

Smoking Amplifies Cardiovascular Risk in Patients With Hypertension and Diabetes

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Smoking is considered an important “risk factor” for arterial hypertension and diabetes management, according to, respectively, the current guidelines of the European Society of Hypertension and the European Society of Cardiology on the management of arterial hypertension (1) and the guidelines on diabetes of the European Society of Cardiology and the European Association for the Study of Diabetes (2). The aim of the current article is to further evaluate the effect of smoking on mortality and cause-specific cardiovascular events in hypertension and in diabetes and to assess whether there is a significant interaction between the effects of smoking and diabetes.

SMOKING AND HYPERTENSION

— To assess the effect of smoking on mortality and cause-specific cardiovascular events, and the interaction between smoking and diabetes, we analyzed a database of 3,468 hypertensive patients without major cardiovascular disease at baseline and with prospective follow-up for morbidity and mortality (3). The database consists of individual data of hypertensive patients from four prospective studies performed in Europe (4–7). Age of the subjects averaged 61 ± 13 years (mean \pm SD), 45% were men, and 61% were under antihypertensive treatment at baseline. Office blood pressure averaged $159.0 \pm 19.9/91.0 \pm 11.7$ mmHg and 24-h ambulatory blood pressure $138.1 \pm 16.4/82.3 \pm 11.0$ mmHg. Current smoking and diabetes were coded as yes or no at the baseline examination; 13.7% of the patients smoked and 8.4% had diabetes. We used Cox proportional hazards regression

analysis to assess the prognostic significance of smoking, with stratification for study and adjustment for age, sex, diabetes, total cholesterol, 24-h systolic blood pressure, antihypertensive treatment, and BMI. The average 24-h blood pressure was used because its predictive power has been shown to be superior to that of office blood pressure (3). Median follow-up time was 6.57 years (range 0.08–13.1) and total follow-up time amounted to 23,164 patient-years. Table 1 shows the results for all-cause mortality, noncardiovascular mortality, and cardiovascular mortality, which includes all fatal cardiovascular events and sudden death. Table 2 shows the results for fatal and nonfatal coronary heart disease, congestive heart failure, and stroke. Coronary heart disease included sudden death and fatal and nonfatal myocardial infarction. Congestive heart failure required the presence of three disorders: symptoms such as dyspnoea, clinical signs such as ankle edema or crepitations, and the necessity of treatment. Stroke was defined as a neurological deficit with symptoms continuing for >24 h or leading to death with no apparent cause other than vascular; transient ischemic attack was not an end point. As shown in Tables 1 and 2, smoking was a significant and independent risk factor for all-cause, cardiovascular, and noncardiovascular mortality and for fatal and nonfatal coronary heart disease and congestive heart failure ($P < 0.01$ for all end points), but not for stroke ($P = 0.71$). In view of the negative finding on stroke, we performed sensitivity analyses in which we consecutively excluded each of the four studies; these analyses gave similar results, so that the negative finding could not be attributed to the impact of one par-

ticular study. In addition, an appropriate interaction term indicated that the absence of predictive power of smoking did not differ among the four studies.

Because of lack of consensus among studies on the possible risks of stroke from cigarette smoking, Shinton and Beevers (8) performed a meta-analysis of 32 studies and found the overall risk of stroke associated with smoking to be 1.5 (95% CI 1.4–1.6). However, the risk was lower at older age and was not significant for cerebral hemorrhage, so that the higher age in our study and the usually higher prevalence of cerebral hemorrhage in hypertension, although not assessed in our patients, may have contributed to the negative finding. The authors (8) also noted a significant dose response between the number of cigarettes smoked and the relative risk of stroke. It is of note that the prevalence of smoking was only 13.7% in our hypertensive study population, and it is possible that smokers were in general lighter smokers in view of the advice to hypertensive patients to reduce and quit smoking; in fact, 18.5% of the study population were past smokers. Whereas smoking is usually considered a risk factor for stroke in population-based studies (9), the relative risk of smoking appears to be lower for stroke than for coronary heart disease (10). Results are less consistent in hypertension; for example, smoking was a significant risk factor for coronary heart disease but not for stroke in the Medical Research Council trial in older hypertensive subjects (11), whereas smoking contributed significantly to the incidence of the two outcomes in the Medical Research Council trial of mild hypertension (12).

Finally, we tested the interaction between smoking and diabetes and observed that the relative risk of smoking was not greater in diabetic subjects than in nondiabetic subjects ($P > 0.6$). In addition, interaction terms between smoking and 24-h systolic blood pressure, age, sex, total cholesterol, and antihypertensive treatment, respectively, were not significant within our study population.

SMOKING AND DIABETES — To find out about the effect of smoking on mortality and cause-specific cardiovascu-

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Table 1—Multivariable Cox regression analysis for all-cause, cardiovascular, and noncardiovascular mortality in 3,468 hypertensive patients

	All-cause	Cardiovascular	Noncardiovascular
Number of events	324	145	179
Smoking	1.76 (1.29–2.39)*	1.89 (1.19–3.01)†	1.68 (1.12–2.52)†
24-h systolic blood pressure	1.35 (1.21–1.51)*	1.44 (1.22–1.71)*	1.28 (1.10–1.50)†
Diabetes	1.87 (1.38–2.55)*	1.69 (1.06–2.69)‡	2.03 (1.35–3.06)*
Age	1.09 (1.08–1.11)*	1.10 (1.08–1.12)*	1.09 (1.07–1.11)*
Male sex	1.93 (1.52–2.46)*	1.27 (0.88–1.82) ^{NS}	2.70 (1.95–3.75)*

Data are hazard ratios and 95% CIs associated with smoking and diabetes (coded as 1 if yes and 0 if no), 1 SD higher blood pressure, 1 year of age, and male sex (men = 1 and women = 0); total cholesterol, antihypertensive treatment, and BMI are not significant. * $P \leq 0.001$; † $P \leq 0.01$; ‡ $P \leq 0.05$.

Table 2—Multivariable Cox regression analysis for fatal and nonfatal coronary heart disease, congestive heart failure, and stroke in 3,468 patients with hypertension

	Coronary heart disease	Congestive heart failure	Stroke
Number of events	129	99	113
Smoking	1.87 (1.20–2.91)†	2.14 (1.22–3.76)†	0.89 (0.49–1.62) ^{NS}
24-h systolic blood pressure	1.44 (1.21–1.71)*	1.45 (1.19–1.78)*	1.73 (1.45–2.06)*
Diabetes	1.15 (0.64–2.04) ^{NS}	2.05 (1.19–3.53)†	2.19 (1.34–3.57)†
Cholesterol	1.20 (1.07–1.35)†	1.05 (0.86–1.26) ^{NS}	1.07 (0.91–1.27) ^{NS}
Age	1.07 (1.05–1.09)*	1.11 (1.08–1.14)*	1.07 (1.05–1.09)*
Male sex	2.70 (1.85–3.94)*	1.32 (0.84–2.07) ^{NS}	2.03 (1.36–3.02)*

Data are hazard ratios and 95% CIs associated with smoking and diabetes (coded as 1 if yes and 0 if no), 1 SD higher blood pressure or total cholesterol level, 1 year of age, and male sex (men = 1 and women = 0); antihypertensive treatment and BMI are not significant. * $P \leq 0.001$; † $P \leq 0.01$; ^{NS} $P > 0.05$.

lar events, and the interaction between the effects of smoking and diabetes, we conducted a literature search with the PubMed computerized database for relevant studies and examined the reference lists of the original articles and of reviews on the topic. Selection criteria to be included in this review were as follows: studies on subjects with type 2 diabetes or with undefined diabetes (assuming a majority of patients with type 2 diabetes), with or without inclusion of nondiabetic subjects, which assessed the relative risk of smoking, taking into account age, sex, and other relevant covariates in unequiv-

ocal multivariable analyses. The studies include the First National Health and Nutrition Examination Survey (13), a large case-control study (14), the World Health Organization Multinational Study of Vascular Disease in Diabetes (15,16), the U.K. Prospective Diabetes Study (UKPDS) (17–19), the Nurses' Health Study Cohort (20,21), and the Swedish National Diabetes Registry (22). Past smoking was usually not a risk factor in these studies (13–15,21), with few exceptions (20), but the results showed that current smoking is a significant and independent risk factor for all-cause mortality (13,20),

Table 3—Risk of smoking for coronary heart disease and stroke in the Nurses' Health Study

	Coronary heart disease*	Stroke
Never smokers	1.00	1.00
Past smokers	1.21 (0.97–1.51)	0.69 (0.48–1.00)
Current smokers		
1–14 cigarettes/day	1.66 (1.10–2.52)	1.04 (0.50–2.17)
≥ 15 cigarettes/day	2.68 (2.07–3.48)	1.84 (1.21–2.81)
P for trend	<0.001	0.004

*Coronary heart disease includes fatal CHD and non-fatal myocardial infarction. Data are relative risks vs. never smokers, adjusted for age, period, alcohol consumption, duration of diabetes, postmenopausal hormone use, diabetes medication use, BMI, family history of myocardial infarction, physical activity, high cholesterol, and high blood pressure. Adapted from Al-Delaimy et al. (21).

coronary heart disease mortality (13,14), and cardiovascular disease mortality (16,20) and for fatal and nonfatal coronary heart disease (15,17,18,21) and aggregates of cardiovascular disease (21,22). The adjusted relative risks ranged from ~ 1.5 to ~ 2.0 . In the UKPDS (18), the risk of smoking at diagnosis of diabetes amounted to 1.55 (95% CI 1.08–2.01) for stroke. However, in one study, the risk of smoking was not significant for cerebrovascular disease (15) and in the Nurses' Health Study, the relative risk for stroke appeared to be less than the risk for coronary heart disease, as illustrated in Table 3 (21).

Finally, we looked for articles that compared the adjusted relative risks of smoking in diabetic and nondiabetic subjects and/or reported interaction terms between smoking and diabetes. Ford and DeStefano (13) reported that the relative risk for all-cause mortality of current smokers versus never-smokers amounted to 1.60 (95% CI 1.34–1.90) in diabetic subjects and to 1.79 (1.10–2.91) in nondiabetic subjects. The interaction term between smoking and diabetes was not significant, and this was also the case for coronary heart disease. Similarly, DeStefano et al. (14) reported that the relative risk for coronary heart disease mortality was 1.8 (1.3–2.6) in older diabetic patients and 2.2 (1.8–2.5) in older nondiabetic patients (P for interaction = 0.45), and the risk of smoking was even less in younger diabetic subjects than in control subjects ($P < 0.001$). In the Nurses' Health Study, the test for interaction between diabetes status and smoking categories (i.e., never-smokers, past smokers, light and heavy smokers) was not significant for all-cause mortality ($P = 0.83$) (20) and the relative risk for fatal and nonfatal coronary heart disease of current smoking versus never smoking was 2.65 (2.06–3.40) for diabetic women and 5.13 (4.53–5.80) for nondiabetic subjects (21).

CONCLUSIONS — Smoking is a risk factor for mortality and coronary heart disease in hypertension and in diabetes. The risk for stroke is less consistent in hypertension and appears to be smaller than that of CHD in diabetes. Finally, there is no evidence that the relative risk of smoking is greater in diabetic subjects than in nondiabetic subjects. However, because diabetes is a risk factor for morbidity and mortality, the absolute risk of

smoking is usually greater in diabetic subjects than in nondiabetic subjects.

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