Acoustic Shadowing on B-Mode Ultrasound of the Carotid Artery Predicts Ischemic Stroke

The Atherosclerosis Risk in Communities (ARIC) Study

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Background and Purpose—We examined the relationship of carotid artery lesions (CALs), with and without acoustic shadowing (AS), to incident ischemic stroke events in the Atherosclerosis Risk in Communities study cohort.

Methods—The study population consisted of 13 123 men and women aged 45 to 64 years, and free of stroke, examined during 1986–1989. Over an average follow-up time of 8.0 years, 226 incident ischemic stroke cases (thromboembolic brain infarctions) were identified and classified by a standardized protocol. Three levels of exposure were defined on the basis of the presence of B-mode ultrasound–detected CALs and AS in a 3-cm segment of the carotid arteries centered at the bifurcation.

Results—The hazard ratio for ischemic stroke adjusted for age, ethnicity, and study site for women with a CAL without AS, compared with those without a CAL, was 1.92 (95% CI, 1.23, 3.01), and the hazard ratio comparing those with a CAL with AS with those without a CAL was 4.01 (95% CI, 2.28, 7.06). The corresponding hazard ratios for men were 1.99 (95% CI, 1.36, 2.91) and 2.23 (95% CI, 1.32, 3.79). Although adjustment for diabetes, hypertension medication, systolic blood pressure, left ventricular hypertrophy score, fibrinogen, von Willebrand factor antigen, and smoking status attenuated these associations somewhat, when compared with no evidence of CALs, CALs with AS remained statistically significant predictors of ischemic stroke in women, while CALs without AS were predictive of ischemic stroke in men.

Conclusions—B-mode ultrasound–detected CALs and AS serve as markers of atherosclerosis and thus are predictive of ischemic stroke. (Stroke. 2001;32:1120-1126.)

Key Words: carotid arteries □ cerebral infarction □ incidence □ risk factors □ ultrasonography

Many clinical studies have reported relationships between carotid artery plaque characteristics and cerebrovascular events.1–16 Histology studies have characterized the constituents of carotid artery plaques, while B-mode ultrasound has been used for the noninvasive assessment of plaque morphology.16–26 A number of classification systems have been developed to describe B-mode ultrasound plaque morphology; the most commonly used is attributed to Gray-Weale et al21 and defines 4 mutually exclusive categories based on intensity (echolucent versus echogenic) and pattern (homogeneous versus heterogeneous) of reflections. Generally, studies involving the relationship of plaque composition and morphology with cerebrovascular events have focused on plaque ulceration, hemorrhage, and lipid content. In contrast, despite the recent interest in coronary calcification,27,28 the implications of calcification or mineralization within carotid artery plaques remain largely unexplored. Acoustic shadowing (AS) on B-mode ultrasound is commonly accepted as a marker of arterial mineralization or calcification26,29–32 and is defined as a reduction in amplitude of echoes caused by intervening structures with high attenuation.

We report on the relationship between carotid artery plaque, with and without mineralization, as indexed by AS, and incident ischemic cerebrovascular events in the Atherosclerosis Risk in Communities (ARIC) Study cohort.

Subjects and Methods

Study Population

The ARIC Study is an ongoing population-based study of the etiology and natural history of atherosclerosis and its sequelae. The ARIC Study cohort consists of 15 792 men and women aged 45 to 64 years who were examined at baseline during 1986–1989 in 4 communities: Jackson, Mississippi; Forsyth County, North Carolina; northwest suburbs of Minneapolis, Minnesota; and Washington County, Maryland. Probability sampling was used to select ARIC...
cohort participants from these communities; blacks were over-
sampled in Forsyth County and exclusively sampled in Jackson. Response rates for the ARIC baseline examination were 66%, 46%, 67%, and 65% for Forsyth County, Jackson, Minneapolis, and Washington County, respectively. Detailed sampling procedures and the study design have been published.³³ The study was approved by an institutional review committee, and subjects gave informed consent.

Baseline ARIC Examination

The baseline ARIC cohort examination consisted of a standardized medical examination that included interviews, measurement of blood pressure, an ECG, anthropometry, a fasting venipuncture, and an ultrasound examination.³⁴ Trained interviewers ascertained information on basic demographic variables, medical history, medication use, and habits, including smoking history. Medical history included information on diagnoses of stroke, hypertension, and diabetes. In addition, participants were asked to bring the containers of all medications they had used during the 2 weeks before their visit.

Systolic and diastolic (fifth phase) blood pressures were measured 3 times with a random zero sphygmomanometer after the participant was at rest and seated for 5 minutes. The average of the second and third measurements was used in the analysis. Left ventricular hypertrophy (LVH) score was determined by Cornell voltage criteria for the resting ECG.³⁵ All anthropometric measurements were obtained while the participant was fasting, wearing a scrub suit, wearing nonconstricting underwear, and had an empty bladder. Body mass index (BMI) was calculated as weight (kg) divided by the square of height (m).

Lipids, hemostatic factors, and clinical chemistries were measured at the ARIC Central Lipid Laboratory, the ARIC Central Hemostasis Laboratory, and the ARIC Central Clinical Chemistries Laboratory, respectively. Participants were asked to fast for 12 hours before their examination. A Cobas-Bio centrifugal analyzer using commercial reagents determined total cholesterol.³⁶ HDL cholesterol level was measured after precipitation of apolipoprotein B–containing lipopro-
teins with magnesium chloride and dextran sulfate. The hexokinase/ glucose-6-phosphate dehydrogenase method was used to measure serum glucose. Fibrinogen was measured by the thrombin-time titration method originally described by Clauss,³⁷ and von Wille-
brand factor (vWF) antigen was determined by a commercially obtained ELISA kit. Automated hematologic procedures were used to determine hematocrit and hemoglobin at each field center. Prevalent stroke at baseline was defined, for exclusion, as a positive response to the following question: “Has a doctor ever said you had any of the following: stroke?” Prevalent diabetes was defined as a fasting blood glucose value ≥11.1 mmol/L (200 mg/dL), reported evidence of a lesion and whether or not AS was present. Lesions were not defined explicitly; readers were asked to judge the presence of a lesion on the basis of abnormal arterial wall thickness, shape, or texture. AS was defined as a reduction in amplitude of echoes caused by intervening structures with high attenuation.

AS on ultrasound is commonly accepted as a marker of arterial mineralization. Although studies have not validated that AS only occurs in the presence of mineralization, the only reported nonarti-
factual cause of AS is mineralization.³⁶-³⁹,⁴²-⁴³ In addition, studies comparing histology with ultrasound findings have reported a positive correlation between mineral and the echogenicity of lesions.³⁶-³⁹,⁴²-⁴³

On the basis of the aforementioned definitions and information from the 6 available sites, 3 levels of carotid atherosclerosis status were defined: (1) individuals without carotid artery lesion (CAL) or AS identified at any site, (2) those with lesions identified at 1 or more sites but no evidence of AS associated with those lesions, and (3) those with 1 or more lesions characterized by AS. Because arterial mineralization does not develop in the absence of a lesion and AS can occur as an artifact of the imaging process, individuals who had evidence of AS but no record of lesions were excluded (n = 86). Furthermore, “among individuals ‘without lesions or AS at any site,’ those who were missing lesion and/or AS information at either the right or left bifurcation, or at any 2 or more of the 6 sites, were excluded (n = 1526). In contrast, individuals ‘with lesions at any site’ remained in the analysis regardless of missing ultrasound information at other sites.

In addition, mean far wall extracranial carotid IMT was derived on the basis of information available from the 6 carotid artery sites.⁴⁰-⁴³ Because 38% of individuals were missing IMT information at some carotid artery site, IMT was imputed for missing sites on the basis of sex- and race-specific multivariate linear models of mean IMT as a function of age, BMI, and arterial depth. On average, values were imputed for 2.3 sites per person. Additionally, mean far wall IMT was adjusted for site-specific reader differences and downward measurement drifts over the baseline visit. Detailed information on mean far wall IMT in ARIC has been previously published.⁴⁰-⁴³

Incident Events

The ARIC surveillance component provided standardized ascertain-
ment and classification of incident cerebrovascular events for all cohort members.³⁴,³⁵,⁴³ Information concerning events was obtained during annual follow-up telephone interviews, by reviewing local hospital discharge lists, and by checking death certificates. A computer algorithm and an expert reviewer independently classified each eligible case using criteria adapted from the National Survey of Stroke.³⁴,³⁵ These criteria included autopsy evidence, results of neuro-
imaging and other diagnostic procedures, and information on com-
binations of symptom type, duration, and severity. Differences in diagnosis were adjudicated by another reviewer.

Cerebrovascular events in this analysis were restricted to definite or probable hospitalized ischemic stroke events, including throm-
botic brain infarction and embolic brain infarction.³⁴,³⁵,⁴³ Definite thombotic brain infarction required either autopsy evidence of nonhemorrhagic infarct of the brain, or 1 major or 2 minor neuro-
logical symptoms lasting at least 24 hours or until death, and CT or MRI showing evidence of infarct without evidence of hemorrhage. Events were classified as probable thrombotic brain infarctions when CT or MRI evidence obtained within 48 hours of event onset was negative or nonspecific but indicated no evidence of hemorrhage, and any information obtained from a spinal tap provided further evidence that the stroke was not hemorrhagic. The distinction between lacunar and nonlacunar infarcts was only made in the case of definite thrombotic brain infarctions. Because of the small number of lacunar strokes (n = 68), for purposes of these analyses thrombotic brain infarctions included lacunar and nonlacunar strokes. Definite and probable embolic brain infarction required the evidence previ-
ously mentioned for thrombotic brain infarction as well as an identifiable source of cerebral embolus. Incident cerebrovascular events were defined as events occurring after a participant’s initial
entry into the ARIC cohort through the end of 1996, among those without prevalent stroke at baseline.

**Statistical Analyses**

Prospective analyses were performed in which the presence of CALs, with and without AS as an index of plaque mineralization, determined a participant’s exposure status. Two indicator variables defined the 3 levels of carotid atherosclerosis status, and comparisons were made between each of these 3 levels. The outcome of interest was incident ischemic stroke.

Covariates of interest included age, sex, ethnicity center (Forsyth County whites, Forsyth County blacks, Minneapolis whites, Jackson blacks, and Washington whites), total cholesterol, HDL cholesterol, systolic blood pressure, LVH score, fibrinogen (dichotomized at the mean: 3.013 g/L), vWF antigen, BMI, hemoglobin, hematocrit, smoking status (current, former, and never), use of hypertension medication, diabetes status, and mean far wall IMT. The linear and logistic regression methods proposed by Zhao47 were used to determine age-, sex-, and ethnicity center–adjusted baseline means and proportions for covariates at each level of carotid atherosclerosis status. The distribution of mean far wall IMT for each level of carotid atherosclerosis status was examined with the use of histograms. Furthermore, Poisson regression was used to determine adjusted sex-specific stratified rates of incident ischemic stroke for each level of carotid atherosclerosis status.

Cox proportional hazard models were used to calculate sex-specific hazard ratios for ischemic stroke in relation to carotid atherosclerosis status. Throughout the analyses, interaction terms between sex and the carotid atherosclerosis status variables were used to determine sex-specific hazard ratios within a single model. The association between carotid atherosclerosis status and incident ischemic stroke was then assessed after controlling for covariates. Age, total cholesterol, HDL cholesterol, systolic blood pressure, LVH score, BMI, hemoglobin, hematocrit, vWF antigen, and mean far wall IMT were modeled as linear in the log (hazard) scale. Models with and without the appropriate interaction terms were compared to identify interactions within each sex category between covariates and the 3 levels of carotid atherosclerosis; a P-value of 0.05 was used as a nominal value of statistically significant interaction. The assumption of proportional hazards was evaluated for each of the covariates of interest and the main exposure variable with the use of log(-log survivorship) plots and by testing differences between hazard ratios estimated for each of 3 periods of follow-up (first 3 years, next 3 years, and afterward).

**Results**

Exclusions for these analyses included individuals with prevalent stroke or unknown stroke status at baseline (n=329), individuals without ultrasound information on lesion and/or AS (n=1526), individuals with evidence of AS without evidence of a lesion (n=86), and those of neither black nor white descent, plus blacks from either the Minneapolis or Washington County field center (n=80), those missing other key baseline variables (n=647), and 1 individual lost to follow-up. Hence, the study population for these analyses included 13 123 ARIC Study participants who had been followed an average of 8.0 years. At the end of 1996 this cohort had experienced 226 incident ischemic stroke events.

Baseline means and proportions, stratified by carotid atherosclerosis status and adjusted for age, sex, and ethnicity center, were calculated for covariates (Table 1). Of the 13 123 participants, 8464 (64%) had no evidence of CALs, 3755 (29%) had CALs without AS, and 904 (7%) had CALs with AS.

The distribution of mean far wall IMT for each level of carotid atherosclerosis status is shown in Figure 1 (analysis was limited to the 12 756 individuals with mean far wall IMT information available). Of the 1058 individuals with a mean far wall IMT of $\geq 1.00$ mm, 94.4% had evidence of a CAL either with (or without) AS; however, only 42.4% of the individuals with a CAL with AS and 16.6% of the individuals with a CAL without AS had a mean far wall IMT of $\geq 1.00$ mm.
During the follow-up period, 45, 34, and 17 ischemic stroke events occurred, respectively, in the 5085 women without evidence of CALs, the 1762 with a CAL without AS, and the 391 with a CAL with AS; corresponding counts for men were 48 of 3379, 62 of 1993, and 20 of 513. Age- and ethnicity center–adjusted rates of incident ischemic stroke for each level of carotid atherosclerosis status stratified by sex are illustrated in Figure 2. Rates of incident ischemic stroke were higher in those with CALs compared with those without CALs; among those with CALs, rates of incident ischemic stroke were higher in those with evidence of AS.

The hazard ratio for ischemic stroke adjusted for age and ethnicity center for women with a CAL without AS, compared with those without a CAL, was 1.92 (95% CI, 1.23, 3.01); the hazard ratio comparing those with a CAL with AS with those without a CAL was 4.01 (95% CI, 2.28, 7.06) (Table 2). The corresponding hazard ratios for men were 1.99 (95% CI, 1.36, 2.91) and 2.23 (95% CI, 1.32, 3.79). Furthermore, the global P-value for the interaction between the carotid atherosclerosis variables and sex was 0.25.

Evaluation of covariates indicated that sex, age, diabetes status, smoking status, systolic blood pressure, hypertension medication, LVH score, fibrinogen, and vWF antigen were independent predictors of incident stroke. Sex-specific hazard ratios for incident ischemic stroke in relation to carotid atherosclerosis were somewhat attenuated after adjustment for these independent predictors of stroke and were substantially attenuated after further adjustment for mean far wall IMT, an established marker of subclinical atherosclerosis (Table 2). After adjustment for mean far wall IMT, although not statistically significant, women and men with a CAL without AS had a 38% to 42% increased hazard for ischemic stroke compared with women and men without evidence of a CAL. Additionally, women with a CAL with AS had a 112% increased hazard for ischemic stroke compared with women without evidence of a CAL (statistically significant), while the corresponding hazard in men was increased only 10%.

### Discussion

#### Overview

We were interested in the ability of carotid artery atherosclerosis status, as defined by evidence of CALs and AS at 6 carotid artery sites, to predict ischemic stroke incidence. In women, CALs with AS were significantly stronger predictors of ischemic stroke than CALs without AS, whereas in men, CALs with and without AS predicted ischemic stroke equally well. Although adjustment for age, ethnicity center, diabetes, hypertension medication, systolic blood pressure, LVH score, fibrinogen, vWF antigen, and smoking status attenuated these associations somewhat, when compared with no evidence of CALs, CALs with AS remained significant predictors of ischemic stroke in women, while CALs without AS were predictive of ischemic stroke in men.

Additionally, we compared how the 3 discrete levels of carotid atherosclerosis status defined in this report compared with an established measure of subclinical atherosclerosis on a continuous scale, namely, mean far wall IMT. Although 94.4% of individuals with a mean far wall IMT ≥1.00 mm had evidence of a CAL (with or without AS), the majority of

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**TABLE 2. Adjusted Hazard Rate Ratios for Ischemic Stroke by Sex in Relation to Carotid Atherosclerosis Status**

<table>
<thead>
<tr>
<th>Lesions</th>
<th>Women</th>
<th>Men</th>
<th>Women</th>
<th>Men</th>
<th>Women</th>
<th>Men</th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>No lesion</td>
<td>1.92 (1.23, 3.01)</td>
<td>1.99 (1.36, 2.91)</td>
<td>1.52 (0.97, 2.39)</td>
<td>1.77 (1.21, 2.60)</td>
<td>1.38 (0.86, 2.22)</td>
<td>1.42 (0.95, 2.13)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lesion with AS vs no lesion</td>
<td>4.01 (2.28, 7.06)</td>
<td>2.23 (1.32, 3.79)</td>
<td>2.85 (1.60, 5.06)</td>
<td>1.53 (0.89, 2.62)</td>
<td>2.12 (1.13, 3.96)</td>
<td>1.10 (0.61, 1.97)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lesion with AS vs lesion without AS</td>
<td>2.09 (1.16, 3.74)</td>
<td>1.12 (0.68, 1.86)</td>
<td>1.88 (1.04, 3.38)</td>
<td>0.86 (0.51, 1.44)</td>
<td>1.53 (0.84, 2.82)</td>
<td>0.77 (0.46, 1.31)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values in parentheses are 95% CIs. All models were adjusted for age, ethnicity, and study site. Within each model appropriate interaction terms were used for stratification by sex (model 1, global P=0.25; model 2, global P=0.14; model 3, global P=0.19). In addition, model 2 was adjusted for hypertension medication, systolic blood pressure, LVH score, diabetes, fibrinogen, vWF antigen, and smoking status. Model 3 was adjusted for mean far wall IMT and model 2 covariates.

†P<0.05, †P<0.10, †P<0.15 for specific sex interactions within each model.
individuals with CALs both with and without AS had a mean far wall IMT < 1.00 mm. After adjustment for mean far wall IMT, when compared with no evidence of CALs, CALs without AS were not significant predictors of stroke in women or men, while CALs with AS were significant predictors of stroke in women but not in men.

Historically, arterial mineralization has been accepted as a marker of advanced atherosclerosis. However, it has not been determined whether mineralization, independent of atherosclerosis status, plays a protective or deleterious role relative to incident ischemic stroke events. Arguments for a protective role include the ability of mineralization to stabilize soft lipid plaques; arguments for a deleterious role include loss of distensibility of the arterial wall and a weakening at the interface between the arterial wall and fibrous material. Studies indicate that although mineralization is correlated with overall plaque burden, individuals with similar levels of atherosclerosis have varying levels of mineralization; they also indicate that advanced nonmineralized lesions do occur, indicating that lesion formation does not always trigger the process of mineralization. Furthermore, a differential risk factor profile was found for those with CALs with and without AS in an earlier study of the baseline ARIC cohort and in Table 1. Male sex and increased total and LDL cholesterol levels were associated only with the presence of a CAL, while smoking and hypertension were associated both with the presence of a CAL and with the presence of AS among those with a CAL. If mineralization is a regulated process similar to bone formation, as current evidence suggests, the process of arterial mineralization could be the body’s protective response to the development of atherosclerosis.

Unfortunately, epidemiological studies are limited in their ability to control for overall level of atherosclerosis in assessing the effects of arterial mineralization at specific arterial sites. Hence, it is hard to determine whether mineralization within any individual lesion is protective or deleterious. First, we established that CAL with AS and CAL without AS were predictive of ischemic stroke in both women and men (Table 2, model 1). Next, we attempted to control for the established stroke risk factors, despite the fact that many of these risk factors are atherosclerotic risk factors, to determine whether CAL with AS and CAL without AS were independent predictors of ischemic stroke (Table 2, model 2). Finally, we attempted to control for overall level of atherosclerosis, while assessing the predictive value of AS within CALs, by controlling for mean far wall IMT; however, residual confounding by atherosclerosis level may be responsible for the elevated risk in women associated with CAL with AS (Table 2, model 3).

The present results are similar in both magnitude and direction to the results of a parallel analysis of carotid atherosclerosis status and incident coronary heart disease (K.J. Hunt, PhD, unpublished data, 2000). The risk factor-adjusted hazard ratios for CAL without AS compared with no CAL were similar for women and men: 1.78 and 1.59 for CHD and 1.52 and 1.77 for ischemic stroke (sex-related differences were not significant). Thus, CALs without AS predict disease similarly in women and men. However, the comparison of CALs with AS to CALs without AS is quite different: hazard ratios are 1.73 in women versus 1.04 in men for coronary heart disease (sex interaction, \( P < 0.10 \)) and 1.88 in women versus 0.86 in men for ischemic stroke (sex interaction, \( P < 0.05 \)). The sex-related differences persist for both coronary heart disease and ischemic stroke after further adjustment for IMT. Biological differences are one potential explanation for the differential associations consistently observed between women and men. For example, in postmenopausal women arterial mineralization may serve as a marker for the extent of estrogen deficiency.

Finally, lesions in the extracranial carotid arteries may be related to cerebrovascular events either directly or primarily because they represent a measure of overall level of atherosclerosis. Atherosclerosis, the same process we have imaged in the carotid arteries, is almost always the pathology underlying coronary heart disease, whereas various fibrotic and other atherosclerotic processes affect the very small intracranial arteries and arterioles responsible for many of the stroke events. Yet cerebral arteries, unlike the coronaries, are downstream from the carotid arteries. Therefore, the strength of the carotid lesion association with coronary heart disease and its similarity to the association with stroke we report here imply that the carotid lesions serve as good markers of the general extent of atherosclerosis.

**Strengths and Limitations**

The present study is one of the first population-based studies to examine carotid artery calcification, as indexed by AS, in relation to incident ischemic stroke. As end points we included only validated definite or probable thromboembolic brain infarctions. A participant’s physician was notified when a residual carotid artery lumen of \( \geq 2 \) mm or a lesion of potential clinical significance, in the opinion of an experienced neurologist, was found, such as the presence of a mobile component or large ulceration. The combined frequency of these referrals was 1.5% of all scans.

Unfortunately, the B-mode ultrasound information available to us provided only a crude indicator of the presence or absence of mineralization in identified CALs. CAL morphology could not be further characterized on the basis of intensity (echolucent versus echogenic) and pattern (homogeneous versus heterogeneous) of reflections with the use of an accepted classification system. The role mineralization plays as atherosclerosis develops may be dependent on the pattern in which it is distributed throughout a lesion. New methods, such as electron beam CT, subsecond helical CT, and modified MRI have been developed with an enhanced ability to detect and quantify calcification in various arterial territories, but their use is not as widespread as that of B-mode ultrasound.

The ARIC ultrasound scanning and reading protocols were developed with the aim of measuring IMT precisely, not identifying and characterizing lesions in the carotid arteries. Nevertheless, lesions and AS identified during the ARIC examination are believed to represent true findings of lesions and AS; hence, the false-positive rate is expected to be low. By contrast, the false-negative rate may be high. Repeatability of the carotid atherosclerosis status variable has been
determined on the basis of repeated ultrasound readings in a subset of the population; however, repeated information was not available on the ultrasound scanning procedure. Kappa statistics based on 974 repeat ultrasound readings were 0.65 (95% CI, 0.60, 0.69) for the carotid atherosclerosis status variable (weighted for the degree of agreement across the 3 defined levels of carotid atherosclerosis status), 0.56 (95% CI, 0.47, 0.66) for the determination of AS, and 0.55 (95% CI, 0.44, 0.66) for the determination of AS among the 297 individuals with evidence of CALS.8,59

Future Studies

Atherosclerosis typically leads to multiple lesions and to various degrees of involvement in different arterial beds. Hence, findings of prospective studies based on a single arterial bed are not specific enough to determine the mechanisms through which morphological attributes of lesions promote or inhibit cardiovascular events. Prospective studies that follow multiple arterial sites and detailed morphological characteristics of lesions identified over time could be informative.60 To date, epidemiological studies of subclinical atherosclerosis indicate that the presence of atherosclerosis is largely explained by known risk factors. However, what causes some individuals with atherosclerosis to develop ischemic stroke, while most silently carry the disease, remains unknown. Understanding both the mechanism(s) through which arterial mineralization develops and how the morphology of a lesion influences the likelihood of an ischemic event may provide insight into who will sustain strokes.

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