Implications for the use of FPG and HbA1c for cost–effective screening DAVID R. JESUDASON, MBBS, FRACP1 KERRIE DUNSTAN, RN1 DARRYL LEONG, MBBS1 GARY A. WITTERT, MBBCH, MD, FRACP1,2 OBJECTIVE –– The use of fasting plasma glucose (FPG) level 7.0 mmol/l leads to under–diagnosis of type 2 diabetes compared with the oral glucose tolerance test (OGTT).The aims of this study were 1) to com– pare the utility of HbA1c and FPG at dif– ferent thresholds as screening tests for diagnosing type 2 diabetes, as defined by OGTT criteria; 2) to determine the rela– tionship between HbA1c and FPG and cardiovascular risk; and 3) to compare HbA1c measured by HPLC with the result obtained using a portable device (DCA2000; Bayer Diagnostics, Mulgrave, Australia) to assess the potential utility of the latter in screening for type 2 diabetes. RESEARCH DESIGN AND METHODS Subjects Subjects were recruited for this study by community advertisement for people with obesity, family history of diabetes, history of gestational diabetes, or symp– toms such as polyuria and polydipsia. All individuals older than 18 years of age without a previous diagnosis of type 2 di– abetes were tested if they responded to the advertisement with a request for screen– ing. Pregnant women were excluded from the study. Patients referred by general practitioners and other hospital special– ists for an OGTT were offered the oppor– tunity to participate in the study. The Ethics Com– mittee of the Royal Adelaide Hospital approved the protocol. Informed consent was obtained from all volunteers. Study design Subjects fasted from food and fluid from 11:00 P.M. the previous night and at– tended the Endocrine Test Unit at the Royal Adelaide Hospital between 8:00 A.M. and 9:00 A.M. Subjects were asked to complete a questionnaire to document the presence of ischemic heart disease, hypertension, and hyperlipidemia and whether there was a family history of type 2 diabetes. Height, weight, and waist cir– cumference were measured. A forearm vein was then cannulated with a 19–g but– terfly and 5 ml of venous blood was col– lected for measurement of glucose and HbA1c. Thereafter, 75 g of glucose was administered orally and 5 ml of blood was collected at 120 min for measurement of plasma glucose. All patients and their general practitioners were sent a letter in– forming them of the results, and patients were advised by telephone and by letter to seek follow–up whenever either diabetes or IGT was detected. Assays Plasma glucose was measured by the hex– okinase method, which has an interassay CV of 1.9% at a glucose level of 4.8 mmol/l. HbA1c was measured by HPLC using a spherical cation exchange gel, which has an interassay CV of 2% at an HbA1c level of 6%. HbA1c results from our laboratory (Institute of Medical and Vet– erinary Science) were referenced to the National Glycohemoglobin Standardisa– tion Program.Abbreviations: ADA, American Diabetes Association; CV, coefficient of variation; FPG, fasting plasma glucose; HPLC, high–performance liquid chromatography; IFG, impaired fasting glycemia; IGT, impaired glucose tolerance; OGTT, oral glucose tolerance test; ROC, receiver operating characteristic; WHO, World Health Organization.Guerci B, Durain D, Leblanc H, Rouland JC, Passa P, Godeau T, Charbonnel B, Mathieu–Daude JC, Boniface H, Monnier L, Dauchy F, Slama G, Drouin P: Multi– centre evaluation of the DCA 2000 system for measuring glycated haemoglobin: DCA 2000 study group.Diabete Metab 23: 195–201, 1997 18.Macrovascular risk and diagnostic criteria for type 2 diabetes 488 DIABETES CARE, VOLUME 26, NUMBER 2, FEBRUARY 2003 used self–reported data to evaluate cardio– vascular risk, our data relating to cardio– vascular risk are consistent with the results of other studies demonstrating an association between cardiovascular

dis- ease and increasing FPG and HbA1c, even in the nondiabetic range (18,20,29).McCance DR, Hanson RL, Charles MA, Lennart THJ, Pettitt DJ, Bennett PH, Knowler WC: Comparison of tests for gly- cated haemoglobin and fasting and two hour plasma glucose concentrations as di- agnostic methods for diabetes.More- over, data from the Diabetes Control and Complications Trial (DCCT) (21) and U.K. Prospective Diabetes Study (UK- PDS) (22) demonstrate that there remains a significant risk of microvascular disease with HbA1c levels well below 8%, and even at an HbA1c of 6%, there is a 75% Figure 1--ROC curves comparing FPG (F), HbA1c by HPLC (OE), and HbA1c by DCA2000 () as diagnostic indicators for diabetes.In situations in which fasting blood glucose can be readily obtained, a cutoff of 6.4 mmol/l results in diagnosis of more diabetic subjects than HbA1c as well as identification of those at significant risk for cardiovascular disease, in whom max- imal intervention, whether pharmacolog- ical or nonpharmacological, should be targeted.Wahl PW, Savage PJ, Psaty BM, Orchard TJ, Robbins JA, Tracey RP: Diabetes in older adults: comparison of 1997 Ameri- can Diabetes Association classification of diabetes mellitus with 1985 WHO classi- fication.Khaw KT, Wareham N, Luben R, Bing- ham S, Oakes S, Welch A, Day N: Glycated haemoglobin, diabetes, and mortality in men in Norfolk cohort of Eu- ropean Prospective Investigation of Can- cer and Nutrition.Rohlfing CL, Little RR, Wiedmeyer HM, England JD, Madsen R, Harris MI, Flegal KM, Eberhardt MS, Goldstein DE: Use of GHb (HbA1c) in screening for undiag- nosed diabetes in the U.S. population.Perry RC, Shankar RR, Fineberg N, McGill J, Baron AD: HbA1c measurement im- proves the detection of type 2 diabetes in high risk individuals with non-diagnostic levels of fasting plasma glucose.The ADA also created a new category termed im- paired fasting glycemia (IFG) to describe patients with FPG levels of 6.1-6.9 mmol/l (5) to categorize individuals at in- creased risk for type 2 diabetes and those who may be at increased cardiovascular risk.Gabir MM, Hanson WC, Dabelea D, Im- peratore G, Roumain J, Bennett PH, Knowler WC: The 1997 American Diabe- tes Association and 1999 WHO criteria for hyperglycaemia in the diagnosis and prediction of diabetes.The current OGTT and FPG thresh- olds for diagnosis of diabetes are based on their association with microvascular dis- ease, the incidence of which increases sharply above currently defined glycemic thresholds.We hy- pothesized that levels of HbA1c may in- crease progressively with increasing plasma glucose levels, even below con- ventionally defined diabetic thresholds, and are associated with the risk of macro- vascular disease.Statistical analysis Results are presented as means SD. The receiver operating characteristic (ROC) was used to describe the ability of HbA1c (HPLC or DCA2000) and FPG to deter- mine the presence or absence of type 2 diabetes as defined by the OGTT.Harris MI, Eastman RC, Cowie CC, Flegal KM, Eberhardt MS: Comparison of diabe- tes diagnostic categories in the U.S. pop- ulation according to 1997 American Diabetes association and 1980-85 World Health Organization diagnostic criteria.Gabir MM, Hanson RL, Dabelea D, Im- peratore G, Roumain J, Bennett PH, Knowler WC: Plasma glucose and predic- tion of microvascular disease and mortal- ity.Franse LV, Di Bari M, Shorr RI, Resnick HE, Van Eijk JTM, Bauer DC, Newman AB, Pahor M: Type 2 diabetes in older well-functioning people: who is undiag- nosed?In contrast to other studies that have evaluated the use of glucose and HbA1c as screening tests, we studied smaller num- bers of subjects prospectively rather than derived data retrospectively but obtained consistent results.The OGTT is a time-consuming, poorly reproducible, inconvenient, and expensive test

that we would argue can largely be avoided in favor of an HbA1c or FPG, using lower diagnostic thresholds and risk factor assessment to provide the most rational approach to subsequent management.The first subset should be considered diabetic because they are at increased risk for cardiovascular and mi- crovascular complications; these subjects should receive standard diabetic assess- ment (e.g., for retinopathy, neuropathy, and nephropathy) as well as for cardio- vascular disease.The aim of this study was to evaluate the use of HbA1c and FPG as predictors of type 2 diabetes and cardiovascular risk and, accordingly, to develop a rational approach to screening for abnormalities of glucose tolerance.Problems with the use of HbA1c for screening have included vari- ability and poor standardization of assays, biological variability of HbA1c levels, overlap between subjects with and with- out diabetes as compared with fasting or 2-h glucose levels (5,14–17), and poor sensitivity (12).Based on an ROC analysis, the areas under the curve (predictive values) of HbA1c as measured by HPLC and DCA2000 for detecting type 2 diabetes, compared with OGTT, were 0.893 and 0.911, respectively (2 0.53, df 2, P 0.77) (Fig.CONCLUSIONS -- These results show that FPG and HbA1c (by either method) will diagnose or exclude diabe- tes with certainty in only a minority (15%) of subjects when the OGTT, with currently defined cutoffs, is used as the gold standard.Wiener K, Roberts NB: The relative merits of haemoglobin A1c and fasting plasma glucose as first line diagnostic tests for di- abetes mellitus in non-pregnant subjects.The World Health Organization (WHO) and subsequently the Australian Diabetes Society similarly adopted an FPG level of 7 mmol/l as the threshold for diagnosing type 2 diabetes (6,7); how- ever, these organizations continue to rec- ommend use of the OGTT, because patients with type 2 diabetes based on an OGTT often have a nondiabetic FPG level (1,8,9).Log-binomial regression was used to determine the risk ratios (and 95% CIs) for the presence of ischemic heart disease for each SD increase in HbA1c, as mea- sured by either HPLC or using the DCA2000 method and the FPG.The regression data for HbA1c by DCA2000 versus HPLC reveals a small in- Macrovascular risk and diagnostic criteria for type 2 diabetes 486 DIABETES CARE, VOLUME 26, NUMBER 2, FEBRUARY 2003 tercept of 0.2 but no change in slope.Neither HbA1c (HPLC or DCA2000) nor FPG remained independent risk factors for cardiovascular disease after adjust- ment for age, waist circumference, hyper- tension, and high cholesterol.Table 1--The sensitivity, specificity, and cardiovascular risk ratio at each cutoff of HbA1c (by HPLC), HbA1c (by DCA2000), and FPG HbA1c by HPLC HbA1c by DCA2000 FPG (mmol/l) HbA1c (%) Sen (%) Spec (%) CV HbA1c (%) Sen (%) Spec (%) CV FPG Sen (%) Spec (%) CV 3.9 100 0.22 1 4.0 100 0.2 1 3.0 100 0 1.0 4.7 100 10.0 1.3 5.0 100 11.1 1.3 4.7 100 23.1 1.4 5.6 85.2 80.5 1.8 5.8 85.2 77.8 1.6 5.6 79.6 85.8 1.7 6.2 42.6 99.1 2.3 6.8 42.6 99.6 2.1 6.4 59.3 99.1 2.0 6.8 22.2 100 2.8 7.3 20.4 100 2.4 7.7 31.5 100 2.5 Sen, sensitivity; Spec, specificity.Peters AL, Davidson MB, Schringer DL, Hasselblad V: A clinical approach for the diagnosis of diabetes mellitus: an analysis using glycosylated haemoglobin levels.Colman PG, Goodall GI, Garcia- Webb P, Williams PF, Dunlop ME: Glycohaemo- globin: a crucial measurement in modern diabetes measurement.The Diabetes Control and Complications Trial Research Group: The effect of inten- sive treatment of diabetes on the develop- ment and progression of long term complications of insulin- dependant dia- betes mellitus.N Engl J Med 329:977–986, 1993 23.Measurement of HbA1c is used to determine average glycemic control over an 8- to 12-week period, and HbA1c level has been linked to

develop- ment of microvascular complications such as neuropathy, nephropathy, and retinopathy (7).Pathophysiology/Complications ORIGINAL ARTICLE DIABETES CARE, VOLUME 26, NUMBER 2, FEBRUARY 2003 485 the-spot results comparable to those obtained with HPLC can be obtained us- ing automated and portable devices (17).HbA1c was also measured using the DCA2000 (Bayer Diagnostics), a portable device that uses an immunoas- say technique with a monoclonal anti- body directed against a sequence of the HbA1c molecule (19).When measured by DCA2000, HbA1c 6.2% (sensitivity 72.2%, specificity 94.7%) was the best predictor of diabetes, and HbA1c levels 5.0 and 6.8% pre- dict the absence or presence of diabetes, respectively, with almost 100% certainty (Table 1).Kilpatrick ES, Maylor PW, Keevil BG: Bi- ological variation of glycated haemoglo- bin.The corresponding cutoffs were 5.0 and 6.8% for HbA1c (DCA2000 HPLC device; Bayer Diagnostics, Mulgrave, Australia) and 4.7 and 6.4 mmol/l for FPG.The American Diabetes Asso- ciation (ADA) based diagnosis of diabetes on a fasting plasma glucose (FPG) level of 7.0 mmol/l because this level correlates with a 2-h (post-75 g glucose) level of 11.1 mmol/l (5).Given that a major part of the morbidity and mortality from type 2 diabetes arises from macrovascular disease such as ischemic heart disease and not just microvascular disease, any screening test for diabetes would be more meaningful if it could also predict cardiovascular disease.The repro- ducibility of measurements of FPG, 2-h glucose, and HbA1c by each method was calculated for the 41 subjects, who were tested twice, and the intrasubject CV was determined (15).Accordingly, we propose that there is a rational basis for using either FPG or HbA1c for purposes of screening and assigning risk and, therefore, target- ing the most appropriate group of indi- viduals for further investigation and intervention.As with FPG, the risk of microvascular disease is low with an HbA1c 6.1%, but a relatively high risk of macrovascular disease remains and accordingly aggres- sive risk factor reduction is warranted.There is a relationship between HbA1c and FPG and the risk of both microvascu- lar (4) and macrovascular disease (1,20), although the increased risk of macrovas- cular disease occurs at lower glycemic thresholds.Davidson MB, Schriger DL, Peters AL, Lorber B: Relationship between fasting plasma glucose and glycosylated haemo- globin.RESEARCH DESIGN AND METHODS -- OGTT and measurement of HbA1c and FPG levels were performed in 505 subjects screened for type 2 diabetes.When measured using high-performance liquid chromatogra- phy (HPLC), however, the test has high precision (interassay coefficient of varia- tion [CV] 1-2%).Sensitivity is the fraction of individuals at or above the HbA1c cutoff point who have diabetes, whereas specificity is the fraction of indi- viduals with an HbA1c level below the cut- off point who do not have diabetes.Reproducibility There was a within-subject CV of 2.2% for HbA1c by HPLC, 2.7% for HbA1c by DCA2000, 4.9% for FPG, and 16.0% for 120-min plasma glucose after a 75-g oral glucose load.The detection of type 2 di- abetes has been reported by others to halve when ADA as opposed to WHO cri- teria are applied (1).Wahl et al. (1) showed that at an FPG level of 6.38 mmol/l, the prevalence of diabetes by ADA and 1985 WHO criteria were simi- lar.References 1. 1).2).