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Progression of varicose veins and chronic venous insufficiency in the general population in the Edinburgh Vein Study

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Objective: **The natural history in the general population of chronic venous disease in the legs is not well understood. This has limited our ability to predict which patients will deteriorate and to assign clinical priorities. The aims of this study were to describe the progression of trunk varicose veins and chronic venous insufficiency (CVI) in the general population, to identify important lifestyle and clinical prognostic factors, and to determine the relationship between venous reflux and progression.**

Methods: **The Edinburgh Vein Study is a population-based cohort study in which randomly selected adults aged 18 to 64 years had an examination at baseline. This included a questionnaire on lifestyle and clinical factors, standardized assessment and classification of venous disease in the legs, and duplex scan to detect venous reflux in eight segments of each leg. A follow-up examination 13 years later included a reclassification of venous disease to ascertain progression in the development or increase in severity of varicose veins and CVI.**

Results: **Among 1566 adults seen at baseline, 880 had a follow-up examination, of whom 334 had trunk varicose veins or CVI at baseline and composed the study sample. The mean (standard deviation) duration of follow-up was 13.4 (0.4) years. Progression was found in 193 (57.8%), equivalent to 4.3% (95% confidence interval [CI], 3.7-4.9) annually. In 270 subjects with only varicose veins at baseline, 86 (31.9%) developed CVI, with the rate increasing consistently with age ($P = .04$). Almost all subjects (98%) with both varicose veins and CVI at baseline deteriorated. Progression of chronic venous disease did not differ by gender or leg, but a family history of varicose veins and history of deep venous thrombosis increased risk (odds ratio [OR], 1.85 [95% CI, 1.14-1.30] and 4.10 [95% CI, 1.07-15.71], respectively). Overweight was associated with increased risk of CVI in those with varicose veins (OR, 1.85; 95% CI, 1.10-3.12). Reflux in the superficial system increased the likelihood of progression, especially in combination with deep reflux (OR, 2.57; 95% CI, 1.55-4.25) and when located in the small saphenous vein (OR, 4.73; 95% CI, 1.37-16.39).**

Conclusions: **Nearly half of the general population with chronic venous disease deteriorated during 13 years, and almost one third with varicose veins developed skin changes of CVI, increasing their risk of ulceration. Age, family history of varicose veins, history of deep venous thrombosis, overweight, and superficial reflux, especially in the small saphenous vein and with deep reflux, might influence the risk of progression.**

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Chronic venous disease in the legs occurs commonly in Western countries,[1] with varicose veins affecting around one quarter to one third of adults.[2,3] Chronic venous insufficiency (CVI) comprising skin changes is less frequent,[1,2] but ulceration is serious, is difficult to heal, and recurs in at least two thirds of patients.[4] Demands for treatment are often not easily met.[5]

Little is known about the natural history of chronic venous disease in the general population. A major longitudinal study was conducted in pharmaceutical workers in Basle, Switzerland,[6] but this was some years ago before the use of current, more stringent methods of measurement. This lack of knowledge of natural history and of prognostic factors has meant that few advances have been made in identifying patients who might benefit from early intervention and in evaluating preventive measures.

The aims of our study were to describe the progression of trunk varicose veins and CVI in the general population, to identify important lifestyle and clinical prognostic factors, and to determine the relationship between presence of venous reflux and progression.

METHODS

Study design. The Edinburgh Vein Study is a population-based cohort study in which subjects examined at baseline from 1994 to 1996 underwent a follow-up examination from 2007 to 2009. The study was approved by

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the Lothian Research Ethics Committee, and each participant gave informed written consent at baseline and follow-up.

Baseline examination. The recruitment, response, and methods at baseline have been described in detail.[2,7] Briefly, an age- and sex-stratified random sample of adults aged 18 to 64 years was selected from general practice registers in Edinburgh. A total of 1566 subjects took part (response of 53.8%). Participants had a social class distribution similar to that of residents in Edinburgh but were slightly older, from more affluent areas, and more likely to be female than nonresponders.

The baseline examination comprised administration of a questionnaire on age, gender, and social class according to occupation[8]; family history of varicose veins or ulcer in grandparents, parents, or siblings; history of deep venous thrombosis (DVT); cigarette smoking; bowel habit; and mobility at work. Women provided an obstetric history including number of pregnancies experienced. Measurements of height to the nearest 5 mm, with a freestanding metal ruler on a heavy base, and weight to the nearest 100 g, with a digital Soehnle scale (Nassau, Germany), were taken for calculation of body mass index. Legs were inspected with subjects standing on a raised platform with their feet in three standard positions: (1) facing the observer with heels together and forefeet apart, (2) facing away from the observer in a similar position, and (3) facing away from the observer with feet parallel. After at least 2 minutes to allow pooling of blood in the legs, venous disease was classified by the Basle system.[6] Photographs of the legs were taken in the three standard positions and later classified by two observers independently of each other and the clinical classification.

Duplex scans were performed by a Prisma VST scanner (Diasonics Sonotron, Zug, Switzerland) with a pneumatic cuff around the calf and automatic inflator (Oak Medical, Scunthorpe, UK) providing some standardization of applied pressure. Examination was on a tilting couch at a 45-degree angle with measurements made at eight points in each leg: common femoral vein proximal to the saphenofemoral junction; femoral vein (1) 2 cm distal to the confluence with the profunda femoris vein and (2) lower third of thigh; popliteal vein (1) above and (2) below the knee crease; great saphenous vein (1) distal to the saphenofemoral junction and (2) lower third of thigh; and small saphenous vein just distal to the saphenofemoral junction. Duration of reflux was recorded and the mean of two readings used in the analysis.

Follow-up examination. The recruitment process and methods at follow-up have been reported.[9,10] Briefly, information on the 1566 subjects in the baseline study was sent to the Practitioner Services Division of NHS National Services Scotland to link subjects' names and dates of birth to the Lothian Community Health Index (Edinburgh, Scotland). This linkage provided updated addresses and general practices where subjects were registered. For those no longer resident in Scotland but still in the United Kingdom, the health authority of registration was provided so they could be traced. Subjects who had died or emigrated were removed from the invitation list. Up to two invitation letters and three telephone calls were made to the remaining subjects.

The follow-up examination was held in the Wellcome Trust Clinical Research Facility in Edinburgh. Subjects were examined by a research fellow and nurses trained in classification of venous disease and duplex scanning. The examination, including the taking of photographs, was similar to the examination at baseline[7] except that as well as the Basle system,[6] the clinical categories of the more recent Clinical, Etiological, Anatomical, Pathophysiological (CEAP) classification[11] were used to permit comparability with other studies. The CEAP class C2 varicose veins (diameter of 3 mm or more) correspond to Basle trunk varices (dilated tortuous trunks of great and small saphenous veins and their branches of the first and second order) and were graded for severity according to the Basle system of 1 (mild), 2 (moderate), and 3 (severe), depending on degree and extent of tortuosity and prominence of the veins. Standard photographs from the Basle study were used for reference when necessary. CVI was classified by only the CEAP system because the classes correspond closely to Basle grades: CEAP class C3 (corona, edema) corresponds to Basle grade 1; C4 (a. pigmentation, eczema; b. lipodermatosclerosis, atrophie blanche), to grade 2; and C5 (healed ulcer) and C6 (active ulcer), to grade 3.

Quality control. During the baseline and follow-up examinations, several quality control mechanisms[2,7,9,10] were carried out. These included periodic training for staff, interobserver and intraobserver variability checks of venous classification and duplex scanning, and comparisons of clinical classifications and photographic findings.

For this current analysis of longitudinal changes, a highly pertinent quality parameter was observer variability between baseline and follow-up. A subsample of 100 baseline participants was created by selecting every 15th of the 1566 participants. Baseline photographs were independently classified by two follow-up observers. Consensus of these observers was then compared with the classifications made by the baseline observers. Very good agreement was found.[10] Level of agreement was 96% ($\kappa = 0.90$) for C2 varicose veins, 99% ($\kappa = 0.88$) for corona phlebectatica, and 100% ($\kappa = 1.00$) for both edema and pigmentation.

Statistical analysis. Data collected at baseline and follow-up were checked, coded, and double entered onto the University of Edinburgh mainframe computer system for analysis with SPSS-X (SPSS Inc, Chicago, Ill). Subjects with trunk varicose veins or CVI at baseline composed the current study sample. A definition of progression of chronic venous disease required at least one of the following: increase in grade of varicose veins or CVI; development of CVI in those with varicose veins (or vice versa); or change from unilateral to bilateral disease. Presence of reflux was defined as retrograde flow $\geq$0.5 second.

Characteristics of participants were described by mean and standard deviation or percentage (number) and compared by *t*-test or χ^2 test, respectively. Logistic regression analyses were used to calculate unadjusted odds ratios