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Research Article

Five-Year Risk of Cardiovascular Events after Transient Ischemic Attack: Results from a Prospective Cohort

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Objectives. There are few contemporary, prospective studies reporting on the long-term risk of stroke and other cardiovascular (CV) events after transient ischemic attack (TIA). The primary aim was to examine the risk of new CV events within 5 years after TIA. The secondary aim was to identify baseline predictors of long-term CV events, including inflammatory biomarkers in a subgroup analysis. *Materials and Methods.* In a prospective, multicenter study, we enrolled 577 TIA patients between 2012 and 2014. The primary outcome was a composite of stroke, acute coronary syndrome, and CV death. We used data from the Norwegian Cardiovascular Disease Registry. In a subgroup of 112 patients, blood samples were analyzed for inflammatory biomarkers. *Results.* The primary outcome occurred in 108 patients (18.7%), of which 69 patients (12.0%) had a stroke. Sixty-one (56.5%) of the events occurred during year two through five. Increasing age (HR 1.05; 95% CI, 1.03-1.08), male sex (HR 1.82; 95% CI, 1.16-2.85), hypertension (HR 1.67; 95% CI, 1.04-2.67), and acute infarction on brain imaging (HR 1.84; 95% CI, 1.17-2.91) were significant predictors for the primary outcome. In the subgroup analysis, none of the blood inflammatory biomarkers were associated with CV events. *Conclusions.* The risk of CV events was highest during the first year after TIA, with a lower but sustained risk throughout the follow-up. This emphasizes the importance of both early initiation of and long-term continuation of secondary preventive treatment after TIA. Inflammatory biomarkers are probably not important as prognostic markers of cardiovascular disease in TIA patients.

1. Introduction

The age-standardized stroke mortality rates have declined worldwide during the last decades, but the number of new strokes is increasing every year, and stroke remains one of the leading causes of disability and death [1, 2]. Previous landmark studies have shown a high rate of subsequent stroke in the early phase after transient ischemic attack

(TIA) [3–5], and that TIA patients are more prone to myocardial infarctions (MI) [6] and vascular death [7, 8]. A combination of urgent diagnosis and treatment, improved secondary prevention, and a reduction of risk factors in the population probably explain the observed reduction in the risk of stroke and other CV events after TIA during the last decades [9–14]. We have previously demonstrated a low risk of subsequent stroke, both within 1 week and until 1 year after TIA [15]. However, only a few prospective studies have been reporting on the risk of subsequent stroke and other vascular events as well as all-cause mortality beyond 1 year after TIA [16, 17].

Another focus area in stroke and TIA research has been the development of different clinical risk score models to predict short- and long-term stroke recurrence after TIA. Validation studies for these risk scores, including the ABCD2 and ABCD3-I scores, have given conflicting results. Several meta-analysis and guidelines have stated that such scores are limited in their performance and clinical utilities [18, 19]. An increasing body of evidence suggests that inflammation plays a key role in pathogenesis and outcome of ischemic injury [20–22]. There is an ongoing search for candidate biomarkers being able to predict cardiovascular (CV) outcomes after stroke and TIA. Blood-based biomarkers may provide incremental value over established prognostic markers, but whereas inflammatory biomarkers like C-reactive protein (CRP) is established as a risk marker for future MI, the clinical usefulness of such markers in relation to TIA is still limited and uncertain [23–27].

Our primary aim was to examine the risk of new CV events within 5 years after TIA. Our secondary aim was to evaluate predictors of long-term CV events after TIA, including inflammatory biomarkers.

2. Methods

2.1. Study Design and Study Population. A detailed description of our prospective cohort study, MIDNOR TIA, has been given previously [15]. In brief, this is a multicenter study where all eight hospitals in the region of Central Norway recruited patients between 2012 and 2014. Patients eligible for enrollment had a TIA within the previous 14 days. We used the TIA diagnosis based on the World Health Organization criteria [28], which defines a TIA as an acute loss of focal cerebral or ocular function lasting less than 24 hours, without an apparent nonvascular cause. TIA patients were residents of Central Norway, aged 18 to 90 years, and living at home with a modified Rankin scale of ≤3. Most patients were hospitalized after their acute event and recruited during their short stay in the stroke unit. All patients underwent a standardized diagnostic work-up containing as a minimum a thorough patient history, a physical examination, brain diffusion-weighted imaging MR (DWI-MR) or CT, carotid Doppler ultrasound or CT angiography, blood test, and ECG. Patients were treated according to current guidelines for TIA [29].

2.2. Biochemical Analyses. In all 577 TIA patients, blood tests, including lipid status and HbA1c, were taken. In 112 of the patients, additional serum and plasma samples were collected and stored in a regional biobank. All patients were eligible for biobanking, but the capacity and staff in the investigating stroke unit put a restriction on the number of tests. All samples were taken in the acute phase, during the first 1-2 days after the qualifying TIA. Samples were analyzed for inflammatory biomarkers at Oslo University Hospital, Rikshospitalet. The *a priori* specified biomarkers were CD40L (cluster of differentiation 40 ligand), reflecting platelet-mediated inflammation; CRP (C-reactive protein), a reliable marker of systemic inflammation; VWF (von Willebrand factor), a marker of endothelial cell activation; TGFβ1 (transforming growth factor-beta 1), a marker related to extracellular matrix remodeling; TCC (terminal complement complex), a marker of complement activation; IL-6, IL-8, and IL-10 (interleukins); MCP-1 (monocyte chemoattractant protein 1); TNF-α (tumor necrosis factor-alpha); and IL-1 RA (IL-1 receptor antagonist), all reflecting activation of prototypical inflammatory cytokines and chemokines, and IL-10, a prototypical anti-inflammatory cytokine. In addition to their relevant properties, the panel of biomarkers was chosen based on evidence of potential prognostic value from previous studies [30–32].

Plasma levels of IL-6, IL-8, MCP-1, TNF, IL-1 RA, and IL-10 were analyzed on a multiplex platform (Bio-Plex Human Cytokine Panel; Bio-Rad Laboratories Inc., Hercules, CA, USA). Plasma CD40L, CRP, and TGFβ1 were analyzed with matched antibodies from R&D systems (Stillwater, MN, USA), while VWF was analyzed using antibodies from Dako Cytomation (Agilent, MN, USA) in a 384 format using a combination of a SELMA (Jena, Germany) pipetting robot and a BioTek (Winooski, VT, USA) dispenser/washer. Absorption was read at 450 nm with wavelength correction set to 540 nm using an ELISA plate reader (Bio-Rad, Hercules, CA, USA). Intra- and interassay coefficients of variation were <10% for all EIAs.

2.3. Outcomes, Definitions, and Ethical Approval. The primary composite outcome was the cumulative post-TIA risk of stroke, acute coronary syndrome (ACS), and CV death. The secondary outcome was baseline predictors of long-term CV events and in a subgroup analysis assessment of any association between prespecified blood inflammatory biomarkers and CV events. In the present 5-year follow-up, data on subsequent strokes, ACS, CV death, and all-cause mortality were retrieved from the Norwegian Cardiovascular Disease Registry, with the associated Norwegian Stroke Registry and Norwegian Myocardial Infarction Registry. We used the WHO criteria for stroke [33]. The definition of death from cardiovascular causes was based on the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) and included fatal ischemic, hemorrhagic or unspecified strokes, acute coronary syndrome, heart failure, cardiac arrest, pulmonary embolism, deep venous thrombosis, and aortic disease.

The study was approved (REC no. 2012/1224; REC no. 28560) by the Regional Committee of Medical and Health Research Ethics of Møre og Romsdal and Trøndelag, Norway (REC Central, Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology). All the

subjects gave written informed consent before inclusion in the original 1-year follow-up study. Permission to use data from the Norwegian Cardiovascular Disease Registry was granted by the Norwegian Institute of Public Health, which is the data controller for these registries.

2.4. Statistical Analysis. Baseline characteristics are given in means with standard deviations (SD) or as numbers and percentages as appropriate. The long-term cumulative incidence of the composite outcome consisting of stroke, ACS, and CV death was estimated by the Kaplan-Meier plots. The log rank test was used to assess for statistical differences in event-free survival for the presence or absence of baseline risk factors. In the composite outcome, if more than one event occurred, the event occurring closest in time to the index TIA was used, and all causes of death other than by stroke and other cardiovascular events were treated as censoring events. Events that occurred after the 5-year follow-up period were not included in the analyses. Predictors of outcome events were assessed using univariable and multivariable Cox proportional hazard regression analysis. All variables assessed to be of clinical relevance were included in the multivariable analysis, regardless of significance value.

In the subgroup analysis of serum biomarkers, a Cox proportional hazard regression analysis (adjusted for age) was used to calculate hazard ratios (HR) and 95% CI per unit increase in biomarker for the dependent binomial outcomes of recurrent stroke and the composite outcome of stroke, ACS, and CV death. To reduce the level of confounding, all patients with CRP above 10 mg/L were analyzed for comorbidities involving increased immune response. On this basis, six patients were excluded from the final analysis (two because of ongoing urinary tract infections, one because of ongoing vasculitis, one because of active seronegative rheumatoid arthritis, one with newly diagnosed esophageal cancer, and one because of recent orthopedic surgery). In the few cases where the biomarker results were below detection values, we imputed random values between 0 and the lower detection number.

All analyses were carried out using IBM SPSS Statistics (version 25).

3. Results

Our prospective study included 577 patients of which 467 (82.5%) experienced their first ever TIA. Table 1 summarizes the baseline characteristics of all patients, divided into those who had and those who did not have a CV event during follow-up. Mean (SD) age was 71.5 years (11.0), and 56.7% were male. A high-risk ABCD2 score (4-7) was registered in 371 patients (64.3%). Extracranial imaging (carotid ultrasound and/or CT angiography) was performed in 520 patients, and 48 (9.2%) had a symptomatic >50% carotid stenosis. A DWI-MR was performed in 361 patients, and 26.9% (97/361) of these showed acute infarction. CT scan was performed in 564 patients, of which 2.3% (13/564) showed an acute infarction. All patients had either MRI or CT, or both, performed.

Most patients (85.4%) were examined by a stroke specialist within 24 hours from TIA. Median time from onset until stroke specialist assessment was 3.8 hours (interquartile range, 0.8-6.8 hours). Only 27 patients (4.7%) were evaluated at the outpatient clinic. Median length of hospital stay was 2 days. All investigations, including additional blood sampling for inflammatory biomarkers, were done during this time.

3.1. CV Events. The primary composite outcome occurred in 108 patients (18.7%), where 47 of the events (43.5%) occurred during the first year (Table 2). The cumulative rate of stroke was 12.0% ($n = 69$), of which 84% ($n = 57$) were ischemic strokes. The rate of stroke was 5.4% during the first year and 6.6% after the first year through the fifth year. In total, 30 patients (5.2%) had an acute coronary event, and 35 patients (6.1%) had a fatal CV event. Multiple CV events were registered in 25 patients.

All-cause mortality was 15.1% (87 patients), meaning that 52 patients (52/87–59.8%) died from non-CV causes. Of these, 25 patients died from cancer, 15 from infections, 5 from complications to dementia, 4 from unspecified accidents, 1 from kidney failure, and 1 from liver cirrhosis.

The clinical predictors of the primary composite outcome in multivariable analyses were increasing age (HR 1.05; 95% CI, 1.03 to 1.08), male sex (HR 1.82; 95% CI, 1.16 to 2.85), hypertension (HR 1.67; 95% CI, 1.04 to 2.67), and acute infarction on brain imaging (HR 1.84; 95% CI, 1.17 to 2.91) (Figure 1 and Table 3).

The discrimination value of the aforementioned ABCD2 score for predicting subsequent strokes after TIA within 5 years is shown in Figure 2. The low-risk group showed a higher probability of stroke-free survival than the high-risk group, although the difference was not statistically significant ($p = 0.055$ at 5 years, log rank test). The area under the curve (AUC) of a receiver operating characteristic analysis was 0.59 (95%CI = 0.52 to 0.66) at 5 years.

3.2. Inflammatory Biomarkers. In the subgroup of 112 patients analyzed for inflammatory biomarkers, the composite outcome occurred in 27 patients (24.1%) of which 20 of them (17.9%) had a stroke. None of the tested inflammatory biomarkers at baseline were associated with the composite outcome or stroke (see Table 4). Furthermore, there was no association between biomarker levels and the presence or absence of potential high-risk baseline clinical characteristics (acute infarction on MRI, >50% carotid stenosis, ABCD2 score 4-7) (results not shown).

4. Discussion

Our primary aim was to examine the long-term rates of CV events (i.e., stroke, ACS, and CV mortality) in a prospective cohort of 577 patients with 5-year follow-up, where almost nine out of ten patients had been assessed within 24 hours of their index TIA. The cumulative incidence of total CV event and stroke was 18.7% and 12.0%, respectively, giving an average annual risk of 3.7% and 2.4%, respectively. Approximately half of the CV events as well as strokes

Table 1: Baseline clinical characteristics and results from main investigations for the subjects with vascular events (composite outcome of stroke, acute coronary syndrome, or cardiovascular death) and no vascular events, *n* (%) or mean (SD).

Variable	Vascular event (*n* = 108)	No vascular event (*n* = 469)
Male	72 (66.7)	255 (54.4)
Age in years, mean (SD)	75.0 (8.5)	69.5 (11.3)
Medical history		
Former ischemic stroke	25 (23.1)	62 (13.2)
Former TIA	28 (25.9)	73 (15.6)
Former myocardial infarction	23 (21.3)	44 (9.4)
Diabetes mellitus	13 (12.0)	53 (11.3)
Hypertension[†]	70 (64.8)	213 (45.4)
Hypercholesterolemia[‡]	51 (47.2)	163 (34.8)
Current smoker	16 (14.8)	78 (16.6)
Investigations		
Extracranial imaging	98 (90.7)	422 (90)
>50% stenosis or occlusion	16/98 (16.3)	36/422 (8.5)
Either brain CT or DWI-MR	108 (100)	469 (100)
Acute infarction	28 (25.9)	75/469 (16.0)
ECG and/or 24-h Holter ECG	108 (100)	469 (100)
Newly diagnosed and known atrial fibrillation	22/108 (20.4)	57/469 (12.2)
ABCD2 score high risk (4-7)	81 (75)	290 (61.8)

[†]Using blood pressure-lowering medication. [‡]Using lipid-lowering medication.

occurred during the first year after TIA. Furthermore, beyond one year after TIA, the annual rate of CV events and stroke remained relatively low but constant.

Our 5-year CV event rates are similar to those reported in comparable large post-TIA risk studies, which show relatively highest risk of subsequent strokes and other CV events during the first year, and then constant annual event rates not diminishing over time [7, 8, 16, 34–36], and even increasing towards 10-15 years after TIA [36]. In contrast, the stroke rate trends in the short-term period after TIA (1 year) have been shown to decrease during the last decades. In a retrospective cohort study of prospectively collected data in the Framingham Heart Study, following 14059 patients from 1948 until 2017, the risk of stroke after TIA was significantly lower in the most recent epoch from 2000 until 2017 compared with the earliest period [35] [5, 12]. The importance of rapid evaluation and treatment of TIA patients has been emphasized by several studies. Most likely, the lower stroke recurrences after TIA through the last two decades can be attributed to improved urgent treatment and secondary prevention strategies [13].

Table 2: Cumulative event rates within 5 years of TIA.

Outcome	Patients No.	%
Primary composite outcome	108/577[†]	18.7
Stroke	69/577 (67 occurring as the first event)[†]	12.0
Fatal	11/69	15.9
Nonfatal	58/69	84.1
Acute coronary syndrome	30/577 (27 occurring as the first event)[†]	5.2
Fatal	3/30	10
Nonfatal	27/30	90
Cardiovascular death	35/577 (14 occurring as the first event)[†]	6.1
All-cause death	87/577	15.1
Noncardiovascular death	52/577	9.0

[†]In the primary composite outcome, a patient could have no more than one outcome event, whichever occurred first. Some patients had multiple events; 20 patients had either a stroke or acute coronary syndrome before dying from cardiovascular causes, 4 patients had both stroke and acute coronary syndrome, and one patient had stroke and acute coronary syndrome and died due to cardiovascular disease.

As demonstrated in multivariable analyses, patients with new CV events were likely to be older males with hypertension and acute infarction on brain imaging. Age was a strong predictor of CV events and CV death with a 5% increase in outcome risk for each year. There is strong evidence for an association between undertreated hypertension and CV events including stroke [35], and the association seems to persist in contemporary TIA cohorts. Although we did not control the patients' blood pressure in the follow-up period and therefore cannot strictly conclude, the results support the importance of blood pressure as an important risk factor for subsequent stroke in TIA patients and the need for ambitious monitoring and treatment of blood pressure.

There is conflicting evidence regarding the predictive ability of DWI positives for stroke recurrence in the long-term evaluation [16, 37]. In our study, DWI was performed in two-thirds of the patients, and almost all recognized acute infarctions on brain imaging were found on this modality. A positive DWI predicted both the composite outcome and stroke separately. Importantly, a positive DWI was predictive of subsequent stroke, not only at one year but also for strokes occurring during the entire period until 5 years. It is reasonable to conclude that an acute ischemic lesion after TIA should be regarded as a clinical important event comparable with acute MI and stroke.

Lower risk of major vascular events after TIA in women than in men has been shown in other studies [38]. In our study, there were small differences in proportions of stroke outcomes and CV deaths in women and men, but women had fewer acute coronary events. 14.4% of women, versus 22.0% of men, had at least one CV event during follow-up, which may explain why male sex was a significant predictor of the composite outcome event. An explanation for the increased risk of CV events in males might be that more

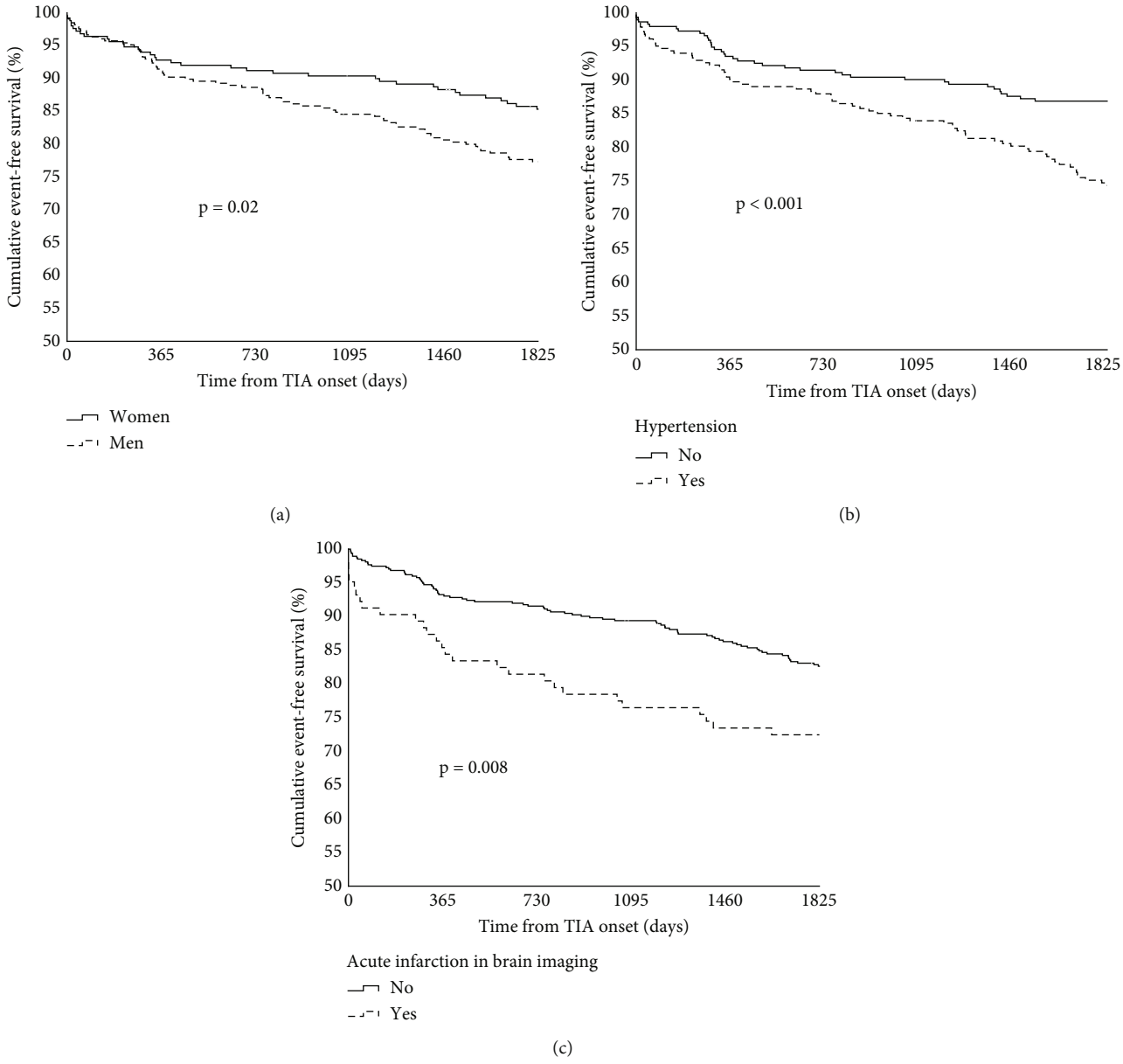

FIGURE 1: Kaplan-Meier plots of patients surviving free from the composite endpoint stroke, acute coronary syndrome, or cardiovascular death stratified by (a) sex, (b) hypertension, and (c) acute infarction on brain imaging (MRI and CT). Log rank test for differences between groups.

TIA events in women were due to nonischemic transient neurological events like migraine. This is supported by the finding that a higher proportion of men had positive DWI (22.3% vs. 12.0% in women).

Diabetes mellitus is established as an important risk factor for CV disease, but the reason for not predicting vascular events may be the fact that the proportion of diabetes patients in our cohort was rather low and that those who had diabetes were relatively well treated at the time of their TIA (median HbA1c 7.2 mmol/L, SD ± 1.3). Similar explanations can probably be used for atrial fibrillation and carotid stenosis. Nearly all patients with atrial fibrillation were on anticoagulation therapy at discharge. Over half of the patients with significant carotid stenosis underwent carotid endarterectomy within 2 weeks of their TIA. Additionally, nearly 9 of 10 of all patients were on lipid-lowering medication at discharge and nearly all patients received antithrombotic medication, either antiplatelet treatment or anticoagulation, with a potential to stabilize a carotid stenosis.

The ABCD2 score was not developed for long-term prediction of stroke after TIA. Nevertheless, we showed that the low-risk group had a higher probability of stroke-free survival than the high-risk group, which may partly be explained by the score's potential diagnostic value in differing between real TIA's and mimics, and that it involves important risk factors like hypertension and age. The AUC value for the score was however low.

Table 3: The association between baseline risk factors and the composite outcome of stroke, acute coronary syndrome, or cardiovascular death within 5 years after TIA.

Variable[†]	Univariable			Multivariable		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Age	1.05	1.03 to 1.07	<0.001	1.05	1.03 to 1.08	<0.001
Male	1.60	1.08 to 2.39	0.021	1.82	1.16 to 2.85	0.009
Former ischemic stroke	1.75	1.12 to 2.73	0.015	1.53	0.90 to 2.59	0.12
Former TIA	1.77	1.15 to 2.72	0.010	1.17	0.70 to 1.93	0.55
Former AMI	2.33	1.47 to 3.69	<0.001	1.58	0.91 to 2.74	0.10
Diabetes mellitus	1.11	0.62 to 1.98	0.73	0.98	0.53 to 1.80	0.95
Hypertension[‡]	2.04	1.38 to 3.03	<0.001	1.67	1.04 to 2.67	0.034
Hypercholesterolemia[§]	1.56	1.07 to 2.27	0.22	0.82	0.53 to 1.29	0.40
Atrial fibrillation	1.80	1.12 to 2.87	0.014	1.25	0.74 to 2.13	0.41
Present or former smoking	0.88	0.52 to 1.50	0.64	1.13	0.62 to 2.07	0.69
Acute ischemia on MRI or CT	1.77	1.15 to 2.72	0.009	1.84	1.17 to 2.91	0.009
Carotid stenosis > 50%	1.82	1.07 to 3.11	0.028	1.10	0.61 to 1.96	0.76

[†]Risk factors present versus absent. [‡]Using blood pressure-lowering medication. [§]Using lipid-lowering medication. HR = hazard ratio from Cox regression analysis; AMI = acute myocardial infarction.

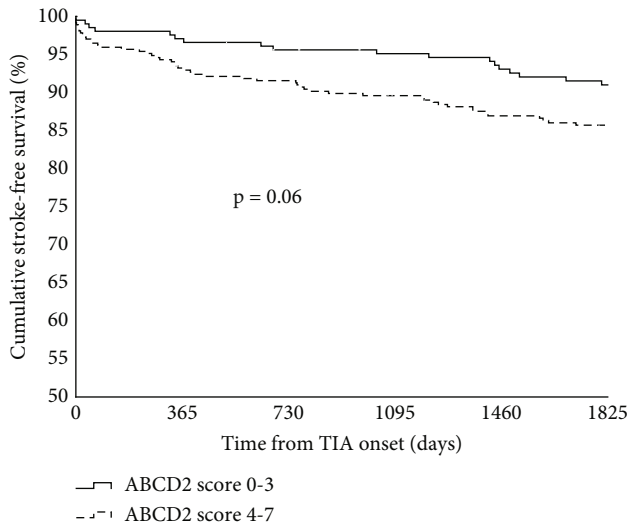

Figure 2: Kaplan-Meier plots of patients surviving free from stroke from time of presenting TIA within 5 years stratified according to ABCD2 scores 0-3 and 4-7. Log rank test for differences between groups.

In a subgroup analysis, we wanted to investigate whether inflammatory biomarkers could predict subsequent stroke, ACS, and CV death within 5 years after TIA. Of the twelve inflammatory biomarkers tested in the Cox proportional hazard regression analyses, no associations between neither the primary composite outcome nor stroke were revealed. Neither were there any associations between the inflammatory markers and the presence of previous CV events (other than TIA) at baseline, a high ABCD2 risk score of 4-7, a positive DWI-MR scan, and/or carotid stenosis. Inflammatory markers have been associated with a poor functional outcome and clinical complications after stroke and a marker of a poor prognosis after CV events in general [30, 31, 39]. However, there are considerable methodological variations between studies [26], and there is conflicting evidence of their prognostic usefulness and incremental value over established prognostic markers. Analyses of inflammatory markers in the acute phase of TIA may be problematic. It is not clear if their prognostic value is during the acute phase (usually considered as the first two days) or in the stable phase after TIA. Even if TIA is a clinical event, it may be too small to trigger an enhanced inflammatory response, and some TIAs may not be true cerebrovascular ischemic events but rather caused by other neurological conditions or represent TIA mimics. Nonetheless, our findings do not support the use of inflammatory biomarkers in the risk assessment following TIA.

The strength of our post-TIA risk study lies in the prospective and multicenter design, involving all hospitals in our region. All participating hospitals adhered to the current guidelines for management of TIA patients. Trained study nurses at each center prospectively registered data using standardized web-based case report forms, and there were no missing data regarding baseline clinical characteristics.

Our study has some limitations. It is inevitable that some enrolled patients might have had a nonischemic transient episode, or "TIA mimic." Upon starting enrollment, we sent a brochure to all the general practitioners and other referring physicians in the region, informing about the study in general and specifying the most typical symptoms of a TIA. Also, inclusion was performed by trained stroke physicians working in stroke units with several years of experience with TIA and stroke, and the baseline risk profile of the cohort was similar to other TIA studies [13]. Second, using health registries for identification of outcome events might have led to underreporting, since patients enrolled in the registries are hospitalized. However, most patients with CV events are hospitalized, and the Norwegian Cardiovascular Disease Registry is well functioning with coverage above 90%. Third, in the follow-up period, we did not collect any

Table 4: Univariable (adjusted only for age) Cox proportional hazard regression for associations between serum biomarkers and stroke and the composite outcome of stroke, acute coronary syndrome, or cardiovascular death within 5 years after TIA.

Biomarker	Stroke			Composite outcome		
	HR[†]	95% CI	*p*	HR[†]	95% CI	*p*
CD40	1.04	0.74 to 1.45	0.82	0.95	0.66 to 1.37	0.78
IL-1 RA	0.09	0.001 to 6.29	0.26	0.53	0.05 to 6.35	0.62
CRP	0.99	0.92 to 1.07	0.76	0.99	0.92 to 1.05	0.66
VWF	0.58	0.14 to 2.38	0.45	0.72	0.22 to 2.34	0.59
TGF-β1	0.94	0.85 to 1.04	0.21	0.92	0.85 to 1.01	0.07
TCC	0.90	0.36 to 2.29	0.83	0.83	0.35 to 1.95	0.66
IL-1β	1.09	0.30 to 4.00	0.89	1.96	0.77 to 5.00	0.16
IL-6	0.86	0.62 to 1.18	0.34	1.03	0.85 to 1.26	0.75
IL-8	0.92	0.82 to 1.05	0.21	1.02	0.96 to 1.08	0.59
IL-10	0.73	0.50 to 1.07	0.11	1.02	0.89 to 1.16	0.81
MCP	0.99	0.94 to 1.04	0.67	1.01	0.97 to 1.06	0,58
TNF-α	0.97	0.93 to 1.02	0.27	1.00	0.98 to 1.01	0.48

[†]Outcome event occurring versus not occurring. OR = odds ratio; CD40 = cluster of differentiation 40; IL-1 RA = interleukin-1 receptor antagonist; CRP = C-reactive protein; VWF = von Willebrand factor; TGFβ1 = transforming growth factor-beta 1; TCC = terminal complement complex; IL- = interleukin-; MCP = monocyte chemoattractant protein; TNF-α = tumor necrosis factor-alpha.

information on possible changes in risk exposure, for instance, adherence to or change in prophylactic medications. Nor did we have any data on long-term treatment effects of, for instance, blood pressure-lowering and lipid-lowering medications. The low association between classical risk factors as diabetes, atrial fibrillation, and hypercholesterolemia and CV events might however imply that patients with these conditions were well treated during the follow-up period. Finally, as in many other studies hampered by small sample size, the number of patients that were included in the biomarker substudy was rather low. The capacity and staff in the recruiting stroke units put a restriction on the number of tests that were taken, especially in the smaller hospitals involved. It is uncertain if this could have biased the biomarker results. However, baseline demographic and vascular risk factor data of the sampled patients were very similar to that of the entire cohort. Still, any firm conclusion will need larger study populations.

In conclusion, the risk of major vascular events, and especially stroke, was highest in the first year after TIA. The findings emphasize that TIA is a vascular event with potential serious short-term recurrent vascular events. Even though the risk of cardiovascular events was lower during the next years, and the general long-term prognosis for TIA patients seems to be quite good, the risk remained steady over the next years. These findings highlight the importance of both early initiation of and long-term continuation of secondary preventive treatment after TIA. The all over favorable prognosis in our study population might indicate that both the acute treatment and the follow-up have been of high quality. There was no association between levels of blood inflammatory biomarkers taken in the acute phase and CV events within 5 years. Inflammatory biomarkers may not be important as prognostic markers of CV disease in TIA patients.

Data Availability

Deposition of patient-level data in a public repository was not specified in the study protocol, which was approved by the ethics committee before the study began. Patient-level data will be available on request, provided that the Regional Ethics Committee gives approval.

Disclosure

A part of this manuscript, including the title, authors, and their affiliations, has previously been published in the doctoral thesis of the corresponding author [40]. The funders had no role in study design, data collection and analysis, or preparation of the manuscript.

Conflicts of Interest

The authors report no competing interests.

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