Long-term cardiovascular prognosis after Transient Ischemic Attack. Associated predictors.

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ABSTRACT

Objective: The aim of our study was to determine long-term cardiovascular risk after transient ischemic attack (TIA) and to identify the factors associated with increased risk.

Methods: Prospective observational registry of TIA patients admitted to the emergency room of our tertiary stroke center from June 2006 to January 2016. New vascular events (NVEs) were recorded from 3 months after TIA onset until June 2017, including both stroke and non-stroke events (coronary and peripheral disease). We registered TIA etiology, age, sex, vascular risk factors, radiological data, and clinical TIA features and analyzed these variables in relation to NVE long-term risk.

Results: In total, 676 patients aged 71.7±13.7 years were included, with a mean follow-up of 48.8±32.7 months. A NVE was detected in 173 patients (25.6%), without significant differences between event types (p=0.84). Univariate analysis associated NVEs with etiologic subgroup, male sex, diabetes, hypertension, previous vascular disease, duration and clinical features of TIA, and signs of acute infarction. Multivariable analysis showed an independent association of NVEs with etiologic TIA subgroup, signs of acute infarction, and duration of TIA symptoms. Large-artery atherosclerosis and cardioaortic embolism had the highest NVE risk, with a slightly higher percentage of non-stroke events. The small-artery disease subgroup had the lowest NVE risk, with a higher percentage of stroke events.

Conclusions: Etiology subgroup was the main factor determining high long-term risk of vascular events in TIA patients. Large-artery atherosclerosis carried the highest vascular risk, both non-stroke and stroke, followed by cardioaortic embolism.

Introduction

In recent years, early recurrence after TIA has decreased from up to 20% to 3.7%, due to the implementation of secondary stroke prevention efforts, such as immediate initiation of antiplatelet drugs or urgent revascularization.[1] Moreover the use of clinical scores (mainly ABCD, ABCD2 and ABCD 3-i)[2-4] have improved the stratification of early TIA recurrence (within 3 months). Although this risk is now well studied, the long-term vascular stroke risk in stable patients with a TIA is not well described.

The aim of the present study was to determine the long-term risk of developing a stroke or non-stroke vascular event beyond the first 3 months post-TIA and to identify the factors associated with an increased risk.

Materials and Methods

Participants

Hospital del Mar is a tertiary stroke center with an on-call neurologist and a stroke unit, as well as capabilities for systemic thrombolysis and neurovascular interventions. It is the only hospital in its catchment area, which comprises the 330,000 inhabitants of 3 of the 10 city districts of Barcelona that can provide urgent imaging studies in patients with TIA as recommended. A prospective observational registry was designed, including all patients with TIA evaluated in the emergency room of our center from January 2006 to January 2016. TIA was defined according to the World Health Organization (WHO) criteria as rapidly developing clinical symptoms and/or signs of focal loss of cerebral function with reversal symptoms within 24 hours (classical criteria)[5] with no apparent cause other than of vascular origin.[6]

All patients with suspect acute neurological symptoms were directly evaluated by a neurologist trained in vascular pathologies, who determined the nature of the symptoms and made the final diagnosis. If patients had fully recovered from symptoms upon arrival to hospital, they or their family members or other caregivers were interviewed to determine the precise neurological symptoms and their duration. Patients with doubtful symptoms, alternative non-vascular origin of symptoms, or a final diagnosis of TIA mimic (n=23) were not included in this study. Other exclusion criteria were residence outside the hospital catchment area, due to the difficulty of long-term follow-up (n=26), and absence of informed consent to participate (n=3). The hospital follows patient care methods and secondary prevention measures according to current European and American guidelines.[7]

Endpoint

The methodology has been described in depth by a previous study.[8] The study endpoint was presentation with a first new vascular event (NVE) more than 3 months after TIA onset, defined according to the Reduction of Atherothrombosis for Continued Health Registry (REACH) study criteria: vascular death, nonfatal stroke, nonfatal myocardial infarction, or hospitalization due to an atherothrombotic event, including vascular interventions.[9] We did not include in this analysis early recurrences (96 patients, 95.8% with stroke) and/or interventions that occurred within 3 months of TIA onset, as the present study focused on long-term risk in stable patients. Of 683 patients with TIA, 7 patients were excluded due to death (n=5) or loss of contact (n=2) within first 3 months of follow-up (**Supplementary figure e-I: Flow-chart**).

Follow-up consisted of a clinic visit with a vascular-trained neurologist at 3 months post-TIA (start of follow-up) and then, at the physician's discretion, a clinic

appointment and/or telephone contact every 3-6 months thereafter. Follow-up lasted until study conclusion (1 June 2017); we reviewed all patient events, death records, and electronic medical records, hospital admissions records, and consulted the primary care physician before considering patients lost to follow-up. For all NVEs, we compiled from medical records all tests, procedures, and events certified by a neurologist, cardiologist, or vascular surgeon (in case of cardiac or peripheral events). A member of our research team confirmed every event, contacting the attending doctor when necessary.

Measures

A structured questionnaire was used to record the following variables, defined according to REACH criteria: age, sex, vascular risk factors (hypertension, diabetes mellitus, hyperlipidemia, current smoking habit), and previous vascular disease, including documented coronary artery disease (CAD) and peripheral artery disease (PAD). A vascular neurologist determined the TIA etiology subgroup at the 3-month follow-up visit, after evaluating all available test results. For each patient, we assigned TIA subtype according to the Stop Stroke Study Trial of Org 10172 in Acute Stroke Treatment (SSS-TOAST, an evidence-based causative classification system for ischemic stroke):[10] large-artery atherosclerosis (LAA), small-artery disease, cardioaortic embolism (CE), undetermined causes (unclassified strokes, more than one apparent mechanism) and other (infrequent) causes. We applied the small-artery disease classification to patients with no evidence of atherothrombotic or cardioembolic TIA who reported classical lacunar syndrome (pure motor, pure sensory, and sensorimotor syndrome involving at least 2 of 3 specific body parts (face, arm, and leg) and ataxic hemiparesis or dysarthria-clumsy hand syndrome.[11]

We analyzed clinical variables extracted from ABCD2[2] score criteria, with a total score of 7 points: speech impairment without weakness - 1 point, weakness - 2 points; duration of symptoms 10 to 59 minutes - 1 point, ≥60 minutes - 2 points; age ≥60 years, 1 point; initial hypertension >140 mmHg (systolic) and/or ≥90 mmHg (diastolic), 1 point; and diabetes mellitus (DM), 1 point. We also registered previous TIA, defined as a TIA in the 7 days preceding the index TIA. Emergency room protocols determined the presence of acute infarction by computer tomography in all patients, as shown by signs of acute ischemic changes in radiological studies, but images for 24 patients were not available for analysis. About half of the population (52.8%, n=357) also had magnetic resonance studies. A trained radiologist with access to clinical information but blinded to patient outcomes analyzed all images.

Standard protocol approvals, registrations, and patient consent

The local ethics committee approved the TIA registry. We obtained written informed consent from all participants or their designated representative.

Statistical analysis

Assuming 10% losses to follow-up and accepting an alpha risk=0.05 and a beta risk<0.05 in a two-sided contrast, the study required a sample size of 96 patients with recurrence and 480 controls to detect a minimum relative risk of 2 with a recurrence rate of 0.2 in the control group. We present data as frequencies and percentages.

We used Kaplan-Meier log rank to perform univariate survival analysis for a NVE and describe variables. We calculated the relative average rate (NVEs per patient-year) as the number of events found during follow-up, divided by the number of years at-risk patients were followed up. ABCD2 risk score was stratified using well-validated reference values: high (6-7 points), medium (4-5 points), and low risk (0-3 points).

Reference subgroups were those with duration of symptoms <10 minutes, a low ABCD2 score (0-3) and the TIA subtype with the lowest percentage of events (lacunar TIA). We used Cox regression survival analysis to estimate multivariate hazard ratio (HR) with 95% confidence interval (CI) for a NVE. We adjusted all multivariate models by those variables that achieved significance in univariate analysis and considered two-sided p-values <0.05 as significant.

Results

A total of 676 patients completed the follow-up to June 2017; 116 cases were censored: 20 discharged home outside the hospital area, 5 lost for unknown reasons, and 91 deaths due to nonvascular causes (**Supplementary figure e-1**). A NVE was detected in 173 patients (25.6%); 40 patients had a NVE within the first year (5.9%) of follow-up (**Figure 1**). Mean follow-up was 48.8±32.7 months, but differed significantly (p<0.001) between patients with no event (55.2±32.9 months) and those with a NVE (30.5±24.2 months).

Types of NVE and etiological subgroups

Event distribution by type (stroke vs non-stroke; p=0.84) was non-significant (p=0.072): **1)** vascular deaths, n=37 (5.5% of the patient cohort), 10 due to fatal stroke disease (4 hemorrhagic), 2 to fatal myocardial infarction, and 18 to other cardiovascular deaths, as defined by REACH (3 other cardiac origin, 3 vascular or limb infarction origin, and 12 sudden death or death without definite nonvascular cause; **2)** non-fatal strokes, n=60 (8.9%), 2 hemorrhagic; **3)** non-fatal myocardial infarction, n=21 (3.1%); **4)** hospitalizations for atherothrombotic events or vascular interventions, n=55 (5.3%), 18 TIA, 14 CAD, and 12 PAD. Of these 173 patients, 93 (13.8%) had cerebrovascular events (fatal stroke, non-fatal stroke) and were hospitalized.

Baseline characteristics and predictors of NVE

The mean age was 71.7±13.7 years, and was not related to NVE (p=0.323). Other baseline characteristics and relationship to NVE in univariate analysis (sex, vascular risk factors, and previous vascular events) are described in **Table 1**. We found associations between NVE and male sex, arterial hypertension, diabetes mellitus, and previous vascular disease. **Table 2** shows the relationship between etiological subgroup of TIA and NVE occurrence. The small-artery disease subgroup had the lowest NVE risk but a greater percentage of stroke events, while LAA and CE had the highest NVE risk, with a slightly higher percentage of non-stroke events. **Table 3** shows univariate analysis of NVE related to clinical and radiological data. We found associations between NVE risk and duration of symptoms, clinical features, and signs of acute infarction. Multivariate Cox analysis showed independent associations of NVE risk with etiological subgroups, signs of acute infarction, and duration of symptoms **(Table 4)**. ABCD2 risk score was associated with NVE in univariate analysis as follows: moderate risk, HR=1.5 (95%CI:1-2.26) and high risk, HR=2.46 (95%CI:1.54-3.93) (**Figure e-2)**. Finally, multivariate analysis (adjusted by previous factors) found an independent association only with a high ABCD2 risk score, HR=1.89 (95%CI:1.08-3.31).

Discussion

To our knowledge, this TIA registry offers the longest follow-up, with cerebrovascular and non-cerebrovascular events identified and evaluated by neurologists, that is currently available for analysis. Our results showed that the risk of cardiovascular complications in these patients is high, based on the Framingham study's cut-off for high coronary risk (≥20% after 10 years).[12] Regarding the number of NVEs within 1 year of follow-up, our results agree with previous studies in our population[13] and with a

more recent multicenter study with a cohort of 4789 patients that showed a cardiovascular risk of 6.2% at 1-year follow-up.[1] In our study, protocols were similar: urgent management in specialized units, immediate implementation of imaging studies, and rapid treatment with stroke-prevention strategies.

Most studies evaluating vascular risk after TIA have focused on early recurrence; very few, with a limited number of patients, have studied the long-term vascular risk after TIA.[14–17] Heterogeneous data have been reported, depending on study design and TIA etiologies.[14–17] Few studies have included non-cerebrovascular events in their patient follow-up and no factors that stratify long-term risk of vascular events in these patients have been described.[18] A 2009 study of TIA and stroke shows a higher acute risk of stroke recurrence, decreasing over a 10-year maximum follow-up, whereas the risk of coronary events remains constant.[19] Our observations regarding NVE risk after TIA are at the lower end of the range described by previous studies (17.4%-41.3%) at 4 or 5 years. In our data, cumulative NVE risk remained constant over the follow-up period, with similar trends for stroke and non-stroke events beyond 3 months post-TIA.

The strongest relationship in our series was with stroke subtype. We applied the recently described SSS-TOAST classification, and found that patients with LAA, CE, and undetermined subtype had a higher vascular risk than those with small-vessel disease etiology, with the highest HR found in the LAA subgroup. The relationship between TIA subtype, the early risk of recurrence after TIA,[1,20] and NVE after stroke[8] has been previously described. In our study, LAA TIA were the main established predictor of subsequent stroke in long-term follow-up after TIA despite preventive treatments.[4,21] Our results underline the importance of developing new preventive strategies to lower the long-term vascular risk in these high-risk patients. Moreover, we

would emphasize the importance of completing a vascular study and correctly classifying the stroke etiology, given the prognostic implications of the etiological subtype. The subgroup of patients with small-artery disease had a higher percentage of stroke than non-stroke events, while patients in the CE and LAA subgroups had very similar risk, but a higher percentage of non-stroke events. This finding distinguishes patients with small-artery disease from all other TIA etiologies, as many of them have no atherosclerosis or related cardiopathologies and cardiovascular recurrences are related to the cerebral small-artery pathology itself. Previous studies describe an increased risk of stroke recurrence in patients with longer duration of symptoms, presence of specific clinical features, previous vascular cerebral pathology, infarctions on neuroimaging, and several vascular risk factors.[1,13,16,22] Furthermore, we detected a univariate relationship between several of these factors and NVE risk; however, only duration of symptoms and signs of acute infarction remained independently associated with NVE.

Although risk scores were originally designed to predict short-term recurrence after TIA, few studies have reported the predictive value of the ABCD2 score for long-term stroke recurrence after TIA.[16,23] Thus, only one study, in a small cohort, has described the capacity of ABCD2 to predict the risk of NVE (both cerebrovascular and non-cerebrovascular).[16] Our study showed that the punctuation of ABCD2 score stratified in: high (6-7 points), medium (4-5 points), and low risk (0-3 points) is useful to identify NVE risk after TIA in long-term follow-up, although the reason why it is able to predict the risk of non-cerebrovascular events remains elusive. Moreover, in the analysis of NVE risk related to the individual component of the ABCD2 score, we found that only

the duration of symptoms was independently associated with a NVE; classical cardiovascular risk factors such as hypertension or diabetes were not.

Our study has several limitations. Participants were recruited from emergency room patients at a single urban hospital, and therefore may have characteristics that are not representative of other populations. The patients were relatively older and had high non-cerebrovascular mortality over the course of a prolonged follow-up. Resonance imaging, which has greater sensitivity to assess acute infarction than computed tomography, was only available for half of the patients. Nonetheless, the detection of acute infarction was independently associated with NVEs in our series. This underlines the known importance of detecting acute ischemic lesions in patients to identify early recurrence risk and extends it to longer-term follow-up.

Our results suggest that etiology subgroup was the main factor determining high long-term risk of vascular events in TIA patients. Large-artery atherosclerosis carried the highest vascular risk, both non-stroke and stroke events, followed by cardioaortic embolism.

REFERENCES

1. Amarenco P, Lavallée PC, Labreuche J, et al. One-Year Risk of Stroke after Transient Ischemic Attack or Minor Stroke. The New England journal of medicine. 2016;374:1533–1542.

2. Johnston SC, Rothwell PM, Nguyen-Huynh MN, et al. Validation and refinement of scores to predict very early stroke risk after transient ischaemic attack. Lancet. 2007;369:283–292.

3. Rothwell PM, Giles MF, Flossmann E, et al. A simple score (ABCD) to identify individuals at high early risk of stroke after transient ischaemic attack. Lancet. 2005;366:29–36.

4. Merwick Á, Albers GW, Amarenco P, et al. Addition of brain and carotid imaging to the ABCD2 score to identify patients at early risk of stroke after transient ischaemic attack: A multicentre observational study. The Lancet Neurology. 2010;9:1060–1069.

5. W. AG, R. CL, Donald EJ, et al. Transient Ischemic Attack — Proposal for a New Definition. New England Journal of Medicine. 2002;347:1713–1716.

6. Aho K, Harmsen P, Hatano S, Marquardsen J, Smirnov VE, Strasser T. Cerebrovascular disease in the community: results of a WHO Collaborative Study. Bulletin of the World Health Organization. 1980;58:113–130.

7. Kernan WN, Ovbiagele B, Black HR, et al. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the american heart association/american stroke association. Stroke. 2014;45:2160-2236.

8. Ois A, Cuadrado-Godia E, Rodríguez-Campello A, et al. Relevance of stroke subtype in vascular risk prediction. Neurology. 2013;81:575–580.

9. Ohman EM, Bhatt DL, Steg PG, et al. The REduction of Atherothrombosis for Continued Health (REACH) Registry: An international, prospective, observational investigation in subjects at risk for atherothrombotic events-study design. American Heart Journal. 2006;151.786.e1-786.e10.

10. Ay H, Furie KL, Singhal A, Smith WS, Sorensen AG, Koroshetz WJ. An evidence-based causative classification system for acute ischemic stroke. Annals of Neurology. 2005;58:688–697.

11. Herve D, Gautier-Bertrand M, Labreuche J, Amarenco P. Predictive values of lacunar transient ischemic attacks. Stroke. 2004;35:1430–1435.

12. Sullivan LM, Wilson P. Validation of the Framingham Coronary Heart Disease prediction score. JAMA. 2001;286:180–187.

13. Purroy F, Montaner J, Rovira Á, Delgado P, Quintana M, Álvarez-Sabín J. Higher risk of further vascular events among transient ischemic attack patients with diffusion-weighted imaging acute ischemic lesions. Stroke. 2004;35:2313–2319.

14. Wardlaw JM, Brazzelli M, Chappell FM, et al. ABCD2 score and secondary stroke prevention: Meta-analysis and effect per 1,000 patients triaged. Neurology. 2015;373–380.

15. Guarino M, Rondelli F, Favaretto E, et al. Short-and long-term stroke risk after urgent management of transient ischaemic attack: The bologna TIA clinical

pathway. European Neurology. 2015;74:1–7.

16. Holzer K, Feurer R, Sadikovic S, et al. Prognostic value of the ABCD 2 score beyond short-term follow-up after transient ischemic attack (TIA) - a cohort study. BioMed Central. 2010;10:50:1–7.

17. Kiyohara T, Kamouchi M, Kumai Y, et al. ABCD3 and ABCD3-I Scores Are Superior to ABCD2 Score in the Prediction of Short- and Long-Term Risks of Stroke After Transient Ischemic Attack. Stroke. 2014;45:418–425.

18. Degan D, Ornello R, Tiseo C, et al. Epidemiology of Transient Ischemic Attacks Using Time- or Tissue-Based Definitions. Stroke. 2017;48:530-536.

19. Pendlebury ST, Rothwell PM. Risk of recurrent stroke, other vascular events and dementia after transient ischaemic attack and stroke. Cerebrovascular Diseases. 2009;27:1–11.

20. Ois A, Gomis M, Rodríguez-Campello A, et al. Factors associated with a high risk of recurrence in patients with transient ischemic attack or minor stroke. Stroke. 2008;39:1717–1721.

21. Purroy F, Montaner J, Molina C a., Delgado P, Ribo M, Álvarez-Sabín J. Patterns and predictors of early risk of recurrence after transient ischemic attack with respect to etiologic subtypes. Stroke. 2007;38:3225–3229.

22. Yang J, Fu JH, Chen XY, et al. Validation of the abcd2 score to identify the patients with high risk of late stroke after a transient ischemic attack or minor ischemic stroke. Stroke. 2010;41:1298–1300.

23. Harrison JK, Sloan B, Dawson J, Lees KR, Morrison DS. The ABCD and

ABCD2 as predictors of stroke in transient ischemic attack clinic outpatients: A retrospective cohort study over 14 years. QJM. 2010;103:679–685.

Table 1. Baseline characteristics related to new vascular events (NVEs).

Variable, No. (%)	Total n=676	NVE n=173	No NVE N=503	*p*
Male sex	358 (53)	103 (59.5)	255 (40.7)	**0.040**
Arterial hypertension	4587 (72)	132 (76.3)	355 (70.6)	**0.048**
Diabetes mellitus	188 (27.8)	64 (37)	124 (24.7)	**0.001**
Hyperlipidemia	336 (49.7)	92 (53.2)	244 (48.5)	0.233
Current smoking	55 (8.1)	18 (10.4)	37 (7.4)	0.171
Previous vascular disease*	139 (20.6)	51 (29.5)	88 (17.5)	**<0.001**

*** Coronary or peripheral artery disease**

Table 2. Etiological classification related to new vascular events (NVEs), stratified by stroke/non-stroke events (p<0.001).

Variable, No. (% of subgroup)	Total n=676	NVE n=173	Stroke n=93	Non-stroke n=80
Etiological subgroup:				
Small-artery disease *	183 (27.1)	20 (10.9)	15 (8.2)	5 (2.7)
Large-artery atherosclerosis	119 (17.6)	55 (46.2)	26 (21.8)	29 (24.4)
Cardioaortic embolism	179 (26.5)	55 (30.7)	26 (14.5)	29 (16.2)
Undetermined causes	178 (26.3)	41 (23)	24 (13.5)	17 (9.6)
Other causes	17 (2.5)	2 (11.8)	2 (11.8)	0

***Reference subgroup**

Table 3. Univariate analysis of new vascular events according to clinical and radiological data.

Variable, No. (%)	Total n=676	NVE n=173	No NVE N=503	*p*
Duration of symptoms				
<10 minutes *	138 (20.4)	24 (13.9)	114 (22.7)	
10-59 minutes	303 (44.8)	78 (45.1)	225 (44.7)	
≥60 minutes	235 (34.8)	71 (41)	164 (32.6)	**0.005**
Clinical features				
Speech impairment *	248 (36.7)	55 (31.8)	193 (38.4)	
Weakness	327 (48.4)	98 (56.6)	229 (45.5)	**0.035**
Blood pressure >140/90	476 (70.4)	117 (67.6)	359 (71.4)	0.270
Age >60 years	537 (79.4)	141 (81.5)	396 (78.7)	0.699
Previous TIA	126 (19.8)	32 (18.5)	94 (18.7)	0.699
Signs of acute infarction	130 (19.9)	50 (29.9)	80 (16.5)	**<0.001**

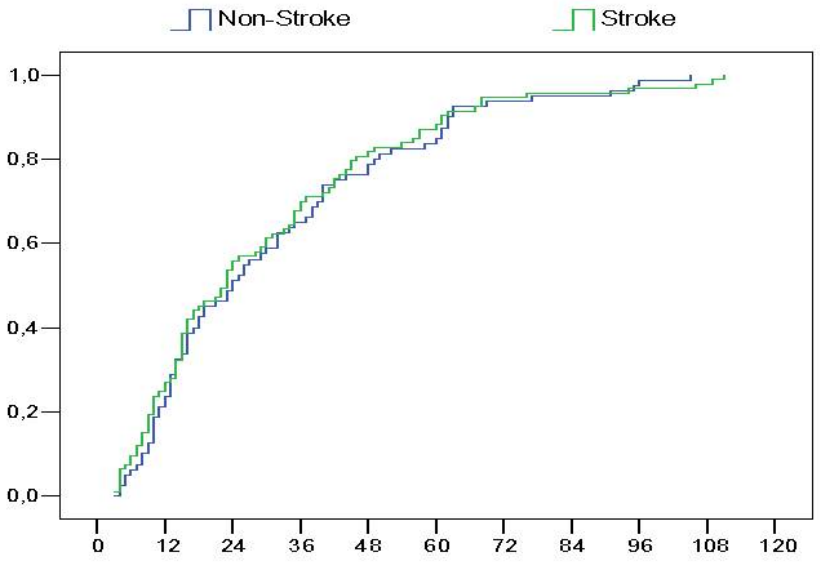
***Reference subgroup**

Table 4. Factors independently associated with NVEs in multivariate Cox regression analysis * (n=652).

	HR 95% CI
Large-artery atherosclerosis	3.97 (2.29-6.87)
Cardioaortic embolism	3.42 (2-5.83)
Undetermined causes	2.60 (1.5-4.5)
Signs of acute infarction	1.53 (1.1-2.15)
Duration of symptoms 10 to 59 minutes	1.62 (1-2.58)
Duration of symptoms ≥60 minutes	2 (1.24-3.25)

***Reference subgroups were those with small-artery disease and duration of symptoms <10 minutes respectively**

Figure 1. Distribution of new vascular events by types (stroke/non stroke) each 12 months.



Patients at risk (n)	669	586	457	350	261	194	140	102	65	37	23
Events (n)	40	49	26	21	12	15	2	3	3	2	0
(%)	(0.06)	(0.08)	(0.06)	(0.06)	(0.05)	(0.08)	(0.01)	(0.03)	(0.05)	(0.05)	