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Table 2. Radiologic findings (means ± SD)

Variables	Symptomatic	Asymptomatic	p value
Lesions, n	17	11	
RI	1.67 ± 0.62	1.12 ± 0.38	<0.05
RR	3.55 ± 1.61	1.90 ± 0.80	<0.05
rSI on T1WI	1.54 ± 0.26	1.27 ± 0.35	<0.05

Statistical Analysis

All statistical analyses were performed using PASW Statistic 18.0 for Windows (SPSS, Chicago, Ill., USA). All data are given as means ± SD. Mann-Whitney U tests were used to compare scores between the symptomatic and asymptomatic groups for unpaired samples. Correlations between two factors were analyzed by Spearman's rank correlation. Statistical significance was preset at $p < 0.05$.

Results

Patient Characteristics

Table 1 shows the characteristics of the 23 patients with 28 atherosclerotic plaque lesions registered in this study. All patients were male. The average degree of stenosis (NASCET score) was >70%, suggesting an indication for surgical intervention, such as CAS or CEA. There were no significant differences between the symptomatic and asymptomatic groups regarding age, degree of stenosis or prevalence of stroke risk factors (hypertension, dyslipidemia, diabetes mellitus and smoking).

Remodeling Characteristics in Symptomatic and Asymptomatic Atherosclerotic Plaques

Table 2 shows the RIs, RRs and signal intensities of plaques relative to those of the sternocleidomastoid muscle on BB T1WI (rSI). RI and RR were both significantly higher in symptomatic lesions than in asymptomatic lesions (both $p < 0.05$). The rSI on BB T1WI in symptomatic lesions was significantly higher than in asymptomatic lesions, indicating the presence of lipid-rich plaques in symptomatic lesions compared with asymptomatic lesions ($p < 0.05$).

The correlations between RI, RR and rSI were calculated to elucidate the relationship between remodeling and plaque lipid content. There were significant correlations between both RI and rSI ($r = 0.41$, $p = 0.03$), and between RR and rSI ($r = 0.50$, $p = 0.01$). These results suggest that plaques with positive remodeling in internal carotid arteries contained more lipid than those in arteries with luminal narrowing (fig. 3).

To validate these results, 10 plaque lesions obtained by CEA were selected, and differences in RI, RR and rSI between type VI and non-type VI plaques were calculated. There were significant differences in RI, RR and rSI between the two groups ($p < 0.05$), but no significant differences in age or percent of luminal stenosis. These histologic results confirmed the validity of the imaging results (table 3).

Remodeling Characteristics and Biochemical Markers

No significant differences in the levels of the biochemical markers, hsCRP, HbA1C, total cholesterol, LDL-C and HDL-C, were detected between the symptomatic and asymptomatic groups (table 4). No correlations between RI or RR and each biochemical marker were detected (data not shown).

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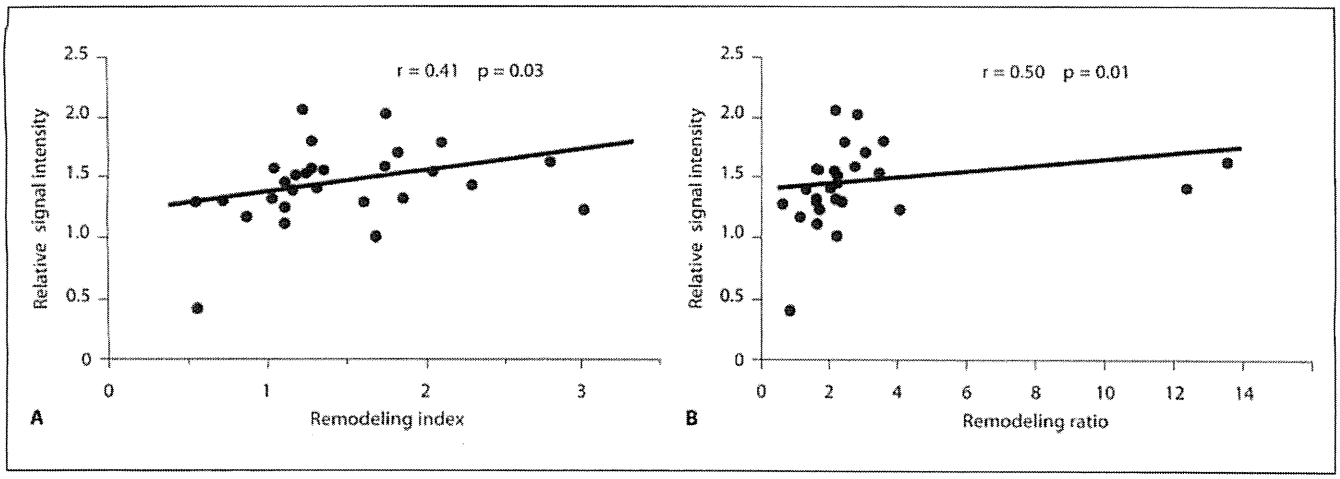

Fig. 3. Correlations between rSI and RI (**A**)/RR (**B**) were calculated, and significant correlations were found between both RI and rSI (r = 0.41, p = 0.03), and between RR and rSI (r = 0.50, p = 0.01).

Discussion

This study demonstrated three main findings. Firstly, plaques in the carotid artery with positive remodeling were associated with a significantly higher stroke prevalence than plaques with negative remodeling. Secondly, plaques with positive remodeling appeared to have significantly higher lipid contents than those with negative remodeling in both radiologic and histologic analysis. We also demonstrated that levels of biological markers, such as hsCRP, HbA1C, total cholesterol, LDL-C and HDL-C, were not useful for predicting stroke events, even though they have been shown to be significantly associated with coronary events [8].

Extensive vascular remodeling in the coronary circulation may be an indicator of plaque vulnerability to rupture [4]. Vulnerable plaques may contain a large necrotic lipid core with a thin or disrupted fibrous cap, with the potential to cause embolization or thrombosis. A previous report also found that plaques with positive remodeling had significantly larger lipid cores and higher macrophage counts than negatively or less positively remodeled plaques, also indicating increased vulnerability of more extensively remodeled plaques using a combination of functional and morphologic mechanisms [6].

MDCT angiography can clearly depict the various layers constituting the arterial wall. This technique has previously been used as an accurate method of assessing the percent luminal narrowing in the carotid artery [19]. The curved multiplanar reconstruction analysis technique used in the current study has the advantage of being able to evaluate luminal narrowing throughout the carotid artery, making identification of the point of maximum narrowing easier. A previous study proposed two potentially useful parameters for demonstrating the degree of arteriosclerosis in the coronary artery. The plaque RI is calculated as the ratio of CSA at the point of maximal vessel stenosis, measured from the luminal-intimal boundary to the outer vessel wall, to the mean reference CSA [17]. The plaque RR is calculated as the ratio of CSA at the point of maximal vessel stenosis to the reference CSA at the distal portion [18]. RR is similar to the use of NASCET criteria to assess the degree of luminal narrowing. RI is less likely to be subject to artificial variation (compared with RR) and might thus represent a more stable and accurate assessment scale. In the current study, we calculated correlations using both measures to exclude any discrepancies

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Table 3. Comparison of radiologic parameters between type-VI and non-type-VI groups (means ± SD)

Variables	Type-VI group	Non-type-VI group	p value
Lesions, n	5	5	
Age, years	66.4 ± 5.32	67.2 ± 5.26	>0.05
NASCET, %	76.5 ± 11.7	74.9 ± 9.5	>0.05
RI	1.35 ± 0.34	0.88 ± 0.25	<0.05
RR	2.29 ± 0.49	1.30 ± 0.33	<0.05
rSI on T1WI	1.50 ± 0.15	1.07 ± 0.38	<0.05

Table 4. Comparison of biological markers between symptomatic and asymptomatic groups (means ± SD)

Markers	Symptomatic (n = 17)	Asymptomatic (n = 11)	p value
hsCRP, mg/dl	0.18 ± 0.21	0.25 ± 0.30	>0.05
T-Chol, mg/dl	180.3 ± 37.7	165.9 ± 30.3	>0.05
HDL-C, mg/dl	48.3 ± 13.6	42.0 ± 11.6	>0.05
LDL-C, mg/dl	105.7 ± 34.2	104.2 ± 27.0	>0.05
HbA1c, %	6.2 ± 0.76	7.0 ± 2.18	>0.05

T-Chol = Total cholesterol.

associated with the analytical method, and the results suggested that positive RR and RI values were both predictive of stroke events, as in coronary arteries. These results are in accord with those of another recent report, which showed that a positive RR value indicated underlying atherosclerotic plaque vulnerability in carotid arteries using MDCT angiography [9].

A previous study of positive remodeling of the internal carotid artery was limited by the lack of correlations between histologic vessel wall measurements and MDCT values [9]. Complicated and vulnerable plaques are defined by histologic analysis as plaques with surface rupture or intraplaque/intraluminal hemorrhage, indicative of stage VI by histologic AHA criteria [20]. Previous reports demonstrated that T1WI of carotid arteries may be useful for identifying histologically complicated plaques with hemorrhage or thrombus, because the formation of methemoglobin is associated with shortening of T_1 in the acute to subacute phase of rupture [21]. Furthermore, new MRI techniques may be able to differentiate between atherosclerotic plaques in terms of the presence of lipid-rich necrotic cores, hemorrhage and calcification [22]. In the current study, the qualitative contents of plaques were estimated using the BB technique, suppressing the signal from flowing blood, based on pulse sequences designed for vascular imaging [13]. These sequences are ideal for plaque imaging because the conspicuity of the vessel wall is increased when adjacent to a hypointense lumen, in which the echo and repetition times can be varied to optimize visualization of specific plaque components [23]. The ratio of plaque intensity to that of the sternocleidomastoid muscle was calculated to eliminate variations in intensity among images [14]. Our results showed that rSI was higher in symptomatic than in asymptomatic plaques. We also confirmed that rSI correlated significantly with both RI and RR. These results suggest that

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plaques in positively remodeled internal carotid arteries, indicative of type VI stage by AHA criteria, may be more vulnerable to stroke than those in arteries with luminal narrowing. Thus, combined analysis of both RI and RR using MDCT angiography and rSI using BB MRI may be useful for predicting stroke events. We confirmed the validity of this conclusion by histologic analysis of plaques obtained by CEA. The indications for surgical interventions, including CEA and CAS, might be reconsidered on the basis of histologic alterations, represented by RI, RR or rSI, because low-grade stenosis with vulnerable lesions may result in cerebrovascular events [24].

Numerous potential risk factors for the development of atherosclerotic plaques in coronary events have been reported [8]. hsCRP, in particular, has been focused on as an independent risk factor for ischemic stroke in Japanese men [25]. In the current study, we calculated the correlations between the degree of positive remodeling and levels of hsCRP, HbA1C, total cholesterol, LDL-C and HDL-C; however, the results suggested that these markers were of little value in predicting future stroke events.

This study had several potential limitations. First, the retrospective design of the study meant that the parameters being measured could be the results, rather than the causes of the cerebral events. In addition, although the assessed plaques may have been the source of the symptoms, imaging only assessed a representative selection of previously ruptured plaques. These factors imply that it is difficult to draw firm conclusions about the predictive value of remodeling parameters for future stroke events. Secondly, the number of patients assessed in this study was small and further prospective studies with more patients are needed to validate the results of this preliminary study.

Conclusions

In the current series of patients with significant carotid stenosis, the degree of positive remodeling, represented by both RI and RR, was significantly greater in symptomatic lesions with cerebral ischemic events than in asymptomatic lesions. In both radiologic and histologic analyses, these lesions were confirmed as vulnerable plaques with underlying surface rupture or intraplaque/intraluminal hemorrhage, indicative of stage VI according to histologic AHA criteria. These results suggest that the combined analysis of RR, RI and rSI might help to predict future stroke events.

Disclosure Statement

The authors have no conflicts of interest to disclose.

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脳卒中高リスク群の診断及び治療による循環器疾患制圧に関する研究

平成２４年度～平成２６年度総合研究報告書

別冊2　研究成果の刊行物・別刷り

研究代表者 峰松 一夫

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Guidelines for Management of Patients with Transient Ischemic Attack

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Abstract

A transient ischemic attack (TIA) is a medical emergency that is associated with a high risk of early ischemic stroke and other vascular events. Several evidence-based guidelines have been published to provide recommendations for the evaluation and treatment of patients with TIA. These guidelines underline the need for the urgent referral of patients with TIA so that they can access expert evaluation and immediate treatment. The distinction between TIA and ischemic stroke has recently become less important because these two conditions share pathophysiological mechanisms and many of the preventive approaches are applicable to both. Therefore, current guidelines are often described without a distinction between TIA and ischemic stroke. However, the applicability of recommendations for applying treatment for ischemic stroke to TIA has not been proven. Further studies are required to determine the effects of urgent intervention or treatment early after TIA.

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A transient ischemic attack (TIA) is a medical emergency that is associated with a high risk of early ischemic stroke and other vascular events. Among patients with TIA, 10–15% develop stroke within 90 days, with about half occurring within 48 h [1–4]. Urgent assessment and management of patients in a dedicated TIA clinic has decreased the 90-day stroke risk by almost 80% [5, 6]. Patients with TIA are also at high risk of cardiovascular events [1]. A previous study found that 2.6% of patients were hospitalized for major cardiovascular events including myocardial infarction, unstable angina, or ventricular arrhythmia within 90 days of TIA [7]. These findings underline the need for the urgent referral of patients with TIA so that they can access expert evaluations and immediate treatment. Several evidenced-based guidelines have provided recommendations for the evaluation and treatment of patients with TIA [8–24].

T.U. and K.M. contributed equally to this chapter.

The classical definition of TIA is the presence of focal neurological symptoms ascribable to a vascular etiology lasting <24 h irrespective of imaging findings [25]. The advent of brain imaging techniques has led to the understanding that up to one third of patients with symptoms lasting <24 h actually has an infarction [1]. This has led to a new tissue-based definition of TIA, that is 'a transient episode of neurological dysfunction caused by focal brain, spinal cord or retinal ischemia, without acute infarction' [1], which is different from the traditional time-based definition. According to this definition, the diagnostic certainty of TIA would depend on the extent of evaluations that a patient undergoes. A brain imaging procedure is prerequisite for concluding a diagnosis of TIA or ischemic stroke.

In contrast, the distinction between TIA and ischemic stroke has become less important because these two conditions share the same pathophysiological mechanisms, and many of the preventive approaches are applicable to both [1]. Acute ischemic stroke and TIA in the acute setting are considered to span the same spectrum, and a new clinical concept termed acute cerebrovascular syndrome has been proposed [26]. Current guidelines are usually presented without a distinction between TIA and ischemic stroke.

We present representative guidelines for the management of patients with TIA [8–24].

Representative Guidelines for the Management of Transient Ischemic Attack

A panel of the American Heart Association (AHA) Stroke Council published 'Guidelines for the management of transient ischemic attacks' in 1994 and a supplement in 1999, and both were separate from the guidelines for the management of stroke [8, 9]. The AHA/American Stroke Association (ASA) issued a scientific statement for the definition and evaluation of TIA in 2009 [1]. The National Stroke Association (NSA) published guidelines for the management of TIA in 2006, and recommendations for systems of care for TIA in 2011 [10, 11]. Guidelines for the assessment and management of people with recent TIA were published in New Zealand in 2008 [12]. A chapter for TIA management was newly added in the second edition of the guidelines for management of stroke in Japan in 2009. The English version of the Japanese guidelines was published recently [13]. A separate chapter for the management of TIA was similarly described in guidelines for management of stroke in the UK [14, 15] and Australia [16]. The AHA/ASA published a scientific statement for 'Coronary risk evaluation in patients with transient ischemic attack and ischemic stroke' in 2003 [17], and 'Guidelines for the prevention of stroke in patients with stroke or transient ischemic attack' in 2006, 2008 and 2011 [18–20], without a distinction between stroke and TIA. 'Guidelines for management of ischaemic stroke and transient ischaemic attack' published in 2008 by the European Stroke Organization (ESO) [21] is an update of the European Stroke Initiative (EUSI) Recommendations for Stroke Management pub-

lished in 2000. The American College of Chest Physicians evidence-based clinical practice guidelines for antithrombotic and thrombolytic therapy for ischemic stroke [22], a Science Advisory of AHA/ASA for oral antithrombotic agents for the prevention of stroke in nonvalvular atrial fibrillation (AF) [23], and an update of the 2010 ESC guidelines for the management of AF [24] covered both ischemic stroke and TIA.

Risk Stratification for Referral to a Specialized Hospital

Patients with suspected TIA require a differential diagnosis from TIA mimics, an assessment of vascular risk factors, and investigations to determine the potential causes of TIA. Magnetic resonance imaging (MRI), including diffusion-weighted imaging (DWI) sequences should be the preferred diagnostic test for patients with suspected TIA. An additional diagnostic workup, including vessel imaging, cardiac evaluation and laboratory testing, should be completed as soon as possible, preferably within hours or a day or two.

To determine the short-term risk of stroke facing the individual patient is important. Patients at high risk of subsequent stroke would benefit more by urgent referral to a specialized stroke center, timely identification of the underlying etiology, and preventive measures such as antiplatelet agents, anticoagulants, and carotid endarterectomy (CEA). Admitting high-risk patients to specialized stroke centers might also provide opportunities to administer acute timely treatments in the event of a subsequent stroke [27].

Simple stratification scores are used to estimate the individual risk for patients with TIA. The most popular tool is the $ABCD^2$ score [28]. The $ABCD^2$ score is recommended to identify patients at high risk of stroke in several guidelines [1, 10, 12, 14–16], and it can be used in primary care to select patients for referral to specialized stroke centers. The presence of ischemic lesions on DWI and TIA etiology, such as large artery atherosclerosis and AF, could improve stroke risk prediction after TIA. However, clinical plus imaging scores, such as the $ABCD^2$-I [29], require additional estimations, and are more difficult to apply. Although these scores could be used in specialized stroke centers to individualize TIA management, they cannot be applied in primary care.

Initial Management and Estimations

Guidelines of the ESO [21]

The ESO guidelines recommend that patients with suspected TIA be referred without delay to a TIA clinic or to a medical center with a stroke unit that can provide expert evaluation and immediate treatment. An immediate diagnostic workup, including urgent vascular imaging (ultrasound, CT or MR angiography), is recommended for patients with TIA, minor stroke or early spontaneous recovery.

National Clinical Guidelines of the National Institute for Clinical Excellence [14]
The National Institute for Clinical Excellence (NICE) guidelines recommend that all patients with TIA should be given immediate antiplatelet therapy with 300 mg/day of aspirin and then referred for urgent specialist assessment. The NICE guidelines recommend that individuals with suspected TIA and at high risk for stroke (for example, $ABCD^2$ score ≥4 or with crescendo TIA) in whom the vascular territory or pathology is uncertain should undergo urgent (within 24 h) brain imaging studies (preferably DWI). Those with suspected TIA at low risk for stroke (for example, $ABCD^2$ <4) in whom the vascular territory or pathology is uncertain should undergo brain imaging studies (preferably DWI) within 7 days. Individuals with suspected TIA who require brain imaging due to uncertain vascular territory or pathology should undergo DWI except where contraindicated, in which case CT scanning should be used (fig. 1a).

National Stroke Strategy of the Department of Health (UK) in 2007 [15]
This strategy recommends immediate referral for appropriately urgent specialist assessment and an assessment of all patients presenting with recent TIA or minor stroke. All higher-risk patients with TIA and minor stroke (e.g. $ABCD^2$ score ≥4) need to be assessed by a specialist and treated within 24 h. Immediate hospital admission might be justified for those at highest risk. High-risk patients who are not considered to require immediate hospital admission have better outcomes if they are assessed, investigated and treated within 24 h of referral. Lower-risk patients with TIA or minor stroke are best assessed within 7 days of the event. Non-urgent referral for TIA or minor stroke is appropriate only for very low-risk patients, such as those presenting with events that occurred several weeks or months previously (fig. 1b).

Clinical Guidelines by National Stroke Foundation (Australia) in 2010 [16]
These guidelines recommend that all patients with suspected TIA should have a full assessment including a detailed history and clinical, prognostic (e.g. $ABCD^2$ score) and investigative tests (e.g. blood tests, brain and carotid imaging and electrocardiography, ECG) at the initial point of healthcare contact, regardless of whether it is in primary or secondary care. Patients identified as being at high risk (e.g. $ABCD^2$ score ≥4 and/or any one of AF, carotid territory symptoms or crescendo TIA) should undergo urgent brain assessment preferably MRI with DWI and carotid imaging within 24 h. In settings with limited access to such modalities, patients should be referred within 24 h to the nearest center where such assessments can be quickly conducted. Patients classified as low risk (e.g. $ABCD^2$ score <4 without AF or carotid territory symptoms or who present more than one week after the last symptoms) should be assessed by brain and carotid imaging as soon as possible, preferably within 48 h (fig. 1c).

Guidelines of Stroke Foundation of New Zealand [12]
The New Zealand guidelines recommend an assessment of stroke risk for all patients with suspected TIA using the $ABCD^2$ tool at the initial point of health care contact

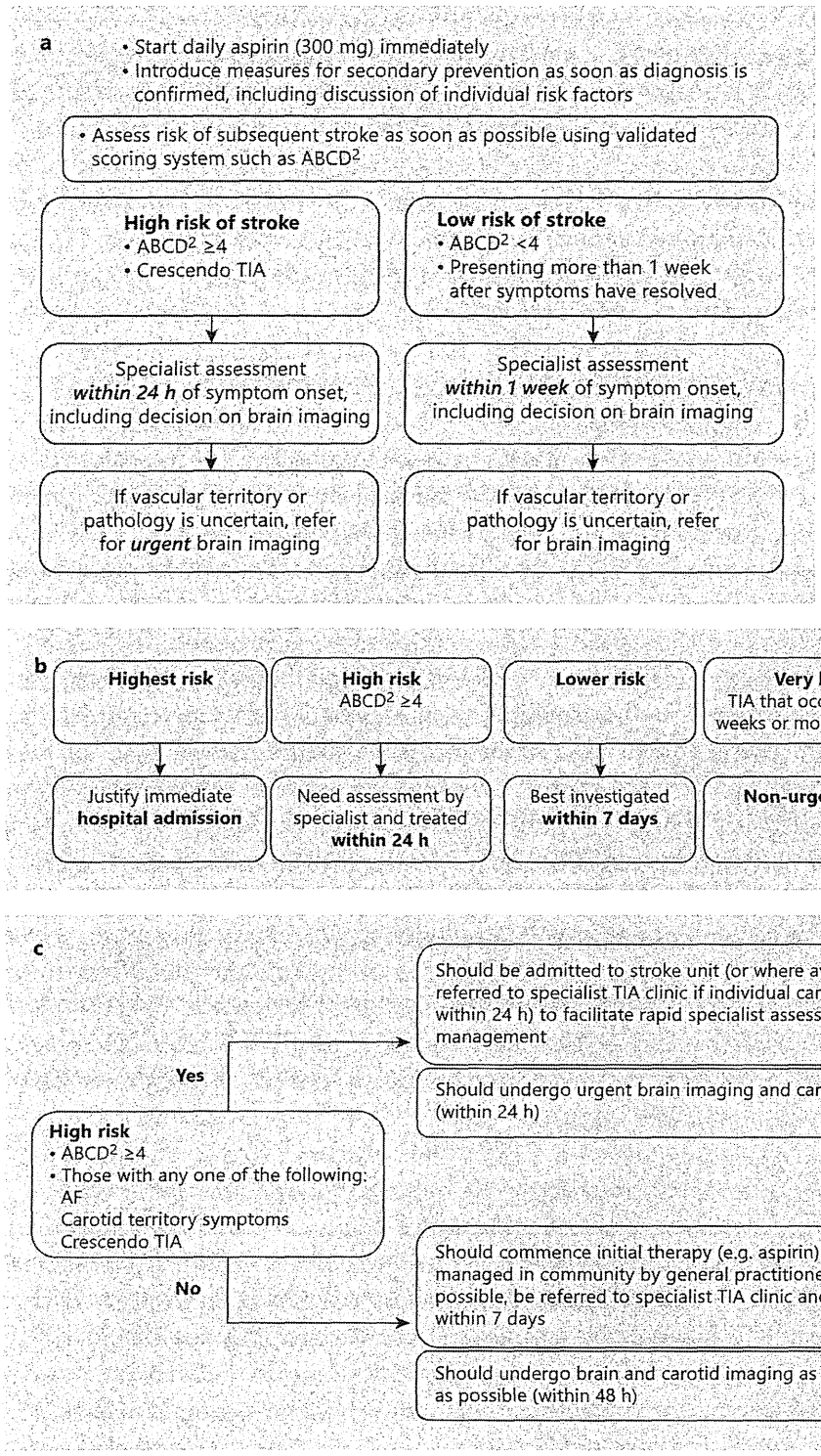

Fig. 1. Algorithms for initial management and estimations. **a** Guidelines of NICE [14]. **b** National Stroke Strategy (UK) [15]. **c** Guidelines of National Stroke Foundation (Australia) [16].

regardless of whether in primary or secondary care. High risk is indicated by any of the following: presence of symptoms at first contact; $ABCD^2$ score ≥4; crescendo TIAs, AF or already receiving anticoagulation therapy. Low risk is indicated by any of the following: $ABCD^2$ score <4 and late presentation (one week after symptoms appear).

Guidelines in Japan [13]
The Japanese guidelines recommend evaluating patients with suspected TIA to identify the onset mechanism and initiating treatment as soon as possible after TIA onset to prevent subsequent cerebral infarction.

Scientific Statement for Definition and Evaluation of Transient Ischemic Attack Published by AHA/ASA in 2009 [1]
This statement recommends evaluating patients with suspected TIA as soon as possible after an event. Patients with TIA should preferably undergo neuroimaging evaluation within 24 h of symptom onset, and MRI, including DWI, is the preferred brain diagnostic imaging modality. If MRI is not available, head CT should be performed. The cervicocephalic vessels should be imaged noninvasively as part of the routine evaluation of patients with suspected TIAs. Noninvasive assessment of the intracranial vasculature reliably excludes intracranial stenosis, and the likelihood of intracranial steno-occlusive disease that would alter management can be determined. Patients should be assessed by ECG as soon as possible after TIA. Prolonged cardiac monitoring (inpatient telemetry or Holter monitoring) is useful for patients with an unclear origin after initial brain imaging and electrocardiography. At least transthoracic echocardiography is reasonable when evaluating patients with suspected TIAs, especially when no cause has been identified by other elements of the workup. Transesophageal echocardiography is useful in identifying patent foramen ovale, aortic arch atherosclerosis and valvular disease, and is reasonable when identification of these conditions will alter management. Routine blood tests, including complete blood count, chemistry panel, prothrombin time and partial thromboplastin time, and fasting lipid panel, are reasonable in the evaluation of patients with suspected TIAs.

National Stroke Association Guidelines for the Management of Transient Ischemic Attacks [10]
These guidelines recommend establishing specialized clinics for the rapid assessment of TIA within 24–48 h of diagnosis. Physicians and institutions that provide care for patients with recent TIA should have same-day access to imaging modalities such as CT/CTA, MR/MR angiography and ultrasound for patients who need it. Patients with suspected TIA who are not admitted to hospital should have rapid (within 12 h) access for urgent assessment and investigation by CT or MRI brain scanning, ECG and carotid Doppler ultrasonography. Patients should be initially assessed within 24–48 h if they are not already assessed by cross-sectional imaging, ECG, or carotid ultrasound

in the emergency department. If they have been performed and the findings are negative, up to 7 days might be appropriate. Patients with a TIA within the past 2 weeks but who were not hospitalized, should undergo prompt (within 24–48 h) assessments by means of carotid Doppler ultrasonography for TIA consistent with carotid territory, blood work and cardiac evaluation using ECG, rhythm strip, and echocardiography to determine the mechanism of ischemia and subsequent preventive therapy.

Hospital Admission

Ideally, all patients with suspected TIA should be immediately hospitalized to ensure rapid diagnostic evaluation and acute stroke therapies. However, admitting all patients with suspected TIA would probably be problematic, as hospital resources (staff and beds) would become insufficient and costs would soar. Neither 100% hospitalization nor 100% outpatient evaluation of patients with TIA is ideal. For acute hospitalization after suspected TIA, risk stratification in the emergency room might help triage patients (high risk) for hospitalization and outpatient (low risk) management [30]. The $ABCD^2$ score can function in this role. In addition, the presence of ischemic lesions on DWI and an apparent TIA etiology, such as large artery atherosclerosis and AF, could improve stroke risk predictions after TIA.

The NSA evidence-based guidelines for TIA management [10] state that hospitalization should be considered for patients with a first TIA within the past 24–48 h to facilitate the possible early deployment of lytic therapy and other medical management strategies if symptoms recur and to expedite the institution of definitive secondary prevention. Additionally, timely hospital referral for a recent TIA (within one week) is always advisable, and hospital admission is generally recommended in the case of crescendo TIAs or duration of symptoms for more than 1 h, symptomatic internal carotid artery stenosis >50% in diameter, a known cardiac source of embolus such as AF, a known hypercoagulable state, or an appropriate combination of the California or ABCD scores.

The scientific statement of AHA/ASA [1] recommends admitting patients with TIA to hospital if they present within 72 h of the event and if any of the following criteria are present: $ABCD^2$ score of ≥3, $ABCD^2$ score 0–2 and uncertainty that diagnostic workup can be completed within 2 days as an outpatient, or $ABCD^2$ score 0–2 and other evidence indicating that focal ischemia caused the event.

The Clinical Guidelines for Acute Stroke Management published by the National Stroke Foundation [16] describe that all patients with suspected TIA presenting to a general practitioner or emergency department should be rapidly assessed. Those identified as high risk ($ABCD^2$ score ≥4 and/or those with any of AF, carotid territory symptoms or crescendo TIA) should be admitted to a stroke unit (or where available, referred to a specialist TIA clinic if they can be assessed within 24 h) to facilitate rapid specialist assessment and management. Those identified as low risk ($ABCD^2$ score <4

and without AF or carotid territory symptoms or crescendo TIA) should start initial therapy (e.g. aspirin) and then be managed in the community setting by a general practitioner or private specialist or, where possible, be referred to a specialist TIA clinic and seen within 7 days (fig. 1c).

Treatment

All patients with TIA are at risk of subsequent stroke and cardiovascular events including myocardial infarction and death. Several interventions that have proven effective in preventing these events are covered by international guidelines and include anticoagulation for cardioembolic TIA, antiplatelet therapy for non-cardioembolic TIA, CEA for >50% symptomatic carotid stenosis, blood pressure (BP)-lowering drugs, statins, improved glycemic control, dietary modification, exercise and smoking cessation [12]. Patients with suspected TIA should be evaluated to determine etiology and be treated to prevent subsequent stroke as soon as possible after TIA onset.

Antiplatelet Therapy

The NICE [14] and Stroke Foundation of New Zealand [12] guidelines recommended starting antiplatelet therapy immediately for all individuals with suspected TIA until brain imaging results are available. Primary intracerebral hemorrhage (ICH) is a rare cause of TIA, and 99% of strokes after TIA are due to cerebral infarction, and no clear evidence indicates that the inadvertent administration of aspirin to patients with ICH before imaging is harmful [12]. Japanese guidelines recommend administering 160–300 mg/day of aspirin for patients with acute TIA (within 48 h) [13]. Daily long-term antiplatelet therapy should be prescribed immediately for the secondary prevention of stroke and other vascular events in patients with non-cardioembolic TIA. Aspirin monotherapy (50–325 mg/day), aspirin (25 mg) combined with extended-release dipyridamole (200 mg) twice daily, and monotherapy with clopidogrel (75 mg) are all acceptable options for initial therapy [10, 20–22]. In addition, cilostazol (200 mg/day) is recommended by the American College of Chest Physicians Evidence-based Clinical Practice Guidelines [22]. Antiplatelet agents that can be applied in Japan comprise aspirin (75–150 mg/day), clopidogrel (75 mg), cilostazol (200 mg/day) and ticlopidine (200 mg/day) [13]. Combining aspirin with clopidogrel increases risk of hemorrhage and is not recommended for long-term secondary prevention after TIA [16, 20, 21].

Anticoagulation Therapy

Long-term oral anticoagulation with a target international normalized ratio (INR) of 2.5 (range, 2.0–3.0) is recommended for patients with TIA and emboligenic cardiac diseases such as persistent or paroxysmal valvular or nonvalvular AF [10, 12, 16, 20–23]. The Japanese guidelines recommend a target INR range of 2.0–3.0 for patients

aged <70 years of age and 1.6–2.6 in those aged ≥70 years [13]. The American College of Chest Physicians Evidence-based Clinical Practice Guidelines [22] recommend oral anticoagulation therapy with dabigatran (150 mg b.i.d.) over adjusted-dose vitamin K antagonist therapy for patients with a history of ischemic stroke or TIA and AF, including paroxysmal AF. The AHA/ASA Science Advisory for oral antithrombotic agents for the prevention of stroke in nonvalvular AF recommends warfarin, dabigatran, apixaban, and rivaroxaban to prevent a first and recurrent stroke in patients with nonvalvular AF [23]. The selection of an antithrombotic agent should be individualized on the basis of risk factors, cost, tolerability, patient preference, potential for drug interactions and other clinical characteristics, including time in the INR therapeutic range if the patient has been treated with warfarin [23]. An update of the 2010 ESC guidelines for the management of AF recommends that novel oral anticoagulant drugs, including dabigatran, apixaban, and rivaroxaban, should be considered instead of adjusted-dose vitamin K antagonist [24].

Carotid Revascularization

CEA is recommended for patients with recent TIA and ipsilateral severe carotid artery stenosis (70–99%). For patients with recent TIA and ipsilateral moderate carotid stenosis (50–69%), CEA is recommended depending on patient-specific factors such as age, sex, and comorbidities. When the degree of stenosis is <50%, there is no indication for CEA. Carotid artery stenting is indicated in patients at a high risk of CEA, such as those with coronary artery disease [10, 12, 13, 16, 20, 21]. In patients with symptomatic internal carotid artery stenosis for whom CEA is a reasonable option, surgery should be performed as soon as the patient is fit for the procedure, preferably within 2 weeks of TIA (cerebral or retinal) [10, 14, 16, 20].

Treatment to Reduce the Cardiovascular Risk

All individuals with a history of TIA should be considered for treatment to reduce cardiovascular risk, and risk factors for recurrent cerebrovascular ischemic events should be appropriately treated. This includes lowering BP and blood cholesterol (with lifestyle modifications and/or drug therapy) for all patients with atherothrombotic TIA, regardless of baseline BP and cholesterol values [10]. The New Zealand guidelines recommend assessing every individual with TIA and informing them of their risk factors for stroke and adverse cardiovascular events, and of possible strategies to modify identified risk factors [12].

Blood Pressure Lowering

Reducing BP is recommended to prevent both recurrent stroke and other vascular events from arising in persons who have had an ischemic stroke or TIA and are beyond the first 24 h [20]. The absolute target BP is uncertain but a benefit has been associated with an average reduction of about 10/5 mm Hg, and normal BP levels have been defined as <120/80 mm Hg [20, 21]. After TIA that is not due to dissection or

cardiogenic embolism, BP should be reduced to <140/90 or <130/80 mm Hg for diabetics, regardless of the initial level, unless the patient has symptomatic hypotension. An angiotensin-converting enzyme inhibitor alone or in combination with a diuretic, or with an angiotensin receptor blocker is useful [10, 20].

Cholesterol Lowering

Statin therapy with intensive lipid-lowering effects is recommended to reduce the risk of stroke and cardiovascular events among patients with ischemic stroke or TIA who have evidence of atherosclerosis, an LDL-C level of >100 mg/dl, and who are without known coronary heart disease [20].

Diabetes Management

Fasting blood glucose levels of <126 mg/dl (7 mmol/l) are recommended. Diet, exercise at least three times a week and oral hypoglycemic agents or insulin should be prescribed as needed to control diabetes for the long-term secondary prevention of stroke [9]. Diabetes should be managed with lifestyle modification and individualized pharmacological therapy [21].

Behavioral Changes

Cessation of smoking, maintaining an appropriate body weight, and enforced exercise are recommended to reduce the risk of recurrent TIA or stroke [10, 12–16, 20].

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