8. 糖尿病連携手帳所持とHbA1c認知度の関連

HbA1cを知らないと答えた割合は，手帳所持者で3.8％，非所持者で11.6％（P<0.01）であり，手帳所持群で有意に少なかった．各年齢カテゴリー別にHbA1cの認知度を見ると80歳未満では，どの年代でも，糖尿病連携手帳を所持している場合は（非所持者に比較して）自身のHbA1c値認知度が高かった（Fig. 2B）．特に，60歳未満では連携手帳所持者にHbA1cを「知らない」と答えた患者はいなかった（手帳非所持者では11.3％がHbA1cを知らなかった）．一方，80歳以上では，連携手帳所持とHbA1c認知度に関連を認めなかった（Fig. 2B）．

多変量解析では，HbA1c値の把握と手帳所持との相関関係は，年齢，性別，入院歴とは独立して有意であった（調整後オッズ比2.75（1.19-8.00），p＝0.034）．入院歴と手帳所持の間に交互作用を認めなかった．入院歴のある患者では，HbA1cを知らない割合は手帳所持者の2.8％（非所持者では6.3％），眼科定期受診をしていない割合は手帳所持者の10.1％（非所持者では25.4％）であったが，入院歴のない患者では，HbA1cを知らない割合は手帳所持者の4.1％（非所持者では13.5％），眼科定期受診をしていない割合は手帳所持者の26.5％（非所持者では39.9％）であり，入院歴があり連携手帳を所持している患者が最も療養行動において優れていた．

考　察

大阪府豊能医療圏において，保険薬局に院外処方箋を持参した患者を対象に，糖尿病診療実態を調査した結果を報告した．血糖コントロール指標における優・良の範囲は，全患者の約3割にとどまっており，薬剤療法による積極的介入にもかかわらず，合併症を防止するための血糖管理はまだまだ不十分であることが明らかになった．年齢層別にHbA1c値を検討したところ，血糖コントロール不可の割合は，男性で50歳代後半，女性で50代前半と60代前半に高くなっていた．この年齢では，仕事や家族の世話・介護などで多忙のため，十分な療養行動がとれていないことが考えられる．糖尿病コントロール良好群に比し不十分以上の群では合併症が多く寿命も短い[9]ことが明らかになっており，糖尿病患者の健康寿命の延伸のために，今後，職場，家庭，施設や地域でのさらに積極的な介入と支援の必要性を示唆する結果である．

糖尿病は，専門医の数に比較して患者数が多く大多数が非専門医に診療されている，また，合併症が多岐にわたるため多くの専門科や多職種での連携が必要である，などの特徴から，地域での診療連携が重要[4,10]であるが，我が国における連携実態の把握は不十分であり，その有用性のエビデンスの報告は少ない．また，日本糖尿病協会の糖尿病連携手帳は異なる医療機関同士で診療情報を共有できる有益なツールであるが，その普及率や効果に関する臨床データは報告されていない．本調査では，医療先進地区と考えられる豊能圏においてすら連携手帳所持率は薬剤治療中の糖尿病患者の15.6％にとどまっていることを明らかにした．この率はお薬手帳（平成23年1月大阪府調査結果[11]では普及率54.2％）に比較してまだまだ低く，今後さらに普及活動を展開してゆく必要があると考えられた．このため，国立循環器病研究センターや大阪大学，市域の中核病院および医師会・歯科医師会・薬剤師会・保健所から構成される豊能医療圏糖尿病地域連携クリティカルパス検討会議では，連携手帳啓発のためのポスター（Fig. 2Cに示す）を作成し，診療所1,330，歯科600，保険薬局365カ所に配布して啓発に努め，連携手帳を用いた地域での診療ネットワークの構築に努力している．

本研究では，糖尿病療養と自己管理のマーカーとして地域におけるHbA1c認知度と眼科定期受診の割合を検討した．HbA1c値を「知らない」と答えた患者は全体の約1割で，その割合は，80歳以上の高齢者，50歳未満の若年者，通院歴が短い（1-2年）患者に多かった．また，患者の約3割が眼科受診していないと答えており，特に糖尿病入院歴のない若年男性に多い結果であった．これらより，高齢者の糖尿病診療では自己管理に限界があり周囲のサポートが必要であることや，糖尿病の通院治療を初めた当初において糖尿病教育がまだ不十分であることが示唆されている．80歳未満では，糖尿病連携手帳所持は，HbA1c認知度（調整オッズ比4.78）や眼科定期受診行動（調整オッズ比2.49）と有意な関連があった．この相関関係は，年齢，性別，糖尿病入院歴，血糖コントロール，処方箋交付元とは，独立しており，連携手帳による糖尿病教育効果が適切な療養行動につながっていると考えられ，連携手帳の効用を示す結果であると考えられる．

本研究は，自由意思に基づくアンケート調査であり糖尿病連携手帳を活用している患者やコントロールが比較的良い患者が，多く回答している可能性がある．また，HbA1cの値は自己申告であり必ずしも正確または直近の値ではない可能性がある．しかしながら，本調査で得られた血糖コントロール各カテゴリーの割合[3]や男女比[2]，眼科受診率[5]は，今までの報告と同程度であり，おおよその糖尿病地域診療実態を反映しているものと考えられる．今回は院外処方箋を交付されている糖尿病患者に限定した調査であるが，糖尿病専門医での調査を主体とした既報に比し，非専門医を主体とした地域の診療実態をより反映できていると考えら

れる．本研究ではHbA1c認知度や眼科定期受診と処方箋交付元とは全く相関がなく，かかりつけ医が診療所であっても病院であってもその自己管理に関する知識や行動に差を認めなかった．

本研究では，豊能医療圏域における糖尿病実態を調査し，地域における血糖コントロールがまだまだ不十分であること，糖尿病連携手帳普及が6人に1人の割合であることを明らかにした．一方，連携手帳所持が適切な自己管理・療養行動と関連していることが示唆されており，今後，さらに連携手帳の普及を含めた啓発活動を展開し，糖尿病専門医，かかりつけ医や地域行政が一丸となり，糖尿病の教育と診療を一層強化する必要があると考えられた．

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・アンケートを収集いただいた吹田市・豊中市・箕面市・池田市の薬剤師会員の方々

・豊能医療圏糖尿病地域連携クリティカルパス検討会議のメンバー

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Abstract

Surveillance and Evaluation of Diabetes Management in the Toyono Medical District

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Critical Path Meeting for Diabetes in Toyono Medical District

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The implementation of programs for diabetes control and complication prevention depends on reliable data. A survey of diabetes conducted at local pharmacies in the Toyono area to evaluate the severity of disease and capacity for self-management revealed that, among 1,026 participants (mean age: 66.9 years, 36.6 % women, an approximate duration of therapy of 10 years and mean HbA1c: 7.2 %), only 31 % had the required HbA1c level (below 6.9 %) recommended by the Japan Diabetes Society. A substantial proportion (12.8 %) of the patients had an HbA1c level of more than 8.4 %. In addition, 9.8 % of the patients were unaware of their HbA1c level and 32.1 % did not undergo regular eye examinations to check for diabetic retinopathy. Multivariate analyses revealed that a higher HbA1c level was associated with a younger age, female gender and longer duration of therapy. Having regular eye examinations was found to be associated with an older age, female gender, longer duration of therapy and possession of the Diabetes "Renkei" Notebook. The Diabetes "Renkei" Notebook is a notebook with instructions and patient records that helps in sharing information among clinics, hospitals, caregivers and the patient. Although the "Renkei" Notebook is thought to make it easier to stay organized in the management of diabetes, this has yet to be proven. The present study demonstrated that the use of a "Renkei" Notebook is associated with favorable improvements in self-care, such as knowledge of one's HbA1c level and attendance at regular eye checkups. The results indicate the need for a continuous, systematic analysis of patient knowledge and education along with the widespread use of the "Renkei" Notebook for diabetes management and self-care.

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Epidemiology of Transient Ischemic Attack

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Abstract

Few epidemiologic data are available regarding the prevalence and incidence of transient ischemic attack (TIA). Here, the incidence of TIA and that of subsequent stroke events were reviewed. The incidences of TIA in Europe were 0.52–2.37 and 0.05–1.14 in men and women aged 55–64, 0.94–3.39 and 0.71–1.47 in those aged 65–74, and 3.04–7.20 and 2.18–6.06 in those aged 75–84, respectively. The corresponding incidences are similar in the United States, and lower in Japan. Higher incidences were revealed in men compared with women. The incidence of TIA increased very markedly with age, regardless of race or gender. The evidence of risk factors for TIA excluding ischemic strokes is very limited. The ABCD/ABCD^2 score was developed to predict individual risk and to triage patients on the first presentation. In prognostic TIA, the crude rate of stroke risks (%) for general populations were 1.7, 4.8, 6.6, 8.5, and 11.4 at 2 days, 1 week, 1 month, 3 and 6 months, whereas those for hospital patients were 13.7 and 12.4 at 1 and 3 months, respectively. There is very limited evidence of an association between a family history of stroke and the incidence of stroke after TIA, which showed that family history of stroke does not predict the risk of ischemic stroke after TIA. There is also limited evidence of seasonal variation in TIA incidence. TIAs were reported to be most frequent in autumn or spring and less common in winter or spring to summer, and most frequent on Mondays. There seems to be no consensus regarding seasonal differences in TIA incidence.

Transient ischemic attack (TIA) is an acute episode of temporary neurologic impairment lasting <24 h, caused by focal ischemia in the brain or retina. TIAs are variable in duration, commonly lasting from 5 to 60 min, but they occasionally last as long as 24 h, but may leave no persistent neurological deficit [1]. According

Table 1. Prevalence of TIA according to age, sex, and race/ethnic group

Population	Age, years	TIA, %		Year and reference
		men	women	
African-Americans				
Jackson, Miss., US				1996 [2]
	45–54	1.5	3.2	
	55–64	1.7	3.2	
	Total	1.6	3.2	
Forsyth, N.C., US				1996 [1]
	45–54	4.0	7.6	
	55–64	4.6	7.8	
	Total	4.3	7.7	
Evans, Ga., US				1973 [3]
	45–54	12.1	0.0	
	55–64	8.9	13.8	
	65	12.1	8.6	
European-Americans				
Forsyth, N.C., US				1996 [2]
	45–54	3.2	5.1	
	55–64	2.5	6.4	
	Total	2.9	5.7	
Evans, G.A., US				1973 [3]
	45–54	20.8	4.9	
	55–64	15.5	10.4	
	65	30.3	18.2	

to the recent American Heart Association/American Stroke Association diagnostic recommendations, TIA patients should undergo a neuroimaging evaluation within 24 h of symptom onset. Patients who have experienced a TIA are at high risk of stroke. However, there are few epidemiologic data on TIA, especially reviews of the incidence and prognostic value of TIAs. In this review, I will focus on the incidence of TIA and subsequent stroke events from an epidemiological point of view.

Prevalence and Incidence of Transient Ischemic Attack

The prevalence of TIA according to age, sex, and race/ethnic group is shown in table 1 [2, 3]. Among African-Americans, the prevalence of TIA does not seem to increase according to age in both men and women. According to the Atherosclerosis Risk in Communities (ARIC) Study, the prevalence of TIA in African-American

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men and women per 1,000 persons was 1.5–1.7 and around 3.2 in Jackson, Miss., but 4.0–4.6 and 7.6–7.8 in Forsyth, N.C., respectively [2]. However, in Evans County, Ga., the prevalence of TIA in the age groups 45–54, 55–64, and 65+ years was 12.1, 8.9, and 12.1 in men and 0, 13.8, and 8.6 in women per 1,000 persons, respectively [3]. These prevalence results are much higher than those obtained in Jackson and Forsyth. The data for Jackson and Forsyth are from 1996, which is 23 years after the Evans data. These two sets of data may not be compared simply because of a different generation.

In the ARIC study, the diagnosis of TIA was categorized as *definite* for a sudden onset of transient limb paralysis, with or without other signs, lasting up to 24 h and leaving no significant deficit; *probable* for other transient focal neurologic deficits lasting up to 24 h; *possible* for a less clear-cut history of symptoms or non-focal symptoms, or *vague* for anxiety and/or emotional symptoms. Evans County, is located in 'the Stroke Belt' in the south-eastern United States, which shows relatively higher stroke incidence. Therefore the prevalence of TIA in Evans County seems to be greater than in other areas.

In a European-American population in Forsyth, the prevalence of TIA was 2.9 and 5.7 in men and women per 1,000 persons, respectively. In Evans, the TIA prevalence of a European-American population was 20.8, 15.5, and 30.3 in men and 4.9, 10.4, and 18.2 in women per 1,000 persons according to the 45–54, 55–64, and 65 or older (65+) age groups, respectively. The prevalence of TIA tends to increase according to age in both men and women.

The Hisayama study examined the prevalence of TIA in the Japanese population [4]. The prevalence of TIA in the Hisayama study was 4.9 per 1,000 persons [4], less than half that in the European-American population in Evans. (13.8 per 1,000 persons) [3]. The etiology of incident TIA in Japan may be different from that in Western countries. Among the Hisayama participants with TIA, 11 subsequent cerebral infarctions were observed; they were diagnosed as 6 lacunar infarctions, 3 embolisms, and 2 atherothromboses by clinical and/or pathological finding or autopsy. The ARIC study showed that TIA due to atherosclerosis was attributable to myocardial infarction in 57% and to stroke in 38% of mortality patients (n = 37) [2]. TIAs due to atherosclerosis (which is usually of carotid artery origin) are estimated to be less common in Japan than in Western countries, and lacunar stroke might be important as an etiology of TIA in Japan [2].

As illustrated in figure 1 [4–11] and table 2, [4, 5, 7, 8, 10, 12–15] the Hisayama study found that the average incidence of the first TIA was 0.78 and 0.38 per 1,000 person-years in men and women, respectively [4]. According to community studies in the US, the average incidence rate for the first TIA was 0.31 per 1,000 person-years (0.93 per 1,000 person-years for those aged >65 years) in Rochester, Minn. [16], and 1.1 per 1,000 person-years in Seal Beach, Californian community [11], where the incidence of all strokes and TIA with previous cerebrovascular events were 7.1 and 1.4 per 1,000 person-years during the period 1963–1967, respectively.

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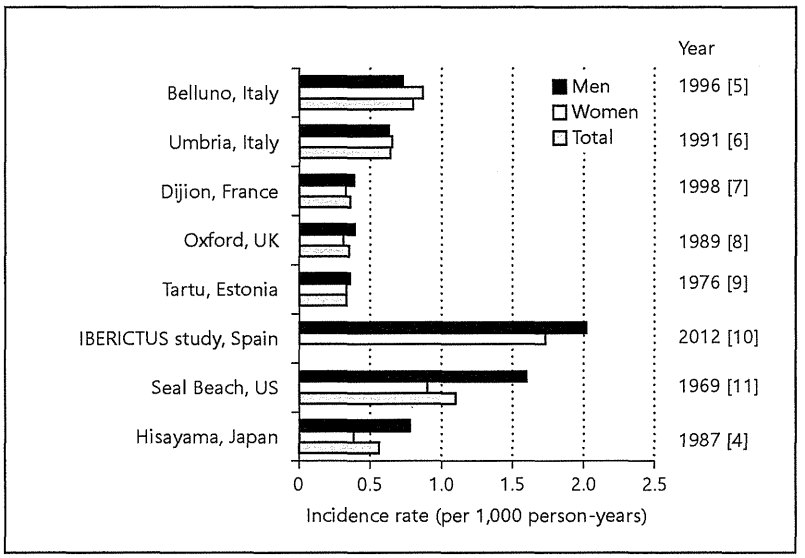

Fig. 1. Incidence of TIA in several countries.

The incidence for men was 9.7, 1.7 times the incidence of 5.7 for women per 1,000 person-years.

The incidence rate of TIA in Belluno, Italy, was 0.80 per 1,000 person-years, and the incidence was non-significantly higher in women than in men (0.73 per 1,000, 95% confidence interval, CI: 0.57–0.91 in men, and 0.87 per 1,000, 95% CI: 0.70–1.06 in women) [5]. After adjustment for the European population, the overall incidence rate decreased to 0.58 per 1,000 inhabitants per year. The mean age of new TIA patients was 73.9 years, and the women were significantly older than the men ($p < 0.001$). The SEPIVAC study of a population in Umbria, Italy revealed a crude rate of 0.64 per 1,000 per year (95% CI: 0.52–0.78), and the authors reported that the rate adjusted to the European population is 0.42 (95% CI: 0.33–0.54) [6]. It is of note that in the Umbria population, one third of the new TIA patients was cared for at home [6]. In Tartu, Estonia, USSR, from 1970 to 1973, the incidence of TIA was 0.33 per 1,000 person-years [9], and the mortality rate for stroke for this population was 0.98 per 1,000 person-years [9]. The Italian and Estonian data on the incidence of TIA, its dependence on age and sex, and mortality rate are close to the corresponding data reported from other countries.

The Oxfordshire Community Stroke Project showed that the crude TIA incidence rate and the TIA rate standardized to the 1981 population of England and Wales were 0.35 and 0.42 per 1,000 person-years, respectively [8]. The incidence of TIA increased sharply with increasing age, and the overall incidence in men was very similar to that

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Table 2. Incidence and mortality of TIA according to age, sex, and race/ethnic group (per 1,000 person-years)

a Asia: Hisayama, Japan

Age group	Incidence		
	men	women	total
40–49 years	0.41	0.00	0.18
50–59 years	1.16	0.57	0.84
60–69 years	0.89	0.52	0.69
70– years	0.45	0.66	0.66
Total	0.78	0.38	0.56

b Europe

Age group	Incidence			Mortality		
	men	women	total	men	women	total
Udine District, Italy [5], 2007–2009						
<45 years	0.03	0.01	0.02			
45–54 years	0.29	0.05	0.16			
55–64 years	0.52	0.05	0.26			
65–74 years	0.94	0.71	0.81			
75–84 years	3.93	2.51	3.04			
85– years	5.34	3.44	3.95			
Total	0.56	0.49	0.52			
IBERICTUS, Spain [7]						
18–24 years	0.03	0.03	0.03	0.00	0.00	0.00
25–34 years	0.08	0.09	0.08	0.00	0.00	0.00
35–44 years	0.35	0.22	0.29	0.06	0.03	0.05
45–54 years	0.96	0.36	0.66	0.07	0.13	0.09
55–64 years	2.37	1.14	1.75	0.10	0.10	0.10
65–74 years	4.91	2.58	3.67	0.06	0.12	0.09
75–84 years	10.13	6.93	8.27	0.13	0.08	0.10
85– years	14.45	13.60	13.88	0.22	0.20	0.02
Total	2.02	1.73	1.87	0.11	0.12	0.12
Central Spain (the NEDICES study) [7]						
65–69 years	9.47	3.29	6.06			
70–74 years	11.27	15.25	13.49			
75–79 years	22.33	18.02	19.83			
80–84 years	10.75	15.22	13.53			
85– years	30.61	21.47	24.90			
Total	14.30	12.83	13.45			
Belluno, Italy [8]						
0–54 years	0.06	0.01	0.03			
55–64 years	1.09	1.04	1.06			
65–74 years	3.39	1.47	2.24			
75–84 years	7.20	6.06	6.39			
85– years	7.57	10.54	10.06			
Total	0.73	0.87	0.80			

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Table 2. Continued

b Europe

Age group	Incidence			Mortality		
	men	women	total	men	women	total
Dijon, France [10]						
<34 years	0.00	0.01				
35–44 years	0.08	0.02				
45–54 years	0.27	0.00				
55–64 years	0.27	0.33				
65–74 years	1.50	1.03				
75–84 years	3.04	2.18				
85– years	4.68	2.20				
Total	0.39	0.33				
Oxfordshire, UK [12]						
<15 years	0.00	0.00	0.00			
15–44 years	0.02	0.02	0.02			
45–54 years	0.25	0.26	0.25			
55–64 years	1.22	0.63	0.92			
65–74 years	2.43	0.90	1.61			
75–84 years	3.01	2.29	2.57			
85– years	0.70	2.87	2.32			
Total	0.39	0.31	0.35			

Novosibirsk, Russia [13]

Age group	Incidence, 1987–1988			Incidence, 1996–1997		
	men	women	total	men	women	total
<45 years	0.02	0.02	0.02	0.02	0.01	0.01
45–64 years	0.49	0.40	0.44	0.68	0.47	0.56
65–74 years	1.26	0.38	0.68	1.24	1.39	1.34
75– years	0.34	0.56	0.51	2.27	1.74	1.85
Total	0.17	0.15	0.16	0.25	0.32	0.29

c America: Greater Cincinnati, Ohio [15]

Age group	Incidence (White)			Incidence (Black)		
	men	women	total	men	women	total
<35 years	0.01	0.02	–	0.02	0.03	–
35–44 years	0.05	0.12	–	0.16	0.13	–
45–54 years	0.85	0.72	–	1.30	0.30	–
55–64 years	1.55	0.96	–	2.06	2.49	–
65–74 years	4.68	2.47	–	3.38	3.30	–
75–84 years	7.5	5.21	–	6.13	6.47	–
85– years	7.19	5.89	–	15.60	8.47	–
Total	1.01	0.68	–	1.07	0.93	–

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in women (incidence ratio 1.3). However, in middle age, men were 2.6 times more likely to suffer a TIA.

In Dijon, France, crude TIA incidence rates of 0.39 and 0.33 per 1,000 person-years were revealed for men and women, respectively [7]. The mean age of first-ever TIA was higher in women (71.8 years) than in men (70.4 years). CT scans were performed in 97% of the cases. These incidence rates were similar to those of previous population-based studies, such as Belluno [5], Tartu [9], and Oxford [8].

The IBERICTUS study results published in 2006 (2,257 strokes and 443 TIAs in patients aged >17 years) demonstrated that the incidence rates for the first TIA were 2.02 and 1.73 per 1,000 person-years in men and women [10], respectively, which are relatively higher than those in Japan. The IBERICTUS age-standardized (to the European population) incidence rates of TIA were 0.30 and 0.27, and those of all strokes (non-TIA) were 1.6 and 1.3 per 1,000 person-years in men and women, respectively; those of ischemic stroke were 4 times that of TIA and approximately one quarter that of intracerebral hemorrhage [10]. In addition, the in-hospital mortality rate of TIA patients was 0.11 and 0.12 per 1,000 person-years in men and women, respectively. However, a limitation of this study was that it is very difficult to detect TIA when there has only been a very short duration of TIA symptoms.

The Greater Cincinnati/Northern Kentucky Stroke Study reported that the age-adjusted rate was significantly lower for white women than for all other race/gender groups [14]. The total incidences of TIA were 1.01 and 0.68 per 1,000 in white men and women, and 1.07 and 0.93 in black men and women, respectively. The highest incidence of TIA of any group was seen in the very elderly black men (15.6 events per 1,000 person-years). The incidence of TIA increased very markedly with age, regardless of race or gender.

Symptoms of Transient Ischemic Attack

The ARIC study of several US populations found that 46.6% of the patients experienced at least one sudden-onset symptom of TIA, with 12.9% receiving a final diagnosis of TIA. The most common symptom among the TIA sudden-onset symptoms was dizziness (35.9%), but only 1.2% of the patients with dizziness had a final diagnosis of TIA, for a prevalence of 0.4% in all patients [2].

The Risk Factors for Transient Ischemic Attack

The risk factors for TIA or stroke are the same as those for other vascular diseases, similar to heart attack (coronary artery disease) or peripheral vascular disease, which causes decreased blood flow to the legs. However, the evidence of risk factors for TIA

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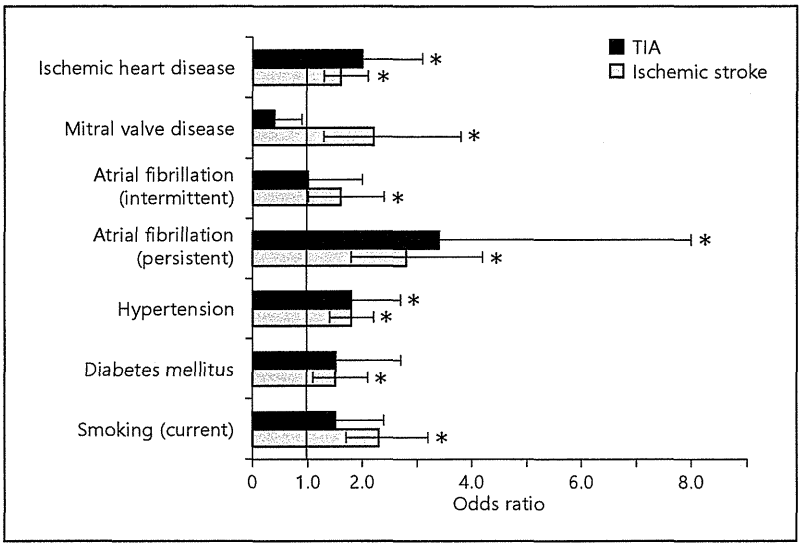

Fig. 2. Risk factors and their odds ratios for ischemic stroke and TIA.

excluding ischemic strokes has been very limited. In a case-control study from Mayo Clinic [16] odds ratios of strokes and TIA for various risk factors were calculated (fig. 2). For both ischemic heart disease and hypertension, the odds ratios of ischemic stroke were similar to those of TIA. Persistent and intermittent atrial fibrillations were found to be risk factors for ischemic stroke, while persistent atrial fibrillation was a risk factor only for TIA.

The Mayo Clinic data, which were collected over a 25-year period (1955–1979) show that TIA is a risk factor not only for stroke but also for death, especially death due to cardiovascular disease [16]. A 2010 meta-analysis revealed that there were no significant differences in sleep disorder breathing prevalence by event type, timing after stroke, or type of monitoring, although obstructive sleep apnea is very common in patients with TIA and stroke [17].

The ABCD score was developed to predict individuals at high early risk of stroke after TIA and to triage patients on the first presentation for medical attention [18]. The score is based on clinical characteristics detected at the time of first assessment for the following variables: Age ≥60 years, Blood pressure ≥140/90 mm Hg, Clinical features of TIA (weakness and speech impairment), and Duration of symptoms (≥60 or <60 min). This score was further validated and refined with the addition of a point for diabetes ($ABCD^2$ score) [19]. Details are described in the chapter by Wolf et al.

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Prognosis of Stroke Events after Onset of Transient Ischemic Attack

Several risk scores have been developed to help stratify short-term stroke risk in patients with TIA [20]. The California score predicts the risk of stroke within 90 days. The ABCD score predicts the risk within 90 days and at 7 days, and the ABCD^2 score predicts the risk at 90, 30, 7, and 2 days.

A 2007 systematic review for early stroke risk after the onset of TIA demonstrated that the pooled stroke risks were 3.1 and 5.2% (95% CI: 2.0–4.1 and 3.9–6.5) at 2 and 7 days, respectively [21]. The lowest and highest risks were observed in studies of emergency treatment by stroke specialists (0.9%) and in population-based studies without emergency medications (11%), respectively.

There are very few studies on the long-term prognosis after the onset of TIA. A prospective study showed that the 10-year risks of stroke, myocardial infarction, and cardiovascular disease (stroke, myocardial infarction, or vascular death) were 18.8% (95% CI: 13.6–23.7), 27.8% (95% CI: 21.8–33.3), and 42.8% (95% CI: 36.4–48.5), respectively [22].

A review table shows prognosis stroke events after the onset of TIA according to race/ethnic group by time course (table 3) [14, 15, 17, 23–33]. A large study in Northern California noted that the 3-month stroke risk was 10.5% after the onset of TIA [31]. The risk of stroke after TIA in Canada was 9.5% at 3 months, and 14.5% at 1 year [26]. However, these studies were not performed with physician confirmation.

For many years, population-based data in Rochester have shown temporal trends in TIA incidence in the US [24]. However, black patients were only 1% of the Rochester study population, compared with 15.2% for the Greater Cincinnati/Northern Kentucky population mentioned earlier [14].

A meta-analysis of observational studies estimated the risk of stroke at 2, 30, and 90 days after TIA [34]. In that analysis, the pooled early risk of stroke was 3.5, 8.0, and 9.2% at 2, 30, and 90 days after TIA, respectively. This prognostic information is very valuable to patients and health care providers.

In the general population, the crude rates of stroke risk (%) were 1.7, 4.8, 6.6, 8.5, and 11.4 for 2 days, 1 week, 1 month, 3 and 6 months, respectively. In hospital patients, the rates were 13.7 and 12.4 for 1 and 3 months, respectively.

Family History

There is a very limited number of articles on the association between family history of stroke and the incidence of stroke after TIA. The Oxfordshire Community Stroke Project has shown that a family history of stroke does not predict the risk of ischemic stroke after TIA (odds ratio, 0.87; 95% CI: 0.57–1.32) [35]. Thus, the current available data show that the risk of ischemic stroke after TIA is not highly heritable.

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Table 3. Prognosis of stroke events after onset of TIA according to race/ethnic groups

	Total	Stroke risk, %						Year and reference
		2 days	1 week	1 month	2 months	3 months	6 months	
General population								
Europe								
Rochester, Minn.	198			7.6		10.1		1973 [15]
Oxfordshire, UK	209		8.6	12.0				1990 [23]
								2003 [24]
Southwest Germany	1,150						13.0	2004 [25]
America								
Nueces County, Tex.	612	1.6		3.2		4.0		2010 [17]
Alberta, Canada	2,285	1.4		6.7		9.5		2004 [26]
Greater Cincinnati, Ohio	927	2.4	3.9	6.9	7.8	8.6	9.5	2005 [14]
Crude averages		1.7	4.8	6.6		8.5	11.4	
Hospital-based population								
Europe								
London, UK	234						29.0	1981 [27]
Iowa City, Iowa	74		6.8[1]					1985 [28]
	62					8.1		1985 [28]
Oxford, UK	209			12.0				2003 [24]
Oxfordshire, UK	87			11.5		17.3		2004 [29]
Northern Portugal	141	9.9		17.7				2006 [30]
America								
Northern California	1,707					10.5		2000 [31]
Ontario, Canada	265					6.0		2004 [32]
NASCET	603					20.1		2004 [33]
Crude averages				13.7		12.4		

[1] Six days, 16.2% for recurrent TIA.

Diurnal and Seasonal Variations in Stroke and Transient Ischemic Attack Incidence

A seasonal variation in stroke incidence has been reported; increases in the stroke incidence, mortality, and the hospitalization of stroke patients during the winter season and a decrease during the warmer or summer seasons in the US [36] and Japan [37]. The Framingham Heart Study revealed that stroke events occurred significantly more often on Mondays than any other days, particularly for working men, and that during the day strokes occurred more frequently between 8 am and noon [36]. The Hisayama Study described a significant seasonality in the incidence of stroke subtypes (except for subarachnoid hemorrhage). In addition, the incidences of intracerebral hemorrhage and cerebral infarction were negatively associated with mean ambient temperature [37]. Karagiannis et al. [38] studying over 8,000 patients in a 10-year study in Greece, found that there was a significant seasonal variation for ischemic strokes with

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the average of 8.4% above peak incidence in spring and the average 10.4% below the lowest rate in summer.

The evidence for seasonal variations in TIA incidence is limited, in contrast to the many significant associations between stroke and seasonal variables. Manfredini et al. [39] showed that TIAs were most frequent in autumn and winter (the highest number of cases was in October), less common in spring and summer (the lowest number of cases was in February), and most frequent on Monday (all p values <0.0001). A large Hungarian registration study (n = 12,556) between 2005 and 2007 revealed that the peak period of TIA incidence was during spring (in May and April for men and women, respectively), whereas lowest number of events occurred in December for both sexes ($p < 0.001$), and that the highest morbidity from TIA occurred on Mondays for men and women [40]. There was no significant seasonal variation in the occurrence of intracerebral hemorrhage, subarachnoid hemorrhage, or TIA in northern Greece [38]. In a large stroke registry study in Japan (n = 12,660 patients), no seasonal difference was observed in stroke patients with a past history of stroke/TIA [41].

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Original Article

Small Dense Low-Density Lipoproteins Cholesterol can Predict Incident Cardiovascular Disease in an Urban Japanese Cohort: The Suita Study

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Aim: **Several lines of evidence indicate that small dense low-density lipoproteins (sd-LDL) are more atherogenic than large buoyant LDL; however, few prospective studies have addressed the role of sd-LDL in cardiovascular disease (CVD). We therefore examined the association between sd-LDL cholesterol (sd-LDL-C) and CVD in a Japanese cohort.**

Methods: **An 11.7-year prospective study was performed using a general population aged 30-79 without a history of cardiovascular disease. Direct LDL-C and sd-LDL-C were measured in samples from 2034 participants (968 men and 1066 women).**

Results: **During the follow-up period, there were 116 incident cases of CVD. The multivariable-adjusted hazard ratios (HRs) of sd-LDL-C for CVD were calculated using a proportional hazards regression model after adjusting for age, hypertension, diabetes, use of lipid-lowering drugs, body mass index, and current smoking and alcohol drinking, and found that increasing quartiles of sd-LDL-C were associated with increased risk of CVD. We also determined that age and sex-adjusted HRs per 10 mg/dL of sd-LDL-C and HRs for CVD, stroke, cerebral infarction, and coronary artery disease were 1.21 (95% CI: 1.12-1.31), 1.17 (95% CI: 1.05-1.30), 1.15 (95% CI: 1.00-1.33), and 1.29 (95% CI: 1.14-1.45), respectively.**

Conclusions: **It was demonstrated that sd-LDL-C was significantly associated with CVD in a Japanese population, providing evidence of sd-LDL-C as an important biomarker to predict CVD.**

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Key words; Cardiovascular disease, Lipoproteins, Lipids, Risk factors, Epidemiology

Introduction

The causal relationship between high levels of serum low-density lipoprotein cholesterol (LDL-C) and cardiovascular disease (CVD) has been well established in previous cohort studies[1-5]. Recent clinical trials have also indicated significant event reduction by statins in the primary and secondary prevention of CVD[6-8]; therefore, LDL-C is one of the most important risk factors of CVD and many guidelines, including ours, recommend certain target LDL-C goals for risk management to prevent the development of CVD[5].

Although we use LDL-C as the primary target for cholesterol-lowering therapy, LDL particles are heterogeneous with respect to size and density. Compared to large, buoyant LDL, small dense LDL (sd-LDL) particles exhibit a prolonged plasma residence time, increased penetration into the arterial wall, lower affinity for the LDL receptor, and increased sus-

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ceptibility to oxidation[9]. Thus, sd-LDL particles possess elevated atherogenic potential. Furthermore, elevated concentrations of sd-LDL can be found in patients with type 2 diabetes, metabolic syndrome, chronic kidney disease, and familial combined hyperlipidemia[10-14], all of which have been found as highly atherogenic conditions. Although Hirano *et al.* showed that sd-LDL-C is significantly higher in patients with coronary artery disease (CAD) in a cross-sectional study[14], no prospective study has addressed whether sd-LDL-C can predict a risk for CVD in non-Western populations. Recently, the Québec Cardiovascular Study has shown prospectively that men with an elevated proportion of LDL with a diameter less than 25.5 nm had a 3.6-fold increased risk of CAD compared with men with relatively normal LDL[15], indicating the strong link of sd-LDL to CVD as a biomarker of cardiovascular disease. Due to its atherogenic properties it is useful to measure sd-LDL for risk assessment; however, a reliable routine method is lacking.

sd-LDL has been measured by ultracentrifugation[16] or gradient gel electrophoresis[17]; however, these methods are both unsuitable for routine analysis, because each requires expensive equipment, complicated techniques, and long assay times. Hirano *et al.* have recently developed a simple precipitation method for sd-LDL-C quantification consisting of 2 steps: removal of apolipoprotein B-containing sd-LDL-free lipoproteins by precipitation with heparin and magnesium, followed by LDL-C measurement by the homogeneous method[18, 19]. This assay allowed us to screen sd-LDL-C in a large cohort. Using this assay, Ai *et al.* recently performed a case control study using samples from the Framingham Offspring Study and found significantly higher sd-LDL-C in women with CAD[20]. Koba *et al.* also showed that sd-LDL-C is more powerful than LDL-C for the determination of CAD[21]; however, these are cross-sectional studies and a prospective study is required to determine whether sd-LDL is an independent predictor of CVD. Therefore, the aim of this study was to address the role of sd-LDL-C for incident CVD in a large cohort study in Japan, the Suita study.

Methods

Population

The Suita study, a cohort study on CVD of urban residents, was established in 1989. The details of this study have been described elsewhere[22]. Briefly, 6485 men and women aged 30-79 years underwent a baseline survey at the National Cerebral and Cardiovascular Center between September 1989 and March 1994, and received medical examinations every 2 years. For these participants, we set the baseline of the present study at medical examinations held between April 1994 and February 1995, since at that time serum samples were collected and stored at −80℃. During this period, 2,437 participants attended the medical examination and were followed until the end of 2007. Of these, 403 participants were excluded due to the following reasons: history of CAD or stroke (n=106), lost to follow-up (n=132), and other reasons such as missing data (n=165). Data from the remaining 2,034 participants (968 men and 1,066 women) were included in the analysis. Informed consent was obtained from all participants. This cohort study was approved by the Institutional Review Board of the National Cerebral and Cardiovascular Center.

Baseline Examination

Blood samples were collected after the participants had fasted for at least 10 hours. The samples were centrifuged immediately. Blood pressure was measured in triplicate on the right arm after 5 min of rest by well-trained physicians using a standard mercury sphygmomanometer. The average of the second and third measurements was used for analysis. At baseline examination, subjects were classified into one of the 5 blood pressure categories based on the criteria of ESH-ESC 2007: optimal (SBP <120 mmHg and DBP <80 mmHg), normal (SBP 120-129 mmHg or DBP 80-84 mmHg), high-normal blood pressure (SBP 130-139 mmHg or DBP 85-89 mmHg), hypertension grade 1 (SBP 140-159 mmHg or DBP 90-99 mmHg), or hypertension grade ≥2 (SBP ≥160 mmHg or DBP ≥100 mmHg). Antihypertensive drug users were classified according to their blood pressure at the baseline survey. Diabetes was defined as fasting serum glucose ≥7.0 mmol/L (126 mg/dL) or current use of medications for diabetes. Body mass index (BMI) was calculated as weight (kilograms) divided by height (meters) squared. Well-trained health nurses obtained information on smoking, drinking, and medical histories.

Laboratory Measurements

Serum total cholesterol, triglyceride, and HDL cholesterol (HDL-C) were determined by standard enzymatic methods. Serum glucose was also measured. For the purposes of this study, we used archived plasma samples that had been frozen at −80℃ and never previously thawed for the assessment of direct LDL-C and sd-LDL-C by homogeneous methods on a Hitachi 7180 automated analyzer (Hitachi, Tokyo, Japan)[18, 19]. The kits used for these tests (LDL-C and sd-LDL-C) were provided by Denka Seiken (Tokyo, Japan). Assays

for direct LDL-C and sd-LDL-C were previously calibrated and directly compared with concentrations obtained after isolation of LDL and sd-LDL by ultracentrifugation.

Endpoint Determination

As previously reported, the endpoints of the present study were (1) date of first CAD or stroke event; (2) date of death; (3) date of leaving Suita city; and (4) the end of December 2007. The first step in the survey for CAD and stroke involved checking the health status of all participants by repeated clinical visits every two years and yearly questionnaires by mail or telephone. In the second step, in-hospital medical records of participants who were suspected of having CAD were reviewed by registered hospital physicians or research physicians who were blinded to the baseline information. The criteria for a diagnosis of CAD included first-ever acute myocardial infarction, sudden cardiac death within 24 h after the onset of acute illness, or coronary artery disease followed by coronary artery bypass surgery or angioplasty. The criteria for definite and probable MI were defined according to the criteria of the MONICA (Monitoring Trends and Determinants of Cardiovascular Disease) project[23]. The criteria for stroke were defined according to the US National Survey of Stroke criteria[24]. Classification of patients into stroke subtypes was based on examination of computed tomography, magnetic resonance imaging, or autopsy.

Statistical Analysis

Continuous variables between groups were compared by analysis of variance and categorical variables were compared by a chi-square test. Triglyceride levels were logarithmically transformed to improve the skewed distribution. The hazard ratio (HR) for MI or stroke was calculated using a proportional hazards model adjusted for age, sex, hypertension (dichotomous variable), diabetes, HDL-C, BMI, smoking (never-smoked; ex-smoker; current smoker) and drinking (never-drank; ex-drinker; regular drinker). All confidence intervals were estimated at the 95% level and significance was set at $p<0.05$. All statistical analyses were conducted using the SAS statistical software package (release version 8.2; SAS Institute, Cary, NC, USA).

Results

Baseline Clinical Characteristics According to sd-LDL-C Quartiles

To study the role of sd-LDL in the incidence of CVD, we divided the cohort into quartiles according to the basal level of sd-LDL-C. **Table 1** shows the clinical characteristics and cardiovascular risk factors of the study population according to the quartiles of sd-LDL-C. BMI, total cholesterol, LDL-C, and triglyceride significantly increased across the sd-LDL-C quartiles both in men and women, while HDL-C decreased in both genders. A significant trend was observed across the quartiles for the severity of high blood pressure, lipid-lowering drug use, and prevalence of diabetes at baseline both in men and women; however, a significant trend for age was only found in women, not in men.

Incidence of CVD According to sd-LDL-C Quartiles

To confirm our previous study, the association between LDL-C and CAD was examined by dividing the cohort into quartiles according to the baseline LDL-C. It was found that age- and multivariable-adjusted HRs for CAD were statistically significant only in men, not in women or the total cohort. The HR of the 4th quartile in men was 3.53 (95% confidence intervals (CIs): 1.31-9.54) in an age-adjusted model and 3.56 (95% CIs: 1.28-9.86) in a multivariable-adjusted model, consistent with our previous report[1]. We then performed analysis to examine the effect of sd-LDL-C. During the observation period, 116 cases of CVD, 53 cases of stroke, 36 cases of cerebral infarction, and 63 cases of CAD were reported. As shown in **Table 2**, increasing quartiles of sd-LDL-C were significantly associated with increased risks of CVD (stroke + CAD), stroke, cerebral infarction, and CAD after age and multivariable adjustment. Age and sex-adjusted HRs per 10 mg/dL of sd-LDL-C for CVD, stroke, cerebral infarction, and CAD were 1.21 (95% CI: 1.12-1.31), 1.17 (95% CI: 1.05-1.30), 1.15 (95% CI: 1.00-1.33), and 1.29 (95% CI: 1.14-1.45), respectively. HRs after multivariable adjustment were almost the same. When we analyzed each gender, age-adjusted HRs per 10 mg/dL of sd-LDL-C for CVD, stroke, cerebral infarction, and CAD were significant in women, while those for CVD and CAD were significant in men. HR for CAD of the fourth quartile was almost 4 after age and multivariable adjustment in men.

After putting LDL-C into the multivariable adjusted-models (Model A), sd-LDL-C was still associated with increased risk for CVD, stroke, cerebral infarction, and CAD in the total cohort, for CVD in men, and CVD, stroke, and cerebral infarction in women. After further putting logarithmically transformed triglyceride and HDL-C variables into Model A (Model B), sd-LDL-C was still associated with

Table 1. Baseline characteristics of cardiovascular risk factors according to small dense LDL cholesterol quartiles

	Small dense LDL Cholesterol				*p* value for Trend
	Q1	Q2	Q3	Q4	
Men					
Number of subjects	241	243	242	242	
Small dense LDL, range (mean), mg/dL	6.3-27.8 (21.1)	27.9-38.2 (32.7)	38.3-53.4 (45.3)	53.5-119.6 (67.3)	
Age, year	60.9 ± 13.1	59.7 ± 12.5	59.1 ± 12.3	59.4 ± 11.3	0.421
Body mass index, kg/m^2	21.5 ± 2.5	22.4 ± 2.8	23.4 ± 2.4	24.0 ± 2.7	< 0.001
TC, mg/dL	170 ± 25	189 ± 24	199 ± 25	220 ± 27	< 0.001
HDL-C, mg/dL	60 ± 15	57 ± 14	51 ± 11	48 ± 11	< 0.001
LDL-C, mg/dL	86 ± 20	111 ± 21	124 ± 23	140 ± 26	< 0.001
Triglyceride, (median) mg/dL	66	87	112	167	< 0.001
Large-LDL-C, mg/dL	65 ± 17	78 ± 21	79 ± 22	72 ± 24	< 0.001
Sd-LDL-C/LDL-C ratio	0.25 ± 0.05	0.31 ± 0.07	0.38 ± 0.08	0.50 ± 0.11	< 0.001
Blood pressure category, %					0.002
Optimal blood pressure	31	26	25	19	
Normal blood pressure	30	24	19	26	
High-normal blood pressure	16	30	25	29	
Hypertension grade 1-3	19	26	29	28	
Antilipidemic drug use, %	1	4	5	8	0.003
Diabetes, %	3	5	7	9	0.023
Current Smoking, %	44	41	41	44	0.021
Current Drinking, %	66	71	72	74	0.577
Women					
Number of subjects	266	267	266	267	
Small dense LDL, range (mean), mg/dL	7.5-23.9 (18.7)	24.0-33.0 (28.6)	33.1-44.6 (38.5)	44.7-136.6 (59.7)	
Age, year	51.7 ± 13.0	57.3 ± 11.9	60.2 ± 11.2	60.4 ± 9.1	< 0.001
Body mass index, kg/m^2	21.0 ± 2.5	21.8 ± 3.2	22.5 ± 3.1	23.2 ± 2.8	< 0.001
TC, mg/dL	175 ± 23	200 ± 22	216 ± 25	234 ± 32	< 0.001
HDL-C, mg/dL	67 ± 13	64 ± 12	60 ± 13	54 ± 12	< 0.001
LDL-C, mg/dL	83 ± 17	109 ± 17	130 ± 18	153 ± 30	< 0.001
Triglyceride, (median) mg/dL	61	78	97	140	< 0.001
Large-LDL-C, mg/dL	64 ± 14	81 ± 15	92 ± 17	93 ± 25	< 0.001
Sd-LDL-C/LDL-C ratio	0.23 ± 0.04	0.27 ± 0.04	0.30 ± 0.05	0.40 ± 0.08	< 0.001
Blood pressure category, %					< 0.001
Optimal blood pressure	34	27	22	17	
Normal blood pressure	25	24	26	25	
High-normal blood pressure	16	29	20	35	
Hypertension grade 1-3	16	21	31	32	
Antilipidemic drug use, %	4	5	6	12	0.002
Diabetes, %	0	1	3	6	< 0.001
Current Smoking, %	13	10	6	7	0.056
Current Drinking, %	34	30	22	23	0.014

TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol. Large LDL-C, LDL-C-Sd-LDL-C. Hypertension was defined as described in methods. Diabetes was defined as fasting serum glucose ≥ 7.0mmol/L (126 mg/dL), the use of anti-diabetic agents, or both.