地域として、心臓突然死に関する様々な形の啓発を行い、地域における突然死に対する認識と救命意識の変化を検証するものである。あわせて、啓発方法の違いによる効果を調べ、効果的・効率的な啓発方法を検討することを目的としている。

今回は平成 24 年 1 月に地域介入前のベースラインデータ調査を実施した。その結果、当該地域では、倒れていた人に対して心肺蘇生を実施すると回答した人は約 1/3、AED を使用すると回答した人は約 1/2 であった。このデータを基に、啓発介入による地域での救命意識の変化について調査する。

また、日本で発生する交通事故死数と突然死数を正しく出来た人は約 1/5 にすぎなかった。院外で発生する突然死数は交通事故死の約 10 倍であるにも関わらず、突然死のほうが少ないと解答するものが多く、突然死に対する正しい知識を伝え、身近に感じさせることが重要であると思われた。

平成 24 年 4 月からは、研究期間中に目標とする舞鶴市人口の 16%に心臓突然死に関する啓発を達成できるように、簡易型心肺蘇生講習会などを様々な活動を実施し、地域住民の救命意識の向上についての効果検証を進めていく予定である。

E. 結論

現在進行中のため未確定。

F. 健康危険情報

特になし。

G. 研究発表

1. 論文発表

なし。

2. 学会発表

なし。

H. 知的財産権の出願・登録状況

特になし

舞鶴地域抽出

救命意識に関するアンケート（地域抽出）

このアンケートでは皆様の救命意識に関する調査をさせていただきたいと思います。本研究は厚生労働省科学研究として行われています。**この調査結果については、完全に秘密を守ります。これから得られる情報は調査結果の分析のためにのみ使用し、いかなる場合にもあなたの個人的なことが外にもれることはありません**のでありのままにお答え下さい。よろしくお願いします。

問 1 もし見知らぬ人があなたの目の前で倒れていて意識がないようなら、あなた自ら心肺蘇生（人工呼吸や心臓マッサージ）を試みようと思いますか。（1つだけ○印）

1 そう思う
2 まあそう思う
3 どちらともいえない
4 あまり思わない
5 そうは思わない

（問 1 で 2～5 を選択された方にうかがいます）

問 1-1 あなたが心肺蘇生をためらう一番の理由は何ですか。（1つだけ○印）

1 何をしたらいいか分からない
2 口をつけて人工呼吸はしたくない
3 救急隊を待ったほうがよいから
4 うまくいかなかった時が心配
5 心臓マッサージはしたくない
6 その他（　　）

（問 1 で 2～5 を選択された方にうかがいます）

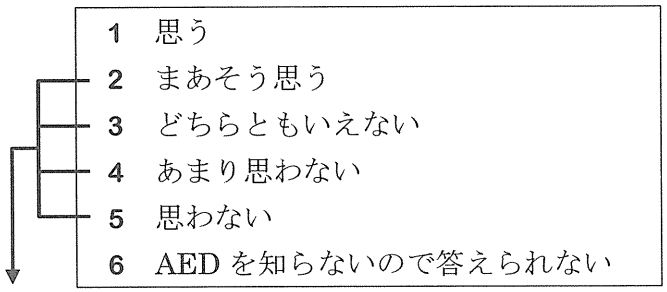
問 1-2 もし心臓マッサージだけで良いならばやってみようと思いますか。（1つだけ○印）

1 そう思う
2 まあそう思う
3 どちらともいえない
4 あまりそう思わない
5 そう思わない

問 2 胸骨圧迫（心臓マッサージ）のみの心肺蘇生でも、人工呼吸をする心肺蘇生と同じぐらいの効果があるということを、今まで聞いたことがありますか。（1つだけ○印）

1 はい　　2 いいえ

問 3 実際に目の前で人が倒れたら AED があれば使用してみようと思いますか。
（1つだけ○印）



（問 3 で 2～5 を選択された方にうかがいます）

問 3-1 あなたが AED の使用をためらう一番の理由は何ですか。（1つだけ○印）

1 AED を正しく使えるかどうか不安	4 誤ったことをして、自分に危険が及ぶことが心配
2 誤ったことをして、倒れている人を傷つけるのが心配	5 その他（　　）
3 AED は医師や救急隊員など専門の人にやってもらったほうがいい	

問 4 日本で 1 年間に交通事故で死亡する人は、およそ何人だと思われますか？（1つだけ○印）

1 およそ 5 千人	3 およそ 5 万人
2 およそ 1 万人	4 分らない

問 5 日本で 1 年間に心臓突然死で死亡する人は、およそ何人だと思われますか？（1つだけ○印）

1 およそ 5 千人	3 およそ 5 万人
2 およそ 1 万人	4 分らない

＊＊

- **年齢:** _____ **歳**
- **性別:** □ 男　□ 女
- **職業:** □医療従事者、□教職員　□公共交通機関、□会社員、□自営業、
  □学生、□主婦、□その他（　　）

- **心肺蘇生の現場に居合わせたことがありますか:** □ はい □ いいえ
- **今までに実際に心肺蘇生を実施したことはありますか？** □ はい □ いいえ
- **今までに心肺蘇生講習を受けたことがありますか？** □ はい □ いいえ

（「はい」を選択された方にうかがいます）

胸骨圧迫（心臓マッサージ）のみの講習会でしたか？ □ はい □ いいえ

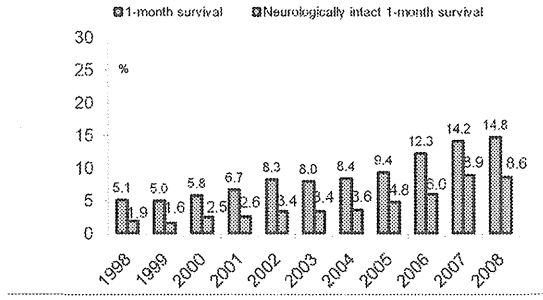
厚生労働省科学研究班
院外心停止の一次救命処置に関する啓発を進める手法の検討
H24年～H25年度

仮称：舞鶴PUSHプロジェクト

分担研究者：京都大学　石見拓
研究協力者：川村孝、北村哲久、西山知佳
舞鶴市・・・

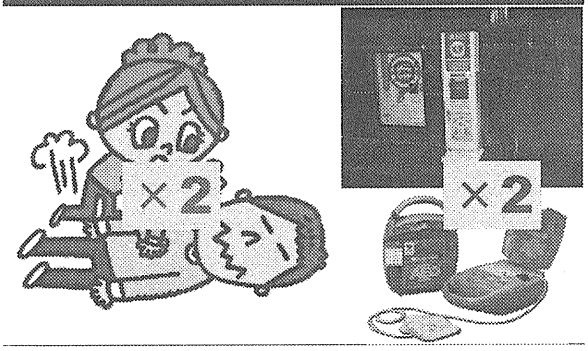
心臓突然死　年間6万人
院外心停止からの救命率はまだまだ低い

目撃心原性心停止からの救命率



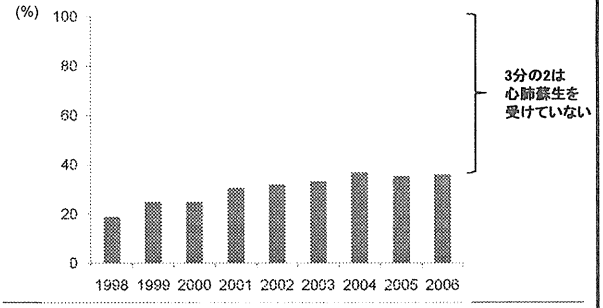
Iwami et al. Circulation 2009.

AEDを用いて救命するために



市民による心肺蘇生の現状

年間約200万人に対して心肺蘇生講習会を実施



Iwami et al. Circulation 2009.

心臓突然死に対する認識の低さ

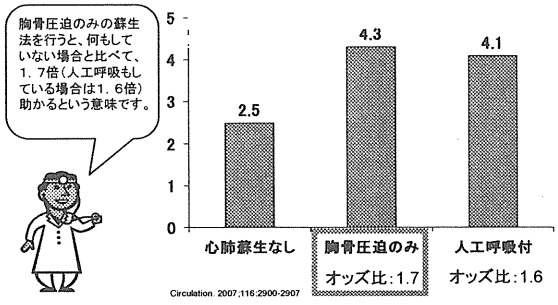
心臓突然死で亡くなる人の数は？
1．5000人／年
2．1万人／年
3．5万人／年

※交通事故死　5000人以下

心臓突然死対策のカギ
市民のちからを活かす

胸骨圧迫（心臓マッサージ）
のみの心肺蘇生
＋
AED

日本発
胸骨圧迫のみの蘇生法の効果



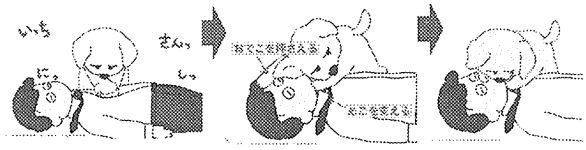
Iwami et al. Circulation 2007.

まず胸骨圧迫
胸骨圧迫＝心臓マッサージが一番大事

C: compressions
（胸骨圧迫）

A: airway
（気道の確保）

B: breathing
（人工呼吸）

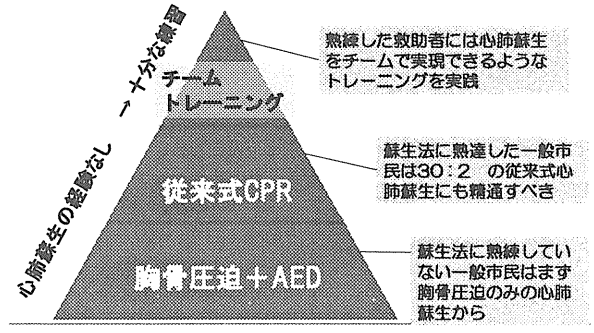


日本版
新しい心肺蘇生ガイドラインでの推奨

- バイスタンダーCPRを増加させるために、胸骨圧迫のみのCPR講習を推奨
- 心肺蘇生講習を体系的に展開する手段として、学術団体、消防、日本赤十字社、その他の心肺蘇生普及団体が教育現場と連携して、心肺蘇生講習を学校教育に導入することを推奨

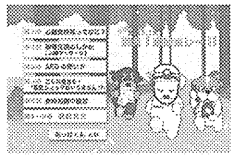
ガイドラインで、胸骨圧迫だけの心肺蘇生の教育を推奨したのは日本だけ！

これからの心肺蘇生教育

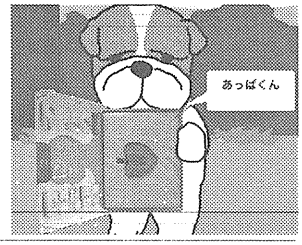


PUSH講習会
簡易型講習会のモデル化

1. 1人1体のトレーニングキット



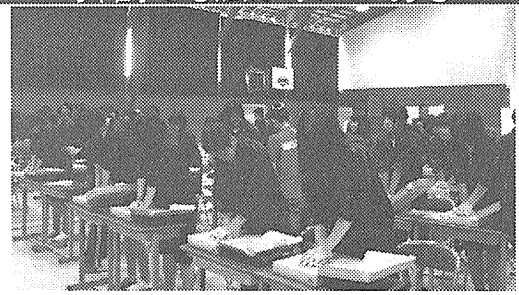
安い
頑丈
使い回し自由
収納しやすい



2. 45分＝授業の時間内

3. DVD教材で質を担保

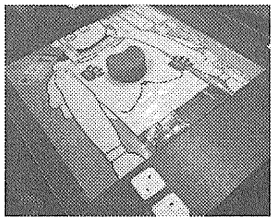
PUSH講習会
舞鶴でも広がりつつある

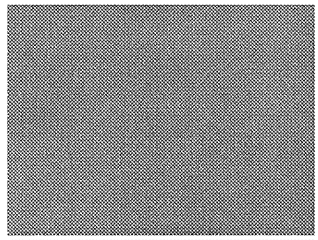


学校における心肺蘇生教育の実施を促すことで、「いのちを大切にするこころ」を育てたい

新しいコンテンツの活用

より簡易型の教材。持ち帰り可能

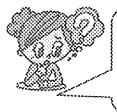




舞鶴市のバックグラウンド

- PUSH講習会を地域・学校で地道に拡げてきた実績
- PUSH講習会の学校での実施環境の整備
- ICLS講習会等で培ったネットワーク・基幹施設の存在
- 効果検証に適度な人口
- 全市的な取り組みの可能性

舞鶴PUSHプロジェクト計画
地域介入　前後比較試験

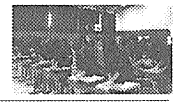


突然死に対する様々な形の啓発（胸骨圧迫とAEDに絞った簡易型講習／啓発ちらし／イベント／ネット情報）を地域で行うことで、地域住民の救命意識・知識およびBystander CPR実施割合が上昇するか？

これまでの約2倍

人口の15%に対して、突然死に関する啓発を実施

- 研究デザイン: 前後比較試験
- 研究期間:　2012年4月– 2014年3月
- 対象地域:　舞鶴市（人口9万人）
- 対象者:　10歳以上の市民

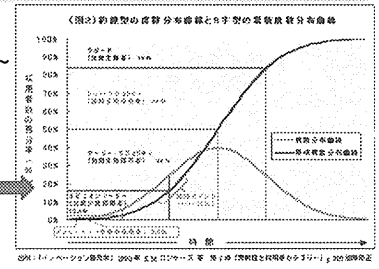


舞鶴PUSHプロジェクト実施計画

“心臓突然死に関する啓発”を、短期間で、地域の人口の15%に対して指導し、その効果を検証する。

イノベーション普及学
～S字の普及曲線と16%の論理～

ブレークスルーのポイント　16%



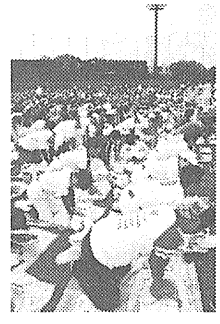
参考：
豊中PUSHプロジェクト

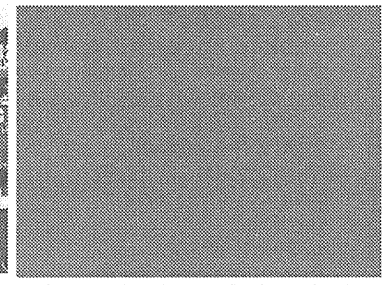
“胸骨圧迫のみの蘇生法”を、毎年、地域の人口の5%に対して指導し、その効果を検証する。

毎年、豊中市の人口38万人の5%である19000人に講習会を提供

“救命力世界一”チャレンジ防災フェスタ

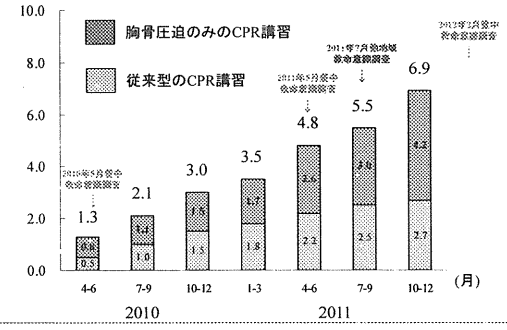
平成23年10月15日（土）　大阪府豊中市の豊島公園





子どもから大人まで3250人（一度に行った救命講習の受講人数で日本最多）

参考：豊中市　累積CPR講習受講者割合の経過



舞鶴PUSHプロジェクト実施計画

毎年、舞鶴市の人口9万人の8%（7200人）に講習会やちらし・イベントなどを通じて、心臓突然死に対する情報を提供

通常の心肺蘇生講習（ベース）	約500名
その他講習	約3000名
小学校5年生　半分	450名
家族等周囲の人への伝達（×2）	900名
中学生　1年生、3年生　半分	350名
家族等周囲への伝達（×2）	1700名
自治会等	1700名
イベント・チラシ等による啓発	1100名

3000名のその他講習をPUSHに切り替える うち1300名は学校

500名＋6700名＝目標達成

効果の検証

- 心停止患者の社会復帰率
- バイスタンダーCPRの実施割合
- 地域住民の意識変化
- 啓発方法による意識・行動変化の違い

本研究で検討

H23年度の取り組み

- ウツタイン統計による院外心停止の実態把握と学校での簡易講習会実施に向けた準備
  - NPO大阪ライフサポート協会に委託
- 舞鶴市の住民の意識調査（地域介入前・ランダムサンプル）
  - サンプル数　200程度
  - 心臓突然死に対する認知度、救命意欲を調査（別紙参照）
  - コントロール地域についても調査　（今回は別研究のコントロールを活用）
- 舞鶴地区の基幹病院・舞鶴市消防本部との調整
  - 舞鶴共済病院の協力確保。消防本部に協力打診中。
  - 舞鶴市長とも面談し、協力要請予定。
- 教員向け簡易講習会と指導者研修会
  - 1月18日予定

H24年度実施案

- 舞鶴市の住民の意識調査（地域介入1年後・ランダムサンプル）
  - サンプル数　200程度
  - 心臓突然死に対する認知度、救命意欲を調査
  - コントロール地域についても調査
- 舞鶴地区の学校での生徒向け簡易講習会＋伝達講習
  - あっぱくん　1000個　（25校に40個づつ）。繰り返し使用で1学年を網羅。持ち帰りで2名以上に伝達。
- 講習会およびイベントの展開
  - 自治会？　企業？？　自衛隊？？？
  - ミュージカル？
  - インターネットの活用？
  - メッセージビデオの提供・積極的な配布・・・

Ⅳ. 研究成果の刊行に関する一覧表

研究成果の刊行に関する一覧表

書　籍

著者氏名	論文タイトル名	書籍全体の編集者名	書　籍　名	出版社名	出版地	出版年	ページ
槇野久士 宮本恵宏 岸本一郎	メタボリックシンドロームの病態診断　インスリン抵抗性の評価法　高インスリン正常血糖クランプ法、SSPG法、ミニマルモデル法.	中尾一和	メタボリックシンドローム （第２版）	日本臨牀社	日本	2011	473-7
豊田一則	rt-PA静注療法の現状と今後	坂井信幸 瓢子敏夫 松丸祐司 宮地　茂 吉村紳一　編	脳血管内治療の進歩2011：最新の機器をどう活かすか？	診断と治療社	東京	2011	70-6
豊田一則	頸動脈狭窄症の疫学	永田泉 峰松一夫 坂井信幸　編	頸動脈狭窄症の診療とステント留置術の実際	永井書店	東京	2011	1-5
宮下史生 豊田一則	頸動脈狭窄症の病因	永田泉、 峰松一夫、 坂井信幸　編	頸動脈狭窄症の診療とステント留置術の実際	永井書店	東京	2011	6-10
古賀政利 豊田一則	頸動脈狭窄症の症候	永田泉、 峰松一夫、 坂井信幸　編	頸動脈狭窄症の診療とステント留置術の実際	永井書店	東京	2011	11-5
豊田一則 （JRCガイドライン作成合同委員会委員として分担執筆）		JRC蘇生ガイドライン2010　JRCガイドライン作成合同委員会,編	JRC蘇生ガイドライン2010	へるす出版	東京	2011	
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発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Higashiyama A, Wakabayashi I,Ono, Y; Watanabe M, Kokubo Y,Okayama A, Miyamoto Y ,Okamura, T	Association With Serum Gamma-Glutamyltransferase Levels and Alcohol Consumption on Stroke and Coronary Artery Disease The Suita Study	STROKE	42 (6)	1764-7	2011
Okamura T, Kokubo Y Watanabe M Higashiyama A, Ono Y, Nishimura, K, Okayama A, Miyamoto Y.	A revised definition of the metabolic syndrome predicts coronary artery disease and ischemic stroke after adjusting for low density lipoprotein cholesterol in a 13-year cohort study of Japanese: The Suita Study	ATHEROSC LEROSIS	217 (1)	201-6	2011
Watanabe M, Kokubo Y, Higashiyama A, Ono Y, Miyamoto Y, Okamura T.	Serum 1,5-anhydro-D-glucitol levels redict first-ever cardiovascular disease: An 11-year population-based Cohort study in Japan, the Suita study	ATHEROSC LEROSIS	216 (2)	477-83	2011
Ichioka M, Suganami T, Tsuda N, Shirakawa,I, Hirata Y, Satoh-Asahara N, Shimoda Y, TanakaM, Kim-Saijo M, Miyamoto Y, Kamei, Y; Sata M, gawa Y.	Increased Expression of Macrophage-Inducible C-type Lectin in Adipose Tissue of Obese Mice and Humans.	DIABETES	60 (3)	819-26	2011
Kajino K, Iwami T, Kitamura T, Daya M, Ong ME, Nishiuchi T, Hayashi Y, Sakai T, Shimazu T, Hiraide A, Kishi M, Yamayoshi S.	Comparison of supraglottic airway versus endotracheal intubation for the pre-hospital treatment of out-of-hospital cardiac arrest.	Crit Care.	15 (5)	R236	2011
Sasaki M, Iwami T, Kitamura T, Nomoto S, Nishiyama C, Sakai T, Tanigawa K, Kajino K, Irisawa T, Nishiuchi T, Hayashida S, Hiraide A, Kawamura T.	Incidence and outcome of out-of-hospital cardiac arrest with public-access defibrillation. A descriptive epidemiological study in a large urban community.	Circ J.	75	2821-6	2011

Nitta M, Iwami T, Kitamura T, Nadkarni VM, Berg RA, Shimizu N, Ohta K, Nishiuchi T, Hayashi Y, Hiraide A,Tamai H, Kobayashi M, Morita H; Utstein Osaka Project.	Age-specific differences in outcomes after out-of-hospital cardiac arrests.	Pediatrics.	128	e812-20	2011
Kubota Y, Yano Y, Seki S, Takada K, Sakuma M, Morimoto T, Akaike A, Hiraide A.	Assessment of pharmacy students' communication competence using the Roter Interaction Analysis System during objective structured clinical examinations.	Am J Pharm Educ.	75	43	2011
Nishiyama C, Iwami T, Nichol G, Kitamura T, Hiraide A,Nishiuchi T, Hayashi Y, Nonogi H, Kawamura T.	Association of out-of-hospital cardiac arrest with prior activity and ambient temperature.	Resuscitation.	82	1008-12	2011
Hayakawa K, Tasaki O, Hamasaki T, Sakai T, Shiozaki T, Nakagawa Y, Ogura H, Kuwagata Y, Kajino K, IwamiT, Nishiuchi T, Hayashi Y, Hiraide A, Sugimoto H, Shimazu T.	Prognostic indicators and outcome prediction model for patients with return of spontaneous circulation from cardiopulmonary arrest: the Utstein Osaka Project.	Resuscitation.	82	874-80	2011
Sakuma M, Morimoto T, Matsui K, Seki S, Kuramoto N, Toshiro J, Murakami J, Fukui T, Saito M, Hiraide A, Bates DW.	Epidemiology of potentially Inappropriate medication use in elderly patients in Japanese acute care hospitals.	Pharmacoepidemiol Drug Saf.	20	386-92	2011
Kitamura T, Iwam T, Kawamura T, Nagao K, Tanaka H,Berg RA, Hiraide A; Implementation Working Group for All-Japan Utstein Registry of the Fire and Disaster Management Agency.	Time-dependent effectiveness of chest compression-only and Conventional cardiopulmonary resuscitation for out-of-hospital cardiac arrest of cardiac origin.	Resuscitation.	82	3-9	2011

Fujimoto S, Toyoda K, Jinnouchi J, Yasaka M, Kitazono T, Okada Y	Differences in Diffusion-Weighted Image and Transesophageal Echocardiographical Findingsin Cardiogenic, Paradoxical and Aortogenic Brain Embolism.	Cerebrovasc Dis.	32 (2)	148-54	2011
Kawano H, Yamamoto H, Miyata S, Izumi M, Hirano T, Toratani N, Kakutani I, Sheppard JA, Warkentin TE, Kada A, Sato S, Okamoto S, Nagatsuka K, Naritomi H, Toyoda K, Uchino M, Minematsu K.	Prospective multicentre cohort study of heparin-induced thrombocytopenia in acute is chaemic stroke patients.	Br J Haematol.	154 (3)	378-86	2011
Koga M, Kimura K, Shibazaki K, Shiokawa Y, Nakagawara J, Furui E, Yamagami H, Okada Y, Hasegawa Y, Kario K, Okuda S, Naganuma M, Nezu T, Maeda K, Minematsu K, Toyoda K.	CHADS2 score is associated with 3-month clinical outcomes after intravenousrt-PA therapy in stroke patients with atrial fibrillation: SAMURAI rt-PA Registry.	J Neurol Sci	306 (1-2)	49-53	2011
Koga M, Toyoda K, Nakashima T, Hyun B-H, Uehara T, Yokota C, Nagatsuka K, Minematsu K.	Carotid duplex ultrasonography can predict safety and outcome of intravenous rt-PA therapy for hyperacute stroke.	J Stroke Cerebrovasc Dis	20	24-29	2011
Mori M, Yamamoto H, Koga M, Okatsu H, Shono Y, Toyoda K, Fukuda K, Iihara K, Yamada N, Minematsu K.	Hyoid bone compression induced repetitive occlusion and recanalization of th internal carotid artery in a patient with ipsilateral brain and retinal ischemia.	Arch Neurol	68	258-59	2011
Nagasawa H, Yokota C, Toyoda K, Ito A, Minematsu K.	High Level of Plasma Adiponectin in Acute Stroke Patients is Associated with Stroke Mortality.	J Neurol Sci,	304	102-06	2011

Naganuma M, Koga M, Shiokawa Y, Nakagawara J, Furui E, Kimura K, Yamagami H, Okada Y, Hasegawa Y, Kario K, Okuda S, Nishiyama K, Minematsu K, Toyoda K.	Reduced estimated glomerular filtration rate is associated with stroke outcomes after intravenous rt-PA: the Stroke Acute Management with Urgent Risk-factor Assessment and Improvement (SAMURAI) Study.	Cerebrovasc Dis	31	123-29	2011
Naganuma M, Mori M, Nezu T, Makihara N, Koga M, Okada Y, Minematsu K, Toyoda K on behalf of the Stroke Acute Management with Urgent Risk-factor Assessment and Improvement(SAMURAI) Study Investigators.	Intravenous recombinant tissue plasminogen activator therapy for stroke patients Receiving maintenance hemodialysis: the Stroke Acute Management with Urgent Risk-factor Assessment and Improvement (SAMURAI) rt-PA Registry.	Eur Neurol	66 (1)	37-41	2011
Nezu T, Koga M, Nakagawara J, Shiokawa Y, YamagamiH, Furui E, Kimura K, Hasegawa Y, Okada Y, Okuda S, Kario K, Naganuma M, Maeda K, Minematsu K, Toyoda K.	Early ischemic change on CT versus DWI for stroke patients receiving Intravenous rt-PA therapy: SAMURAI rt-PA Registry.	Stroke	42	2196-200	2011
Tomii Y, Matsuoka H, Torii T, Uehara T, Toyoda K, Minematsu K.	A new ultrasound method for evaluating dysphagia in acute stroke patients.	Int J Stroke.	6(3)	279-80	2011
Tomii Y, Toyoda K, Nakashima T, Nezu T, Koga M, Yokota C, Nagatsuka K, Minematsu K.	Effects of hyperacute blood pressure and heart rate on stroke outcomes after intravenous tissue plasminogen activator.	J Hypertens	29	1980-87	2011
Tomii Y, Toyoda K, Suzuki R, Naganuma M, Fujinami J, Yokota C, Minematsu K	Effects of 24-hour blood pressure and heart rate recorded with a bpm on recovery from acute ischemic stroke.	Stroke	42	3511-17	2011

Saito Y, Kishimoto I, Nakao K.	Roles of guanylyl cyclase-A signaling in the cardiovascular system.	Can J Physiol Pharmacol.	89 (8)	551-56	2011
Mitomi H, Fukui N, Kishimoto I, Tanabe S, Kikuchi S, Saito T, Hayashi T, Yao T.	Role for p16(INK4a) in progression of gastrointestinal stromal tumors of the stomach: alteration of p16(INK4a) network members.	Hum Pathol.	42 (10)	1505-13	2011
Kishimoto I, Tokudome T, Nakao K, and Kangawa K.	Natriuretic peptide system: an overview of studies using genetically engineered animal models.	FEBS jornal.	278	1830-41	2011
Kishimoto I, Tokudome T, Hosoda H, Miyazato M, Kangawa K.	Ghrelin and cardiovascular diseases.	J Cardiology.	59	8-13	2012
Miyamatsu N, Kimura K, Okamura T, Iguchi Y, Nakayama H, Toyota A, Watanabe M, Morimoto A, Morinaga M, Yamaguchi T.	Effects of public education by television on knowledge of early stroke symptoms among a Japanese population aged 40 to 74 years: a controlled study.	Stroke	43 (2)	545-9	2012
関本裕美、小森勝也 嘉田晃子、宮本恵宏、 鎌倉史郎.	アミオダロン誘発性甲状腺機能低下症のリスクファクターについて.	医療.	65 (5)	258-64	2011
関本裕美、小森勝也、 嘉田晃子、宮本恵宏、 鎌倉史郎.	アミオダロン誘発性甲状腺機能低下症の発症頻度とその治療.	Progress in Medicine.	31 (Suppl. 1)	689-94	2011
宮本恵宏	わが国の心筋梗塞死亡率の低下要因】わが国の心筋梗塞致命率の改善は心筋梗塞死亡率の低下に影響したか.	動脈硬化予防.	10 (2)	44-50	2011
宮本恵宏	【内科疾患の予防戦略】 その他の疾患の予防戦略 糖尿病の進展予防の戦略.	Medicina.	48 (7)	1242-45	2011
宮本恵宏、中山博文、 岡村智教、豊田一則	脳卒中予防のイノベーション－早期発見・早期受診・早期介入	Medicina	48	1254-66	2011
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徳留健、岸本一郎、寒川賢治	内因性ナトリウム利尿ペプチドの虚血組織血管新生促進作用	治療	93	686-88	2011
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橋本洋一郎、中山博文	新規経口抗凝固薬時代のインフォームド・コンセント	Life Style Medicine	6	28-34	2012

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Serum 1,5-anhydro-D-glucitol levels predict first-ever cardiovascular disease: An 11-year population-based Cohort study in Japan, the Suita study

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ABSTRACT

Objective: Serum 1,5-anhydro-D-glucitol (1,5-AG) is well-known to be a useful clinical marker of both short-term glycemic status and postprandial hyperglycemia. In addition, previous epidemiological studies have shown that an increased postload glucose level in an oral glucose tolerance test is a risk factor for cardiovascular diseases (CVD). However, no previous prospective study has reported the association between serum 1,5-AG levels and the risk of CVD. In this study, we examined whether serum 1,5-AG levels can predict the incidence of first-ever CVD.

Methods: Our study was a population-based cohort study in an urban area of Japan. Study subjects comprised 2095 initially healthy Japanese (991 men and 1104 women, mean age: 58.5 years) with no history of coronary heart disease (CHD) or stroke. They were followed up for an average of 11.1 years, and 147 CVD events (64 CHD and 83 strokes) were observed.

Results: The adjusted hazard ratios (HRs) of all CVD in men increased linearly ($p = 0.004$). The HR in the category with serum 1,5-AG levels of 14.0 μg/mL or less was 2.22 (95% confidence interval; 1.24–3.98) compared to the reference category (24.5 μg/mL or greater). Similar results were also shown with a sensitivity analysis in non-diabetic men. Conversely, no significant relationship between serum 1,5-AG levels and CVD risks was observed in women.

Conclusions: Our results suggest that measurement of serum 1,5-AG levels is useful to detect individuals, especially men, at higher risk for CVD, regardless of the presence or absence of diabetes.

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1. Introduction

Serum 1,5-anhydro-D-glucitol (1,5-AG) levels are well-known to rapidly decrease concomitantly with the excretion of glucose in urine, and serum 1,5-AG is a useful clinical marker for short-term glycemic status and postprandial hyperglycemia [1–3].

Previous epidemiological studies have shown that an increased postload glucose level in an oral glucose tolerance test (OGTT) is a risk factor for cardiovascular diseases (CVD) [4,5]. A randomized controlled trial of individuals with impaired glucose tolerance also reported that acarbose, an α-glycosidase inhibitor that suppresses the elevation of postprandial glucose levels, reduced the incidence of CVD as well as type 2 diabetes [6]. These findings suggest that detection and improvement of postprandial hyperglycemia is important for CVD prevention.

An OGTT is useful for the detection of postprandial hyperglycemia, however, it requires overnight fasting, long time, additional costs, and is not always feasible in routine clinical settings or during health check-ups. In contrast, measurement of serum 1,5-AG levels can be performed using a single non-fasting blood sample, relatively costs less, and may be an alternative to OGTT. However, to our knowledge, no previous prospective study has shown the association between serum 1,5-AG levels and the risk of CVD in initially healthy individuals. We examined whether serum 1,5-AG levels can predict the incidence of first-ever CVD in a population-based cohort study of an urban area in Japan.

2. Methods

2.1. Study design and samples

The details of the Suita study have been described elsewhere [7–9]. Briefly, the Suita study is a prospective population-based cohort study of an urban area in Japan. In 1989, 6485 Suita city residents (age, 30–79 years) were randomly sampled and enrolled as study participants. They underwent medical examinations every 2 years. Among these participants, 2406 participants underwent medical examinations between April 1994 and February 1995, and their serum samples were collected and stored at −80 °C. In this

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study, we measured serum 1,5-AG levels in these stored samples. Of these 2406 participants, 289 were excluded from the present analysis for the following reasons: history of coronary heart disease (CHD) or stroke (n = 78), lost to follow-up (n = 132), serum creatinine level of 176.8 mmol/L (2.0 mg/dL) or more (n = 4), and data missing (n = 97). Finally, the remaining 2095 participants (991 men and 1104 women) with serum 1,5-AG measurements were included as subjects in the baseline study and were followed up until December 31, 2007. Informed consent was obtained from all subjects, and the institutional review board at the National Cerebral and Cardiovascular Center approved this study.

2.2. Baseline data collection

The baseline survey included questionnaires, anthropometric measurements, and blood sample tests. Height and weight were measured in light clothing, and body mass index (BMI) was calculated as weight (kg) divided by the square of height (m). Blood pressure was measured 3 times in more than 1-min intervals by well-trained physicians in a sitting position after at least 5 min of rest, using a standard mercury sphygmomanometer [7], and the third measurement of blood pressure was adopted for the present analyses. The levels of total serum cholesterol, high-density-lipoprotein (HDL)-cholesterol and creatinine were determined using an automatic analyzer in the laboratory of the National Cerebral and Cardiovascular Center. Estimated glomerular filtration rates (eGFR) were estimated with a following equation for the Japanese: eGFR (mL/min/1.73 m^2) = 194 × serum creatinine$^{-1.094}$ × Age$^{-0.287}$ (×0.739: if women) [10].

2.3. Measurement of 1,5-AG

In 2009, stored frozen serum samples were shipped to the clinical laboratory company for measurement of 1,5-AG (Mitsubishi Chemical Medience Corporation, Tokyo, Japan). 1,5-AG was measured using the enzymatic method with the "Determiner L 1,5-AG" measurement kit manufactured by the Kyowa Medex Co., Ltd. (Tokyo, Japan) and an H7700 Clinical auto-analyzer, manufactured by the Hitachi High-Technologies Corporation (Tokyo, Japan). The coefficient of variation was less than 5%.

2.4. Ascertainment of outcomes

Outcome ascertainment has been previously described elsewhere [7–9]. The main outcome is the incidence of first-ever CVD events (stroke and CHD). Physicians or nurses checked the health status of each subject at biennial clinical visits to the National Cerebral and Cardiovascular Center, and all participants also completed yearly questionnaires by either mail or telephone. The patients suspected of developing stroke or CHD were confirmed by a review of medical records performed by either the registered hospital physicians or the cohort study research physicians. In addition, to complete the surveillance, we also conducted a systematic search of death certificates for fatal stroke and MI. In Japan, all death certificates are forwarded to the Ministry of Health, Welfare, and Labor and coded for the National Vital Statistics.

A stroke was defined according to criteria from the US National Survey of Stroke [11]. Classification of stroke subtypes (ischemic stroke, intracerebral hemorrhage, subarachnoid hemorrhage) was based on the examination of computed tomographic scans, magnetic resonance images, or autopsies (subarachnoid hemorrhages were excluded from the present analyses). With regard to myocardial infarction (MI), definite and probable MI were defined according to the criteria of the MONICA project [12]. The criteria for CHD were first-ever MI, coronary angioplasty, coronary artery bypass grafting and sudden cardiac death.

2.5. Statistical analysis

A previous report from Japan proposed a serum 1,5-AG level of 14.0 μg/mL, irrespective of sex, as the cut-off for the diagnosis of diabetes [13]. The distribution of serum 1,5-AG levels differed between sexes. Accordingly, we adopted a serum 1,5-AG level of 14.0 μg/mL as the lower cut-off in common, and set the median of those who had serum 1,5-AG of more than 14.0 μg/mL as the upper cut-off (overall and according to sex), overall: 23.1 μg/mL, men: 24.5 μg/mL, women: 21.3 μg/mL. These cut-offs were used to compare baseline characteristics, crude incidence rates, and hazard ratios (HRs). To calculate p values for continuous variables, one-way analysis of variance was used, and for categorical variables, Chi-square test was used. To compare in women the prevalence of medication for diabetes and current alcohol drinking status, Fisher's exact test was used. The p values to test for a linear trend in HRs were calculated.

A Cox proportional hazard model was used to estimate age- and multivariate-adjusted HRs with 95% confidence intervals (CIs). The HRs were adjusted for the following baseline covariates as follows for model 1, age; for model 2, model 1 plus BMI, hypertension (systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or the use of antihypertensive medication), hypercholesterolemia (total cholesterol ≥5.7 mmol/L (220 mg/dL) or the use of antihypercholesterolemic medication) [14], HDL-cholesterol, eGFR, current cigarette smoking (non-current and current) and current alcohol drinking (men; non-current/light to moderate/heavy, women: non-current/current);, for model 3, model 2 plus diabetes (fasting plasma glucose (FPG) ≥7.0 mmol/L (126 mg/dL), postprandial plasma glucose (PPG) ≥11.1 mmol/L (200 mg/dL), or use of anti-diabetic medication). Fasting was defined as fasting time of 8 h or more (n = 1401, 67%), and postprandial was defined as that of less than 8 h (n = 694, 33%). We defined current alcohol drinking as non-current drinking, light to moderate drinking (alcohol consumption of less than 46 g/day), or heavy drinking (that of 46 g/day or more). However, because women with heavy alcohol drinking were few (n = 8, 0.7%) and had no CVD incidence, we treated current alcohol drinking as non-current/current drinking in the multivariate analyses of women. Menopause was added to model 2 and model 3 in women. Combined analyses of women and men adjusting for sex were conducted only in CHD and ischemic strokes because significant interactions between sex and serum 1,5-AG levels were observed in all CVD (p = 0.03) and all strokes (p = 0.01).

In addition, three sensitivity analyses were conducted: First, similar analyses were performed in non-diabetic men with FPG or PPG less than 6.1 mmol/L (110 mg/dL). Second, the definition of postprandial in the diagnostic criteria for diabetes was changed to a fasting time of 2 h or less (postprandial: n = 28, 1%), and similar analyses were conducted to confirm the influence of diabetes diagnostic criteria by PPG. Third, adjustment for waist circumferences in model 2, instead of BMI, was conducted to estimate the influence of insulin resistance. We did not enter both BMI and waist circumferences into the models to avoid the colinearity problem because waist circumferences highly correlated with BMI (correlation coefficient: 0.84). In addition, triglycerides levels were categorized by tertile and added to the model 2 in the combined analysis of women and men with fasting time of 8 h or more (n = 1401), and similar analyses for CHD and ischemic strokes were conducted.

All p values were two-tailed, and $p < 0.05$ was considered statistically significant. All analyses were conducted using SAS version 8.2 (SAS Institute, Cary, Carolina, USA).

3. Results

The mean (standard deviation) of serum 1,5-AG was 23.0 μg/mL (9.2) in men and 20.0 μg/mL (7.0) in women. The overall dis-

Table 1
Baseline characteristics by sex and serum 1,5-anhydro-D-glucitol levels, the Suita study, Japan, 1994–2007.

	Men			
	1,5-Anhydro-D-glucitol (μg/mL)			p
	≥24.5	14.1–24.4	≤14.0	
Number of subjects	423	416	152	
Age (years)	58 (12)	61 (12)	63 (11)	<0.001
Body mass index (kg/m^2)	22.7 (2.7)	22.8 (2.9)	23.1 (2.9)	0.24
HDL cholesterol (mmol/L)	1.4 (0.3)	1.4 (0.4)	1.4 (0.4)	0.48
1,5-Anhydro-D-glucitol (μg/mL)	31.3 (5.6)	19.7 (3.0)	8.8 (3.6)	<0.001
Estimated GFR (mL/min/1.73 m^2)	80.2 (15.6)	78.1 (16.0)	79.0 (18.1)	0.19
Hypertension (%)[a]	32	37	45	0.01
Hypercholesterolemia (%)[b]	23	23	21	0.85
Diabetes (%)[c]	0	3	30	<0.001
Current cigarette smoking (%)	44	39	41	0.36
Alcohol drinking (non/light to moderate/heavy) (%)	29/53/18	29/55/16	35/47/18	0.55
Hypertension medication (%)	13	15	20	0.09
Hypercholesterolemia medication (%)	4	4	5	0.81
Diabetes medication (%)	0	0	20	<0.001
	Women			
	1,5-Anhydro-D-glucitol (μg/mL)			p
	≥21.3	14.1–21.2	≤14.0	
Number of subjects	442	438	224	
Age (years)	59 (12)	55 (12)	58 (12)	<0.001
Body mass index (kg/m^2)	22.2 (3.2)	21.9 (2.7)	22.3 (3.2)	0.12
HDL cholesterol (mmol/L)	1.6 (0.4)	1.6 (0.3)	1.6 (0.3)	0.001
1,5-Anhydro-D-glucitol (μg/mL)	26.7 (4.1)	18.0 (2.0)	10.5 (3.2)	<0.001
Estimated GFR (mL/min/1.73 m^2)	80.2 (19.7)	81.2 (16.8)	81.1 (15.2)	0.71
Hypertension (%)[a]	33	26	31	0.06
Hypercholesterolemia (%)[b]	39	37	38	0.80
Diabetes (%)[c]	1	1	12	<0.001
Current cigarette smoking (%)	11	8	8	0.42
Current alcohol drinking (non/light to moderate/heavy) (%)	75/25/0	72/27/1	72/28/0	0.31
Menopause (%)	76	63	71	<0.001
Hypertension medication (%)	14	12	17	0.17
Hypercholesterolemia medication (%)	7	7	5	0.46
Diabetes medication (%)	0	0	4	<0.001

Mean (standard deviations), or percentage is shown. GFR means glomerular filtration rate.

[a] Hypertension is defined by systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg or the use of antihypertensive medication.

[b] Hypercholesterolemia is defined by total cholesterol ≥5.7 mmol/L (220 mg/dL) or the use of antihypercholesterolemic medication.

[c] Diabetes is defined by fasting plasma glucose ≥7.0 mmol/L (126 mg/dL) in those with fasting time of 8 h or more, postprandial plasma glucose ≥11.1 mmol/L (200 mg/dL) in those with fasting time of less than 8 h, or the use of antidiabetic medication.

tribution (minimum, 25th percentile, median, 75th percentile, maximum) of serum 1,5-AG by sex was 1.2, 17.0, 23.1, 28.9, and 55.3 μg/mL, respectively in men, and 1.7, 15.2, 19.8, 24.8, and 41.5 μg/mL, respectively in women (data not shown). The prevalence of diabetes and medication for diabetes at baseline was highest in the category with the lowest serum 1,5-AG (≤14.0 μg/mL) in both sexes, and was much higher in men (Table 1). Age and prevalence of hypertension increased as serum 1,5-AG decreased in men only.

During the follow-up period (11.1 years average), 147 CVD events (64 CHD and 83 strokes) were observed. The CHD included 14 percutaneous coronary angioplasty, 5 coronary artery bypass grafting, 1 sudden death, 41 myocardial infarctions and 3 unclassified CHD. The strokes included 53 ischemic strokes, 14 hemorrhagic strokes and 16 unclassified strokes. The incidence rates of all CVD and each CVD subtype increased as 1,5-AG levels decreased in men, and the incidence rate of all CVD was 15.1 per 1000 person-years in the lowest 1,5-AG category (Table 2). In model 2, there was a statistically significant linear increase in the adjusted HRs of all CVD in men ($p = 0.004$), and the adjusted HR was 2.22 (95% CI 1.24–3.98) in the lowest 1,5-AG category. In model 3, the adjusted HR of all CVD in the lowest 1,5-AG category was less than model 2. However, the adjusted HR of the middle category (14.1–24.4 μg/mL) was not very different and the elevation of risk was still significant, 1.74 (95% CI 1.07–2.84). In men, similar results were observed for each CVD subtype, although the HRs of CHD were much lower than of all strokes and were not statistically significant. In women, similar results were not observed, although, for CHD, similar trends were observed (Table 3). In the combined analysis of women and men for CHD, the HRs in model 2 increased linearly with decrease in serum 1,5-AG levels ($p = 0.03$), and the adjusted HR in the lowest 1,5-AG category was 2.10 (95% CI 1.10–4.02) (Table 4).

A sensitivity analysis for non-diabetic men with FPG or PPG less than 6.1 mmol/L (110 mg/dL) showed that the adjusted HRs for all CVD in model 2 increased as 1,5-AG levels decreased ($p = 0.03$), and the adjusted HR was 2.00 (95% CI 0.88–4.55) in the lowest 1,5-AG category (Table 5). Similar results were observed with all strokes and ischemic strokes, but such a relationship was not clear in CHD.

In the sensitivity analyses, altering the definition of postprandial, entering waist circumferences or adding triglycerides levels to the models hardly alter the results. In addition, waist circumferences or triglycerides levels were not related with the risk for CVD or each CVD subtype.

Table 2
Incidence rates and adjusted hazard ratios for cardiovascular diseases by serum 1,5-anhydro-D-glucitol levels in men, the Suita study, Japan, 1994–2007.

	1,5-Anhydro-D-glucitol (μg/mL)			p for trend
	≥24.5	14.1–24.4	≤14.0	
Person-years	4727	4322	1455	
All cardiovascular diseases				
Cases, *n*	26	49	22	
Incidence rates/1000 person-years	5.5	11.3	15.1	
Model 1[a]	1	1.76 (1.09–2.86)	2.29 (1.29–4.07)	0.003
Model 2[a]	1	1.79 (1.10–2.91)	2.22 (1.24–3.98)	0.004
Model 3[a]	1	1.74 (1.07–2.84)	1.72 (0.89–3.34)	0.049
Coronary heart disease				
Cases, *n*	16	19	10	
Incidence rates/1000 person-years	3.4	4.4	6.9	
Model 1[a]	1	1.21 (0.61–2.38)	1.81 (0.81–4.05)	0.17
Model 2[a]	1	1.14 (0.57–2.25)	1.59 (0.70–3.59)	0.29
Model 3[a]	1	1.13 (0.57–2.24)	1.47 (0.59–3.68)	0.44
All strokes				
Cases, *n*	10	30	12	
Incidence rates/1000 person-years	2.1	6.9	8.2	
Model 1[a]	1	2.56 (1.25–5.25)	3.02 (1.31–7.01)	0.006
Model 2[a]	1	2.64 (1.28–5.45)	3.32 (1.41–7.79)	0.003
Model 3[a]	1	2.53 (1.23–5.23)	2.29 (0.87–6.01)	0.04
Ischemic strokes				
Cases, *n*	8	20	9	
Incidence rates/1000 person-years	1.7	4.6	6.2	
Model 1[a]	1	2.16 (0.95–4.92)	2.84 (1.09–7.37)	0.02
Model 2[a]	1	2.15 (0.94–4.93)	2.86 (1.09–7.49)	0.03
Model 3[a]	1	2.10 (0.92–4.82)	2.28 (0.78–6.67)	0.09

Parentheses indicate 95% confidence intervals.
[a] Model 1: adjusted for age, model 2: adjusted for model 1 plus body mass index, hypertension, hypercholesterolemia, HDL cholesterol, estimated glomerular filtration rate, current cigarette smoking, current alcohol drinking, model 3: adjusted for model 2 plus diabetes.

4. Discussion

This is the first report of a prospective cohort study showing that serum 1,5-AG levels predict CVD incidence in men, similar to HbA_{1c} [15–17] or postload glucose levels in OGTT [4,5]. More subjects with overt diabetes were included in the category with serum 1,5-AG levels of 14.0 μg/mL or less, which would lead to the greatest risk. Those with serum 1,5-AG levels of 14.1 to 24.4 μg/mL, whose preva-

Table 3
Incidence rates and adjusted hazard ratios for cardiovascular diseases by serum 1,5-anhydro-D-glucitol levels in women, the Suita study, Japan, 1994–2007.

	1,5-Anhydro-D-glucitol (μg/mL)			p for trend
	≥21.3	14.1–21.2	≤14.0	
Person-years	5077	5293	2424	
All cardiovascular diseases				
Cases, *n*	22	15	13	
Incidence rates/1000 person-years	4.3	2.8	5.4	
Model 1[a]	1	0.83 (0.43–1.60)	1.23 (0.62–2.44)	0.68
Model 2[a]	1	0.92 (0.47–1.79)	1.30 (0.65–2.60)	0.54
Model 3[a]	1	0.91 (0.47–1.77)	1.04 (0.48–2.22)	0.99
Coronary heart disease				
Cases, *n*	7	5	7	
Incidence rates/1000 person-years	1.4	0.9	2.9	
Model 1[a]	1	0.82 (0.26–2.60)	2.09 (0.73–5.96)	0.21
Model 2[a]	1	0.89 (0.28–2.83)	2.33 (0.81–6.71)	0.15
Model 3[a]	1	0.87 (0.27–2.76)	1.74 (0.54–5.56)	0.42
All strokes				
Cases, *n*	15	10	6	
Incidence rates/1000 person-years	3.0	1.9	2.5	
Model 1[a]	1	0.83 (0.37–1.86)	0.83 (0.32–2.14)	0.65
Model 2[a]	1	0.93 (0.41–2.09)	0.88 (0.34–2.27)	0.77
Model 3[a]	1	0.92 (0.41–2.08)	0.75 (0.26–2.12)	0.59
Ischemic strokes				
Cases, *n*	6	7	3	
Incidence rates/1000 person-years	1.2	1.3	1.2	
Model 1[a]	1	1.48 (0.50–4.41)	1.03 (0.26–4.12)	0.84
Model 2[a]	1	2.01 (0.66–6.11)	1.20 (0.29–4.89)	0.60
Model 3[a]	1	1.99 (0.66–6.06)	1.01 (0.22–4.71)	0.71

Parentheses indicate 95% confidence intervals.
[a] Model 1: adjusted for age, model 2: adjusted for model 1 plus body mass index, hypertension, hypercholesterolemia, HDL-cholesterol, estimated glomerular filtration rate, current cigarette smoking, current alcohol drinking, menopause, model 3: adjusted for model 2 plus diabetes.