Appendix 1: Meta-analysis of baseline characteristics of patients included in randomised trials

Summary statistics

Summary statistics were extracted from trial reports. Data were collected for all groups, no matter they were experimental or control groups. For continuous variables, we collected means and standard deviations, or medians and quartiles in case only the latter statistics were reported. For binary variables we collected percentages. We also collected the total number of patients allocated to the groups.

Data transformation

For biological parameters, when baseline characteristics were reported as medians and quartiles, or as geometric means and quartiles, we hypothesized a log-normal distribution, to derive arithmetic means and standard deviations. For the variable *Diabetes duration*, we hypothesized an exponential distribution to derive the mean and standard deviation from the median.

Discarded observations

When variability in data was expressed by means of the minimal and maximal value, we discarded the observation, because there is no possibility to derive a standard deviation from extreme values.

For the UKPDS the diabetes duration variable was 0 with an associate standard deviation also equal to 0, since patients were newly diagnosed as having diabetes. In absence of any variability, such a study would have a weight equal to infinity, and we therefore discarded the UKPDS groups when meta-analyzing the diabetes duration variable.

Meta-analyses

For each baseline characteristics we performed a random effect meta-analysis. Units meta-analyzed were groups, rather than trials. Thus each trial contributed twice (for two parallel group trials), or more (for trials with more than two groups). Indeed, groups obtained from randomisation are independent, which means that meta-analyzing groups rather than trials is correct. For binary variables, we applied Freeman-Tukey double -arcsine transformation [1] and use Miller's back transformation [2]. Data were analyzed using the SAS Metanal macro.

Appendix 2: List of the 23 randomised trials included

1 Action to Control Cardiovascular Risk in Diabetes Study Group, Gerstein HC, Miller ME, *et al.* Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* 2008;**358**:2545–59. doi:10.1056/NEJMoa0802743

2 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 Lond Engl* 2011;**378**:156–67. doi:10.1016/S0140-6736(11)60698-3

3 ADVANCE Collaborative Group, Patel A, MacMahon S, *et al.* Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2008;**358**:2560–72. doi:10.1056/NEJMoa0802987

4 Araki A, Iimuro S, Sakurai T, *et al.* Long-term multiple risk factor interventions in Japanese elderly diabetic patients: the Japanese Elderly Diabetes Intervention Trial--study design, baseline characteristics and effects of intervention. *Geriatr Gerontol Int* 2012;**12 Suppl 1**:7–17. doi:10.1111/j.1447-0594.2011.00808.x

5 Bagg W, Whalley GA, Gamble G, *et al.* Effects of improved glycaemic control on endothelial function in patients with type 2 diabetes. *Intern Med J* 2001;**31**:322–8. doi:10.1046/j.1445-5994.2001.00072.x

6 Becker A, van der Does FEE, van Hinsbergh VWM, *et al.* Improvement of glycaemic control in type 2 diabetes: favourable changes in blood pressure, total cholesterol and triglycerides, but not in HDL cholesterol, fibrinogen, Von Willebrand factor and (pro)insulin. *Neth J Med* 2003;**61**:129–36.

7 Blonde L, Merilainen M, Karwe V, *et al.* Patient-directed titration for achieving glycaemic goals using a once-daily basal insulin analogue: an assessment of two different fasting plasma glucose targets - the TITRATE study. *Diabetes Obes Metab* 2009;**11**:623–31. doi:10.1111/j.1463-1326.2009.01060.x

8 Cao S-G, Ren J-A, Shen B, *et al.* Intensive Versus Conventional Insulin Therapy in Type 2 Diabetes Patients Undergoing D2 Gastrectomy for Gastric Cancer: A Randomized Controlled Trial. *World J Surg* 2011;**35**:85–92. doi:10.1007/s00268-010-0797-5

9 Cooray G, Nilsson E, Wahlin Å, *et al.* Effects of intensified metabolic control on CNS function in type 2 diabetes. *Psychoneuroendocrinology* 2011;**36**:77–86. doi:10.1016/j.psyneuen.2010.06.009

10 Malmberg K, Rydén L, Wedel H, *et al.* Intense metabolic control by means of insulin in patients with diabetes mellitus and acute myocardial infarction (DIGAMI 2): effects on mortality and morbidity. *Eur Heart J* 2005;**26**:650–61. doi:10.1093/eurheartj/ehi199

11 Fantin S de S, Wainstein MV, Polanczyk CA, *et al.* Inflammatory and oxidative stress markers after intravenous insulin in percutaneous coronary intervention with stent in type 2 diabetes mellitus: a randomized controlled trial. *J Clin Endocrinol Metab* 2011;**96**:478–85. doi:10.1210/jc.2010-0256

12 Guo L, Pan Q, Wang X, *et al.* Effect of short term intensive multitherapy on carotid intima-media thickness in patients with newly diagnosed type 2 diabetes mellitus. *Chin Med J (Engl)* 2008;**121**:687–90.

13 Hage C, Norhammar A, Grip L, *et al.* Glycaemic control and restenosis after percutaneous coronary interventions in patients with diabetes mellitus: a report from the Insulin Diabetes Angioplasty study. *Diab Vasc Dis Res* 2009;**6**:71–9. doi:10.1177/1479164109336042

14 Jaber LA, Halapy H, Fernet M, *et al.* Evaluation of a pharmaceutical care model on diabetes management. *Ann Pharmacother* 1996;**30**:238–43. doi:10.1177/106002809603000305

15 Ohkubo Y, Kishikawa H, Araki E, *et al.* Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. *Diabetes Res Clin Pract* 1995;**28**:103–17. doi:10.1016/0168-8227(95)01064-k

16 Melidonis A, Tournis S, Stefanidis A, *et al.* The role of strict metabolic control by insulin infusion on fibrinolytic profile during an acute coronary event in diabetic patients. *Clin Cardiol* 2009;**23**:160–4. doi:10.1002/clc.4960230306

17 Natarajan MK, Strauss BH, Rokoss M, *et al.* Randomized trial of insulin versus usual care in reducing restenosis after coronary intervention in patients with diabetes. the STent

Restenosis And Metabolism (STREAM) study. *Cardiovasc Revascularization Med Mol Interv* 2012;**13**:95–100. doi:10.1016/j.carrev.2011.12.001

18 Stefanidis A, Melidonis A, Tournis S, *et al.* Effect of intravenous insulin administration on left ventricular performance during non-ST-elevation acute coronary events in patients with diabetes mellitus. *Am J Cardiol* 2003;**91**:1237–40. doi:10.1016/s0002-9149(03)00272-8

19 Gaede P, Lund-Andersen H, Parving H-H, *et al.* Effect of a multifactorial intervention on mortality in type 2 diabetes. *N Engl J Med* 2008;**358**:580–91. doi:10.1056/NEJMoa0706245

20 Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet Lond Engl* 1998;**352**:837–53.

21 Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. *Lancet Lond Engl* 1998;**352**:854–65.

22 Abraira C, Emanuele N, Colwell J, *et al.* Glycemic control and complications in type II diabetes. Design of a feasibility trial. VA CS Group (CSDM). *Diabetes Care* 1992;**15**:1560–71. doi:10.2337/diacare.15.11.1560

23 Duckworth W, Abraira C, Moritz T, *et al.* Glucose control and vascular complications in veterans with type 2 diabetes. *N Engl J Med* 2009;**360**:129–39. doi:10.1056/NEJMoa0808431

24 Zhang Q, Zhang N, Hu H-L, *et al.* Effect of intensive blood glucose control on quality of life in elderly patients with type 2 diabetes in Anhui Province. *Chin Med J (Engl)* 2011;**124**:1616–22.

Appendix 3 - Table 1. Characteristics of the randomised trials

Characteristics	**Randomised trials** **N = 24**
Year of publication, median (IQR)	2008 (2001 - 2011)
Continent, n (%)	
Europe	11 (40.7)
North America	7 (25.9)
Asia	6 (22.2)
Oceania	2 (7.4)
South America	1(3.7)
Africa	0 (0)
Sample size, median (IQR)	169.5 (76 - 1366)
Number of center, n (%)	
Monocentric	11 (47.8)
Multicentric	11 (47.8)
Unclear	1 (4.4)
Number of center, median (IQR)	2 (1 - 31)
Setting, n (%)	
Hospital	16 (66.7)
General practice	4 (16.7)
Outpatient clinic	2 (8.3)
Other	1 (4.2)
Unclear	1 (4.2)

*The total number of continent cited exceeded the total number of randomised trials as 1 trial was conducted in several continents

IQR : interquartile range