JACC VOL. 67, NO. 4, 2016
FEBRUARY 2, 2016:455–61

1988, statin therapy was available for 43 (30.3%) of all FH parents before they were 30 years of age. For the remaining 99 (69.7%) parents, statins could have been initiated at the earliest after the age of 30 years.

In the group of affected parents, 64 (41.6%) had a cardiovascular event during follow-up, mostly a myocardial infarction (n = 43; 67.2%). At the age of 30 years, the cumulative CVD survival in the parental FH group was near 90% (**Figure 1**). None of the mothers had died before the age of 30, whereas the cumulative incidence of death due to CVD of the fathers was almost 5%. The youngest parent with a myocardial infarction was 20 years old and deceased from the consequences at the age of 23 years.

Our findings that FH parents experiencing cardiovascular events at a younger age than those FH children treated from childhood onwards are in line with the results of Kusters et al. (5). They found in the same study population that long-term statin treatment initiated during childhood was associated with normalization of carotid intima-media thickness (IMT) progression in FH subjects. Furthermore, earlier initiation of statin therapy was associated with thinner carotid IMT at follow-up. Because carotid IMT is an established marker of early atherosclerosis, these results support the pivotal role of statins in the inhibition of the development of early atherosclerotic lesions in FH children.

Altogether, our results suggest that initiation of statin therapy in childhood may be effective in the prevention of very premature CVD and cardiovascular mortality. These findings underline the importance of early diagnosis and treatment of FH patients that should include initiation of statin treatment as well as modulation of other major CVD risk factors, particularly smoking.

*Marjet J.A.M. Braamskamp, MD, PhD
John J.P. Kastelein, MD, PhD
D. Meeike Kusters, MD
Barbara A. Hutten, MD, PhD
Albert Wiegman, MD, PhD

*Department of Vascular Medicine and
Department of Pediatrics
Academic Medical Center
Meibergdreef 9, Room F4-136
Amsterdam 1105 AZ
the Netherlands
E-mail: j.a.braamskamp@amc.uva.nl

http://dx.doi.org/10.1016/j.jacc.2015.11.021

Please note: The current study is supported by a grant from the Dutch Heart Foundation (2009B059). The Dutch Heart Foundation had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. Dr. Kastelein is a recipient of the Lifetime Achievement Award of the Dutch Heart Foundation (2010T082). Dr. Kastelein is a consultant to and receives honoraria from AstraZeneca, Eli Lilly and Company, Amgen, Sanofi, Regeneron, Genzyme, Isis, Aegerion, and KOWA. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Drs. Hutten and Wiegman are joint senior authors.

REFERENCES

1. Goldstein JL, Hobbs HH, Brown MS. PART 12: LIPIDS chapter 120: familial hypercholesterolemia. In: Scriver CR, Beaudet AL, Sly WS, Valle D, editors. The Metabolic and Molecular Bases of Inherited Disease. 8th edition. New York, NY: McGraw-Hill Professional, 2001:2863–913.

2. Wiegman A, Gidding SS, Watts GF, et al. Familial hypercholesterolaemia in children and adolescents: gaining decades of life by optimizing detection and treatment. Eur Heart J 2015;36:2425–37.

3. Baigent C, Keech A, Kearney PM, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet 2005;366:1267–78.

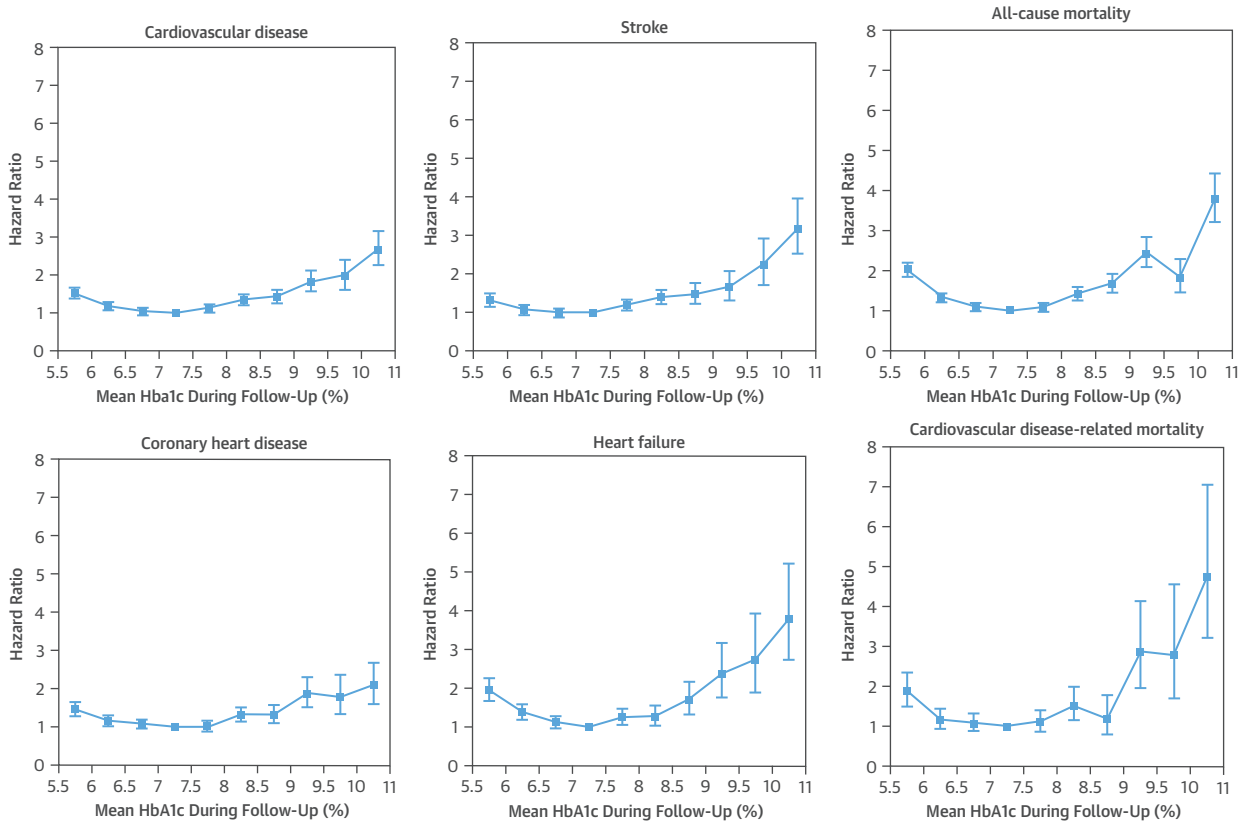
4. Wiegman A, Hutten BA, de Groot E, et al. Efficacy and safety of statin therapy in children with familial hypercholesterolemia: a randomized controlled trial. JAMA 2004;292:331–7.

5. Kusters DM, Avis HJ, de Groot E, et al. Ten-year follow-up after initiation of statin therapy in children with familial hypercholesterolemia. JAMA 2014;312:1055–7.

Association of Hemoglobin A1c Levels With Cardiovascular Disease and Mortality in Chinese Patients With Diabetes

Among diabetic patients, hemoglobin A1c (HbA1c) is an important indicator of glycemic control and, together with blood pressure and cholesterol, is an indicator for risk of complications, including cardiovascular disease (CVD) and mortality. At present, there is no universal consensus on the optimal HbA1c level. Despite this, most international guidelines include a recommended HbA1c target range or level as a treatment goal. Several studies have identified a J-shaped curvilinear relationship between HbA1c and CVD incidence and all-cause mortality, but such a relationship has not yet been confirmed in a Chinese population (1). There are substantial differences in disease risks across racial and ethnic groups due to genetic and environmental factors including life-style and health behaviors, and thus, previous results from Western studies may not be transferable to a Chinese population (2). We sought to examine the association among mean HbA1c, CVD events, and mortality among Chinese primary care patients with type 2 diabetes mellitus (T2DM) in Hong Kong.

FIGURE 1 Adjusted Hazard Ratios for Incidence of CVD, CHD, Stroke, Heart Failure, All-Cause Mortality, and CVD-Related Mortality by Mean HbA1c During Follow-Up



Blue lines refer to the adjusted hazard ratios of Cox proportional hazard regression. **Error bars** indicate 95% confidence intervals. CHD = coronary heart disease; CVD = cardiovascular disease; HbA1c = glycosylated hemoglobin.

A population-based retrospective cohort study was conducted on 117,389 Chinese adult T2DM primary care patients without any CVD history and who had an HbA1c value recorded between August 1, 2008, and December 31, 2009. Data was extracted from the computerized administrative database of Hong Kong Hospital Authority. The date of the first recorded HbA1c was used as the baseline date for each subject. Each subject was then tracked to identify: the date of incidence of an outcome event, the date of all-cause mortality, or until December 31, 2013, whichever came first. The study outcomes included: 1) CVD event with 1 of the following subtype diagnoses: coronary heart disease (CHD), stroke, or heart failure; 2) CHD; 3) stroke; 4) heart failure; 5) all-cause mortality; and 6) CVD-related mortality. Comorbidities were identified by the diagnosis coding system of International Classification of Primary Care-2 and International Classification of Diseases, Ninth Edition, Clinical Modification. A "mean HbA1c" value was determined by calculating the average of all HbA1c measurements collected during follow-up. Baseline covariates included: age; sex; smoking status; drinking habit; body mass index; waist-to-hip ratio; systolic and diastolic blood pressure; low-density lipoprotein cholesterol; total cholesterol to high-density lipoprotein cholesterol ratio; triglycerides; urine albumin-to-creatinine ratio; self-reported duration of diabetes; family history of diabetes; hypertension; the stage of chronic kidney disease; and baseline use of antihypertensive drugs, metformin, sulfonylurea, other oral antidiabetic drugs (acarbose, glitazone, gliptin, glucagon-like peptide-1 agonist, and meglitinides), insulin, and lipid-lowering agents.

Missing data (other than HbA1c) were handled by multiple imputation method. Study subjects were divided into 10 groups according to their mean HbA1c measurement (<6.0%, ≥6.0% to <6.5%, ≥6.5% to <7.0%, ≥7.0% to <7.5%, ≥7.5% to <8.0%, ≥8.0% to <8.5%, ≥8.5% to <9.0%, ≥9.0% to <9.5%, ≥9.5%

to <10.0%, and ≥10.0%). The relationship between HbA1c group and study outcomes were evaluated using multivariable Cox Proportional Hazard regression, adjusting for all baseline covariates. The statistical procedures were repeated using updated HbA1c as a time-updated analysis.

After a median follow-up of 54.5 to 58.5 months, amongst the 10 HbA1c groups, unadjusted incidence rates for CVD events and all-cause mortality were 13.8 to 28.8 and 9.4 to 32.3 per 1,000 person-years, respectively. A J-shaped curvilinear relationship was identified between HbA1c levels and CVD incidence, all-cause mortality, as well as other outcomes (**Figure 1**). An HbA1c range of ≥7.0% to <7.5% had the lowest risk of new CVD, CHD, stroke, heart failure, all-cause mortality, and CVD-related mortality. When compared to a HbA1c range of ≥7.0% to <7.5%, HbA1c <6.5% or ≥8.0% was associated with a significantly higher incidence of CVD and all-cause mortality. Similar results were obtained in the time-updated analysis.

This study had several limitations. This was a retrospective cohort study, which is lower in terms of evidence hierarchy than a randomized controlled trial. Drug exposure over time and life-style behavior risk factors such as diet and exercise were not taken into account in the analyses. This study was undertaken in Hong Kong, and the pattern of association between HbA1c and outcomes may differ in other Chinese populations. The relationship may be subject to temporal changes and modifications in unmeasured risk factors or interventions.

The results of this territory-wide, naturalistic, cohort study of Chinese primary care patients with T2DM supports the findings of previous observational studies conducted in the United States, United Kingdom, Denmark, and the Netherlands, demonstrating a J-shaped pattern of association between HbA1c and CVD and all-cause mortality (1). Similar J-shaped relationships were also identified for CHD, stroke, heart failure, and CVD-related mortality. Although this phenomenon has been postulated to be related to the deleterious effects of severe hypoglycemia (3), this is controversial, and it remains unclear why low levels of HbA1c are associated with a higher risk of CVD and all-cause mortality.

*Eric Yuk Fai Wan, MSc, CStat
Colman Siu Cheung Fung, MBBS, MPH
Carlos King Ho Wong, MPhil, PhD
Weng Yee Chin, MBBS, MD
Cindy Lo Kuen Lam, MBBS, MD

*Department of Family Medicine and Primary Care
The University of Hong Kong
3/F Ap Lei Chau Clinic
161 Main Street, Ap Lei Chau
Hong Kong
E-mail: yfwan@hku.hk

http://dx.doi.org/10.1016/j.jacc.2015.11.020

Please note: This study was funded by the Health Services Research Fund, Food and Health Bureau, HKSAR Commissioned Research on Enhanced Primary Care Study (Ref. no EPC-HKU-2). No funding organization had any role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation of the manuscript. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

REFERENCES

1. Arnold LW, Wang Z. The hba1c and all-cause mortality relationship in patients with type 2 diabetes is j-shaped: a meta-analysis of observational studies. The review of diabetic studies. Rev Diabet Stud 2014;11:138–52.

2. Byrne CD, Wild SH, editors. The Metabolic Syndrome. Chichester, UK: John Wiley & Sons, 2011.

3. Hemmingsen B, Lund SS, Gluud C, et al. Targeting intensive glycaemic control versus targeting conventional glycaemic control for type 2 diabetes mellitus. Cochrane Database Syst Rev 2011;6:CD008143.

Plaque Characterization by Coronary Computed Tomography Angiography and Association With Acute Coronary Syndrome

The study by Motoyama et al. (1) expands on their previous excellent sentinel work (2). The authors showed that in 3,158 patients with a mean follow up of 3.4 ± 2.4 years, computed tomography angiography (CTA)-verified high-risk plaque (HRP) was an independent predictor of acute coronary syndrome (ACS). In addition, in a subgroup of 449 patients who underwent serial CTA, plaque progression was an independent predictor of ACS.

The authors defined HRP on the basis of 2 high-risk features, positive remodeling (remodeling index ≥1.1) and low-attenuation plaque (<30 HU). It would have been of interest whether the addition of other less sensitive, but more specific, high-risk features such as spotty calcification and napkin ring sign (3) would have led to better prediction of ACS.

Secondly, the assessment of plaque volume, which has been the strongest independent predictor of long-term ACS (4), was not reported in this study. Instead of defining plaque progression using quantitative analysis of plaque volume as is standardly done in serial intravascular ultrasound studies, plaque progression was defined as either an increase in stenosis by at least 1 grade or an increase in the remodeling index in this study. In addition, low-attenuation