図１　運動総量の３分位別の大血管症発症リスクの Kaplan-Meier 曲線

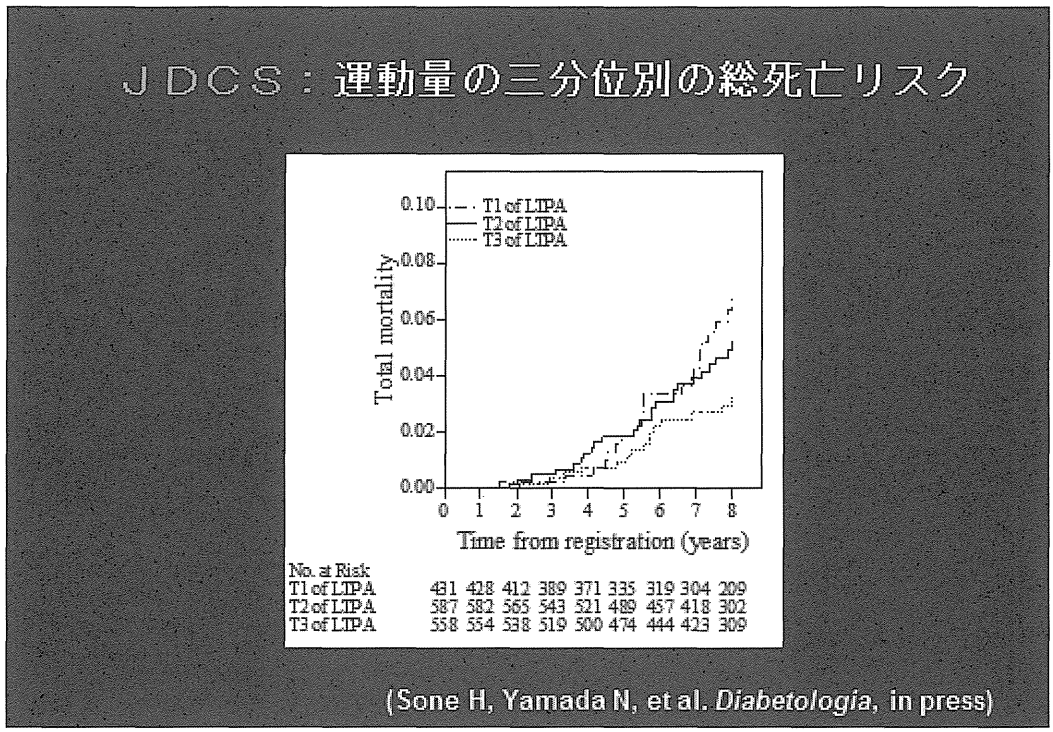
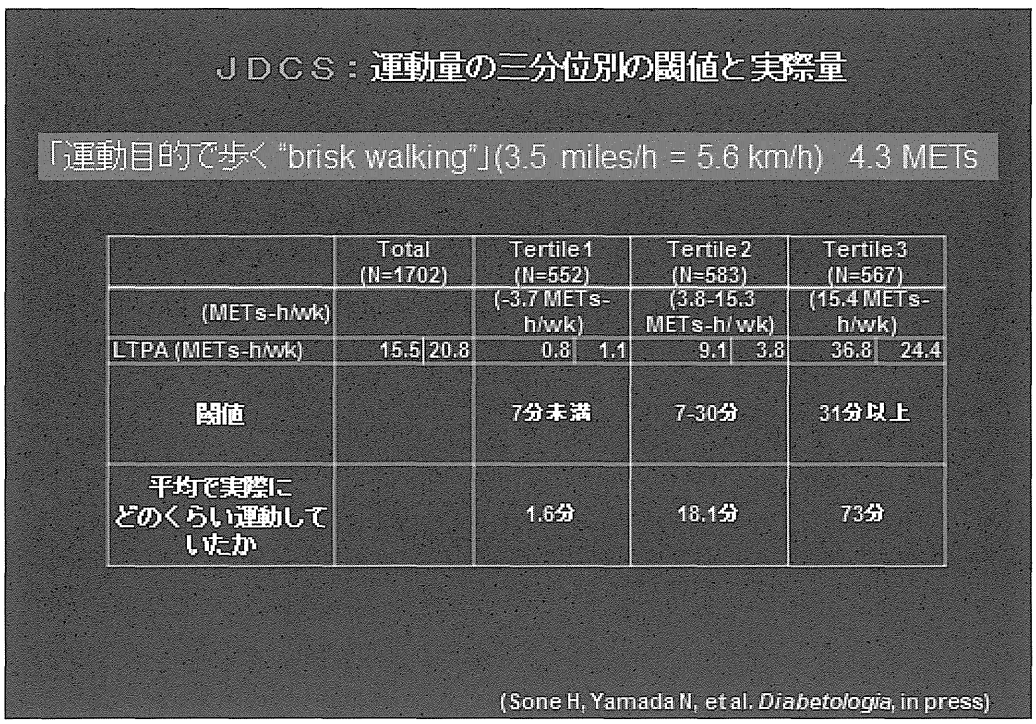


表１　対象者の運動総量の３分位別の臨床的特徴



厚生労働科学研究費補助金(循環器疾患等生活習慣病対策総合研究事業)
日本人2型糖尿病患者における生活習慣介入の長期予後効果
並びに死亡率とその危険因子に関する前向き研究
(Japan Diabetes Complications Study; JDCS)

平成２４年度　分担研究報告書

食物繊維摂取と２型糖尿病患者における脳卒中発症率

吉村幸雄　鎌田智英実　奥村亮太(四国大学)
田中司朗(京都大学医学部附属病院)
堀川千嘉　曽根博仁(新潟大学)

研究要旨

食物繊維摂取は脳卒中発症の関連について2型糖尿病患者を対象とした研究は未だ報告されていない。そこで、本研究では、The Japan Diabetes Complications Study(JDCS)で追跡されたコホートにおいて食物繊維と脳卒中発症の関連を検討した。

本研究対象者は、JDCS に参加した HbA1C6.5%以上で 40～70 歳の 2 型糖尿病患者 1414 人とした。1996 年の登録以降、8 年以上の追跡を行った。Frequency Questionnaire Based on Food Groups (FFQg)を実施し、過去 1～2 カ月の習慣的な栄養素及び食品群摂取状況を調査した。また、主要な評価項目は脳卒中発症までの期間とした。HbA1C、血圧、脂質、エネルギー摂取量、他の交絡因子を調整した Cox 回帰により、食物繊維摂取量のハザード比を推定した。

食物繊維四分位別の平均摂取量は 8.7 から 21.8 g/day の範囲で分布しており、脳卒中発症数は、摂取量が少ない順に 22、15、13、18 人であった。食物繊維摂取の第 1 四分位に比べた第 2、3、4 四分位のハザード比は、0.44 (95%信頼区間:0.20-0.95)、0.37 (95%信頼区間:0.15-0.91) 、0.39 (95%信頼区間:0.12-1.29)であった(傾向 $p<0.01$)。

結論として、食物繊維の摂取は脳卒中発症低下に関連があることが示唆された。

A．研究目的

健常人を対象としたコホート研究の結果、食物繊維摂取は脳卒中発症と負の相関があることが知られており、各国の糖尿病診療ガイドラインでは食物繊維摂取が推奨されている。しかし、2型糖尿病患者を対象とした研究は未だ報告されておらず、脳卒中予防のために食物繊維摂取を推奨する根拠は未だ明らかとなっていない。そこで、本研究では、The Japan Diabetes Complications Study(JDCS)で追跡されたコホートにおいて食物繊維と脳卒中発症の関連を検討した。

B．研究方法

パイロット研究として、PubMed と Embase を用いた系統的レビューを行った。2012/11/31 以前に公表されており、"fiber", "fibre", "stroke", "cerebrovascular disorders", "cardiovascular diseases"または他の疫学関連用語を含む、食物繊維摂取と脳卒中発症の関連を検討した文献を、レビューの対象とした。

本研究対象者は、JDCS に参加した HbA1C6.5%以上で40～70歳の2型糖尿病患者1414人とした。1996年の登録以降、8 年以上の追跡を行った。Frequency Questionnaire Based on Food Groups (FFQg)を実施し、過去1～2カ月の習慣的な栄養素及び食品群摂取状況を調査した。また、主要な評価項目は脳卒中発症までの期間とした。HbA1C、血圧、脂質、エネルギー摂取量、他の交絡因子を調整した Cox 回帰により、食物繊維摂取量のハザード比を推定した。

C．結果

Table 1 に、系統的レビューの結果を示す。6 件の地域ベースコホート研究の文献が確認された。糖尿病患者を対象としたものはなく、糖尿病有病割合は 0 から 9%であった。食物繊維摂取量の第1五分位に対する第2五分位のハザード比は、0.64 から 1.09 倍の範囲であり、6 件で有意な負の相関が見られたものの、研究結果にばらつきが見られた。

Table 2 に、JDCS の 2 型糖尿病患者 1414 人を対象とした食物繊維摂取と脳卒中発症に関する Cox 回帰の結果を示す。食物繊維四分位別の平均摂取量は 8.7 から 21.8 g/day の範囲で分布しており、脳卒中発症数は、摂取量が少ない順に 22、15、13、18 人であった。食物繊維摂取の第 1 四分位に比べた第 2、3、4 四分位のハザード比は、0.44 (95%信頼区間:0.20-0.95)、0.37 (95%信頼区間:0.15-0.91)、0.39 (95%信頼区間:0.12-1.29)であった (傾向 $p<0.01$)。

D．結論

2 型糖尿病患者においても、健常人と同様に、食物繊維の摂取は脳卒中発症低下に関連があることが示唆された。

Table 1. Summary of cohort studies of total dietary fibre and stroke in the literature

Study population	Prevalence of diabetes	Incidence rate per 1000 person-years	Men		Women	
			Total dietary fibre*	HR (95% CI)	Total dietary fibre*	HR (95% CI)
Ascherio et al. 1998	0%	1.01	12.4	Ref	-	-
Circulation 1998		328 strokes	16.6	0.85 (0.61-1.19)	-	-
43738 men		323394 person-years	19.7	0.85 (0.61-1.19)	-	-
USA			23	0.65 (0.45-0.93)	-	-
			28.9	0.70 (0.48-1.00)	-	-
Oh et al. 2005	0%	0.72	-	-	10	Ref
Am J Epidemiol 2005		1020 strokes	-	-	12.8	0.97 (0.79-1.19)
78779 women		1418022 person-years	-	-	14.9	0.89 (0.71-1.10)
USA			-	-	17.1	0.86 (0.69-1.07)
			-	-	21	0.83 (0.66-1.04)
Larsson et al. 2009	4.9 to 7.6%	9.34	16.1	Ref	-	-
Eur J Clin Nutr 2009		3365 strokes	20.9	1.01 (0.82-1.25)	-	-
26556 male smokers		360187 person-years	24.7	1.05 (0.87-1.25)	-	-
Finland			28.9	0.96 (0.84-1.09)	-	-
			35.8	1.00 (0.86-1.17)	-	-
Eshak et al. 2010	3 to 7%	1.32	<7.8	Ref	<8.5	Ref
J Nutr 2010		983 strokes	7.8-9.4	1.14 (0.74-1.76)	8.5-9.9	0.78 (0.55-1.12)
23119 men and 35611 women		743167 person-years	9.5-10.8	1.12 (0.74-1.69)	10.0-11.1	1.08 (0.76-1.54)
Japan			10.9-12.6	1.15 (0.70-1.56)	11.2-12.7	0.89 (0.61-1.30)
			>12.6	1.09 (0.75-1.58)	>12.7	1.05 (0.73-1.51)
Kokubo et al. 2011	2 to 9%	2.84	6	Ref	7.8	Ref

Eur J Clin Nutr. 2011		2553 strokes	9.8	0.94 (0.78-1.14)	11.8	0.89 (0.71-1.11)
40046 men and 46341 women		899141 person-years	11.7	0.89 (0.71-1.11)	13.7	0.85 (0.67-1.08)
Japan			14	0.92 (0.73-1.17)	15.9	0.73 (0.55-0.95)
			19.9	1.00 (0.76-1.32)	21.6	0.64 (0.46-0.88)
Wallstrom et al. 2012	0%	2.71	5.8	Ref	6.5	Ref
PLoS One 2012		755 ischaemic strokes	7.1	0.87 (0.64-1.17)	8.1	0.70 (0.50-0.98)
8139 men and 12535 women		279099 person-years	8.2	0.86 (0.63-1.16)	9.3	0.88 (0.64-1.21)
Sweden			9.3	0.86 (0.63-1.17)	10.6	0.77 (0.55-1.08)
			11.4	0.69 (0.49-0.96)	12.9	0.73 (0.52-1.04)

HR: hazard ratio, CI: confidence interval

*Means in quintiles for Kokubo et al., medians in quintiles for others

Table 2. Cox regression analysis of incidence of stroke and intake of total dietary fibre

	Quartile analysis									
		Q2			Q3			Q4			
	Q1	HR	95%CI	p	HR	95%CI	p	HR	95%CI	p	Trend p
Total dietary fibre, mean±SD	8.7±1.6		12.5±0.9			15.8±1.0			21.8±4.0		
Crude	Ref	0.60	(0.31-1.16)	0.13	0.57	(0.29-1.12)	0.10	0.66	(0.35-1.25)	0.20	0.08
Adjusted for risk factors	Ref	0.46	(0.22-0.98)	0.04	0.41	(0.18-0.95)	0.04	0.45	(0.15-1.35)	0.16	<0.01
Further adjusted for energy	Ref	0.44	(0.20-0.95)	0.04	0.37	(0.15-0.91)	0.03	0.39	(0.12-1.29)	0.12	<0.01

厚生労働科学研究費補助金（循環器疾患等生活習慣病対策総合研究事業）
日本人2型糖尿病患者における生活習慣介入の長期予後効果
並びに死亡率とその危険因子に関する前向き研究
(Japan Diabetes Complications Study; JDCS)

平成２４年度　分担研究報告書

JDCStudy の問題点とその解決

石橋　俊　　自治医科大学内科学講座内分泌代謝学部門

研究要旨
糖尿病における血管合併症の予防、進展抑制を目的とした介入効果についての研究を遂行する上で、問題点を把握、その要因について検討した。

A. 研究目的

本研究は、我が国における糖尿病患者における糖尿病合併症特に血管合併症を把握、その予防、進展抑制をはかるための手段、特にライフスタイルへの介入効果を検討し、我が国独自の大規模臨床として成果を上げつつある。そこでさらに効果的な介入をはかるための、問題点とその対策について検討した。

B. 研究方法

本研究を実施するにあたり、現状と当施設における遂行上の問題点を把握し、その対策について検討した。

C. 研究結果と考察

1）　コホート研究の成果とその解釈：今回の成果報告会では、ベースラインの臨床指標と心血管イベント･総死亡との関連に関する興味深い報告が多数あった。例えば、METS で評価した運動強度を3分位し、最上位は最下位に比較して、脳血管障害の発症と総死亡が有意に低下し、運動の脳血管障害と予防効果と延命効果が示唆された。また、食事調査においても、果物や食物繊維摂取量が高いと心血管イベント発症が低下し、ナトリウムの摂取が多いと心血管イベントの増加が確認された。

２型糖尿病患者の血管合併症予防には一定強度以上の運動、果物や食物繊維の一定量以上の摂取が有効である可能性が示されたことになる。近年、運動の延命効果には注目が集まっている(1)。２型糖尿病患者にも当てはまれば、患者指導に資するところが大きい。ただし、その解釈は慎重である必要がある。例えば、イベント発症予備群は心機能などに問題があり、運動できないという事実を見ている可能性なども慎重に検討する必要がある。

果物については、フルクトース等の

血糖上昇作用に関する懸念から２型糖尿病患者への一定以上の摂取はむしろ制限される傾向があった。一方、食物繊維、ビタミン、ポリフェノール、フラボノイドなど血管合併症抑制的な成分も多く含まれており、摂取量を見直す契機契機となるかもしれない(2)。

２）糖尿病の心血管イベント発症リスク:JDCS と JEDIT のデータを統合して、基本パラメータを入力するとイベントの絶対リスクを算出する JJ リスクスコアエンジンが紹介された。昨年改訂された「動脈硬化性疾患予防ガイドライン 2012 年版」では、同じ糖尿病患者にでも罹病期間、血糖コントロール、細小血管症等の合併症の有無によってイベント発症リスクに差があるとしながら、その定量化に限界があったため、慢性腎臓病(CKD)等と同等のカテゴリーIII に据え置かれた(3)。

この問題に関しては、CKD は２型糖尿病を超えるリスクという報告もされた(4)。JJ リスクスコアの利用によって、更にきめの細かい管理が実現される事が期待される。

３）腎症進展群における eGFR の経年増加：腎症進展患者では eGFR の経年的改善は予想外の結果のため、慎重な考察が必要である。腎症進展患者では栄養状態が徐々に悪化に筋肉量が減少するため、血清クレアチニン値も改善し、みかけ上 eGFR が増加するのかもしれない(5)。シスタチン C やクレアチンクリアランス等の eGFR 以外の、腎機能評価法も併用して総合的に評価すべきであろう。

D. 結論

JDCS によって得られたデータが上記のエビデンス形成に資することを期待したい。

E. 文献

1. Kokkinos, P.F., Faselis, C., Myers, J., Panagiotakos, D., and Doumas, M. 2013. Interactive effects of fitness and statin treatment on mortality risk in veterans with dyslipidaemia: a cohort study. *Lancet* 381:394-399.
2. Dauchet, L., Amouyel, P., and Dallongeville, J. 2009. Fruits, vegetables and coronary heart disease. *Nat Rev Cardiol* 6:599-608.
3. 動脈硬化診療・疫学委員会, 日. 2012. *動脈硬化性疾患予防ガイドライン2012年度版*: 日本動脈硬化学会.
4. Tonelli, M., Muntner, P., Lloyd, A., Manns, B.J., Klarenbach, S., Pannu, N., James, M.T., and Hemmelgarn, B.R. 2012. Risk of coronary events in people with chronic kidney disease compared with those with diabetes: a population-level cohort study. *Lancet* 380:807-814.
5. Wetmore, J.B., Honea, R.A., Vidoni, E.D., Almehmi, A., and Burns, J.M. 2011. Role of lean body mass in estimating glomerular filtration rate in Alzheimer disease. *Nephrol Dial Transplant* 26:2222-2231.

厚生労働科学研究費補助金(循環器疾患等生活習慣病対策総合研究事業)
日本人2型糖尿病患者における生活習慣介入の長期予後効果
並びに死亡率とその危険因子に関する前向き研究
(Japan Diabetes Complications Study; JDCS)

平成２４年度　分担研究報告書

JDCStudy の問題点とその解決

及川眞一
日本医科大学医学部内分泌糖尿病代謝内科学

研究要旨　JDCStudy は糖尿病の血管合併症に対する介入効果を検討するため組織された。動脈硬化性疾患のみならず、細小血管障害に関与する因子について検討することも重要である。細小血管障害に関与する因子を解明することは長期の観察研究によって得られる重要な結果であり、治療を考える上で有用な知見になることが期待される。

A．研究目的

細小血管障害に関与する様々な病態因子を解明する。

B．研究方法

細小血管障害の発症因子、増悪因子を明らかにするため、登録時、および経過中の成績を比較し、合併症の発症要因を解明する。

C．研究結果

年次ごとの臨床成績を、登録時の成績と比較検討することが合併症の発症と進展・増悪に関連する因子の差異を明らかにすることができる。このことにより治療効果の検証が可能となる。さらに長期間の観察を続けることにより、合併症相互の関連性が明らかとなる。

D．考察

臨床成績のまとめから、糖尿病治療の効果が明らかにされる。さらに生活習慣-食事、運動など一の影響を解析すべき因子として加えて行うことは、生活習慣への介入を意義づける上で、重要であると考えられる。

厚生労働科学研究費補助金(循環器疾患等生活習慣病対策総合研究事業)
日本人２型糖尿病患者における生活習慣介入の長期予後効果
並びに死亡率とその危険因子に関する前向き研究
(Japan Diabetes Complications Study; JDCS)

平成２４年度　分担研究報告書

JDCStudy の問題点とその解決

荒木　厚　　井藤　英喜
東京都健康長寿医療センター糖尿病・代謝・内分泌内科

研究要旨
糖尿病における血管合併症の予防、進展抑制を目的とした介入効果についての研究を遂行する上での２つの課題：①栄養と糖尿病合併症、②身体活動量と血管合併症の問題を挙げて、それを解決するための対策や今後の展望について考察を加えた。

A．研究目的

JDCStudy 研究は、我が国における糖尿病患者における糖尿病の血管合併症、およびその危険因子を把握し、血管合併症の予防、進展抑制をはかるための手段、特にライフスタイルへの介入効果を検討してきた。JDCStudy 研究は我が国独自の大規模臨床試験として大きな成果を上げつつある。そこで、さらに効果的な研究を遂行する上での課題、その対策、及び今後の展望について考察を加えてみた。

B．研究方法

本研究を実施するに当っての現状の問題点や課題を把握し、他の介入研究との比較より、研究の解析の上で重要と思われる栄養、身体活動量における課題を抽出し、今後の対策について検討を加えた。

C．研究結果と考察

１．栄養と糖尿病合併症

糖尿病患者の食事における栄養成分は、血糖、血圧、脂質の値に影響を及ぼすが、それが糖尿病合併症の発症、進展にどの程度影響を及ぼすかについては報告が少ない。最近発表された JDCStudy における果実の摂取と網膜症との関連の論文は、その意味で価値があると考えられる[1)]。まだ、未解決の栄養の問題としては、糖尿病患者の蛋白質の摂取と腎症進行との関連、炭水化物の摂取と合併症、死亡との関

連などが考えられる。

とくに、低炭水化物食は糖尿病患者の一部で血糖コントロール改善する一方、過大な宣伝により、多くの患者を惑わしている現状がある。また、低炭水化物食は腎症の悪化やインスリン抵抗性、脂肪肝、心血管疾患、死亡を増やす危険も指摘されている。したがって、JDCStudy においても炭水化物の摂取と血糖、脂質のコントロール、糖尿病合併症との関連について、詳細な検討を加える必要があるであろう。

また、栄養で重要なことは、一つの栄養成分だけでなく、食事のパターンで解析することである。これまで、報告されている食事のパターンとしてはDASH 食、地中海食などがあるが、これらは海外の住民の食事に基づいており、日本人には当てはまらない可能性がある。Nanri らは日本人の食事を主成分分析などにより、健康食、西洋食、シーフード、パン食、デザート食の５つの食事パターンに化して、C ペプチドとの関連を見ている[2]。したがって、JDCStudy においてもこうした手法を用いて、食事パターンと血糖、脂質のコントロール、糖尿病合併症との関連について解析する必要がある。

２．身体活動量と血管合併症：

JDCStudy において身体活動量の増加は、他の従来の危険因子を調整しても総卒中や死亡のリスクの減少につながることが明らかになった。J-EDIT 研究においても同様に、登録時の Baecke の方法による身体活動量と脳卒中発症との関連を検討したが、身体活動量の最大四分位の群は、最小四分位の群と比較しての脳卒中発症のハザード比は 0.44[95％CI:0.20−0.97]であり、身体活動量が少ないことが、脳卒中発症の危険因子であった[3]。

この身体活動量の低下はうつなどの心理的問題や職業などの社会的状況からおこりうる。うつ状態は血小板の活性化、炎症性サイトカインの産生、視床下部、下垂体、副腎系の活性化を介して動脈硬化や血栓形成をきたす可能性がある。J-EDIT 研究でも GDS-15 で評価したうつ症状が多いほど、脳卒中が増えていた。したがって、J-EDIT 研究においても、こうした心理社会的な変数と血管合併症の関連を検討する必要がある。

D．参考文献

1. Tanaka S, et al. Fruit Intake and Incident Diabetic Retinopathy with Type 2 Diabetes. Epidemiology 2013 Jan 23. [Epub ahead of print]

2. Nanri H, et al. Association between dietary pattern and serum C-reactive protein in Japanese men and women. J Epidemiol. 2011; 21: 122-31.

3. Iijima K,et al. Lower physical activity is a strong predictor of cardiovascular events in elderly patients with type 2 diabetes mellitus beyond traditional risk factors: Japanese Elderly Diabetes Intervention Trial (J-EDIT). Geriatr Gerontol Int 12 (Suppl. 1):77-87, 2012 .

E．実用新案登録：なし

Predicting Macro- and Microvascular Complications in Type 2 Diabetes

The Japan Diabetes Complications Study/the Japanese Elderly Diabetes Intervention Trial risk engine

SHIRO TANAKA, PHD[1]
SACHIKO TANAKA, PHD[2]
SATOSHI IIMURO, MD, PHD[3]
HIDETOSHI YAMASHITA, MD, PHD[4]
SHIGEHIRO KATAYAMA, MD, PHD[5]
YASUO AKANUMA, MD, PHD[6]
NOBUHIRO YAMADA, MD, PHD[7]
ATSUSHI ARAKI, MD, PHD[8]
HIDEKI ITO, MD, PHD[8]
HIROHITO SONE, MD, PHD[7]
YASUO OHASHI, PHD[3]
FOR THE JAPAN DIABETES COMPLICATIONS STUDY GROUP
THE JAPANESE ELDERLY DIABETES INTERVENTION TRIAL GROUP

OBJECTIVE—To develop and validate a risk engine that calculates the risks of macro- and microvascular complications in type 2 diabetes.

RESEARCH DESIGN AND METHODS—We analyzed pooled data from two clinical trials on 1,748 Japanese type 2 diabetic patients without diabetes complications other than mild diabetic retinopathy with a median follow-up of 7.2 years. End points were coronary heart disease (CHD), stroke, noncardiovascular mortality, overt nephropathy defined by persistent proteinuria, and progression of retinopathy. We fit a multistate Cox regression model to derive an algorithm for prediction. The predictive accuracy of the calculated 5-year risks was cross-validated.

RESULTS—Sex, age, HbA_{1c}, years after diagnosis, BMI, systolic blood pressure, non-HDL cholesterol, albumin-to-creatinine ratio, atrial fibrillation, current smoker, and leisure-time physical activity were risk factors for macro- and microvascular complications and were incorporated into the risk engine. The observed-to-predicted (O/P) ratios for each event were between 0.93 and 1.08, and Hosmer-Lemeshow tests showed no significant deviations between observed and predicted events. In contrast, the UK Prospective Diabetes Study (UKPDS) risk engine overestimated CHD risk (O/P ratios: 0.30 for CHD and 0.72 for stroke). C statistics in our Japanese patients were high for CHD, noncardiovascular mortality, and overt nephropathy (0.725, 0.696, and 0.767) but moderate for stroke and progression of retinopathy (0.636 and 0.614). By combining macro- and microvascular risks, the classification of low- and high-risk patients was improved by a net reclassification improvement of 5.7% ($P = 0.02$).

CONCLUSIONS—The risk engine accurately predicts macro- and microvascular complications and would provide helpful information in risk classification and health economic simulations.

From the [1]Department of Clinical Trial Design and Management, Translational Research Center, Kyoto University Hospital, Kyoto, Japan; the [2]EBM Research Center, Kyoto University Graduate School of Medicine, Kyoto, Japan; the [3]Department of Biostatistics, School of Public Health, University of Tokyo, Tokyo, Japan; the [4]Department of Ophthalmology, Yamagata University Faculty of Medicine, Yamagata, Japan; the [5]Department of Endocrinology and Diabetes, School of Medicine, Saitama Medical University, Saitama, Japan; The [6] Institute for Adult Diseases, Asahi Life Foundation, Tokyo, Japan; the [7]Department of Internal Medicine, University of Tsukuba Institute of Clinical Medicine, Ibaraki, Japan; and the [8]Tokyo Metropolitan Geriatric Hospital, Tokyo, Japan.
Corresponding author: Yasuo Ohashi, ohashi@epistat.m.u-tokyo.ac.jp.
Received 17 May 2012 and accepted 7 October 2012.
DOI: 10.2337/dc12-0958. Clinical trial reg. no. UMIN CTR C000000222 for the Japan Diabetes Complications Study and UMIN 000000890 for the Japanese Elderly Diabetes Intervention Trial, www.umin.ac.jp/ctr/.
This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc12-0958/-/DC1.

Risk classification for vascular complications is of particular importance in diabetes care, and there is a need for validated diabetes-specific risk engines (1,2). Asian populations account for >60% of the world's diabetes patients (3,4), but data used for most of the engines specific to diabetes include only a limited number of Asians (5–9). Asian patients with diabetes have several important features. We previously reported that Japanese patients have a markedly low prevalence of obesity and low incidence rates of overt nephropathy and diabetic retinopathy (10–13). Furthermore, the risk factor profiles of diabetes complications are quite different between Japanese and Western subjects with diabetes (14). In cohort studies of multiple ethnic groups, lower incidence rates of cardiovascular disease (CVD) were observed in Asian patients than in whites (15,16). Given the overestimation of risks of coronary heart disease (CHD) and stroke in Chinese patients by the UK Prospective Diabetes Study (UKPDS) risk engine (17,18), risk engines for non-Asian populations may not be transportable to Asian patients. To our knowledge, only the Hong Kong Diabetes Registry (HKDR) has developed risk engines for Asian patients with diabetes (17–20).

Most risk engines have focused on classical cardiovascular risk factors such as control of HbA_{1c}, blood pressure, and lipids (5–9,17–20), but, increasingly, studies have suggested the importance of lifestyle factors. In fact, exercise has been shown to reduce all-cause mortality (21,22) and is encouraged by guidelines for type 2 diabetes (23,24). A recent survey of general practitioners in Germany indicated that those physicians thought that to be useful, risk engines should link estimated risks with appropriate recommendations for lifestyle changes (25). Another concern is the lack of capacity to assess multiple diseases simultaneously (25). However, just combining the results of risk engines specific to each vascular complication may yield biased estimates

Diabetes Care Publish Ahead of Print, published online February 12, 2013

of absolute risks since it is likely that each engine was developed independently, and a correlation between incidences of vascular complications is not accounted for in the development process.

Data from the 1,748 patients with type 2 diabetes in the Japan Diabetes Complications Study (JDCS) (26) and the Japanese Elderly Diabetes Intervention Trial (J-EDIT) (27) provide an opportunity to develop a comprehensive risk engine for Asian patients with type 2 diabetes. The aim of the current study was therefore to develop and validate an algorithm that separately calculates each risk of the first occurrence for five events: fatal and nonfatal CHD, fatal and nonfatal stroke, noncardiovascular mortality, overt nephropathy, and progression of retinopathy. This was done by fitting a multistate Cox regression model (28), an extension of the Cox model to multiple time-to-event end points, to the pooled data from these trials.

RESEARCH DESIGN AND METHODS

Patients and measurements

Design of the JDCS and the J-EDIT has been described in detail elsewhere (26,27). In the JDCS, 2,033 Japanese type 2 diabetes patients 40–70 years of age whose HbA_{1c} levels were ≥7.0% were randomized to a conventional treatment group and a lifestyle intervention group; throughout the paper, we present the National Glycohemoglobin Standardization Program value of HbA_{1c} calculated as follows: 0.25 + 1.02 × JDC value (29). The latter group received education on lifestyle modification by telephone counseling and at each outpatient clinic visit in addition to usual care. The J-EDIT is a randomized, controlled trial of intensive and conventional treatments for diabetes that registered a total of 1,173 Japanese type 2 diabetes patients 65–85 years of age whose HbA_{1c} levels were ≥8.1%, or ≥7.5% with at least one of the following criteria: BMI ≥25 kg/m^2; blood pressure ≥130/85 mmHg; serum total cholesterol ≥200 mg/dL (5.17 mmol/L) or LDL cholesterol ≥120 mg/dL (3.10 mmol/L) in participants without CHD; serum total cholesterol ≥180 mg/dL (4.65 mmol/L) or LDL cholesterol ≥100 mg/dL (2.59 mmol/L) in participants with CHD; triglycerides ≥150 mg/dL (1.68 mmol/L); and HDL cholesterol <40 mg/dL (1.03 mmol/L). The protocols of the JDCS and J-EDIT received approval from the ethical committees of all of the participating institutes, and written informed consent was obtained from all patients before enrollment. The present analysis excluded patients who had any history of angina pectoris, myocardial infarction, stroke, peripheral artery disease, familial hypercholesterolemia (diagnosed clinically by markedly elevated LDL cholesterol levels with enlarged Achilles tendons and/or family history of premature coronary artery disease), type III hyperlipidemia (diagnosed by broad β-band on electrophoresis), nephrotic syndrome, serum creatinine levels >1.3 mg/dL (120 μmol/L), mean values of two spot urine examinations for an albumin excretion rate of 150 mg/g creatinine (17.0 mg/mmol) or more, microscopic hematuria, or other clinical findings indicating other renal diseases, preproliferative and proliferative retinopathy, and major ocular disease (e.g., glaucoma, dense cataract, or history of cataract surgery). Baseline data were collected for demographics, results of clinical examinations, laboratory measurements performed at local laboratories, and lifestyle factors such as dietary content and smoking status determined by self-reported questionnaires. Leisure-time physical activity (LTPA) was also assessed at baseline by a self-administered questionnaire, which was almost identical to that used and validated in the Health Professionals' Follow-up Study (30). The patients were asked to report their average frequency (times/week) and duration (min/time) of normal walking, brisk walking, jogging, golfing, tennis, swimming, aerobics dancing, cycling, and other miscellaneous exercise as specified by each patient. The duration engaged in each activity in min/time was multiplied by that activity's typical energy expenditure, expressed in metabolic equivalents (METs), and overall activities were summed to yield a MET/h score per week (31). Data management was conducted by a central data center. Follow-up data were collected through a standardized annual report from each investigator. Non-HDL cholesterol (NHDL-C) levels were calculated by total cholesterol subtracted by HDL cholesterol. LDL cholesterol levels were calculated using the Friedewald formula, that is, NHDL-C subtracted by triglycerides divided by 5 if triglyceride levels are <400 mg/dL (4.48 mmol/L); otherwise, LDL cholesterol levels were treated as missing data.

End points

End points were five time-to-event variables: fatal or nonfatal CHD, fatal or nonfatal stroke, noncardiovascular mortality, overt nephropathy defined by persistent proteinuria, and progression of retinopathy since randomization. The definitions of the events have been described in detail elsewhere (12,13,27,32). In brief, diabetic retinopathy was determined annually by qualified ophthalmologists at each institute using the international diabetic retinopathy and diabetic macular edema disease scales (33) with minor modification: stage 0, no retinopathy; stage 1, hemorrhage and hard exudates; stage 2, soft exudates; stage 3, intraretinal microvascular abnormalities and venous changes, including beading, loop, and duplication; and stage 4, new vessels, vitreous hemorrhage, fibrous proliferation, and retinal detachment. A retinopathy event was progression to stage 3 or 4. A nephropathy event was defined as the development of overt nephropathy (spot urinary albumin excretion >33.9 mg/mmol creatinine in two consecutive samples) (12). Macrovascular events included the occurrence of fatal and nonfatal definite CHD (angina pectoris or myocardial infarction) and fatal and nonfatal stroke. The diagnosis of angina pectoris and myocardial infarction was according to criteria defined by the Multinational Monitoring of Trends and Determinants in Cardiovascular Disease project, and diagnosis of stroke was according to guidelines defined by the Ministry of Health, Labour, and Welfare of Japan (32). Adjudication of end points was performed by central committees comprised of experts in each complication based on additional data such as those obtained by computed tomography or magnetic resonance imaging of the brain or sequential changes in electrocardiograms.

Statistical analysis

The JDCS/J-EDIT (JJ) risk engine calculates each risk of the first occurrence within a user-specified time point for the five events described above. The occurrences of these events are viewed as transitions between disease states and were modeled by a multistate model that follows the Markov renewal process (28). The disease states and transitions assumed in the multistate model are detailed in Supplementary Appendix A. We fit a multistate model using a standard procedure for the stratified Cox regression model. That is, we assumed that baseline intensities for any of the transitions were possibly different but that transition intensities to a disease state share

common hazard ratios (HRs) for risk factors. The following risk factors were screened through a backward variable selection with the critical value of $P = 0.1$: age, sex, HbA_{1c}, years after diagnosis, BMI, systolic blood pressure (SBP), NHDL-C, LDL cholesterol, HDL cholesterol, log-transformed triglycerides, log-transformed urine albumin-to-creatinine ratio (ACR), estimated glomerular filtration rate, atrial fibrillation, smoking status, alcohol intake, and LTPA. BMI was categorized by cutoff points of 18.5 and 25 kg/m^2. LTPA was categorized by the cutoff point of 3.8 METs-h/week, which corresponds to the intensity of home activity or conditioning exercise (31). HRs in this model were estimated by maximizing the partial likelihood, and then baseline intensity functions were calculated by the Breslow estimator. Missing data were substituted using the multiple imputation method.

We assessed the predictive accuracy of the 5-year risks based on the JJ risk engine using 10-fold cross-validation, i.e., we performed 10 rounds of cross-validation using different partitions. One round of cross-validation involved randomly partitioning a sample of data on 1,748 patients into complementary subsets, fitting the stratified Cox regression model to one subset of 90% of patients, and validating the model on the remaining subset with the criteria described below. We compared hazards for end points between tertiles of the calculated 5-year risks from the 10-fold cross-validation by the Cox regression. Calibration, namely, how closely the prediction reflected observed events, was assessed for each event by the Hosmer-Lemeshow test and the mean of observed-to-predicted (O/P) ratios, which was calculated as the mean of ratios of the observed-to-expected events across the strata used in the Hosmer-Lemeshow test. Discrimination, the ability to distinguish between those who experienced the event and those who did not, was evaluated using Harrell C statistics, the proportion of all patient pairs in which the predictions of the model and observed events were concordant. Further, we constructed a reclassification table of macro- and microvascular complications (34).

All analyses were conducted by the central data center with the use of SAS software version 9.2 (SAS Institute, Cary, NC). The authors had full access to the data and take responsibility for their integrity. All reported P values for statistical tests are two tailed, and $P < 0.05$ was taken to indicate statistical significance.

RESULTS—The mean ± SD (range) age and HbA_{1c} level at baseline of the 1,748 Japanese type 2 diabetic patients was 62.1 ± 8.6 (40–84) years and 7.9 ± 1.2 (6.0–15.8)%, respectively, and 49.9% of the subjects were women. Their mean baseline values indicated that the subjects had good control of weight (BMI = 23.2 ± 3.1 kg/m^2; waist circumference = 80.3 ± 9.6 cm), blood pressure (SBP = 132.9 ± 16.0 mmHg), and serum cholesterol levels (NHDL-C = 3.78 ± 0.90 mmol/L; LDL cholesterol = 3.16 ± 0.82 mmol/L; HDL cholesterol = 1.43 ± 0.44 mmol/L; triglycerides = 1.39 ± 0.88 mmol/L). Their baseline ACR levels were quite low, with a median ± IQR of 1.8 ± 3.0 mg/mmol, as we excluded those with ACR of 17.0 g/mmol or more. Current smokers and past smokers accounted for 24.4 and 24.0%, respectively, of patients. The median (IQR) LTPA at baseline was 10.5 (1.6–22.5) METs-h/week, and 34.0% of patients had no exercise habit (<3.8 METs-h/week). During the median follow-up of 7.2 years, among the 1,748 subjects, we observed 96 (5.5%) events of fatal or nonfatal CHD, 89 (5.1%) fatal or nonfatal strokes, 71 (4.1%) overt nephropathies defined by persistent proteinuria, and 64 (3.7%) noncardiovascular deaths. Of the 1,297 patients without retinopathy at baseline, 415 (32.0%) developed retinopathy. Of the 866 patients who had retinopathy or developed retinopathy after baseline, 113 (13.0%) had progression to retinopathy of stage 3 or 4.

The backward variable selection procedure identified 11 baseline risk factors

Table 1—*HRs of risk factors incorporated in the best-fitting multistate Cox regression model*

	CHD				Stroke				Noncardiovascular mortality			
	HR	95% CI		*P*	HR	95% CI		*P*	HR	95% CI		*P*
Sex (woman/man)	0.41	0.24	0.70	<0.01	0.46	0.29	0.73	<0.01	0.55	0.29	1.04	0.07
Age (+10 years)	1.38	1.02	1.85	0.04	1.55	1.17	2.06	<0.01	2.44	1.70	3.50	<0.01
HbA_{1c} (+1%)	1.22	1.02	1.45	0.03	1.23	1.04	1.44	0.02				
BMI (<18.5/18.5–25 kg/m^2)									3.22	1.40	7.37	0.01
BMI (≥ 25/18.5–25 kg/m^2)									1.16	0.60	2.21	0.66
SBP (+10 mmHg)	1.13	0.98	1.31	0.10	1.16	1.00	1.33	0.045				
NHDL-C (+1 mmol/L)	1.56	1.26	1.93	<0.01	1.38	1.10	1.74	0.01				
Atrial fibrillation (yes/no)					12.48	3.77	41.29	<0.01				
Current smoker (yes/no)	1.67	1.00	2.81	0.052					2.11	1.04	4.26	0.04
LTPA (≥3.8/<3.8 METs-h/week)					0.63	0.39	1.01	0.053	0.57	0.33	1.01	0.054
	Overt nephropathy				Retinopathy							
Age (+10 years)					1.16	1.04	1.30	0.01				
HbA_{1c} (+1%)	1.28	1.08	1.53	0.01	1.32	1.25	1.40	<0.01				
Years after diagnosis (+1 years)					1.04	1.03	1.06	<0.01				
BMI (<18.5/18.5–25 kg/m^2)					0.67	0.43	1.03	0.07				
BMI (≥25/18.5–25 kg/m^2)					1.22	0.99	1.49	0.06				
SBP (+10 mmHg)	1.14	0.97	1.33	0.11								
Log ACR (+1 unit)	3.02	2.16	4.23	<0.01	1.11	1.01	1.22	0.03				
Atrial fibrillation (yes/no)	5.54	0.74	41.49	0.10								
Current smoker (yes/no)	2.18	1.28	3.71	<0.01								

for macro- and microvascular complications and noncardiovascular mortality. Table 1 shows the HRs, 95% CIs, and *P* values for these risk factors. Significant modifiable risk factors were HbA_{1c} and NHDL-C for CHD, HbA_{1c}, SBP, and NHDL-C for stroke, BMI <18.5 kg/m^2 and being a current smoker for noncardiovascular mortality, HbA_{1c} and being a current smoker for overt nephropathy, and HbA_{1c} for retinopathy. Having an exercise habit was associated with reduced risks of stroke and mortality, although with only borderline statistical significance. All of the risk factors that were retained through the variable selection procedure were incorporated into the JJ risk engine. The algorithm of the JJ risk engine is described in Supplementary Appendix A.

The performance of the JJ risk engine was evaluated by several validation criteria. Tertile Cox regression showed that the 5-year risks calculated by the JJ risk engine effectively classified populations at low and high risk for each complication. The HRs (95% CI) of the second and third tertiles compared with the first tertile were 2.09 (1.07–4.09) and 5.22 (2.84–9.58) for CHD; 1.78 (0.96–3.30) and 3.32 (1.86–5.92) for stroke; 2.14 (1.09–4.18) and 3.17 (1.65–6.09) for noncardiovascular mortality; 1.54 (0.55–4.34) and 10.59 (4.56–24.59) for overt nephropathy; and 1.18 (0.58–2.40) and 2.56 (1.37–4.81) for progression of retinopathy.

Table 2 shows the predictive accuracy of the JJ risk engine regarding calibration and discrimination. The O/P ratios for each complication, including noncardiovascular mortality, ranged between 0.93 and 1.08, and Hosmer-Lemeshow tests did not show any significant deviations between the observed and predicted events. In contrast, the UKPDS risk engine (5,6) overestimated CHD risk in Japanese patients (O/P ratios [Hosmer-Lemeshow *P*]: 0.30 [$P < 0.01$] for CHD and 0.72 [$P = 0.54$] for stroke) (Table 2). Discrimination according to C statistics was high for CHD, noncardiovascular mortality, and overt nephropathy (0.696–0.767) but was moderate for stroke and progression of retinopathy (0.636 and 0.614).

Table 3 compares risk classification by the 5-year risk of macrovascular disease based on the JJ risk engine with that based on the UKPDS risk engine. By the UKPDS risk engine, more than half of patients had a macrovascular risk of 10% or more (249 of the 376 cases and 697 of the 1,372 noncases), as expected by the tendency of overestimation The sensitivity and specificity of the UKPDS risk engine with a cutoff value of 10% risk were 66.2 and 49.2%, respectively. In contrast, only 101 of the 376 cases (26.9%) who developed any of the events had a macrovascular risk of 10% or more based on the JJ risk engine, yielding sensitivity of 26.9% and specificity of 89.1%.

Table 4 shows how the combination of 5-year risks of macro- and microvascular complications based on the JJ risk engine classified low-risk and high-risk patients. If we combined macro- and microvascular risks, 73 of 376 cases (19.4%) and 187 of 1,372 noncases (13.6%) were newly classified as a high-risk population, and sensitivity increased up to 46.3% while specificity was maintained at 75.4%. The net reclassification improvement (total of sensitivity and specificity in this case) was improved by 5.7% ($P = 0.02$).

To illustrate the use of the JJ risk engine, consider two Japanese men 60 years of age with simple diabetic retinopathy and without atrial fibrillation who do not have smoking and exercise habits. The clinical characteristics of both patients are HbA_{1c} = 9%, duration of diabetes = 20 years, BMI = 23 kg/m^2, NHDL-C = 3.88 mmol/L, and ACR = 6.79 mg/mmol creatinine. The SBP of one patient is 120 mmHg. His leading risk is estimated to be the progression of retinopathy (5-year risk, 15.5%), and his macrovascular risks are moderate (9.2% for CHD and 9.6% for stroke). His 5-year risks of noncardiovascular death and overt nephropathy are low (4.8 and 3.7%, respectively). The other patient has

Table 2—*Predictive accuracy of the JJ risk engine in 1,748 patients*

	Calibration				Discrimination	
	Mean predicted 5-year risk	Observed 5-year risk	O/P ratio	*P*†	C statistic	95% CI
CHD	2.70%	2.92%	1.08	0.14	0.725	0.656–0.793
By the UKPDS risk engine	(9.66%)	—	(0.30)	(<0.01)	(0.695)	(0.626–0.764)
Stroke	3.36%	3.26%	0.97	0.12	0.636	0.564–0.708
By the UKPDS risk engine	(4.52%)	—	(0.72)	(0.54)	(0.638)	(0.566–0.711)
Noncardiovascular mortality	2.08%	2.12%	1.02	0.12	0.696	0.613–0.778
Overt nephropathy	2.28%	2.40%	1.04	0.11	0.767	0.690–0.845
Progression of retinopathy*	10.96%	10.20%	0.93	0.13	0.614	0.524–0.705

*Patients without diabetes retinopathy at baseline were excluded. †The Hosmer-Lemeshow test with eight degrees of freedom. $P < 0.05$ indicates significant deviation between predicted and observed events.

Table 3—*Risk classification of the 1,748 patients according to 5-year risks of macro-vascular disease based on the JJ risk engine and the UKPDS risk engine*

	5-Year risk by the JJ risk engine*						
5-Year risk by the UKPDS risk engine*	<5%		5–10%		10% or more		Total
Patients who developed events							
<5%	37	9.8%	2	0.5%	0	0.0%	39
5–10%	66	17.6%	19	5.1%	3	0.8%	88
10% or more	37	9.8%	114	30.3%	98	26.1%	249
Total	140		135		101		376
Patients who did not develop any events							
<5%	245	17.9%	7	0.5%	0	0.0%	252
5–10%	341	24.9%	78	5.7%	4	0.3%	423
10% or more	202	14.7%	349	25.4%	146	10.6%	697
Total	788		434		150		1,372

*Probability of any occurrence of CHD or stroke within 5 years.

Table 4—*Risk classification of the 1,748 patients according to 5-year risks of macro- and microvascular diseases based on the JJ risk engine*

5-Year risk of microvascular disease†	5-Year risk of macrovascular disease* <5%		5–10%		10% or more		Total
Patients who developed events							
<5%	79	21.0%	48	12.8%	19	5.1%	146
5–10%	40	10.6%	35	9.3%	20	5.3%	95
10% or more	21	5.6%	52	13.8%	62	16.5%	135
Total	140		135		101		376
Patients who did not develop any events							
<5%	601	43.8%	215	15.7%	40	2.9%	865
5–10%	115	8.4%	104	7.6%	34	2.5%	240
10% or more	72	5.2%	115	8.4%	76	5.5%	267
Total	759		434		150		1,372

*Probability of any occurrence of CHD or stroke within 5 years. †Probability of any occurrence of overt nephropathy defined by persistent proteinuria or progression of retinopathy within 5 years.

an SBP of 180 mmHg. His leading risks are macrovascular diseases (16.1% for CHD and 17.6% for stroke), and his microvascular risks are moderate (7.8% for nephropathy and 13.6% for retinopathy). The risk of noncardiovascular mortality is estimated to be 4.0%.

CONCLUSIONS—In this study, we developed a novel risk engine that integrates modifiable lifestyle and clinical risk factors, including HbA_{1c}, BMI, SBP, NHDL-C, current smoking, and LTPA into the risks of a first occurrence of macro- and microvascular complications. We confirmed that the risk engine performed reasonably well and that combining macro- and microvascular risks improved the classification of low-risk and high-risk patients by a net reclassification improvement of 5.7%. In contrast, the UKPDS risk engine overestimated CHD risk, and this tendency is consistent with a previous report in Asian patients (18). A web application for the JJ risk engine, which works in both Windows and Macintosh environments, is available at http://www.biostatistics.jp/prediction/jjre.

With the advent of modern therapeutics, especially hypoglycemic and antihypertensive agents, the early identification of high-risk patients is an appealing strategy (35). A novelty of the JJ risk engine is that it allows risk classification based on the risk not only of CVD but also of renal and eye diseases. Although the prevalence of micro- or macroalbuminuria in Asian hypertensive diabetes is alarmingly high (36), most of the progression to overt nephropathy occurs in a small fraction of patients with elevated HbA_{1c} and SBP values and a smoking habit (12). In this study, patients in the fourth quartile of the calculated risk developed overt nephropathy at a rate 10 times greater than those in the first quartile. Most risk engines are specific to CVD; however, greater emphasis on the risk of microvascular diseases should be placed when assessing risk among diabetic patients given that diabetic nephropathy and retinopathy are major causes of ESRD and blindness, respectively. Combining macro- and microvascular risks resulted in the net reclassification improvement of 5.7% ($P = 0.02$) and a sensitivity and specificity of 46.3 and 75.4%, respectively; only 16.5% of cases were classified as the high-risk population for macro- and microvascular diseases and only 43.8% of noncases were in the low-risk population (Table 4). Thus, the discriminatory power of the JJ risk engine was only moderate, despite the statistically significant improvement in prediction, and exploring novel risk factors would be of particular importance for more accurate risk classification.

The JJ risk engine shares features similar to those with previously developed risk engines. The predictors of CHD are the same as in the UKPDS risk engine (5) except for the inclusion of NHDL-C instead of the total cholesterol–to-HDL cholesterol ratio. Donnan et al. (7) added diabetes duration, treated hypertension, height, and two interaction terms into their model, and the risk equation of the HKDR includes diabetes duration, estimated glomerular filtration rate, and ACR additionally but does not use HbA_{1c} (18). A recent cohort study in Japan also suggested that the progression of the albuminuria stage is a risk factor of CVD (37). In contrast, log ACR was not associated with CHD or stroke in our study. This discordant observation would be attributable to the exclusion of low microalbuminuria in our study. The elevation of ACR within a range of normoalbuminuria may not lead to an increase in the risk of CVD. We also found that the UKPDS risk engine overestimated CHD risk (Table 2) and the C statistic of the JJ risk engine (0.725) was slightly higher than that of the risk equation of the HKDR (0.704) (18), indicating that the JJ risk engine may outperform the previously developed risk engines for the prediction of CHD. For the prediction of stroke, we did not identify smoking status and years after diagnosis as predictors, which are included in the UKPDS risk engine (6). The risk equation from the Swedish National Diabetes Register incorporates the use of antihypertensive drugs and lipid-lowering drugs as predictors (9). However, medical therapies are not considered in the current analysis, since the effects of medications on vascular complications were likely to be confounded by other clinical factors. In contrast to CHD, the C statistic of the JJ risk engine (0.636) was similar to the UKPDS risk engine (0.638) and lower than the risk equation of the HKDR (0.749) (17). With regard to lifestyle factors, we identified LTPA as a risk factor for stroke and noncardiovascular mortality, although the statistical significance was borderline. On the other hand, BMI, which has been recognized as one of the most important risk factors in the deterioration of type 2 diabetes, was not associated with CVD. We previously reported that the BMI of Japanese patients is much lower than that of white patients, although in those reports, other patient characteristics were similar in terms of age, HbA_{1c}, and daily energy intake (10,11). Our findings run contrary to the results of studies of white patients, but data on diet in diabetic patients are sparse, particularly in Asia. In this study, the contribution of lifestyle factors to the risk assessment appears to be limited, and the associations between lifestyle and diabetes complications are worthy of further research.

One important feature of this study is that we analyzed pooled data from two nationwide clinical trials in Japan. The end points were defined similarly in both trials and follow-up was performed by diabetes specialists, ensuring data of relatively high quality. Patients generally

had fair or good glycemic, weight, blood pressure, and lipid control. The major difference between the two trials was eligible age, i.e., age between 40 and 70 years in the JDCS and age between 65 and 85 years in the J-EDIT. Prior to pooling the datasets, we compared important clinical factors between patients in the two trials and found no notable differences except for age; therefore, pooling of the datasets was considered to be valid. Consequently, the study population in the present analysis included subjects spanning several decades, i.e., those from 40 to 84 years. This can be expected to enhance the generalizability of the algorithm.

Statistical modeling can be much more complex if we handle multiple events simultaneously. To the best of our knowledge, this is the first study that applies a multistate model to the construction of a risk engine. It is notable that these events are not inherently independent and the JJ risk engine calculates each probability of the first occurrence for five events. Thus, if the risk of an event (e.g., overt nephropathy) was increased by a risk factor (e.g., log ACR), the probability of the first occurrence of other events (e.g., stroke) can decrease theoretically even if there are no direct associations with the risk factor.

Several limitations warrant mention. First, transportability of prognostic information is critical, but in this study we evaluated only the internal validity. Thus, external validation is required in other populations. Second, updating the algorithm by long-term follow-up data or pooled analysis with other studies in Asia is desirable given that the size of our cohort is relatively small and the observed events of CVD and overt nephropathy in this population were relatively few. Third, we included angina pectoris and transient ischemic attack as components of the cardiovascular events, although they are soft end points. Consequently, the JJ risk engine would provide macrovascular risks higher than those by other risk engines based on only hard cardiovascular events. Fourth, data on peripheral arterial disease and hemoglobin levels were not available. These factors were included as inputs into the HKDR all-cause mortality risk score (19), and peripheral arterial disease is a clinically relevant cardiovascular outcome. Fifth, the use of aspirin, which might increase the risk of hemorrhagic stroke, was not investigated. Finally, we defined overt nephropathy as the presence of persistent proteinuria, since an elevated urinary albumin excretion due to nondiabetic renal lesions or conditions is not rare.

In conclusion, the risk engine allowed accurate and comprehensive risk assessment of macro- and microvascular complications, although external validation is required in other populations. The calculated absolute risks of vascular complications can be used in risk classification for individual patients, health economic simulations, and estimation of the burden of the disease.

Acknowledgments—This work was funded by the Ministry of Health, Labour, and Welfare of Japan.

No potential conflicts of interest relevant to this article were reported.

The sponsor had no role in the design or conduct of the study.

Sh.T., Sa.T., and Y.O. performed statistical analysis and wrote the manuscript. S.I. managed data. H.Y., S.K., Y.A., N.Y., A.A., H.I., and H.S. planned and conducted the JDCS and the J-EDIT. H.S. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

The authors thank the many diabetologists and patients at the 59 participating institutes of the JDCS and 42 participating institutes of the J-EDIT throughout Japan. The authors thank Satomi Fukuya and Yasuko Maruyama (University of Tsukuba Institute of Clinical Medicine) for their excellent secretarial assistance.

References

1. Coleman RL, Stevens RJ, Retnakaran R, Holman RR. Framingham, SCORE, and DECODE risk equations do not provide reliable cardiovascular risk estimates in type 2 diabetes. Diabetes Care 2007;30:1292–1293
2. Chamnan P, Simmons RK, Sharp SJ, Griffin SJ, Wareham NJP. Cardiovascular risk assessment scores for people with diabetes: a systematic review. Diabetologia 2009;52:2001–2014
3. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care 2004;27:1047–1053
4. Chan JC, Malik V, Jia W, et al. Diabetes in Asia: epidemiology, risk factors, and pathophysiology. JAMA 2009;301:2129–2140
5. Stevens RJ, Kothari V, Adler AI, Stratton IM; United Kingdom Prospective Diabetes Study (UKPDS) Group. The UKPDS risk engine: a model for the risk of coronary heart disease in type II diabetes (UKPDS 56). Clin Sci (Lond) 2001;101:671–679
6. Kothari V, Stevens RJ, Adler AI, et al. UKPDS 60: risk of stroke in type 2 diabetes estimated by the UK Prospective Diabetes Study risk engine. Stroke 2002;33:1776–1781
7. Donnan PT, Donnelly L, New JP, Morris AD. Derivation and validation of a prediction score for major coronary heart disease events in a U.K. type 2 diabetic population. Diabetes Care 2006;29:1231–1236
8. Balkau B, Hu G, Qiao Q, Tuomilehto J, Borch-Johnsen K, Pyörälä K; DECODE Study Group; European Diabetes Epidemiology Group. Prediction of the risk of cardiovascular mortality using a score that includes glucose as a risk factor. Diabetologia 2004;47:2118–2128
9. Cederholm J, Eeg-Olofsson K, Eliasson B, Zethelius B, Nilsson PM, Gudbjörnsdottir S; Swedish National Diabetes Register. Risk prediction of cardiovascular disease in type 2 diabetes: a risk equation from the Swedish National Diabetes Register. Diabetes Care 2008;31:2038–2043
10. Sone H, Ito H, Ohashi Y, Akanuma Y, Yamada N; Japan Diabetes Complication Study Group. Obesity and type 2 diabetes in Japanese patients. Lancet 2003;361:85
11. Sone H, Yoshimura Y, Ito H, Ohashi Y, Yamada N; Japan Diabetes Complications Study Group. Energy intake and obesity in Japanese patients with type 2 diabetes. Lancet 2004;363:248–249
12. Katayama S, Moriya T, Tanaka S, et al.; Japan Diabetes Complications Study Group. Low transition rate from normo- and low microalbuminuria to proteinuria in Japanese type 2 diabetic individuals: the Japan Diabetes Complications Study (JDCS). Diabetologia 2011;54:1025–1031
13. Kawasaki R, Tanaka S, Tanaka S, et al.; Japan Diabetes Complications Study Group. Incidence and progression of diabetic retinopathy in Japanese adults with type 2 diabetes: 8 year follow-up study of the Japan Diabetes Complications Study (JDCS). Diabetologia 2011;54:2288–2294
14. Sone H, Mizuno S, Yamada N. Vascular risk factors and diabetic neuropathy. N Engl J Med 2005;352:1925–1927; author reply 1925–1927
15. Lee ET, Keen H, Bennett PH, Fuller JH, Lu M. Follow-up of the WHO Multinational Study of Vascular Disease in Diabetes: general description and morbidity. Diabetologia 2001;44(Suppl. 2):S3–S13
16. Karter AJ, Ferrara A, Liu JY, Moffet HH, Ackerson LM, Selby JV. Ethnic disparities in diabetic complications in an insured population. JAMA 2002;287:2519–2527
17. Yang X, So WY, Kong AP, et al. Development and validation of stroke risk equation for Hong Kong Chinese patients with type 2 diabetes: the Hong Kong Diabetes Registry. Diabetes Care 2007;30:65–70

18. Yang X, So WY, Kong AP, et al. Development and validation of a total coronary heart disease risk score in type 2 diabetes mellitus. Am J Cardiol 2008;101: 596–601
19. Yang X, So WY, Tong PC, et al.; Hong Kong Diabetes Registry. Development and validation of an all-cause mortality risk score in type 2 diabetes. Arch Intern Med 2008;168:451–457
20. Yang X, Ma RC, So WY, et al. Development and validation of a risk score for hospitalization for heart failure in patients with type 2 diabetes mellitus. Cardiovasc Diabetol 2008;7:9
21. Hu G, Jousilahti P, Barengo NC, Qiao Q, Lakka TA, Tuomilehto J. Physical activity, cardiovascular risk factors, and mortality among Finnish adults with diabetes. Diabetes Care 2005;28:799–805
22. Kokkinos P, Myers J, Nylen E, et al. Exercise capacity and all-cause mortality in African American and Caucasian men with type 2 diabetes. Diabetes Care 2009; 32:623–628
23. Marwick TH, Hordern MD, Miller T, et al.; Council on Clinical Cardiology, American Heart Association Exercise, Cardiac Rehabilitation, and Prevention Committee; Council on Cardiovascular Disease in the Young; Council on Cardiovascular Nursing; Council on Nutrition, Physical Activity, and Metabolism; Interdisciplinary Council on Quality of Care and Outcomes Research. Exercise training for type 2 diabetes mellitus: impact on cardiovascular risk: a scientific statement from the American Heart Association. Circulation 2009;119:3244–3262
24. Colberg SR, Sigal RJ, Fernhall B, et al.; American College of Sports Medicine; American Diabetes Association. Exercise and type 2 diabetes: the American College of Sports Medicine and the American Diabetes Association: joint position statement. Diabetes Care 2010;33:e147–e167
25. Müller-Riemenschneider F, Holmberg C, Rieckmann N, et al. Barriers to routine risk-score use for healthy primary care patients: survey and qualitative study. Arch Intern Med 2010;170:719–724
26. Sone H, Tanaka S, Iimuro S, et al.; Japan Diabetes Complications Study Group. Long-term lifestyle intervention lowers the incidence of stroke in Japanese patients with type 2 diabetes: a nationwide multicentre randomised controlled trial (the Japan Diabetes Complications Study). Diabetologia 2010;53:419–428
27. Araki A, Iimuro S, Sakurai T, et al.; Japanese Elderly Diabetes Intervention Trial Study Group. Long-term multiple risk factor interventions in Japanese elderly diabetic patients: the Japanese Elderly Diabetes Intervention Trial—study design, baseline characteristics and effects of intervention. Geriatr Gerontol Int 2012; 12(Suppl. 1):7–17
28. Andersen PK, Keiding N. Multi-state models for event history analysis. Stat Methods Med Res 2002;11:91–115
29. The Committee on the Standardization of Diabetes Mellitus-Related Laboratory Testing of Japan Diabetes Society. International clinical harmonization of hemoglobin A1c in Japan: from JDS to NGSP values [Internet]. Available from http://www.jds.or.jp/jds_or_jp0/uploads/photos/813.pdf. Accessed 31 January 2012
30. Tanasescu M, Leitzmann MF, Rimm EB, Hu FB. Physical activity in relation to cardiovascular disease and total mortality among men with type 2 diabetes. Circulation 2003;107:2435–2439
31. Ainsworth BE, Haskell WL, Herrmann SD, et al. 2011 Compendium of Physical Activities: a second update of codes and MET values. Med Sci Sports Exerc 2011; 43:1575–1581
32. Sone H, Tanaka S, Tanaka S, et al.; Japan Diabetes Complications Study Group. Serum level of triglycerides is a potent risk factor comparable to LDL cholesterol for coronary heart disease in Japanese patients with type 2 diabetes: subanalysis of the Japan Diabetes Complications Study (JDCS). J Clin Endocrinol Metab 2011;96: 3448–3456
33. Wilkinson CP, Ferris FL 3rd, Klein RE, et al.; Global Diabetic Retinopathy Project Group. Proposed international clinical diabetic retinopathy and diabetic macular edema disease severity scales. Ophthalmology 2003;110:1677–1682
34. Pencina MJ, D'Agostino RB Sr, D'Agostino RB Jr, Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. Stat Med 2008;27: 157–172; discussion 207–212
35. National Institute for Clinical Excellence. Inherited Clinical Guideline H. Management of type 2 diabetes: management of blood pressure and blood lipids. London: National Institute for Clinical Excellence [article online], 2002. Available from http://www.nice.org.uk/nicemedia/pdf/NICE_INHERITEd_Hv8.pdf. Accessed at 25 April 2011
36. Wu AY, Kong NC, de Leon FA, et al. An alarmingly high prevalence of diabetic nephropathy in Asian type 2 diabetic patients: the MicroAlbuminuria Prevalence (MAP) Study. Diabetologia 2005;48:17–26
37. Yokoyama H, Araki S, Haneda M, et al.; Japan Diabetes Clinical Data Management Study Group. Chronic kidney disease categories and renal-cardiovascular outcomes in type 2 diabetes without prevalent cardiovascular disease: a prospective cohort study (JDDM25). Diabetologia 2012;55: 1911–1918

Diabetologia
DOI 10.1007/s00125-012-2810-z

ARTICLE

Leisure-time physical activity is a significant predictor of stroke and total mortality in Japanese patients with type 2 diabetes: analysis from the Japan Diabetes Complications Study (JDCS)

H. Sone · S. Tanaka · S. Tanaka · S. Suzuki · H. Seino · O. Hanyu · A. Sato · T. Toyonaga · K. Okita · S. Ishibashi · S. Kodama · Y. Akanuma · N. Yamada · on behalf of the Japan Diabetes Complications Study Group

Received: 29 April 2012 / Accepted: 29 November 2012

Abstract
Aims/hypothesis Our aim was to clarify the association between leisure-time physical activity (LTPA) and cardiovascular events and total mortality in a nationwide cohort of Japanese diabetic patients.

Methods Eligible patients (1,702) with type 2 diabetes (mean age, 58.5 years; 47% women) from 59 institutes were followed for a median of 8.05 years. A comprehensive lifestyle survey including LTPA and occupation was performed using standardised questionnaires. Outcome was

A complete list of members of the JDCS group can be found in the electronic supplementary material (ESM).

Electronic supplementary material The online version of this article (doi:10.1007/s00125-012-2810-z) contains peer-reviewed but unedited supplementary material, which is available to authorised users.

H. Sone (✉) · O. Hanyu
Department of Internal Medicine, Niigata University Faculty of Medicine, 1-757 Asahimachi-dori, Chuoh-ku, Niigata, Japan 951-8510
e-mail: jdcstudy@md.tsukuba.ac.jp

H. Sone · S. Kodama · N. Yamada
Department of Internal Medicine, University of Tsukuba, Ibaraki, Japan

S. Tanaka
Translational Research Center, Kyoto University, Kyoto, Japan

S. Tanaka
EBM Research Center, Kyoto University, Kyoto, Japan

S. Suzuki
Diabetes Center, Ohta General Hospital, Fukushima, Japan

H. Seino
Seino Internal Medicine Clinic, Fukushima, Japan

A. Sato
Diabetes Center, Tokyo Women's Medical University, Tokyo, Japan

T. Toyonaga
Department of Diabetes and Endocrinology, National Hospital Organization Kumamoto Medical Center, Kumamoto, Japan

K. Okita
Department of Metabolic Medicine, Osaka University, Osaka, Japan

S. Ishibashi
Department of Endocrinology and Metabolism, Jichi Medical College, Tochigi, Japan

Y. Akanuma
The Institute for Adult Diseases Asahi Life Foundation, Tokyo, Japan

Published online: 27 February 2013

follow-up for the 1,771 patients was 7.86 years (final follow-up rate was 75%; 1,332/1,771 patients). For this analysis of physical activity, data on the 1,702 patients (901 men, age 58.2±7.0 years; 801 women, age 58.9±6.8 years) who responded to the baseline physical activity survey were used. There was no notable difference in baseline characteristics between responders and non-responders. We analysed follow-up data until March 2003.

Diabetes mellitus and IGT were diagnosed according to the 'Report of the Committee of the Japan Diabetes Society on the Classification and Diagnostic Criteria of Diabetes Mellitus', which is almost identical in terms of thresholds for glucose levels to those of the WHO. The study protocol, which is in accordance with the Declaration of Helsinki and the Ethical Guidelines for Clinical/Epidemiological Studies of the Japanese Ministry of Health Labor and Welfare, received ethics approval from the institutional review boards of all participating institutes. All enrolled patients provided written informed consent.

Assessment of LTPA LTPA was assessed at baseline by a self-administered questionnaire, which was almost identical to that used and validated in the Health Professionals' Follow-up Study [18]. The patients were asked the average frequency (times/week) and duration (min/time) of normal walking, brisk walking, jogging, golf, tennis, swimming, aerobics dancing, cycling and other miscellaneous exercise (specified by each patient). The duration engaged in each activity in min/time was multiplied by that activity's typical energy expenditure, expressed in MET, based on the newest compendium of Ainsworth [23]; then overall activity was summed to yield a MET h score per week. The energy expended by sitting quietly, 1 MET, is equivalent to 3.5 ml oxygen uptake (kg body weight)$^{-1}$ min^{-1} or 4.184 kJ (1 kcal) (kg body weight)$^{-1}$ h^{-1}.

Other lifestyle variables A baseline dietary survey, which was validated and is widely used in Japan [24], was undertaken. This consisted of food records and a food frequency questionnaire, which included questions on alcohol consumption. Information on cigarette smoking was collected using a self-administered questionnaire. Smoking status was classified into one of three categories: current smokers, ex-smokers and never smokers [25]. Occupation was surveyed by a self-administered questionnaire based on the Japan Standard Classification of Occupations [26], which was also used in the National Health and Nutritional Examination Survey in Japan. Occupations were: (1) professional or skilled workers and technicians; (2) administrative or managerial; (3) office or clerical; (4) sales; (5) service; (6) armed force and police; (7) agricultural, forestry and fishery; (8) transport, trades and storage; (9) labourers in manufacturing, mining and construction and (10) no work or housewife. Occupations in categories 1, 2, 3 and 10 were classified as sedentary and the remainder were defined as physically active.

Clinical and laboratory measurements Patients were assessed yearly after the baseline evaluation. Mean values for at least two measurements each year were obtained for HbA_{1c}, fasting plasma glucose and fasting serum lipids. HbA_{1c} assays were performed according to procedures outlined by the Laboratory Test Committee of the JDS, which is known to be converted by the formula HbA_{1c} (JDS) (%)= $0.98 \times HbA_{1c}$ (National Glycohaemoglobin Standardisation Program; NGSP) (%)+0.25%. All other laboratory tests were done at each participating institute. Serum LDL-cholesterol was calculated using Friedewald's equation, except where triacylglycerols exceeded 4.52 mmol/l (400 mg/dl), in which case LDL-cholesterol data were treated as 'missing'. This was applicable to 19 participants. All other measurements, including those for body weight, blood pressure and a 12-lead ECG, were performed at least once yearly.

Outcome measures A fatal or first non-fatal manifestation of CHD (angina pectoris or myocardial infarction) was diagnosed according to criteria defined by the Multinational Monitoring of Trends and Determinants in Cardiovascular Disease (WHO/MONICA) project. A patient with a first percutaneous coronary intervention or coronary artery bypass graft was also counted as having a CHD event. Information regarding primary outcome and other clinical variables for each individual was collected through an annual report that included detailed findings at the time of the event from each participating diabetologist who was providing care to those patients. Adjudication of endpoints was by central committees comprised of experts in diabetology as well as cardiology who were masked to risk factor status, including information on LTPA, and was based on additional data such as a detailed history, sequential changes in ECG and serum cardiac biomarkers and results of coronary angiography. Information regarding vital status and causes of death was also obtained through an annual report form and causes of death were classified based on the ninth revision of the International Classification of Diseases (ICD-9) Clinical Modification codes (www.icd9data.com/2007/Volume1/240-279/250-259/250/default.htm) for cardiovascular disease (diagnosis codes 390–452), cancer (diagnosis codes 140–208) and other miscellaneous causes.

Statistical analysis

All statistical analyses and data management were conducted at a central data centre. Patient characteristics were described as mean ± SD, median and interquartile range or percentage. HRs of the incidence of each outcome for higher tertiles of LTPA compared with the lowest tertile of LTPA

Table 1 Baseline characteristics of the 1,702 Japanese patients with type 2 diabetes according to tertile of LTPA

Characteristic	Total	Tertile 1 (≤3.7 MET h/week)	Tertile 2 (3.8–15.3 MET h/week)	Tertile 3 (≥15.4 MET h/week)	*p* for trend
No. of patients	*n*=1702	*n*=551	*n*=589	*n*=562	
LTPA (MET h/week)	15.5±20.8	0.8±1.1	9.1±3.8	36.8±24.4	<0.01
Women (%)	47.1	48.3	48.4	44.5	0.20
Age (years)	58.5±6.9	57.9±7.2	58.7±6.8	59.0±6.7	0.01
Diabetes duration (years)	11.0±7.1	10.4±6.6	11.0±7.3	11.6±7.4	0.01
Sedentary occupation (%)	74.1	67.1	75.6	77.8	<0.01
BMI (kg/m^2)	23.0±3.0	23.2±3.2	23.0±3.0	22.7±2.9	0.01
Waist circumference (cm)	79.4±9.2	80.0±9.4	79.6±9.1	78.5±9.0	0.01
Systolic blood pressure (mmHg)	131.7±16.3	131.5±16.4	132.1±16.5	131.6±16.1	0.88
Diastolic blood pressure (mmHg)	76.7±9.9	76.8±10.0	76.8±10.0	76.6±9.9	0.71
HbA_{1c} (JDS) (%)	7.9±1.3	8.0±1.4	7.8±1.2	7.8±1.2	<0.01
HbA_{1c} (IFCC) (mmol/mol)	67.0±14.2	68.8±15.6	66.3±13.4	66.0±13.4	<0.01
Fasting plasma glucose (mmol/l)	8.85±2.41	9.10±2.59	8.71±2.18	8.77±2.45	0.03
LDL-cholesterol (mmol/l)	3.17±0.83	3.18±0.84	3.17±0.85	3.16±0.78	0.67
HDL-cholesterol (mmol/l)	1.42±0.44	1.37±0.42	1.41±0.42	1.48±0.45	<0.01
Triacylglycerols[a] (mmol/l)	1.15±0.80	1.21±0.80	1.18±0.84	1.08±0.72	0.05
Treated by insulin/OHA without insulin (%)	22.1/65.7	22.9/68.6	21.3/64.5	22.1/64.2	0.76/0.13
Use of agents for hypertension (%)	25.9	30.7	24.6	22.4	<0.01
Use of agents for dyslipidaemia (%)	24.0	24.9	23.6	23.4	0.55
Current smoker (%)	27.6	31.0	30.2	22.1	<0.01
Energy intake (kJ/day)	7,183±1,469	7,145±1,540	7,217±1,473	7,175±1,415	0.82
Saturated fatty acid intake (g)	15.4±5.1	15.4±5.4	15.5±5.1	15.2±4.9	0.73
Dietary fibre intake (g)	14.6±5.2	14.0±5.4	14.7±5.2	15.1±5.1	<0.01
Ethanol intake (per day): never, 3 drinks or less, more than 3 drinks (%)[b]	62.1/31.5/6.4	66.5/26.9/6.6	61.9/31.7/6.3	57.9/35.8/6.3	<0.01/<0.01/0.83
No. of outcome incidents					
CHD	114	38	42	34	-
Stroke	89	33	33	23	-
Mortality	69	26	27	16	-

Data are means (±SD for continuous variables)

[a] Median (interquartile range)

[b] 'One drink' is equivalent to 12.6 g of ethanol based on the US Department of Agriculture definition

OHA, oral hypoglycaemic agent

than those in Western countries [28, 31]. Furthermore, cardiovascular disease is not necessarily a leading cause of death among diabetic patients in Japan [32], which is in distinct contrast to Western patients with diabetes [1]. Despite these differences, only two studies have prospectively investigated associations between physical activity and mortality and morbidity in Asian populations with diabetes [4, 7]. This is notable, as Asian diabetic patients account for more than 60% of the world's diabetes population [28]. One was a recent report from Taiwan [7] that used a self-reported bivariate response of whether exercise was performed regularly as the only physical activity variable. The other study was from Japan [4] and involved only individuals with diabetes who were more than 65 years of age and demonstrated dose-dependent effects of physical activity that were evaluated and scored, although not by the use of universal MET h units. Therefore, information on the recommended level of physical activity required to prevent complications in Asian patients with diabetes is scarce.

The current results for Japanese individuals with type 2 diabetes revealed that 15.4 MET h/week or more of LTPA was associated with a significant reduction in risk of stroke and total deaths (by approximately half) compared with 3.7 MET h/weekor less of LTPA. The cut-off of 15.4 MET h/week in the current analysis corresponds to 2.2 MET h/day which is, for example, equivalent to 30 min/day of brisk walking (3.5 miles [5.6 km]/h) and is 4.3 MET [23]. This is