OBSERVATIONS

Simvastatin, Fenofibrate, and Rhabdomyolysis

The National Cholesterol Education Program (NCEP) guidelines recommend use of statin-fibrate combinations to treat combined dyslipidemia. Myopathy and rhabdomyolysis are reported side effects, especially with gemfibrozil-statin combinations (1). This risk is recognized to result from both pharmacodynamic and pharmacokinetic interactions. In vitro studies in human hepatocytes have shown that unlike gemfibrozil, fenofibrate has no pharmacokinetic interaction with simvastatin at concentrations achieved with clinical dosing (2). The acid form of simvastatin is partly eliminated by glucuronidation and lactonization, both of which are inhibited by gemfibrozil but not fenofibrate (2). This lack of a pharmacokinetic interaction between simvastatin and fenofibrate relaxed the recommendation in the package insert for simvastatin, allowing all doses to be used in combination with fenofibrate. A recent NCEP guideline update also supports lessening concern regarding this combination (3). Hence, it is frequently prescribed for combined dyslipidemia. We report a case of rhabdomyolysis with this combination that raises questions regarding its safety and suggests that caution is still in order.

A 70-year-old man with a history of type 2 diabetes, dyslipidemia, hypertension, and hypothyroidism presented with 2 weeks of bilateral leg myalgia. Four weeks before presentation, he was started on 160 mg fenofibrate for combined dyslipidemia: total cholesterol 194 mg/dl, LDL cholesterol 115 mg/dl, HDL cholesterol 32 mg/dl, and triglycerides 229 mg/dl. Medications at that time included 40 mg simvastatin, 50 mg atenolol, 0.112 mg levothyroxine, 8 mg rosiglitazone, 150 mg ranitidine twice daily, and 5 mg terazosin. Laboratory values before starting fenofibrate were serum creatinine 1.6 mg/dl, creatinine phosphokinase (CPK) 200 IU/l, and normal liver profile. He denied having any recent illness or alcohol, antibiotic, or over-the-counter medication use. Serum laboratory values at presentation were creatinine 2.7 mg/dl and CPK 10,936 IU/l. Urine was dark yellow with 3+ blood and trace protein. Fenofibrate and simvastatin were discontinued, and the patient was admitted with rhabdomyolysis. With hydration, his myalgia resolved and creatinine returned to baseline within 1 week. Serum CPK peaked at 15,000 IU/l and returned to baseline within 4 weeks.

The mechanism of muscle damage is unclear, but the risk of serious interaction with simvastatin-fenofibrate combination is not completely absent. Trials have shown fewer side effects with this combination, but they are limited by small sample sizes, exclusion of patients predisposed to adverse events, and short-term follow-ups (1,3).

At this juncture, two aspects need to be revisited: evidence of advantage and safety of this combination compared with simvastatin or fenofibrate monotherapy. To date, there is neither evidence to support a reduction in coronary artery disease outcome nor sufficient data to make conclusions regarding the safety of this combination. Hence, physicians need to be aware of potentially fatal side effects such as rhabdomyolysis when prescribing simvastatin-fenofibrate combination. In addition, careful selection and monitoring of patients, patient education on risk and warning symptoms of potential adverse effects, and screening for risk factors such as hepatic impairment, renal insufficiency, serious infections, hypothyroidism, and diabetes, especially in elderly patients, is warranted. Data from large long-term trials like the ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial are needed to establish both the efficacy and the safety of this combination in treating combined dyslipidemia.

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Self-Reported Diabetes in Northland, New Zealand

There is little published community prevalence diabetes data in Northland, an area at the northernmost part of New Zealand containing 3.8% (140,088) of the total population (1). Māori, the indigenous people, are known to be at increased risk of diabetes (2), and Northland has a Māori population (29%) (1) higher than the national average (14.7%) (3). Hospitalization rates for diabetes are high in Northland, with a standardized relative ratio against the national rate of 1.77 (95% CI 1.55–1.92) (4). The purpose of this study was to assess the prevalence of self-reported diabetes in Northland and to calculate a two-factor (obesity and first-degree family history of diabetes) risk-based prevalence rate for undiagnosed diabetes.

In this study, 360 randomly selected cluster-sampled respondents were selected for personal interviews asking whether they had been diagnosed with diabetes, were receiving regular diabetes checks, had a first-degree family history of diabetes, or had self-reported obesity.

A total of 290 (81%) of 360 potential interviews were conducted. The prevalence of self-reported diabetes was 6%, increasing with age and with no statistical difference overall for sex or ethnicity. The prevalence rate for the two-factor risk-

assessed, potentially undiagnosed diabetes pool was a further 4%, with no sex or ethnicity differences and a peak in the 50- to 59-year-old age-group.

National figures from the 1996/1997 National Health Survey show a nationwide diabetes prevalence of 3.7%, with 8.3% for Māori and 3.1% for non-Māori (5). Equivalent data for Northland are sparse. Comparisons with this study and the Northland Diabetes Resource Centre 2001 data show an increase in the overall prevalence rate for diabetes between 2001 and 2003 (from 3.6 to 6.0%, $P = 0.0226$) and a significant increase in non-Māori with diabetes (from 3.0 to 6.4%, $P = 0.0078$) (4).

National figures for the size of the undiagnosed diabetes pool have been broadly estimated at between one-third and one-half of all diabetic patients in the community (6). The fact that we found the same order of magnitude as predicted adds support to our study's validity (6).

Community surveys for diabetes have occurred in other regions, but this is the first Northland survey (7). Self-reported diabetes data generally have inaccuracies, with one study failing to report 11.2% (7). Our study may also underreport prevalence by a similar percentage.

In Northland, the overall diabetes prevalence increase of 66% over 2 years, especially for non-Māori, is substantially higher than the increase of 30% over 10 years predicted by the Ministry of Health (6). Possible explanations would include differential access to medical services (5,8) and increasing diabetes risk factors such as obesity (9). In addition, Māori health providers may have detected the initial "easier to identify" Māori with diabetes, with non-Māori now catching up. Finally, possibly Māori in this study did not self-report diabetes accurately due to cultural aspects of "mana," or pride and self-worth. However, the lead investigator is Māori, and this was not observed. Most of these explanations also are present in other New Zealand communities. Consequently, further studies are warranted to validate the observed increased incidence of diabetes against predicted incidence and the relative ethnicity changes.

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An Inexpensive Method to Diagnose Incipient Diabetic Nephropathy in Developing Countries

Diabetic patients with microalbuminuria are at a high risk for developing overt nephropathy and cardiovascular complications (1). Constant monitoring is mandatory to prevent vascular complications. Due to socioeconomic reasons, many patients in developing countries cannot afford to regularly test their blood glucose. In such a scenario, the test of urine albumin-to-creatinine ratio or albumin excretion rate to diagnose diabetic albuminuria is beyond the reach of many patients. In addition, only a few speciality centers provide facilities for doing these tests. Urine protein dipstick testing is, however, easily available to most patients. We aimed to evaluate whether a dipstick test showing "trace" for urinary protein reliably indicated the presence of microalbuminuria.

Urine dipstick for protein was done in 500 consecutive random urine samples of type 2 diabetic subjects, using Uristik (Bayer Diagnostics India). The results were read visually as "negative" or as "positive," indicated as trace, 1+, 2+, or greater, representing a protein concentration of <0.15, 0.15–0.30, >0.30, or >1 g/l, respectively. Three trained technicians tested all samples, and the interobserver variations were <5%, measured statistically. Urine microscopy was done on all samples, and samples with significant presence of white blood cells and other cell types were excluded.

Among the 500 urine samples, 360 were negative for dipstick, 99 were trace, and 41 were 1+ or greater. In the subjects without clinical proteinuria ($n = 459$), albumin-to-creatinine ratio was determined. The results were ranked as normoalbuminuria (men <2.5, women <3.5 mg/mmol [$n = 356$]) and microalbuminuria (men 2.5–25, women 3.5–35 mg/mmol; $n = 103$). Quantification of urine creatinine (mg/dl) was by the Jaffe method, urine albumin by immunoturbidimetry, and urine protein by the biuret method using a Hitachi 912 analyzer (Roche, Mannheim, Germany).

The data of 459 urine samples were used to determine the sensitivity and specificity of the dipstick to detect a negative or a positive test. The sensitivity, specificity, positive predictive value, and negative predictive value of trace to detect microalbuminuria were 68, 98, 92, and 88%, respectively; the accuracy was 89%.

This study showed that the dipstick test with a reading of trace was highly specific and fairly sensitive in determining the presence of microalbuminuria.

Micral-test II was found to be an effective screening tool in various Caucasian studies (2). However, even micral-test II is an expensive screening tool in develop-

ing countries. In a study by Baskar et al. (3), Combur 5 test D strips (Roche Diagnostics, Vilvoorde, Belgium) were found to have little or no benefit in repeat testing outside the low microalbuminuric range. In our study, we found that the positive test had 98% sensitivity and 100% specificity to determine proteinuria.

In developing countries like India, the cost of doing an albumin-to-creatinine ratio in a random sample is $5.60 U.S. (INR 250), while 100 patients can be screened for albuminuria by a dipstick at the cost of $9.80 U.S. (INR 439). A repeat test is, however, essential in positive cases to ascertain the presence of microalbuminuria or proteinuria. The cost efficiency and the high sensitivity and specificity of the urine dipstick test will encourage its use among primary care physicians and private practitioners as a diagnostic tool for microalbuminuria and proteinuria. This would initiate the first step toward detection of incipient diabetic nephropathy in developing countries.

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Pregestational Diabetes and Pregnancy

An Australian experience

We examined the current status of pregnancy complicated by preexisting diabetes in Australia. Data were collected on 180 pregnancies from 10 teaching hospitals (in NSW, Victoria, and Western Australia) with an interest in pregnancy complicated by diabetes, for the period from July 2003 to June 2004.

The majority of the pregnancies were complicated by type 2 (55%) rather than type 1 diabetes. The women with type 2 diabetes were significantly older (32.8 ± 5.4 years) than those with type 1 diabetes (30.9 ± 5.1 years, $P = 0.014$, independent *t* test). Type 2 diabetic women also had a shorter diabetes duration (4.4 ± 3.3 vs. 13.3 ± 8.2 years, $P < 0.0001$).

The outcomes were 172 (96.6%) live births at 37.1 ± 2.9 (mean ± SD) weeks of gestation. The mean weight was 3,473 ± 820 g (median 3,580 g), a result which would fall within the 87th and 96th centiles using the Gestation Network Centile Calculator (1). Sixty three percent of deliveries were by Caesarean section.

The survey did not capture early miscarriages. There were six (3.4%) neonatal deaths. One of these related to a termination for fear of congenital malformations. There were five stillbirths, giving a stillbirth rate of 2.8%, four times that seen in the general population. (In the NSW Midwives Database, the perinatal mortality, which includes stillbirths and later neonatal deaths, was 0.71 in 2002.) Five of the six deaths occurred in women with type 2 diabetes. Four of these women were of non-English speaking background, and none had received prepregnancy counseling or folate supplementation.

Prepregnancy counseling could be documented in only 19.8% of the women: 27.8% of those with type 1 diabetes and merely 12% of those with type 2 diabetes. Folate supplementation at the time of conception as a surrogate for planned pregnancy was documented in 45.7% of the women: 56.6% of those with type 1 diabetes, 36.4% of those with type 2 diabetes.

Neonatal hypoglycemia was common (25%), as was shoulder dystocia (8.1%). Congenital malformations were also common, with 8.1% major malformations and 12% minor malformations. A first-trimester HbA_{1c} was available for five of the pregnancies with a major congenital malformation and was 7.6 ± 2.1% compared with 7.1 ± 1.8% ($n = 119$) in those without a major congenital abnormality. In the NSW Birth Defects Register, the rate of major birth defects before 2002 was ~2.1%. Thus, the rate of major malformation in our survey was four times that of the background population.

Type 2 diabetes is now the more common type of diabetes in women of reproductive age, and this will continue to increase based on the increasing prevalence of type 2 diabetes in this age-group documented in the AusDiab study (2). Pregnancies in patients with type 2 diabetes have significantly worse outcomes than the general population and are not more benign than pregnancies complicated by type 1 diabetes. We believe that these poor outcomes are at least in part due to the lack of attention directed to these women because of their relative social disadvantage and a perception that type 2 diabetes is not as severe a problem, even in pregnancy. Public health measures need to be taken to educate both the public and the medical profession about the dangers of type 2 diabetes and pregnancy.

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Performance of Glucose Dehydrogenase– and Glucose Oxidase–Based Blood Glucose Meters at High Altitude and Low Temperature

Blood glucose meters using the enzyme glucose oxidase (GO) have been proven unreliable at high altitude (1–6). A new test strip technology, based on the oxygen-insensitive enzyme glucose dehydrogenase (GD), has been utilized by some manufacturers. Our hypothesis was that since oxygen is not involved in the reaction pathway of glucose dehydrogenase, glucose dehydrogenase-based blood glucose meters would perform better than glucose oxidase-based meters at high altitude. To our knowledge, performance of glucose dehydrogenase-based meters at high altitude and low temperature has not been studied.

Five plasma-calibrated blood glucose meters were evaluated in this study, four glucose dehydrogenase based (GD1: Precision Xtra; GD2: Ascensia Contour; GD3: Accu-Chek Compact; and GD4: Freestyle) and one glucose oxidase based (GO1: OneTouch Ultra), with capillary blood samples from one of the investigators (D.Ö.).

First, all meters were tested in a hypobaric chamber at simulated altitudes (at 20°C in chronological order with ~8-min intervals) of 0, 4,500, 2,500, and again 0 m above sea level, with normal (~5.8-mmol/l) and high (~16.5-mmol/l) plasma glucose values ($n = 6$ at all conditions). At 4,500 and 2,500 m altitude, the glucose oxidase-based meter (GO1) overestimated plasma glucose values by 15 ± 0.1% (mean ± SD) at the normal blood glucose level and 6.5 ± 0.5% at the high blood glucose level, as compared with the readings at 0 m.

Comparatively, three glucose dehydrogenase–based meters overestimated readings of normal and high blood glucose levels (GD1 by 6.5 ± 0.2 and 1.5 ± 0.7%, GD3 by 3.7 ± 0.1 and 3.5 ± 0.4%, and GD4 by 0.8 ± 0.2 and 0.8 ± 0.4%, respectively). The fourth, GD2, underestimated readings of normal and high blood glucose levels by 1.9 ± 0.2 and 4.2 ± 0.9%, respectively.

Second, the effect of temperature was tested with ~14.6 mmol/l plasma glucose at high (25°C) and low (8°C) temperature at ground level, allowing 35 min for meters and test strips to acclimate to each temperature. Three meters underestimated, GD1 by 7.9 ± 0.6% (mean ± SD, $n = 6$), GD2 by 8.5 ± 0.7%, and GD4 by 9.7 ± 0.5%, and two meters overestimated, GO1 by 6.7 ± 0.9% and GD3 by 8.4 ± 0.6%, plasma glucose values at 8°C as compared with 25°C.

In addition, three glucose dehydrogenase–based meters (GD1, GD2, and GD3) were tested with blood at up to 5,895 m above sea level during the ascent of Mount Kilimanjaro, Tanzania. In the presence of both high altitude and low temperature, the meters diverged from each other. At the summit, 5,895 m above sea level, the readings of the investigator's plasma glucose concentration were 2.8, 11.9, and 21.0 mmol/l (GD1, GD2, and GD_3, respectively).

In this study, all four glucose dehydrogenase–based meters performed better than the glucose oxidase–based meter at high altitude, as hypothesized. However, at low temperature, all tested meters performed with similar magnitude of discrepancy. The glucose dehydrogenase–based meters showed a within-group variation, where GD3 alone overestimated plasma glucose levels at low temperature. GD3 determines glucose using reflectance photometry, in contrast to the other (electrochemical) blood glucose meters tested in this study. GD4 performed exceptionally well at simulated high altitude but not at low temperature and is based on coulometric measurement technology, in contrast to the other (amperometric) electrochemical meters (GD1, GD2, and GO1).

In conclusion, people with diabetes who intend to participate in activities at high altitude or, in particular, at low temperature, should be informed that blood glucose meters may give totally unreliable false low or high readings.

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Prevalence of Diabetes in Greater Beirut

High rates of diabetes have been observed among Arab populations in the Middle East (1). We aimed to determine the prevalence of previously diagnosed and undiagnosed diabetes in Greater Beirut, which includes Administrative Beirut and its suburban part of Mount Lebanon. This part of Lebanon is home to 53.6% of the population and represents a mixture of urban and rural areas with different socioeconomic classes.

A multistage random probability sample was devised using the population distribution suggested by the Lebanese Central Administration of Statistics. Despite a minor and insignificant deviation, the quota that best represents Greater Beirut was achieved.

A research team conducted a door-to-door survey. A total of 3,000 exclusively Lebanese citizens ≥40 years of age (mean 55.5 [95% CI 55.2–55.9]) were interviewed and asked about prior medical diagnosis of diabetes.

On the next morning, venous blood was collected from subjects who did not report a previous diagnosis of diabetes and accepted enrollment in the study. Blood could not be obtained from people who did not fast for 12 h overnight or could not be available at the scheduled appointment. Venous whole blood was transported within 2 h to our laboratory (affiliated with the Faculty of Medical Sciences of the Lebanese University). Plasma glucose concentrations were measured by an automated glucose oxidase method using Roche Diagnostics Reagents.

The 1997 American Diabetes Association criteria for the diagnosis of diabetes and impaired fasting glucose were used.

All statistical analysis was done using SPSS. The differences between the scalded/ratio variables under consideration were analyzed by z test (Gaussian test). $P < 0.05$ was considered statistically significant.

Of the 3,000 individuals recruited, 339 were found to have previously diagnosed diabetes, representing a prevalence of 11.3% (95% CI 10.2–12.4). Only two subjects met epidemiological criteria for type 1 diabetes. This prevalence increased with age but this increase was not significant for subjects ≥70 years of age. When we took into consideration the whole population studied, the prevalence of previously diagnosed diabetes was significantly higher in men ($P = 0.001$), although the difference was not statistically significant for subjects ≥50 years of age.

In the group that did not report a previous diagnosis of diabetes, fasting plasma glucose was measured in 551 individuals; the remaining subjects were not tested. The sampled and unsampled groups were not statistically different concerning age and sex.

We found 28 individuals with undiagnosed diabetes and 14 with impaired fasting glucose, which constitutes a prevalence of 5.1% (95% CI 3.2–6.9) and 2.5% (95% CI 1.2–3.9), respectively. The combined prevalence of previously diagnosed and newly diagnosed diabetes was 15.8% (95% CI 14.5–17.1); 17.6% (95% CI 15.8–19.4) in men and 13.4% (95% CI 11.5–15.3) in women ($P = 0.002$). In the U.S., 6.3% of the population has diabetes: 4.5% diagnosed and 1.8% undiagnosed (2). The ratio of known to unknown diabetes obtained in our study was similar to the one recognized in the U.S.

These results suggest that the prevalence of diabetes in Greater Beirut is high. Larger samples covering different areas in Lebanon are needed to estimate the national prevalence of diabetes.

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COMMENTS AND RESPONSES

Two-Year Statin Therapy Does Not Alter the Progression of Intima-Media Thickness in Patients With Type 2 Diabetes Without Manifest Cardiovascular Disease

Response to Beishuizen et al.

We read the recent study by Beishuizen et al. (1), which claims that statin treatment had no effect on intima-media thickness (IMT) in diabetic subjects. We agree that contrary to the suggestions made in the Third Report of the Adult Treatment Panel of the National Cholesterol Education Program (2), diabetes is not always a cardiovascular disease equivalent in terms of cardiovascular event risk and that this risk is more related to the individual level of other cardiovascular risk factors.

However, it is hard to conclude that statins are ineffective in reducing IMT in diabetics subjects on the basis of the reported data because of some relevant methodological problems. The main problem is the change in statins tested during the study. In fact, until now, no trial has demonstrated that statin switch is as efficacious as continuous treatment with a single statin on vascular protection. Then, the LDL cholesterol–lowering effect of 0.4 mg cerivastatin is not equal to that of 20 mg simvastatin. The authors admit that mean LDL cholesterolemia significantly increased after statin switch. At the end of the study, the placebo group was smaller than estimated to be sufficient to detect significant differences between groups. Some randomization problems are also foreseeable by the 87% relative risk reduction in cardiovascular disease rates and by the 100% relative risk reduction in coronary artery disease rates in statin-treated patients after only 24 months of treatment, which is much higher than that observed in the diabetic group of the

HPS (Heart Protection Study) (3) or in CARDS (Collaborative Atorvastatin Diabetes Study) (4) (or in any other large statin clinical trial). Moreover, it is not correct to compare the observed results with those obtained with bezafibrate, which is not an antihypercholesterolemic drug and has a completely different pharmacodynamic profile.

In our opinion, on the basis of the reported data, Beishuizen et al. should have concluded that 15.4 months of treatment with 0.4 mg cerivastatin (not generically "statins") is not efficacious in reducing IMT progression in type 2 diabetic subjects.

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Two-Year Statin Therapy Does Not Alter the Progression of Intima-Media Thickness in Patients With Type 2 Diabetes Without Manifest Cardiovascular Disease

Response to Cicero et al.

We thank Cicero et al. (1) for their comments on our article (2). We measured intima-media thickness (IMT) at baseline and after 1 and 2 years. Thus, the assertion by Cicero et al. that we "should have concluded that 15.4 months of treatment with 0.4 mg cerivastatin. . .is not efficacious in reducing IMT progression in type 2 diabetic subjects" cannot, in our view, be drawn from the data as gathered. Although the level of LDL cholesterol was significantly higher during 20-mg simvastatin treatment compared with 0.4-mg cerivastatin treatment (2.56 vs. 2.34 mmol/l), our results did not change after correcting for the duration of cerivastatin treatment. At the end of the study, the placebo group was smaller than in the sample size calculation; however, our actual SD of the changes in IMT was smaller than the SD used for these calculations, thereby (retrospectively) decreasing the needed sample size, which was confirmed by the small confidence interval of the difference between IMT changes in the placebo and statin groups (95% CI −0.0281 to 0.0132 mm).

We disagree with the notion of a randomization problem. We used a computerized randomization scheme, and baseline characteristics, lipid levels, and IMT were very similar between the groups, as shown in Tables 1–3 of our article. Our study was not designed to detect a risk reduction in cardiovascular events. Furthermore, the absolute number of cardiovascular events observed is much too small to draw the conclusions suggested by Cicero et al. The events are, however, relevant in terms of being at odds with the end point IMT. We concluded that in patients with type 2 diabetes, this intermediate end point should be interpreted judiciously. In the absence of other randomized placebo-controlled trials on the effect of lipid-lowering therapy on carotid IMT in patients with type 2 diabetes, we felt it relevant to address the results of the SENDCAP (St. Mary's, Ealing, Northwick Park Diabetes Cardiovascular Disease Prevention) study (3). We are aware of the differences between statin and fibrate interventions and of the modest (9.6%) LDL cholesterol–lowering effect in that study. Given the results of these two studies, we hypothesize that carotid IMT in type 2 diabetes may be less reversible than in nondiabetic subjects. The recent results of the ARBITER (Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol) trial extend this concept to the effects of niacin on IMT (4).

In conclusion, we do not share the concerns of Cicero et al. on the statin switch in our study, nor do we agree with their concerns on randomization or sample size. In view of this, we believe our conclusions are valid.

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Is Atherosclerosis in Diabetes and Impaired Fasting Glucose Driven by Elevated LDL Cholesterol or by Decreased HDL Cholesterol?

Response to Drexel et al.

In the report of Drexel et al. (1), an HDL-related cluster of lipid markers was significantly associated with risk of cardiovascular disease among coronary patients with type 2 diabetes, whereas an LDL-related cluster was not significantly associated. The authors conclude from their observation that "in today's setting of effective LDL cholesterol lowering with statins, HDL cholesterol, triglycerides, and LDL particle diameter are the predominant lipid risk factors determining the fate of coronary patients with diabetes."

Although Drexel et al. briefly discuss the issue of sample size, their substudy of patients with type 2 diabetes appears to be severely underpowered. It would be required to be more than two times larger to provide a power of 80% and at least four times larger to provide a power of 95% at an α level of 5% (2). Clearly, the nonsignificance of the association for the LDL-related pattern does not allow the authors to conclude that there is indeed no association. It seems rather likely that the observed relative risk (RR) for the LDL-related pattern (1.362 [95% CI 0.985–1.883], $P = 0.061$) suggests an association. In addition, point estimates for both patterns are quite similar after reparametrization. Actually, the observed RR of 0.702 for an increase of the HDL-related pattern corresponds to an RR of 1.412 if the risk associated with a reduction of the HDL-related pattern is being modeled. Thus, both patterns have similar predictive value of future vascular events. We expect that this similarity will be even more obvious if odds ratios would be calculated in a restricted analysis by excluding those 41% of diabetic patients receiving lipid-lowering drugs instead of only medication adjustment. Thus, dyslipoproteinemia characterized by high LDL cholesterol still appears to play an important role in the management of cardiovascular risk in diabetic patients. This is also in line with recent evidence from larger cohorts, where LDL cholesterol was a significant predictor of cardiovascular disease events among 746 diabetic men (3) and 921 diabetic women (4), whereas HDL cholesterol appeared to predict risk only among men.

The question remains what combination of lipid markers actually provides the best prediction for future vascular events. Statistical methods other than factor analysis, e.g., canonical discriminant analysis, are possibly more appropriate to derive the biomarker profile with maximal predictive power. Also, non-HDL cholesterol should be included in the analysis as a marker of atherogenic cholesterol because it may be more valuable to quantify atherosclerotic risk among diabetic patients, particularly among those with elevated triglyceride levels (5).

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Is Atherosclerosis in Diabetes and Impaired Fasting Glucose Driven by Elevated LDL Cholesterol or by Decreased HDL Cholesterol?

Response to Schulze and Hoffmann

Our study (1) demonstrates that an LDL-related lipid factor in coronary patients with type 2 diabetes is *1*) not elevated, *2*) not associated with significant coronary stenoses, and *3*) not significantly predictive for future events. Whereas the first two findings did not even show a trend for the LDL-related factor, our prospective data need to be confirmed by a longer follow-up with more end points. We have amply discussed this

in our report, and Schulze and Hoffmann (2) also raise this point.

Since currently ~58% of coronary patients are on statins (3) and lipid-lowering medication very frequently is required in diabetes to achieve the stringent LDL cholesterol goals that have been put forth for this "CAD risk equivalent," exclusion of diabetic patients on lipid-lowering therapy in our investigation would have excluded diabetic coronary patients receiving up-to-date medical care and thus would have rendered the study population utterly unrepresentative of today's clinical setting.

Factor analysis is the appropriate technique to extract an integral factor representing diabetic dyslipidemia from the individual lipid parameters measured. The power of this factor to predict vascular events can be subsequently evaluated in Cox regression models. This approach is novel in the study of lipid risk factors in patients with diabetes but has been previously applied to investigate the metabolic syndrome (4).

We included apolipoprotein B levels in our factorial analysis. Non-HDL cholesterol represents the total cholesterol carried by VLDL, IDL (intermediate-density lipoprotein), and LDL, of which each particle contains one molecule of apolipoprotein B. Serum levels of apolipoprotein B are thus closely related to non-HDL cholesterol.

Even though cardiovascular risk is significantly reduced in diabetic patients by statins, it remains at a very high level in these patients (5). The consistent association of the HDL-related factor with glycemia, with significant stenoses and with the future incidence of vascular events, provides compelling and conclusive evidence that the main lipid risk factor in our patients with diabetes is the triad of low HDL cholesterol, small LDL particles, and high triglycerides.

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Depressive Symptoms, Insulin Resistance, and Risk of Diabetes in Women at Midlife

Response to Everson-Rose et al.

We read with interest the article by Everson-Rose et al. (1), which indicated that depressive symptoms were associated with a greater risk of diabetes at 3-year follow-up. The authors discussed several mechanisms by which depression may contribute to subsequent insulin resistance and type 2 diabetes, in particular, excess cortisol and central adiposity, altered immune function, and behavioral factors such as compliance and physical activity.

In this letter, we would like to suggest two additional explanations for the findings of Everson-Rose et al. First, patients with and without significant depressive symptoms clearly differed at baseline in the homeostasis model assessment of insulin resistance, a difference that remained fairly constant over time instead of accelerating for the depressed group. Therefore, the reverse hypothesis suggesting that insulin resistance results in a higher risk for depression seems more likely.

Second, there may be shared factors that increase the risk for both type 2 diabetes and depression. Notably, an impaired fatty acid metabolism is related to depression and to features of the metabolic syndrome (2). Low consumption of ω-3 fatty acids is associated with hypertriglyceridemia, cardiovascular disease, insulin resistance, and type 2 diabetes (3–5). Moreover, lowered ω-3 levels have been reported in erythrocytes of patients with depression (6). ω-3 fatty acids also have anti-inflammatory effects, and three recent placebo-controlled trials have found ω-3 acid, in particular eicosapentaenoic acid, to be effective in reducing depression (7).

We conclude that in this intriguing field of research, careful attention should be given to accurate controlling for confounders. Specifically, the assessment of fatty acid intake and metabolism should be included in future studies on the associations between depression and features of the metabolic syndrome.

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Depressive Symptoms, Insulin Resistance, and Risk of Diabetes in Women at Midlife

Response to Pouwer and de Jonge

Pouwer and de Jonge (1) raise two interesting points regarding our findings on depressive symptoms, insulin resistance, and diabetes risk (2). First, they suggest that insulin resistance may increase the risk for depression. This may be a plausible hypothesis, but it is an unlikely explanation for our findings. Participants were excluded from our analyses if they had overt diabetes (fasting blood glucose of ≥126 mg/dl or a self-reported history of diabetes) at the baseline examination. Moreover, although 126 (4.7%) participants in our study could be considered to have pre-diabetes, characterized by fasting blood glucose values between 110 and 125 mg/dl and typically considered an insulin-resistant state, the majority of our participants had normal glucose values and were not insulin resistant. For our analyses, we calculated insulin resistance by the revised homeostasis model assessment of insulin resistance (HOMA-IR) (3), which provides a continuum of values; thus, we did not define "cases" of insulin resistance. We did find that depressive symptoms were predictive of incident cases of diabetes over 3 years of follow up. In response to the hypothesis suggested by Pouwer and de Jonge, we reanalyzed our data and found that HOMA-IR values at baseline were not predictive of depression (P = 0.87) over the 3 years of the study among women who were not initially depressed.

Second, Pouwer and de Jonge (1) argue that intake and metabolism of ω-3 fatty acids may be important in the risk for depression and type 2 diabetes. This is an intriguing hypothesis; dietary factors may indeed influence risk for depression and, in turn, insulin resistance and diabetes risk. Data on consumption of ω-3 fatty acids in the SWAN population are available from a food frequency questionnaire completed at baseline. Therefore, we repeated our analyses of diabetes and insulin resistance, with adjustments for age, race, education, study site, and dietary consumption of ω-3 fatty acids. These analyses showed that ω-3 fatty acid consumption was not related to HOMA-IR (P = 0.42) or risk of diabetes (P = 0.65) in our population, and including this factor as a covariate did not affect the observed relationships between depression and either outcome. Nonetheless, dietary interventions may be useful for reducing depression or insulin resistance. Our data do not address that issue.

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Mortality and Causes of Death in a National Sample of Diabetic Patients in Taiwan

Response to Tseng

Tseng's study (1) indicated that only 19.8% of deaths among Taiwanese diabetic patients had an underlying cause of death attributed to cardiovascular disease (CVD), which was relatively low compared with the U.S. (49.4%) and U.K. (49.1%). One possible explanation was that Taiwanese diabetic patients were less likely to experience CVD than their counterparts in western countries. An Asia Pacific Collaboration cohort study did not support this hypothesis: no discernible differences were found between the hazard ratios for CVD deaths in Asian and Australasian populations (2).

The underlying cause of death is determined by a combination of factors, including both the physician's certification and the coder's interpretation of coding rules. Therefore, another explanation was that coders in Taiwan were more likely to assign diabetes as the underlying cause of death than in other countries. An evaluation study revealed that the diabetes death

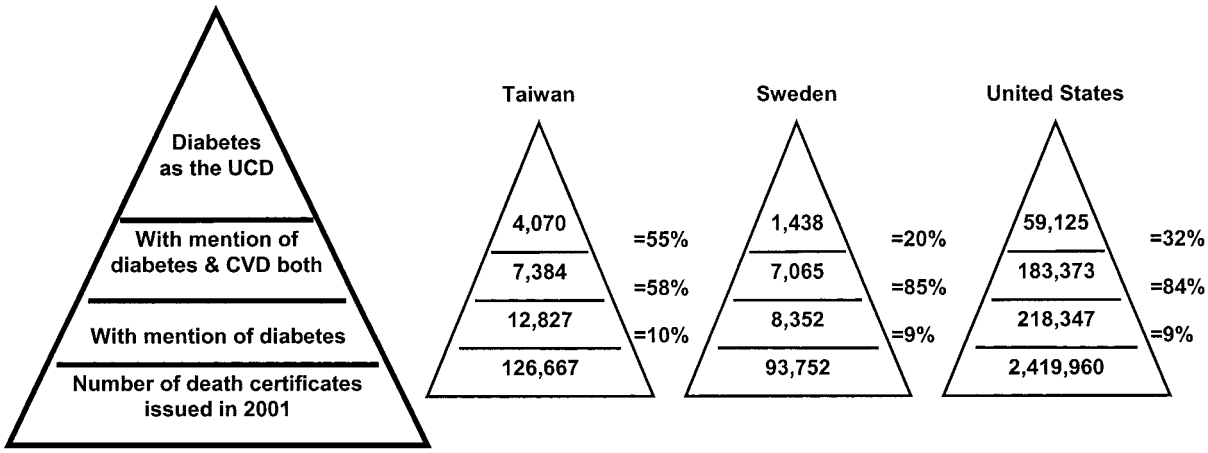

Figure 1—*Number of death certificates with mention of diabetes, with mention of both diabetes and CVD, and with diabetes selected as the underlying cause of death (UCD) in Taiwan, Sweden, and the U.S., 2001.*

rates calculated from manually coded death records did not show significant differences with those based on a widely used standard computerized coding system (3). Lu (3) proposed a third explanation, that Taiwanese physicians were more likely to certify diabetes as the underlying cause of death than physicians in other countries.

To test the first and the third hypotheses, we compared the diabetes-related multiple-cause-of-death mortality data of three countries as part of the International Collaborative Effort on Automating Mortality Statistics (4). The three countries used the same computerized coding system; therefore, there were no discrepancies in assigning the underlying cause of death among the three countries.

The proportion of death certificates with mention of diabetes was similar (9–10%) for Taiwan, Sweden, and the U.S. (Fig. 1). However, among those certificates with mention of diabetes, only 58% of certificates in Taiwan also mentioned CVD, considerably less than in Sweden (85%) and the U.S. (84%). Of those death certificates with mention of both diabetes and CVD in Taiwan, diabetes was selected as the underlying cause of death in 55% of cases, considerably higher than in Sweden (20%) and the U.S. (32%).

For CVD, the death rate calculated according to multiple-cause-of-death mortality data can be a proxy of the prevalence in the decedent population (5). We found a lesser coexistence of CVD among certificates with mention of diabetes in Taiwan than in Sweden and the U.S. Thus, the first explanation was partially supported. Our findings also confirmed the third hypothesis, that Taiwanese physicians were more likely to prefer diabetes over CVD as the underlying cause of death than their counterparts in Sweden and the U.S.

One limitation of using multiple-cause-of-death mortality data as a proxy for prevalence is that in some circumstances, the deceased may have had CVD but the certifying physician chose not to report it on the death certificate. However, we could still conclude that the interpretation of differences in cause-of-death statistics among countries should take into account the differences in cause-of-death certification behaviors among physicians of different countries.

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Mortality and Causes of Death in a National Sample of Diabetic Patients in Taiwan

Response to Lu et al.

The comparison of the coding behaviors of death certificates for diabetic patients among physicians of different countries reported by Lu et al. (1) is interesting and provides some explanations for a lower proportion of mortality from cardiovascular disease (CVD) coded

as the underlying cause of death in Taiwanese diabetic patients (2). However, the data presented should be interpreted with caution in order to avoid overinterpretation.

Based on a lower coexistence of CVD and diabetes in death certificates with mention of diabetes, Lu et al. concluded that their results partially supported the first hypothesis of a less likely experience of CVD death in Taiwanese diabetic patients than in their counterparts in Sweden and the U.S. This conclusion should at least be based on a strict assumption that the behavior of physicians among different countries to simultaneously enter CVD and diabetes in the death certificates for diabetic patients having CVD was not different. However, this presumption was not based on evidence and was actually contradictory to their later conclusion of different behaviors of filling the death certificates among physicians of various countries.

The third hypothesis suggested by Lu et al. that "coders in Taiwan were more likely to assign diabetes as the underlying cause of death than in other countries" was supported by their comparison analyses. However, the use of multiple-cause-of-death data could at most reflect the prevalence of certain diseases in the deceased patients, and it is still unknown whether the actual "cause of death" can be attributed to CVD.

The use of data from the Asia Pacific Collaboration cohort study (3,4) to contradict the first hypothesis could be misleading. First, the hazards ratios reported in that study compared diabetic versus nondiabetic subjects in the Asian and Australasian populations, respectively; Asian diabetic patients were not compared with Australasian diabetic patients (3). Second, the analyses in that study grouped all Asian populations from China, Japan, Hong Kong, Singapore, and Taiwan, not individuals specifically from Taiwan. Third, the two cohorts from Taiwan were not representative of general diabetic patients in Taiwan, because the Kinmen Neurological Disorders Survey recruited residents of Kinmen Island with an age range of 50–93 years and the Cardiovascular Disease Risk Factors Two Township Study recruited residents of two townships (one Hakka community and one Fukienese community) in Taiwan Island Proper with an age range of 20–92 years (4). Both cohorts excluded a significant proportion of younger diabetic patients, and the case numbers of diabetic patients were relatively small (~219 and 155, respectively) (3). With a median follow-up of 2.9 and 6.0 years in the respective cohorts, there would not be sufficient mortality cases for making significant inferences for Taiwanese diabetic patients.

It should also be mentioned that the approach of Lu et al. of studying cause of death of diabetic patients using death certificates without following a cohort of diabetic patients might have neglected a high proportion of the deceased diabetic patients not having diabetes mentioned in their death certificates.

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