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Supplementary webappendix

This webappendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Griffin SJ, Borch-Johnsen K, Davies MJ, et al. Effect of early intensive multifactorial therapy on 5-year cardiovascular outcomes in individuals with type 2 diabetes detected by screening (ADDITION-Europe): a cluster-randomised trial. *Lancet* 2011; published online June 25. DOI:10.1016/S0140-6736(11)60698-3.

Webappendix

Measurement and endpoints

Blood pressure was calculated as the mean of three measurements (one measure at baseline in the Netherlands) performed after at least 10 minutes rest, while participants were seated with the cuff on the right arm at the level of the heart, using Omron blood pressure recorders. Height and weight were measured in light indoor clothing, without shoes, using a fixed rigid stadiometer and a Tanita scale. We recorded the average of two measurements of waist circumference using a tape measure halfway between the lowest point of the rib cage and the anterior superior iliac crests when standing.

Biochemical measures were analysed in five regional laboratories at baseline and follow-up: the Aarhus University Hospital and Steno Diabetes Centre, Gentofte (Denmark); Addenbrookes Hospital (Cambridge); Royal Infirmary (Leicester); and the SHL Center for Diagnostic Support in Primary Care, Etten-Leur (Netherlands). HbA1c was analysed by DCCT aligned ion-exchange high-performance liquid chromatography using Menarini 8160 in the Netherlands, Bio-Rad Variant II in Leicester and Tosoh G7 machines in Denmark and Cambridge. Plasma creatinine was analysed with kinetic colorimetric methods and by enzymatic methods from November 2008 onwards in the Netherlands. Serum total cholesterol, HDL-cholesterol and triglycerides were measured using standard enzymatic techniques on a Roche Hitachi 917 system until 2004 and thereafter a Hitachi 912 in Denmark, a Siemens Dimension RxL in Cambridge, a Siemens ADVIA 2400 in Leicester and a Beckman LX-20 until November 2008 and thereafter a Roche Hitachi Modular P in the Netherlands. Friedewald's formula was used to calculate LDL-cholesterol if serum triglyceride level was ≤4•5 mmol/l. Repeated analyses of standardised control samples for HbA1c, creatinine, cholesterol and triglycerides during follow-up confirmed reliability and precision of laboratory methods (all coefficients of variation were ≤ 1.8%, 6.4%, 3.2% and 8.3% respectively).

We collected information on socio-demographic characteristics (education, employment, and ethnicity), lifestyle habits (smoking status, alcohol consumption) and prescribed medication using standardised self-report questionnaires. We assessed frequency of hypoglycaemic events using the question 'how often have you felt that

your blood sugars have been unacceptably low recently' and 7-point response scale from 'none of the time' to 'most of the time' taken from the Diabetes Treatment Satisfaction Questionnaire.(1) Medication was coded using the WHO Anatomical Therapeutic Chemical (ATC) Classification System by staff unaware of group allocation.

In each centre participants' medical records or national registers were searched for potential endpoints by staff unaware of group allocation. In Denmark the national patient register was searched on 31/12/2009 for deaths and for ICD10 codes for cardiovascular events (I08-I77), and surgical procedures concerning amputations (chapters KNFQ, KNHQ, KNDQ, KNCQ) and revascularisations (chapters KF and KP of the Nomesco Classification of Surgical Procedures. Sundhedsstyrelsen and Munksgaard, Copenhagen, 2005). In Cambridge and Leicester participants were registered with the England and Wales Office of National Statistics, which provided copies of death certificates. Sensitive electronic Read code searches of general practice records were undertaken between March 2009 and February 2010. If a possible event was highlighted, copies were made of medical records, anonymised and reviewed by investigators unaware of group allocation. Additional information was obtained from hospital records and coroner's offices as required. In the Netherlands investigators extracted endpoint and vital status information from general practice records onto standardised forms. After initially refusing a data abstraction visit two practices were visited by an investigator who ascertained endpoints by the same method but was aware of group allocation. We therefore undertook sensitivity analyses excluding participants from these practices. For a further twenty patients who had moved practice, endpoint data were obtained by telephone interview with their current general practitioners.

In 2008 the Independent Data Monitoring and Safety Committee recommended continuation of the study following analysis of data (unaware of group allocation) on mortality rate and frequency of hypoglycaemic events.

1. Bradley C. Handbook of psychology and diabetes: a guide to psychological measurements in diabetes research and practice: Harwood Academic Press; 1994.