.¹²⁴ However, some ST users view NRTs as less palatable or acceptable and more costly than ST.^{124,125} Most NRTs are available over the counter, but some require a prescription (nicotine nasal spray and inhaler).^{126,127}

Is There a Role for ST Use in Reducing Smoking-Associated CV Risk?

Worldwide and in the United States, cigarette smoking is the leading cause of preventable death.¹²⁷ Over the past several decades, there has been a large decline in smoking prevalence; however, the rate of smoking cessation appears to have slowed and reached a plateau.¹²⁷ In the United States, developing interventions to help cigarette smokers quit and reduce total tobacco-related mortality remains a major health concern.¹¹⁶ Among the suggested tobacco harm reduction strategies is the use of ST products for cigarette smokers who are unable or unwilling to quit.¹¹⁷ Compared with cigarette smoking, the CV risk associated with ST use is markedly lower.¹²⁸ Data, however, are lacking to support ST use as a safe and long-term strategy for smoking cessation. This controversial topic has also been addressed by others.^{5,117,129}

Interest in the possibility that ST products could provide a population-based intervention to reduce smoking has been based in part on the Swedish ST experience and the temporally associated decline in smoking rates in Sweden.¹³⁰ The decrease in smoking among men in Sweden from 40% to 15% between 1976 and 2002 has been attributable to the increase in ST snus use from 10% to 23% in the same period.¹³¹ However, in a recent longitudinal study of a national US sample, Zhu et al¹³² found no association between ST use and population smoking cessation rates. In fact, ST users were more likely to switch to cigarettes. Using data from 4 US nationally representative surveys, Tomar et al¹³³ reported that cigarette smoking was

more prevalent among young males who used ST compared with those who did not and that unsuccessful past-year attempts by daily cigarette smokers were more prevalent among daily snuff users (41.5%) compared with never snuff users (29.6%). Others have also reported that cigarette smoking initiation or prevalence does not decline as ST rates increase.¹³⁴ Further, US states with the lowest rates of smoking prevalence have the lowest rates of ST use.^{132,134,135} The findings of Zhu et al¹³² and Tomar et al¹³³ weaken the argument that promoting ST use for harm reduction in countries such as the United States that have established tobacco control programs would be an effective way to increase smoking cessation rates.

To date, there has only been a single randomized trial (N=263) evaluating ST as an intervention to supporting smoking cessation.¹³⁶ Current cigarette smokers were randomly assigned to a control group (group therapy) or ST+group therapy group. At 7 weeks, there was a significant difference in point-prevalence abstinence rates between ST users (36.4%) and the control group (20.8%) ($P=0.001$); however, no differences were found in smoking cessation rates between groups at 6 months (23.1% versus 20.8%; $P>0.05$, ST versus control, respectively).¹³⁶ More randomized studies are needed to determine long-term health outcomes, as well as cessation rates.

The FDA commissioned the Institute of Medicine to explore the science base for tobacco harm reduction. The need for research in this area came about as a result of marketing ST products as PREPs.⁴ The Institute of Medicine report *Clearing the Smoke: Assessing the Science Basis for Tobacco Harm Reduction* examined the potential benefits and risks of tobacco harm reduction strategies and stimulated considerable public discussion about whether the major health risks imposed by CS might be reduced by the use of ST products (specifically Swedish snus), either substituting a ST product for cigarette smoking or using ST products to support reduced cigarette consumption.¹³⁷ The Institute of Medicine report also noted that ST product use had been proposed as a smoking cessation strategy for those smokers for whom cessation efforts using NRT had failed.¹³⁷ In the absence of large, multiple randomized clinical trials, the concept of using ST products and PREPs for harm reduction has generated considerable debate.^{117,129} The debate relates to (1) the observational nature of data supporting ST or PREP for smoking cessation; (2) ethical issues associated with the concept of harm reduction; (3) the possibility that ST use may provide a “gateway” for the initiation of smoking; (4) the possibility that ST use will result in fewer smokers quitting cigarette smoking; and (5) the possibility that the tobacco industry may attempt to manipulate the ST products or environment to weaken the efficacy of tobacco control interventions.

There is concern that promoting ST may promote youth initiation of cigarette smoking. Even though there is an increase in ST product initiation and use among adolescent males, there is no prospective or epidemiological evidence to support the former assertion.^{1,134} Data from 2 studies have shown that young nonsmoking men who were ST product

users were 2 to 3 times more likely to become active cigarette smokers.^{138,139} However, data from other studies have shown little relationship between ST product use and smoking initiation¹⁴⁰ or that associations could be explained by confounding psychosocial factors.^{141,142} There is concern that youth and young people may be lulled into a false sense of security by turning to PREPs or ST products.¹²² There also is concern that marketing one tobacco product as a substitute for others will divert attention from the smoking cessation message.¹⁴³ Given that smokers who are concerned about their health and who may have medical illness are often more interested in trying PREPs, the fear that these tobacco users may be derailed from quitting altogether is of special concern.⁵ Furthermore, some fear that exsmokers may relapse to tobacco use by choosing these PREPs as a safe alternative to cigarettes and an alternative to be used in environments where smoking is prohibited.¹²²

Those opposing the idea of ST product use as a harm reduction method have raised the possibility that the tobacco industry may attempt to manipulate the ST products or environment to weaken the efficacy of tobacco control interventions. As noted in the introduction, a disturbing trend is the recent acquisition of companies producing ST products by the dominant cigarette-producing companies, including the purchase of the parent company of US Smokeless Tobacco Company by Phillip Morris USA and the purchase of Conwood by Reynolds American.^{2,144} If ST products are to be a useful smoking cessation therapy for “hard-core” cigarette users, ST products should deliver as much or a higher nicotine dose and/or faster delivery rate compared with the safer alternative of NRT. However, recently introduced (manufactured) snus products from Phillip Morris produce plasma nicotine levels of only 4 ng/mL (compared with 18 ng/mL when smoking)—a level so low that the use of snus is not likely to be as effective as NRT interventions in enhancing smoking cessation.¹¹

Data from international, European, and US studies overwhelmingly demonstrate that compared with ST users, active smokers are at much greater risk for CV morbidity and mortality and have shorter life spans.^{44–46,52,128} When examining life expectancy, Rodu and Cole¹⁴⁵ found that the life expectancy of a 35-year-old ST user was 35.9 years, only 0.04 years (ie, 15 days) less than a nontobacco user but 7.8 years greater than an active smoker. However, as discussed elsewhere in this report, more recent reports suggest that long-term ST use might be associated with increased risk of mortality owing to MI and stroke, suggesting that ST product use may complicate or reduce the chance for survival after a MI or stroke.^{30,49,54} The main question that remains unanswered is whether individuals who switch from cigarettes to ST products reduce their disease risk. Unfortunately, there is only one study to date that has examined this question, and its findings

revealed that people who switched from cigarette smoking to ST (“switchers”) had a higher rate of death from any cause, including coronary artery disease, than those who quit tobacco use altogether.¹⁴⁶

ST products are also a source of carcinogens, and ST use is associated with cancers of the oral cavity and pancreas, as well as potential adverse effects on reproductive organs.¹⁴⁷ Considering the latter as well as the aforementioned CV risks, NRT represents a safer pathway to smoking cessation compared to ST use.

A concern about using ST for smoking cessation is that it sustains the addiction to nicotine.⁹ Similar to cigarette smokers, ST users find it difficult to quit, and they experience many signs and symptoms of nicotine withdrawal.⁵¹

Conclusions and Policy Implications

As a national nonprofit health organization committed to promoting tobacco control research and policy efforts, the American Heart Association does not recommend the use of ST as an alternative to cigarette smoking or as a smoking cessation product. Although the evidence is consistent with the suggestion that the CV risks are lower with ST products, ST products are not without harm.^{12,145–148} As reviewed in this article, there is evidence that long-term ST product use may be associated with a greater risk of fatal MI^{47,49} and fatal stroke,⁵² suggesting that ST product use may complicate or reduce the chance for survival after a MI or stroke.³¹ In addition to potential CVD risk, ST product use is associated with an increased risk of some cancers and with oral disease, and it is addictive. Furthermore, the promotion of ST may lead to fewer people quitting smoking and more dual use of cigarettes and ST products. Considering the inadequate evidence of smoking cessation efficacy and safety, promoting ST product use as a way for smokers to reduce risk for smoking-related diseases is not appropriate. Another concern is the disturbing trend in the increase in ST product initiation and use among adolescent males. New federal restrictions went into effect in June 2010 that will apply to the sales and marketing of both cigarettes and ST products (Table 1).

Given that ST product use in general has harmful effects on health and is addictive, the scientific community should prioritize strategic efforts to : (1) evaluate factors associated with the initiation and use of ST products; (2) determine to what extent the use of ST products results in continued tobacco use, including dual smoking and ST product use, in smokers who would otherwise have quit; and (3) assess the effect of “reduced risk” messages related to ST products on public perception, tobacco use and cessation, and policy decision making. Based on the findings reviewed in this statement, clinicians should continue to discourage use of all tobacco products and emphasize the prevention of smoking initiation and smoking cessation as primary goals for tobacco control.

Disclosures

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*Modest.

†Significant.

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*Modest.

†Significant.

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Impact of Smokeless Tobacco Products on Cardiovascular Disease: Implications for Policy, Prevention, and Treatment: A Policy Statement From the American Heart Association

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