Atherosclerosis in Trial of Org 10172 in Acute Stroke Treatment Subtypes among Young and Middle-Aged Stroke Patients: The Norwegian Stroke in the Young Study

Annette Fromm, MD, PhD,* Øystein Ariansen Haaland, PhD,† Halvor Naess, MD, PhD,*‡§ Lars Thomassen, MD, PhD,*‡ and Ulrike Waje-Andreassen, MD, PhD*

Background: Ischemic stroke patients subtyped as of undetermined cause (SUC) usually outnumber those with determined cause subtypes. Etiological stroke classifications may lead to neglect of parallel, noncausative findings. Atherosclerosis progresses over decades and is associated with high morbidity and mortality in young stroke patients in long-term follow-up studies. We compared the prevalence of carotid atherosclerosis in all TOAST subtypes among young patients with acute ischemic stroke. *Methods:* We investigated 150 patients aged 15-60 years with documented acute ischemic stroke, and 84 controls free of cardiovascular disease. Stroke etiology was classified according to TOAST criteria. Carotid intima–media thickness (cIMT) measurements were obtained from 12 standardized multiangle measurements in the common carotid artery, carotid bifurcation, and internal carotid artery. *Results:* The causes of stroke were 5.3% large-artery atherosclerosis (LAA), 26.7% cardioembolism, 21.3% small-artery occlusion (SAO), 10% stroke of other determined cause, and 36.7% stroke of undetermined cause (SUC). cIMT was increased in patients with LAA (1.56 mm, $P = .002$), SAO (1.11 mm, $P = .006$), and SUC (1.10 mm, $P = .004$) compared to controls (cIMT 0.86 mm). Segmental cIMT distribution differed across stroke subtypes, age groups, and sexes. *Conclusions:* Atherosclerotic disease is prevalent in the majority of young and middle-aged ischemic stroke patients, requiring determined investigation and aggressive treatment of modifiable risk factors. **Key Words:** Young stroke—ischemic stroke—stroke etiology—TOAST—carotid intima–media thickness—atherosclerosis—ultrasound.

From the *Centre for Neurovascular Diseases, Department of Neurology, Haukeland University Hospital, Bergen, Norway; †Department of Global Public Health and Primary Health Care, University of Bergen, Bergen, Norway; ‡Department of Clinical Medicine, University of Bergen, Bergen, Norway; and §Centre for Age-Related Medicine, Stavanger University Hospital, Stavanger, Norway.

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Address correspondence to Annette Fromm, MD, PhD, Centre for Neurovascular Diseases, Department of Neurology, Haukeland University Hospital, N-5021 Bergen, Norway. E-mail: atfm@helse-bergen.no.

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Introduction

There is evidence for substantial differences in stroke etiology dependent on age.[1,2] Etiological classifications aim to identify the causative subtype of stroke during a decision-making process by integration of symptom characteristics, risk factors, and results of stroke investigation,[3] but relevant parallel findings have a lesser impact on the final determination. The most widely applied classification is the Trial of Org 10172 in Acute Stroke Treatment (TOAST) subtype classification, which organizes stroke into 5 etiological subtypes: large-artery atherosclerosis (LAA), cardioembolism (CE), small-artery occlusion (SAO), stroke of other determined cause (SOC), and stroke of undetermined cause (SUC).[4] LAA has been the reported cause of stroke among young adults in 3%-21%.[5-7] Long-term follow-up data 12 years after stroke revealed a stroke-recurrence rate of 25%, a 5-fold increased rate of vascular comorbidity, a 10-fold increased mortality, mainly associated with cardiovascular disease (CVD), and an 8-fold increased rate of memory impairment compared to controls.[8] Carotid intima–media thickness (cIMT) as surrogate marker of atherosclerosis is frequently used for vascular risk evaluation.[9] The Norwegian Stroke in the Young Study (NOR-SYS) ultrasonographic research protocol includes multisegmental multiangle measurements of cIMT with the purpose to evaluate clinical and subclinical atherosclerotic arterial disease regardless of the cause of stroke.[10]

We aimed to compare the prevalence of carotid artery atherosclerosis in each TOAST subtype among young and middle-aged ischemic stroke patients to that of controls free of CVD. We hypothesized that atherosclerosis is a relevant parallel finding beyond the LAA subtype, indicating the need for thorough workup despite patient age as its discovery may have a valuable impact on secondary prevention.

Materials and Methods

NOR-SYS is a prospective 3-generation long-term follow-up study. Details of the study protocol have recently been published.[10] Medical history, vascular risk factors, and clinical, laboratory, neuroradiological, and cardiological results are combined with ultrasonographic data gathered according to the research protocol. The presented analysis is based on data from 150 patients and 84 controls included in NOR-SYS between September 2010 and June 2012.

Standard Protocol Approvals, Registrations, and Patient Consents

NOR-SYS is conducted according to the Declaration of Helsinki, approved by the Regional Committee for Medical and Health Research Ethics, Western-Norway, and registered in ClinicalTrials.gov (NCT01597453). Written informed consent was obtained from all participants or their legal representatives.

Subject Selection

Patient inclusion criteria were documented acute ischemic stroke, age 15-60 years, and residency in Hordaland county, Norway. Two patients refused study participation. Seven patients were excluded from statistical analyses: three due to incomplete neurosonographic data set and four due to non-Caucasian origin. Partners of included patients served as controls due to their function as reference persons for joint offspring in future analyses. Of 123 available partners, 63 (70.8%) caucasian females and 21 (61.8%) caucasian males with no prior cardiovascular events participated.

Stroke Subtype Classification by TOAST

Etiological classification was performed according to the TOAST criteria by an experienced stroke neurologist (H.N.) [4] who was blinded for results derived from the NOR-SYS ultrasonographic research protocol.

Neurosonology

Ultrasound was performed with Philips iU22 and 9-3 MHz linear array transducer (Philips Medical Systems, Bothell, WA, USA). Two patients were examined at our intensive care unit with a portable Phillips CX50 ultrasound system and a 12-3 MHz linear array transducer (Philips Medical Systems, Bothell, WA, USA). The studied subjects were examined by 2 sonographers (A.F. and U.W.A.), both trained and certified for the NOR-SYS duplex sonography research protocol[10] in collaboration with the Vascular Imaging Centre, University Medical Centre, Utrecht, The Netherlands.

Data Reliability Tests

Reproducibility testing of cIMT measurements within (intraobserver correlation .78-.98) and between (interobserver correlation .83-.93) sonographers of the research group, and between iU22 and CX50 (interequipment correlation .94) were in accordance with other studies.[11-14]

cIMT Measurements

As previously described,[10] a total of 12 far-wall cIMT measurements in the common carotid artery (CCA), carotid bifurcation (BIF), and internal carotid artery (ICA) were performed in each participant in the end-diastolic phase of the cardiac cycle. Mean cIMT values were acquired using Philips QLAB (Philips Medical Systems). Maximum IMT or plaque thickness was measured additionally in case of intrasegmental irregularities.

Statistical Analysis

All statistical analyses were conducted by a statistician (Ø.A.H.). To facilitate comparability to other studies,[6,15] and to assess the influence of age and sex on IMT, our study population was grouped according to age (younger,