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	–

Uchiyama S, Amarenco P, Minematsu K, Wong KSL (eds): TIA as Acute Cerebrovascular Syndrome.
Front Neurol Neurosci. Basel, Karger, 2014, vol 33, pp 69–81 (DOI: 10.1159/000351892)

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

Uchiyama S, Amarenco P, Minematsu K, Wong KSL (eds): TIA as Acute Cerebrovascular Syndrome.
Front Neurol Neurosci. Basel, Karger, 2014, vol 33, pp 69–81 (DOI: 10.1159/000351892)

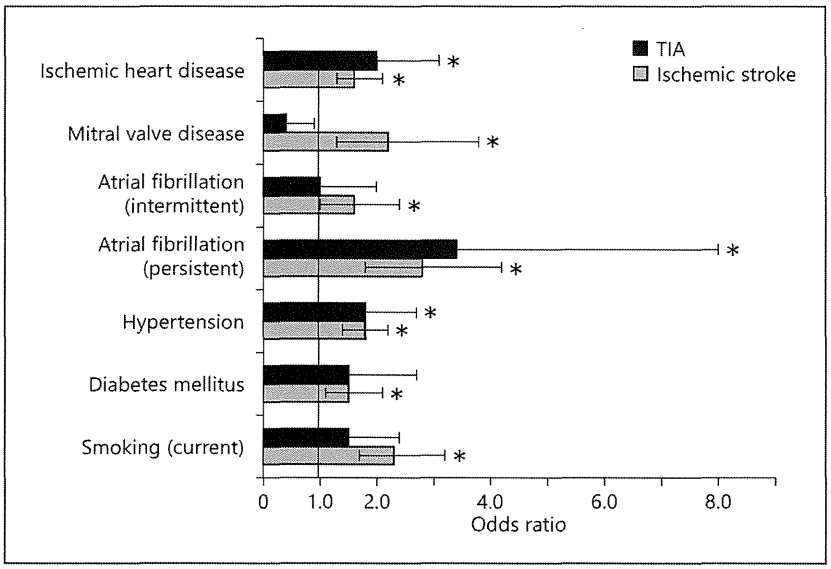

Fig. 2. Risk factors and their odds ratios for ischemic stroke and TIA.

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.

Uchiyama S, Amarenco P, Minematsu K, Wong KSL (eds): TIA as Acute Cerebrovascular Syndrome.
Front Neurol Neurosci. Basel, Karger, 2014, vol 33, pp 69–81 (DOI: 10.1159/000351892)

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.

Uchiyama S, Amarenco P, Minematsu K, Wong KSL (eds): TIA as Acute Cerebrovascular Syndrome.
Front Neurol Neurosci. Basel, Karger, 2014, vol 33, pp 69–81 (DOI: 10.1159/000351892)

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

Uchiyama S, Amarenco P, Minematsu K, Wong KSL (eds): TIA as Acute Cerebrovascular Syndrome.
Front Neurol Neurosci. Basel, Karger, 2014, vol 33, pp 69–81 (DOI: 10.1159/000351892)

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].

References

1 Pokorski RJ: Morbidity and mortality associated with transient ischemic attack (TIA). J Insur Med 1996;28:136–141.

2 Toole JF, Lefkowitz DS, Chambless LE, Wijnberg L, Paton CC, Heiss G: Self-reported transient ischemic attack and stroke symptoms: methods and baseline prevalence. The ARIC Study, 1987–1989. Am J Epidemiol 1996;144:849–856.

3 Karp HR, Heyman A, Heyden S, Bartel AG, Tyroler HA, Hames CG: Transient cerebral ischemia. Prevalence and prognosis in a biracial rural community. JAMA 1973;225:125–128.

4 Ueda K, Kiyohara Y, Hasuo Y, Yanai T, Kawano H, Wada J, Kato I, Kajiwara E, Omae T, Fujishima M: Transient cerebral ischemic attacks in a Japanese community, Hisayama, Japan. Stroke 1987;18:844–848.

5 Lauria G, Gentile M, Fassetta G, Casetta I, Agnoli F, Andreotta G, Barp C, Caneve G, Cavallaro A, Cielo R, Mongillo D, Mosca M, Olivieri P: Incidence of transient ischemic attacks in the Belluno Province, Italy. First-year results of a community-based study. Acta Neurol Scand 1996;93:291–296.

6 Ricci S, Celani MG, La Rosa F, Vitali R, Duca E, Ferraguzzi R, Paolotti M, Seppoloni D, Caputo N, Chiurulla C, et al: A community-based study of incidence, risk factors and outcome of transient ischaemic attacks in Umbria, Italy: the SEPIVAC study. J Neurol 1991;238:87–90.

7 Lemesle M, Madinier G, Menassa M, Billiar T, Becker F, Giroud M: Incidence of transient ischemic attacks in Dijon, France. A 5-year community-based study. Neuroepidemiology 1998;17:74–79.

8 Dennis MS, Bamford JM, Sandercock PA, Warlow CP: Incidence of transient ischemic attacks in Oxfordshire, England. Stroke 1989;20:333–339.

9 Zupping R, Roose M: Epidemiology of cerebrovascular disease in Tartu, Estonia, USSR, 1970 through 1973. Stroke 1976;7:187–190.

10 Diaz-Guzman J, Egido JA, Gabriel-Sanchez R, Barbera-Comes G, Fuentes-Gimeno B, Fernandez-Perez C: Stroke and transient ischemic attack incidence rate in Spain: The IBERICTUS Study. Cerebrovasc Dis 2012;34:272–281.

11 Friedman GD, Wilson WS, Mosier JM, Colandrea MA, Nichaman MZ: Transient ischemic attacks in a community. JAMA 1969;210:1428–1434.

12 Diaz-Guzman J, Bermejo-Pareja F, Benito-Leon J, Vega S, Gabriel R, Medrano MJ, Neurological Disorders in Central Spain Study G: Prevalence of stroke and transient ischemic attack in three elderly populations of central Spain. Neuroepidemiology 2008;30:247–253.

Uchiyama S, Amarenco P, Minematsu K, Wong KSL (eds): TIA as Acute Cerebrovascular Syndrome.
Front Neurol Neurosci. Basel, Karger, 2014, vol 33, pp 69–81 (DOI: 10.1159/000351892)

13 Feigin VL, Shishkin SV, Tzirkin GM, Vinogradova TE, Tarasov AV, Vinogradov SP, Nikitin YP: A population-based study of transient ischemic attack incidence in Novosibirsk, Russia, 1987–1988 and 1996–1997. Stroke 2000;31:9–13.

14 Kleindorfer D, Panagos P, Pancioli A, Khoury J, Kissela B, Woo D, Schneider A, Alwell K, Jauch E, Miller R, Moomaw C, Shukla R, Broderick JP: Incidence and short-term prognosis of transient ischemic attack in a population-based study. Stroke 2005;36: 720–723.

15 Whisnant JP, Matsumoto N, Elveback LR: Transient cerebral ischemic attacks in a community. Rochester, Minnesota, 1955 through 1969. Mayo Clin Proc 1973;48:194–198.

16 Evans BA, Sicks JD, Whisnant JP: Factors affecting survival and occurrence of stroke in patients with transient ischemic attacks. Mayo Clin Proc 1994;69: 416–421.

17 Johnson KG, Johnson DC: Frequency of sleep apnea in stroke and TIA patients: a meta-analysis. J Clin Sleep Med 2010;6:131–137.

18 Rothwell PM, Giles MF, Flossmann E, Lovelock CE, Redgrave JN, Warlow CP, Mehta Z: A simple score (ABCD) to identify individuals at high early risk of stroke after transient ischaemic attack. Lancet 2005; 366:29–36.

19 Johnston SC, Rothwell PM, Nguyen-Huynh MN, Giles MF, Elkins JS, Bernstein AL, Sidney S: Validation and refinement of scores to predict very early stroke risk after transient ischaemic attack. Lancet 2007;369:283–292.

20 Purroy F, Begue R, Quilez A, Pinol-Ripoll G, Sanahuja J, Brieva L, Seto E, Gil MI: The California, ABCD, and unified ABCD2 risk scores and the presence of acute ischemic lesions on diffusion-weighted imaging in TIA patients. Stroke 2009;40:2229–2232.

21 Giles MF, Rothwell PM: Risk of stroke early after transient ischaemic attack: a systematic review and meta-analysis. Lancet Neurol 2007;6:1063–1072.

22 Clark TG, Murphy MF, Rothwell PM: Long term risks of stroke, myocardial infarction, and vascular death in 'low risk' patients with a non-recent transient ischaemic attack. J Neurol Neurosurg Psychiatry 2003;74:577–580.

23 Dennis M, Bamford J, Sandercock P, Warlow C: Prognosis of transient ischemic attacks in the Oxfordshire Community Stroke Project. Stroke 1990; 21:848–853.

24 Lovett JK, Dennis MS, Sandercock PA, Bamford J, Warlow CP, Rothwell PM: Very early risk of stroke after a first transient ischemic attack. Stroke 2003; 34:e138–e140.

25 Daffertshofer M, Mielke O, Pullwitt A, Felsenstein M, Hennerici M: Transient ischemic attacks are more than 'ministrokes'. Stroke 2004;35:2453–2458.

26 Hill MD, Yiannakoulias N, Jeerakathil T, Tu JV, Svenson LW, Schopflocher DP: The high risk of stroke immediately after transient ischemic attack: a population-based study. Neurology 2004;62:2015–2020.

27 Humphrey PR, Marshall J: Transient ischemic attacks and strokes with recovery prognosis and investigation. Stroke 1981;12:765–769.

28 Calandre L, Molina JA: Short-term outcome of medically treated patients with transient ischemic attacks, reversible ischemic neurologic deficits and strokes with minimum residuum. Eur Neurol 1985; 24:281–285.

29 Coull AJ, Lovett JK, Rothwell PM, Oxford Vascular S: Population based study of early risk of stroke after transient ischaemic attack or minor stroke: implications for public education and organisation of services. BMJ 2004;328:326.

30 Correia M, Silva MR, Magalhaes R, Guimaraes L, Silva MC: Transient ischemic attacks in rural and urban northern Portugal: incidence and short-term prognosis. Stroke 2006;37:50–55.

31 Johnston SC, Gress DR, Browner WS, Sidney S: Short-term prognosis after emergency department diagnosis of TIA. JAMA 2000;284:2901–2906.

32 Gladstone DJ, Kapral MK, Fang J, Laupacis A, Tu JV: Management and outcomes of transient ischemic attacks in Ontario. CMAJ 2004;170:1099–1104.

33 Eliasziw M, Kennedy J, Hill MD, Buchan AM, Barnett HJ, North American Symptomatic Carotid Endarterectomy Trial G: Early risk of stroke after a transient ischemic attack in patients with internal carotid artery disease. CMAJ 2004;170:1105–1109.

34 Wu CM, McLaughlin K, Lorenzetti DL, Hill MD, Manns BJ, Ghali WA: Early risk of stroke after transient ischemic attack: a systematic review and meta-analysis. Arch Intern Med 2007;167:2417–2422.

35 Flossmann E, Rothwell PM: Family history of stroke does not predict risk of stroke after transient ischemic attack. Stroke 2006;37:544–546.

36 Kelly-Hayes M, Wolf PA, Kase CS, Brand FN, McGuirk JM, D'Agostino RB: Temporal patterns of stroke onset. The Framingham Study. Stroke 1995; 26:1343–1347.

37 Shinkawa A, Ueda K, Hasuo Y, Kiyohara Y, Fujishima M: Seasonal variation in stroke incidence in Hisayama, Japan. Stroke 1990;21:1262–1267.

Uchiyama S, Amarenco P, Minematsu K, Wong KSL (eds): TIA as Acute Cerebrovascular Syndrome.
Front Neurol Neurosci. Basel, Karger, 2014, vol 33, pp 69–81 (DOI: 10.1159/000351892)

38 Karagiannis A, Tziomalos K, Mikhailidis DP, Semertzidis P, Kountana E, Kakafika AI, Pagourelias ED, Athyros VG: Seasonal variation in the occurrence of stroke in Northern Greece: a 10 year study in 8,204 patients. Neurol Res 2010;32:326–331.

39 Manfredini R, Manfredini F, Boari B, Malagoni AM, Gamberini S, Salmi R, Gallerani M: Temporal patterns of hospital admissions for transient ischemic attack: a retrospective population-based study in the Emilia-Romagna region of Italy. Clin Appl Thromb Hemost 2010;16:153–160.

40 Bodis J, Csoboth I, Gazdag L, Kriszbacher I: Seasonal variation, weekly and daily rhythm of transient ischemic attack in Hungary. Clin Appl Thromb Hemost 2010;16:232.

41 Ogata T, Kimura K, Minematsu K, Kazui S, Yamaguchi T, Japan Multicenter Stroke Investigators C: Variation in ischemic stroke frequency in Japan by season and by other variables. J Neurol Sci 2004;225:85–89.

Yoshihiro Kokubo, MD, PhD, FAHA, FACC, FESC
Department of Preventive Cardiology
National Cerebral and Cardiovascular Center
5-7-1 Fujishiro-dai, Suita, Osaka 565-8565 (Japan)
E-Mail ykokubo@hsp.ncvc.go.jp

Uchiyama S, Amarenco P, Minematsu K, Wong KSL (eds): TIA as Acute Cerebrovascular Syndrome.
Front Neurol Neurosci. Basel, Karger, 2014, vol 33, pp 69–81 (DOI: 10.1159/000351892)

Toyoda K (ed): Brain, Stroke and Kidney.
Contrib Nephrol. Basel, Karger, 2013, vol 179, pp 35–41 (DOI: 10.1159/000346720)

Carotid Atherosclerosis in Kidney Disease

Yoshihiro Kokubo

Department of Preventive Cardiology, National Cerebral and Cardiovascular Disease, Suita, Japan

Abstract

Recently, chronic kidney disease (CKD) has become a major public health problem and a risk factor for all-cause mortality, cardiovascular disease (CVD). To prevent cardiovascular disease as early as possible, subclinical studies for CKD are essential. Recently, carotid atherosclerosis has been evaluated by measurement of the intima-media thickness (IMT) of the carotid artery wall, which is a good predictor of incidence of CVD. In this manuscript, I reviewed subclinical studies on the relationship between the carotid atherosclerosis and kidney dysfunction in a general population. Cross-sectional studies for general populations have shown an inverse association of carotid IMT with renal function. In one large cross-sectional study in a US population, the cystatin C level had no independent association with carotid IMT. However, in cross-sectional studies for outpatients, a significant association was observed between the two in subjects with kidney dysfunction. The association between CKD and carotid IMT tends to be weaker in apparently healthy populations than in patients. A higher level of blood pressure decreases renal function, and a decreased GFR raises blood pressure. In other words, increases in blood pressure and decreases of renal function exacerbate each other. Therefore, an investigation of the incidence of CVD and subclinical analyses of both renal dysfunction and blood pressure categories is called for. The impact of high-normal blood pressure and hypertension on stenosis were more evident in subjects with CKD. Carotid atherosclerosis tended to be more severe in subjects with CKD and high blood pressure. These findings pointed to the importance of early detection of subjects with decreased renal function and the strict management of blood pressure in general populations.

Recently, in prospective follow-up studies for general populations, chronic kidney disease (CKD) has become a major public health problem and a risk factor for all-cause mortality, cardiovascular disease (CVD), and its subtypes such as stroke and myocardial infarction (MI) [1]. In end-stage renal disease, the cardiovascular disease mortality rate is more than 10 times as high as that in the

general population [2]. Even at relatively high glomerular filtration rates (GFRs), renal dysfunction is an independent risk factor for incident CVD [1, 3]. In a large population sample from California (approximately 1.1 million people, mean age 52 years, 2.8 years of mean follow-up), compared with the estimated GFR (eGFR) ≥60 ml/min/1.73 m^2 group, the adjusted hazard ratios (95% CI) of all-cause mortality for eGFR = ranges of 45–59, 30–44, 15–29, and <15 ml/min/1.73 m^2 were 1.2 (1.1–1.2), 1.8 (1.7–1.9), 3.2 (3.1–3.4), and 5.9 (5.4–6.5). In an urban Japanese population sample, compared with the eGFR ≥90 ml/min/1.73 m^2 group, the hazard ratios (95% CIs) for the incidence of CVD and stroke were 1.8 (1.2–2.5) and 1.9 (1.3–3.0) in the eGFR = 50–59 ml/min/1.73 m^2 group and 2.5 (1.6–3.9) and 2.2 (1.2–4.1) in the eGFR <50 ml/min/1.73 m^2 group, respectively.

In order to prevent cardiovascular disease as early as possible, subclinical studies for CKD are essential. Recently, carotid atherosclerosis has been evaluated by measurement of the intima-media thickness (IMT) of the carotid artery wall, which is a good predictor of incidence of CVD [4]. It is important for persons with cardiovascular risk factors to be evaluated for carotid atherosclerosis before the onset of CVD. In this section, I would like to review subclinical studies on the association between carotid atherosclerosis and kidney dysfunction in a general population.

Kidney Dysfunction and Carotid Atherosclerosis

Table 1 shows a review of published articles on the association between kidney dysfunction and carotid atherosclerosis in various general populations. Among the three studies of Westerners, a cross-sectional study for Germany population showed that carotid IMT was increased by 0.02 mm (95% confidence intervals; 0.02 to 0.03 mm) in the 1st quartile, compared with the 4th quartile creatinine clearance [5]. In a study from Finland, carotid IMT was observed to be inversely associated with estimated GFR, although this study had a small sample size [6]. However, in a relatively large US population, the cystatin C level had no independent association with carotid IMT. Due to the wide age ranges in the US population, various cardiovascular risk factors are involved in carotid IMT. In Caucasian populations, kidney dysfunction may be weak but still a significant risk factor for carotid atherosclerosis nonetheless.

On the other hand, in Asian populations, CKD increases the risk of carotid atherosclerosis [7, 8]. A recent Japanese study has examined whether combinations of CKD with blood pressure category were associated with carotid arteriosclerosis. In hypertensive subjects, albuminuria and CKD were each associated with IMT (odds ratios = 1.85 and 1.79; 95% CIs = 1.13–3.03 and 1.09–2.94; p = 0.015 and 0.022, re-

Toyoda K (ed): Brain, Stroke and Kidney.
Contrib Nephrol. Basel, Karger, 2013, vol 179, pp 35–41 (DOI: 10.1159/000346720)

Table 1. Review of the association between renal dysfunction and carotid atherosclerosis (general population)

Population	Number	Sex	Age, years	Study design	Results	Journal
Caucasian						
Germany	3,364	M/F	≥55	cross-sectional	compared with the 4th quartile creatinine clearance, IMT was increased by 0.02 (0.02–0.03) in the 1st quartile.	Am J Kidney Dis 2008;51:584–593
Finland	247 (M) 258 (F)	M/F	40–62	cross-sectional	IMT is inverse associated with eGFR	Nephrol Dial Transplant 2009;24:2767–2772
US	6,557	M/F	45–84	cross-sectional	cystatin C level had no independent association with carotid IMT	Am J Kidney Dis 2009;53:389–398
Asian						
China	1,046	MF	63±9	cross-sectional	IMT = 0.74±0.27 mm (eGFR >90), 0.82±0.30 (eGFR = 60–89), 0.94±0.38 (eGFR <60); p < 0.001	Am J Kidney Dis 2007;49:786–792
Japan	1,351	M	58±10	cross-sectional	hypertension+CKD(+): HR = 1.79 (1.09–2.94, p = 0.022); normotension+CKD(+): no association, albuminuria+CKD(+)+IFG or DM: increase risk of carotid early atherosclerosis, albuminuria+CKD(+)+IFG or DM: no association	Hypertens Res 2007;30:1035–1041

IFG = Impaired fasting glucose; DM = diabetes mellitus; HR = hazard ratio.

spectively), but neither was associated with carotid IMT in subjects with normotension. In addition, combination of albuminuria and CKD was significantly associated with IMT in subjects with impaired fasting glucose (fasting plasma glucose levels ≥110 mg/dl or current use of antidiabetic medication), but not in those without. In order to evaluate the association between CKD and IMT, other cardiovascular risk factors, that is blood pressure should be also considered.

Table 2 summarizes the previous published articles on the association between kidney dysfunction and carotid atherosclerosis in patients. In Caucasian outpatients, a significant association was observed in subjects with kidney dysfunction [9–12]. In Chinese predialysis patients, carotid IMT shows statistically significant increases according to the stage of CKD [13]. Overall, the association between CKD and carotid IMT tend to be weaker in apparently healthy populations than in patients. Therefore, to detect the association between kidney dysfunction and carotid atherosclerosis, present illnesses should be considered, especially cardiovascular disease, i.e., higher blood pressure. The total population-attributable fractions of higher blood pressure for cardiovascular disease have been estimated as approximately 50% in men and 30% in women [14].

Toyoda K (ed): Brain, Stroke and Kidney.
Contrib Nephrol. Basel, Karger, 2013, vol 179, pp 35–41 (DOI: 10.1159/000346720)

Table 2. Review of the association between renal dysfunction and carotid atherosclerosis (outpatients)

Population	Subjects	Number	Sex	Age, years	Study design	Results	Journal
Caucasian							
UK	cases, outpatients plasma creatinine >1.4 mg/dl; control, 13 healthy normotensive	cases/ control: 114/13	MF	66 (55–71)	cross-sectional	common carotid artery-IMT: cases, 0.59±0.22 mm; control, 0.44±0.08 mm; p = 0.0012	Am J Kidney Dis 2005;46:856–862
France	CKD/hypertension /normotension patients	273	MF	58±15/ 59± 11/ 56±6	cross-sectional	IMT: no association; internal diastolic diameter = 6.3±1.1/ 5.8±0.7/5.5±0.6 (p < 0.001)	Kidney Int 2006;69:350–357
Australia	chronic renal failure patients	159:159	MF	64±8	case-control	0.89±0.17 vs. 0.73±0.13 mm, p < 0.05	Clin Exp Pharmacol Physiol 2000;27:639–641
Brazil	outpatients	122	MF	55±11	cross-sectional	IMT = 0.62±0.19 (eGFR <60) vs. 0.53±0.10 mm (eGFR >60); p = 0.030	Nephron Clin Pract 2010;115: c189–194
Asian							
China	predialysis CKD patients	227	MF	56±16	cross-sectional	0.64±0.18 (CKD I-II), 0.74±0.25 (CKD III), 0.81±0.25 (CKD IV), 0.86±0.20 (CKD V), p < 0.01	Eur J Int Med 2012;23:539–544

IFG = Impaired fasting glucose; DM = diabetes mellitus; HR = hazard ratio.

Subclinical Organ Damage

According to the 2007 European Society of Cardiology/European Society of Hypertension (ESC/ESH) Guidelines for the management of arterial hypertension [15] and the Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2009) [16], the risk of CVD was stratified by blood pressure categories and cardiovascular risk factors. The strata of the 2007 ESC/ESH Guideline consist of the first stratum (no risk factors), the second stratum (1–2 risk factors), the third stratum (3 or more risk factors, metabolic syndrome, or subclinical organ damage), and the fourth stratum. CKD is categorized in third stratum as subclinical organ damage (the third stratum), based on slight increases in plasma creatinine (men 1.3–1.5 mg/dl; women 1.2–1.4 mg/dl), microalbuminuria (30–300 mg), and low estimated glomerular filtration rate by the MDRD formula (<60 ml/min/1.73 m^2) or creatinine clearance by the Cockroft Gault formula (<60 ml/min). According to the 2007 ESC/ESH Guideline, the blood pressure category should be optimal blood pressure in order to prevent CVD from contributing to subclinical kidney damage.

Toyoda K (ed): Brain, Stroke and Kidney.
Contrib Nephrol. Basel, Karger, 2013, vol 179, pp 35–41 (DOI: 10.1159/000346720)

In an urban cohort, compared with optimal blood pressure subjects without CKD, the normal blood pressure, high-normal blood pressure, and hypertensive subjects without CKD showed increased risks of CVD, whereas the impact of each blood pressure category on CVD was more evident in subjects with CKD, especially in men (p for interaction = 0.04) [3]. Results of stroke were similar (p for interaction = 0.03 in men).

Recently, in a prospective cohort study, CKD in the high-normal blood pressure category at the baseline survey has been a risk factor for incident hypertension (multivariable-adjusted hazard ratio = 1.41) [17]. In an urban population cohort of Nagoya, Japan, the adjusted hazard ratio (95% CI) of incident hypertension in the highest tertile of GFR (4.4–76.1 ml/min/1.73 m^2) was 1.40 (1.26–1.57) compared with the first tertile [18]. A reduction in GFR of 10 ml/min/1.73 m^2 was associated with an 11% increase in risk for incident hypertension. In other studies, renal dysfunction has been associated with increased levels of inflammatory factors [19, 20], abnormal apolipoprotein levels [19], elevated plasma homocysteine [19], enhanced coagulability [20], anemia, left ventricular hypertrophy, increased arterial calcification, endothelial dysfunction and arterial stiffness [21]. These factors may contribute to elevated blood pressure.

On the other hand, The Multiple Risk Factor Intervention Trial study, one of the coronary heart disease prevention trials recommended to the National Heart and Lung Institute in US, showed that elevations of blood pressure are a strong independent risk factor for end-stage renal disease [22]. Compared with optimal blood pressure, hypertension is a risk factor for end-stage renal disease, with adjusted relative risks (95% CIs) for stages 1–4 hypertension of 3.1 (2.3–4.3), 6.0 (4.3–8.4), 11.2 (7.7–16.2) and 22.1 (14.2–34.3), respectively. A higher level of blood pressure decreases renal function [22], and a decreased GFR raises blood pressure. In other words, increases in blood pressure and decreases of renal function exacerbate each other.

Recently, the Suita Study has shown that CKD is independently associated with carotid atherosclerosis, especially in GFR <50 ml/min/1.73 m^2 (odds ratio = 1.91; 95% CI = 1.16–3.14) in a general urban population (1,602 men and 1,844 women) [23]. The impact of high-normal blood pressure and hypertension on stenosis were more evident in subjects with CKD (high-normal blood pressure: odds ratios (95% CIs) = 1.58 (1.08–2.31) and 2.74 (1.63–4.61); hypertension: odds ratios = 1.94 (1.36–2.77) and 2.36 (1.49–3.73) in non-CKD and CKD groups, respectively). Carotid atherosclerosis tended to be more severe in subjects with CKD and high blood pressure. This study suggests the importance of early detection of subjects with decreased renal function and the strict management of blood pressure in the general population.

Toyoda K (ed): Brain, Stroke and Kidney.
Contrib Nephrol. Basel, Karger, 2013, vol 179, pp 35–41 (DOI: 10.1159/000346720)

Conclusions

This review found that the association between renal function and carotid IMT tends to be weaker in general populations than that in outpatients. Increases in blood pressure and decreases of renal function exacerbate each other. A cross-sectional study in an urban population has shown that the impact of high-normal blood pressure and hypertension on stenosis were more evident in subjects with CKD. These findings stress the importance of early detection of subjects with decreased renal function and the strict management of blood pressure in general populations in order to prevent CVD in early stage. Additional studies are required to assess whether lowering of eGFR can actually increase the risk of carotid atherosclerosis according to blood pressure category in cohort study.

Acknowledgement

The present study was supported by the Intramural Research Fund of the National Cerebral and Cardiovascular Center (22–4–5) and by a grant (No. 23390178) from the Ministry of Education, Science, and Culture of Japan.

References

1 Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY: Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med 2004;351:1296–1305.
2 USRDS: The United States renal data system. Am J Kidney Dis 2003;42:1–230.
3 Kokubo Y, Nakamura S, Okamura T, Yoshimasa Y, Makino H, Watanabe M, et al: Relationship between blood pressure category and incidence of stroke and myocardial infarction in an urban Japanese population with and without chronic kidney disease: the Suita study. Stroke 2009;40:2674–2679.
4 Kokubo Y, Toyoda K, Watanabe M, Ono Y, Miyamoto Y, Nagatsuka K: Impact of carotid plaque on the risk of stroke and ischemic heart disease in a Japanese urban population: the Suita study. Cerebrovasc Dis 2011;31(suppl 2):7.
5 Desbien AM, Chonchol M, Gnahn H, Sander D: Kidney function and progression of carotid intima-media thickness in a community study. Am J Kidney Dis 2008;51:584–593.
6 Kastarinen H, Ukkola O, Kesaniemi YA: Glomerular filtration rate is related to carotid intima-media thickness in middle-aged adults. Nephrol Dial Transplant 2009;24:2767–2772.
7 Zhang L, Zhao F, Yang Y, Qi L, Zhang B, Wang F, et al: Association between carotid artery intima-media thickness and early-stage CKD in a Chinese population. Am J Kidney Dis 2007;49:786–792.
8 Ishizaka N, Ishizaka Y, Toda E, Koike K, Seki G, Nagai R, et al: Association between chronic kidney disease and carotid intima-media thickening in individuals with hypertension and impaired glucose metabolism. Hypertens Res 2007;30:1035–1041.
9 Lemos MM, Jancikic AD, Sanches FM, Christofalo DM, Ajzen SA, Carvalho AB, et al: Intima-media thickness is associated with inflammation and traditional cardiovascular risk factors in non-dialysis-dependent patients with chronic kidney disease. Nephron Clin Pract 2010;115:c189–c194.

Toyoda K (ed): Brain, Stroke and Kidney.
Contrib Nephrol. Basel, Karger, 2013, vol 179, pp 35–41 (DOI: 10.1159/000346720)

10 Zoungas S, Ristevski S, Lightfoot P, Liang YL, Branley P, Shiel LM, et al: Carotid artery intima-medial thickness is increased in chronic renal failure. Clin Exp Pharmacol Physiol 2000;27:639–641.
11 Briet M, Bozec E, Laurent S, Fassot C, London GM, Jacquot C, et al: Arterial stiffness and enlargement in mild-to-moderate chronic kidney disease. Kidney Int 2006;69:350–357.
12 Preston E, Ellis MR, Kulinskaya E, Davies AH, Brown EA: Association between carotid artery intima-media thickness and cardiovascular risk factors in CKD. Am J Kidney Dis 2005;46:856–862.
13 Zhou W, Ni Z, Yu Z, Shi B, Wang Q: Brain natriuretic peptide is related to carotid plaques and predicts atherosclerosis in predialysis patients with chronic kidney disease. Eur J Int Med 2012;23:539–544.
14 Kokubo Y, Kamide K, Okamura T, Watanabe M, Higashiyama A, Kawanishi K, et al: Impact of high-normal blood pressure on the risk of cardiovascular disease in a Japanese urban cohort: the Suita study. Hypertension 2008;52:652–659.
15 Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G, et al: 2007 guidelines for the management of arterial hypertension. The task force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens 2007;25:1105–1187.
16 Ogihara T, Kikuchi K, Matsuoka H, Fujita T, Higaki J, Horiuchi M, et al: The Japanese Society of Hypertension guidelines for the management of hypertension (JSH 2009). Hypertens Res 2009;32:3–107.
17 Kokubo Y, Nakamura S, Watanabe M, Kamide K, Kawano Y, Kawanishi K, et al: Cardiovascular risk factors associated with incident hypertension according to blood pressure categories in non-hypertensive population in the Suita Study: an urban cohort study. Hypertension 2011;58:e100.
18 Takase H, Dohi Y, Toriyama T, Okado T, Tanaka S, Sonoda H, et al: Evaluation of risk for incident hypertension using glomerular filtration rate in the normotensive general population. J Hypertens 2012;30:505–512.
19 Muntner P, Hamm LL, Kusek JW, Chen J, Whelton PK, He J: The prevalence of nontraditional risk factors for coronary heart disease in patients with chronic kidney disease. Ann Intern Med 2004;140:9–17.
20 Shlipak MG, Fried LF, Crump C, Bleyer AJ, Manolio TA, Tracy RP, et al: Elevations of inflammatory and procoagulant biomarkers in elderly persons with renal insufficiency. Circulation 2003;107:87–92.
21 Feldman HI, Appel LJ, Chertow GM, Cifelli D, Cizman B, Daugirdas J, et al: The chronic renal insufficiency cohort (CRIC) study: Design and methods. J Am Soc Nephrol 2003;14:S148–S153.
22 Klag MJ, Whelton PK, Randall BL, Neaton JD, Brancati FL, Ford CE, et al: Blood pressure and end-stage renal disease in men. N Engl J Med 1996;334:13–18.
23 Ohara T, Kokubo Y, Toyoda K, Koga M, Nagatsuka K, Nakamura S, et al: The impact of chronic kidney disease on carotid atherosclerosis in a general Japanese urban population: the Suita study. Stroke 2012;43:A2642.

Yoshihiro Kokubo, MD, PhD, FAHA, FACC, FESC
Department of Preventive Cardiology
National Cerebral and Cardiovascular Center
5-7-1, Fujishiro-dai, Suita, Osaka, 565-8565 (Japan)
E-Mail ykokubo@hsp.ncvc.go.jp

Toyoda K (ed): Brain, Stroke and Kidney.
Contrib Nephrol. Basel, Karger, 2013, vol 179, pp 35–41 (DOI: 10.1159/000346720)

Brief Report

Impact of Chronic Kidney Disease on Carotid Atherosclerosis According to Blood Pressure Category

The Suita Study

Tomoyuki Ohara, MD; Yoshihiro Kokubo, MD; Kazunori Toyoda, MD; Makoto Watanabe, MD; Masatoshi Koga, MD; Satoko Nakamura, MD; Kazuyuki Nagatsuka, MD; Kazuo Minematsu, MD; Masanori Nakagawa, MD; Yoshihiro Miyamoto, MD

Background and Purpose—We aimed to clarify the association of chronic kidney disease (CKD) with carotid atherosclerosis and the impact of CKD on carotid atherosclerosis according to blood pressure categories in an urban general population.

Methods—We studied 3466 Japanese individuals (35–93 years old) in the Suita Study. Carotid atherosclerosis was expressed as the maximum carotid intima-media thickness and the presence of stenosis (>25%). The estimated glomerular filtration rate was calculated using the equations recommended by the Japanese Society of Nephrology. CKD was defined as estimated glomerular filtration rate <60 mL/min per 1.73 m^2. Blood pressure categories were defined by the European Society of Hypertension and European Society of Cardiology 2007 criteria.

Results—The multivariable-adjusted maximum carotid intima-media thickness and odds ratio for stenosis in subjects with estimated glomerular filtration rate <50 mL/min per 1.73 m^2 were greater than those in subjects with estimated glomerular filtration rate ≥90 mL/min per 1.73 m^2. When subjects were stratified according to blood pressure categories, the multivariable-adjusted maximum carotid intima-media thickness was significantly greater in CKD subjects than in non-CKD subjects only in subjects with hypertension. Similarly, the impact of CKD on stenosis was evident only in subjects with hypertension (multivariable-adjusted odds ratios for stenosis [95% confidence interval] were 2.21 [1.53–3.19] in non-CKD/hypertension and 3.16 [2.05–4.88] in CKD/hypertension compared with non-CKD/optimal blood pressure).

Conclusions—In a general population, the association of CKD with carotid atherosclerosis was modest, but CKD was independently associated with carotid atherosclerosis in subjects with hypertension. ***(Stroke. 2013;44:00-00.)***

Key Words: carotid artery diseases ■ carotid intima-media thickness ■ hypertension ■ renal insufficiency, chronic

Chronic kidney disease (CKD) has been shown to be an independent risk factor for cardiovascular disease in general populations.[1] Recently, we have shown that even slight renal dysfunction, with an estimated glomerular filtration rate (eGFR) of 50 to 59 mL/min per 1.73 m^2, results in an increased risk of cardiovascular disease in an urban general population.[2]

One possible explanation for the association of CKD with cardiovascular disease is that CKD-related nontraditional risk factors accelerate atherosclerosis independent of traditional vascular risk factors.[3] However, there is controversy as to whether CKD is independently associated with carotid intima-media thickness (IMT).[4] This may be because the impact of CKD, especially mild kidney disease, on carotid atherosclerosis is somewhat limited. CKD seems to increase the risk of carotid atherosclerosis when hypertension and impaired glucose metabolism are present.[5] We hypothesized that the impact of CKD on carotid atherosclerosis differs according to the presence of concomitant cardiovascular risk factors. Thus, we aimed to clarify the association of CKD with carotid atherosclerosis and the impact of CKD on carotid atherosclerosis according to blood pressure (BP) categories in an urban general population.

Patients and Methods

We sequentially enrolled 3,446 individuals (1,844 women and 1,602 men, 35–93 years old [62±11 years]) who underwent regular health checkups and carotid ultrasonography between April 2002 and March 2004 from the participants in the Suita Study, an epidemiological study of cerebrovascular and cardiovascular diseases. Each index of

Received July 23, 2013; accepted August 19, 2013.

From the Departments of Cerebrovascular Medicine (T.O., K.T., K.M.), Preventive Cardiology (Y.K., M.W., Y.M.), Stroke Care Unit (M.K.), Hypertension and Nephrology (S.N.), and Neurology (K.N.), National Cerebral and Cardiovascular Center, Osaka, Japan; and North Medical Center (M.N.), Kyoto Prefectural University of Medicine, Kyoto, Japan.

This article encompasses the doctoral dissertation of Dr Ohara.

The online-only Data Supplement is available with this article at http://stroke.ahajournals.org/lookup/suppl/doi:10.1161/STROKEAHA.113.002957/-/DC1.

Correspondence to Tomoyuki Ohara, MD, Cerebrovascular Medicine, National Cerebral and Cardiovascular Center, 5-7-1 Fujishirodai, Suita, Osaka 565-8565, Japan. E-mail ohatomo@ncvc.go.jp

Stroke **is available at http://stroke.ahajournals.org** **DOI: 10.1161/STROKEAHA.113.002957**

Table 1. Adjusted Max-IMT According to eGFR Category

	eGFR, mL/min per 1.73 m²				*P* Value for Trend
	≥90	60–89	50–59	<50	
Men	236	1106	174	86	
Age adjusted	1.44±0.04	1.47±0.02	1.52±0.05	1.64±0.07*	0.078
Multivariable adjusted	1.43±0.04	1.48±0.02	1.51±0.05	1.63±0.07*	0.134
Women	436	1214	137	57	
Age adjusted	1.21±0.02	1.20±0.01	1.22±0.03	1.38±0.05†	0.014
Multivariable adjusted	1.21±0.02	1.20±0.01	1.21±0.03	1.34±0.05*	0.079

Means±SD (mm). eGFR indicates estimated glomerular filtration rate; and max-IMT, maximum carotid intima-media thickness.
*P<0.05 and †P<0.01 vs eGFR≥90.

carotid atherosclerosis was defined as follows. Max-IMT was defined as the maximum IMT in the entire scanned area. Stenosis was defined as the presence of a stenotic area ≥25% on a cross-sectional scan. The eGFR was calculated using equations recommended by the Japanese Society of Nephrology.[6] The subjects were categorized into 4 groups (eGFR ≥90, 60–89, 50–59, and <50 mL/min per 1.73 m²) as in our previous study.[2] CKD was defined as an eGFR <60 mL/min per 1.73 m². BP categories (optimal, normal, high-normal BP, and hypertension) were based on the European Society of Hypertension and European Society of Cardiology 2007 criteria.[7] The association of eGFR category with carotid atherosclerosis and the association of CKD with carotid atherosclerosis according to BP categories were examined using analysis of covariance and logistic regression analysis, after adjusting for cardiovascular risk factors as covariates (see Methods in the online-only Data Supplement).

Results

CKD was identified in 16.2% (eGFR=50–59: 10.9%; eGFR<50: 5.3%) of men and in 10.5% (7.4%, 3.1%) of women (see Table I in the online-only Data Supplement.). The multivariable-adjusted max-IMT and odds ratio for stenosis in subjects with eGFR<50 were significantly greater than those in subjects with eGFR≥90; however, the max-IMT and odds ratio in subjects with eGFR=50 to 59 were not significantly different from those in subjects with eGFR≥90 (Tables 1 and 2). Consequently, the max-IMT and odds ratio for stenosis in the whole CKD sample were not significantly greater than those in the eGFR≥90 group.

When subjects were stratified according to BP categories, the multivariable-adjusted max-IMT in the hypertension category was significantly greater in both sexes. The max-IMT was significantly greater in CKD subjects than in non-CKD subjects only in subjects with hypertension (Figure A). The prevalence of stenosis was higher in subjects with high-normal BP and hypertension in all subjects. The impact of CKD on the prevalence of stenosis was more pronounced in subjects with hypertension (multivariable-adjusted odds ratio [95% confidence interval], 2.21 [1.53–3.19] in non-CKD/hypertension and 3.16 [2.05–4.88] in CKD/hypertension; Figure B). Similar trends were found in the analysis of stenosis in men.

Discussion

In our study, CKD was independently associated with carotid atherosclerosis in subjects with hypertension, but not in nonhypertensive subjects. This is the first study to show the combined impact of CKD and hypertension on carotid atherosclerosis in an urban general population.

In previous studies in general populations, only one study reported that reduced kidney function was a strong predictor of greater carotid IMT at baseline and progression of carotid atherosclerosis independent of vascular risk factors.[8] Another study found no independent association of eGFR with carotid IMT.[9] In our study, eGFR <50 mL/min per 1.73 m²

Table 2. Adjusted Odds Ratios (95% CI) for Stenosis According to eGFR Category

	eGFR, mL/min per 1.73 m²				Odds Ratio/10 mL per min eGFR Increase
	≥90	60–89	50–59	<50	
Men and women	672	2320	311	143	
Cases of stenosis	47	318	69	48	
Age adjusted	1	1.09 (0.78–1.53)	1.34 (0.87–2.06)	1.91 (1.16–3.14)	0.94 (0.88–1.01)
Multivariable adjusted	1	1.17 (0.83–1.66)	1.37 (0.88–2.13)	1.79 (1.07–2.98)	0.94 (0.88–1.01)
Men	236	1106	174	86	
Cases of stenosis	22	226	51	32	
Age adjusted	1	1.37 (0.84–2.23)	1.71 (0.96–3.04)	1.86 (0.96–3.04)	0.95 (0.87–1.03)
Multivariable adjusted	1	1.56 (0.94–2.57)	1.85 (1.02–3.36)	1.81 (0.91–3.59)	0.95 (0.87–1.04)
Women	436	1214	137	57	
Cases of stenosis	25	92	18	16	
Age adjusted	1	0.85 (0.52–1.37)	0.99 (0.50–1.96)	2.38 (1.12–5.06)	0.93 (0.84–1.04)
Multivariable adjusted	1	0.84 (0.51–1.38)	0.91 (0.45–1.84)	2.04 (0.93–4.47)	0.95 (0.85–1.06)

CI indicates confidence interval; and eGFR, estimated glomerular filtration rate.

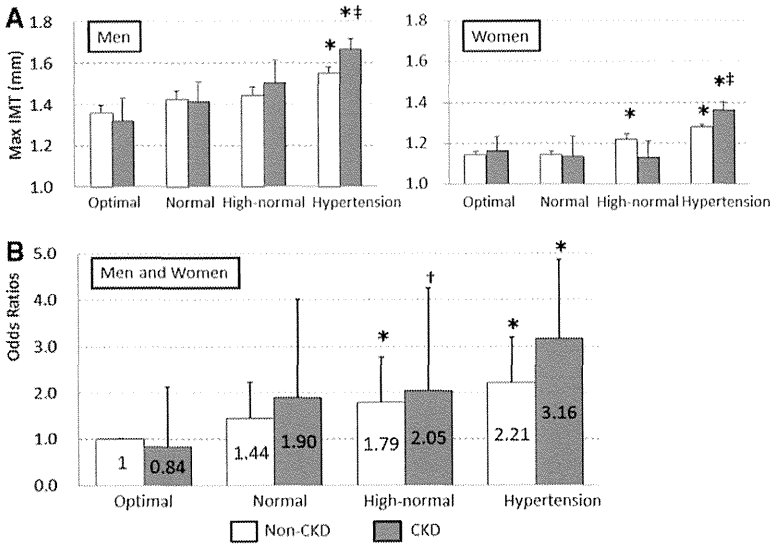

Figure. Multivariable-adjusted maximum carotid intima-media thickness (max-IMT; **A**) and odds ratios for stenosis (**B**) according to blood pressure (BP) category in subjects with and without chronic kidney disease (CKD). **P*<0.05; †*P*=0.053 vs non-CKD/optimal BP; ‡*P*<0.05 vs non-CKD subjects in the same BP category.

was independently associated with carotid atherosclerosis, whereas CKD was not. The inconsistent results of these studies might be attributable in part to different eligibility criteria, background, or methods for evaluating renal function. An alternative explanation is that the association of CKD with carotid atherosclerosis may be somewhat limited.

In a recent Japanese study, CKD was associated with increased IMT only in subjects with hypertension.[5] Similarly, we showed that CKD was independently associated with carotid atherosclerosis in subjects with hypertension, whereas there was no significant impact of CKD in nonhypertensive subjects. Our results suggest that the impact of CKD on carotid atherosclerosis differs according to the presence of concomitant vascular risk factors. CKD may not directly contribute to early carotid atherosclerosis but may rather accelerate the development of atherosclerosis in the setting of progressive endothelial dysfunction in those with hypertension.

We could not demonstrate a causal relationship between CKD, hypertension, and carotid atherosclerosis because of the cross-sectional design of our study. However, carotid atherosclerosis reflects the cumulative effects of cardiovascular risk factors that are present over many years. In the future, we plan to determine whether the coexistence of CKD and hypertension increases the risk of carotid atherosclerosis in a prospective study.

In conclusion, the association of CKD with carotid atherosclerosis was modest, but CKD was independently associated with carotid atherosclerosis in subjects with hypertension in an urban general population. Our results suggest that the presence of hypertension should be considered for risk stratification of CKD for improved stroke prevention.

Acknowledgments

We thank Drs Masao Shinomiya and Katsuyuki Kawanishi, the president and vice-president of the Suita Medical Association, respectively, and all members of the Suita Medical Association, the Suita City Health Center, Satsuki-Junyukai, and the Division of Preventive Cardiology.

Sources of Funding

This study was supported by the Japan Heart Foundation and the Astellas/Pfizer Grant for Research on Atherosclerosis Update, the Intramural Research Fund of the National Cerebral and Cardiovascular Center (22-4-5), and Grant-in-Aid for Scientific Research from the Japan Society for the Promotion of Science (Grant Numbers 23390138/23591288).

Disclosures

None.

References

1. Weiner DE, Tighiouart H, Amin MG, Stark PC, MacLeod B, Griffith JL, et al. Chronic kidney disease as a risk factor for cardiovascular disease and all-cause mortality: a pooled analysis of community-based studies. *J Am Soc Nephrol*. 2004;15:1307–1315.
2. Kokubo Y, Nakamura S, Okamura T, Yoshimasa Y, Makino H, Watanabe M, et al. Relationship between blood pressure category and incidence of stroke and myocardial infarction in an urban Japanese population with and without chronic kidney disease: the Suita Study. *Stroke*. 2009;40:2674–2679.
3. Schiffrin EL, Lipman ML, Mann JF. Chronic kidney disease: effects on the cardiovascular system. *Circulation*. 2007;116:85–97.
4. Kokubo Y. Carotid atherosclerosis in kidney disease. *Contrib Nephrol*. 2013;179:35–41.
5. Ishizaka N, Ishizaka Y, Toda E, Koike K, Seki G, Nagai R, et al. Association between chronic kidney disease and carotid intima-media thickening in individuals with hypertension and impaired glucose metabolism. *Hypertens Res*. 2007;30:1035–1041.
6. Matsuo S, Imai E, Horio M, Yasuda Y, Tomita K, Nitta K, et al; Collaborators developing the Japanese equation for estimated GFR. Revised equations for estimated GFR from serum creatinine in Japan. *Am J Kidney Dis*. 2009;53:982–992.
7. Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G, et al. 2007 Guidelines for the Management of Arterial Hypertension: The Task Force for the Management of Arterial Hypertension of ESH and ESC. *J Hypertens*. 2007;25:1105–1187.
8. Desbien AM, Chonchol M, Gnahn H, Sander D. Kidney function and progression of carotid intima-media thickness in a community study. *Am J Kidney Dis*. 2008;51:584–593.
9. Bui AL, Katz R, Kestenbaum B, de Boer IH, Fried LF, Polak JF, et al. Cystatin C and carotid intima-media thickness in asymptomatic adults: the MESA. *Am J Kidney Dis*. 2009;53:389–398.

SUPPLEMENTAL MATERIAL

Impact of chronic kidney disease on carotid atherosclerosis according to blood pressure: The Suita Study

Supplemental Methods

The Suita Study

Suita City is located adjacent to Osaka City, which belongs to the second largest metropolitan area in Japan. The Suita Study, an epidemiological study of cerebrovascular and cardiovascular diseases, is based on a random sampling of 12,200 Japanese urban residents.[1, 2] The participants have been visiting the National Cerebral and Cardiovascular Center every 2 years since 1989 for regular health checkups. Written informed consent was obtained from all participants. This study was approved by the Institutional Review Board of the National Cerebral and Cardiovascular Center.

Evaluation of renal function

Serum creatinine (Cr) was measured by the kinetic Jaffé method. The estimated glomerular filtration rate (eGFR) was calculated from the Cr value and age, using equations recommended by the Japanese Society of Nephrology.[3]

$$eGFR\ (mL/min/1.73m^2) = 194 \times age^{-0.287} \times Cr^{-1.094}\ (\text{for men})$$

and $$eGFR\ (mL/min/1.73m^2) = 194 \times age^{-0.287} \times Cr^{-1.094} \times 0.739\ (\text{for women}).$$

Carotid Ultrasound Measurements

Carotid atherosclerosis was evaluated by high-resolution ultrasonography with a 7.5-MHz transducer that produced an axial resolution of 0.1 mm. We measured the carotid arteries from the superior border of the collarbone to the inferior margin of the mandible. Details of the methods used for the carotid ultrasonic examination have been previously published.[4]

Measurement of Blood Pressure

Well-trained physicians measured blood pressure (BP) three times with the subject in a seated position using a mercury column sphygmomanometer, an appropriately sized cuff and a standard protocol. Before the initial BP reading was obtained, participants were seated at rest for at least 5 minutes. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were taken as the average of the second and third measurements, which were separated by more than 1 minute. Subjects were classified into one of four BP categories (optimal, normal, high-normal and hypertension) based on BP values according to the European Society of Hypertension and European Society of Cardiology (ESH-ESC) 2007 criteria[5]: optimal (SBP <120 mmHg and DBP <80 mmHg), normal (SBP=120~129 mmHg and DBP=80~84 mmHg), high-normal BP (SBP=130~139 mmHg and DBP=85~89 mmHg), and hypertensive (SBP ≥140 mmHg and DBP ≥90 mmHg or the use of antihypertensive drugs). If the SBP and DBP readings for a subject were in different categories, the subjects were categorized into the higher of the two BP categories.

Covariates

We performed routine blood tests that included serum total cholesterol, HDL cholesterol and glucose levels. Fasting serum glucose categories were defined as follows[6]: diabetes mellitus (DM, fasting serum glucose ≥7.0 mmol/L (126 mg/dL) or the use of medications for DM), impaired fasting glucose (fasting serum glucose levels from 5.6~6.9 mmol/L (100~125 mg/dL), and normoglycemia (fasting serum glucose levels <5.6 mmol/L (<100 mg/dL). Physicians or nurses administered questionnaires covering personal habits and present illness. Smoking and drinking status were divided into current, former and never. Body mass index (BMI) was calculated as weight (kg) divided by height $(m)^2$.

Statistical analysis

The association of GFR category with carotid atherosclerosis index was examined using analysis of covariance (ANCOVA) to compare the maximum intima-media thickness among subjects according to GFR category. In addition, logistic regression analysis was to estimate odds ratios (OR) and 95% confidence intervals (CI) for the relationship between stenosis and each GFR category, adjusting for covariates (age, smoking and drinking status, BP category, blood glucose category, total and HDL cholesterol (quartile), and body mass index). To examine the combined impact of CKD and