

Mortality Rates in Trials of Subjects With Type 2 Diabetes

Ebrahim Barkoudah, MD; Hicham Skali, MD, MSc; Hajime Uno, PhD; Scott D. Solomon, MD; Marc A. Pfeffer, MD, PhD

Background—In randomized controlled trials (RCTs) of subjects with type 2 diabetes mellitus, mortality rates vary substantially. We sought to examine the inclusion and exclusion criteria of these RCTs to explore relationships with mortality.

Methods and Results—MEDLINE database was searched from August 1980 through March 2011. Selection criterion included published RCTs of adults with type 2 diabetes mellitus of at least 1000 patients, reporting all-cause mortality and having follow-up duration of at least 1 year. Twenty-two trials were eligible. Annualized mortality rates were derived. Inclusion and exclusion criteria were tabulated for each trial. Trials were categorized in 4 groups according to annual mortality rates: <1 , ≥ 1 to <2 , ≥ 2 to <4 , and ≥ 4 per 100 patient-years. The analysis cohort included 91 842 patients and 6837 deaths. Mortality rates ranged from 0.28 to 8.24 per 100 patient-years. Patients enrolled in the highest mortality category were more likely to be older and had longer diabetes duration and higher blood pressure. The selection for hypertension was common in the low- as well as high-mortality trials. Although the mortality rates were higher in RCTs with prior cardiovascular morbidity, the selection for chronic kidney disease—defined by either higher serum creatinine or lower estimated glomerular filtration rate and/or the presence of proteinuria—was associated with the highest mortality rates.

Conclusions—In this analysis of RCTs of type 2 diabetes mellitus, a 29-fold difference in annualized mortality was observed. In these RCTs, selection for renal disease, defined by either decline in renal function or presence of proteinuria, portends important mortality risk. (*J Am Heart Assoc* 2012;1:8-15.)

Clinical Trial Registration—URL: <http://www.ClinicalTrials.gov>. Unique identifier: NCT00303979.

Key Words: type 2 diabetes • chronic kidney disease • mortality • controlled clinical trials • randomized

Background

Type 2 diabetes mellitus (T2DM) increases the risk of premature morbidity and mortality in the community and cardiovascular disease (CVD) is the leading cause of death in individuals with diabetes.^{1,2} The burden of diabetes-related CVD is likely to continue to expand with the increasing incidence of diabetes in the population.³

It is clear from epidemiologic studies that concomitant diabetes augments the hazard associated with other risk factors for developing CVD, including hypertension, hyperlipidemia, and renal impairment.^{4,5} Similarly, in patients with established CVD, diabetes portends a greater risk of worse outcomes especially when associated complications such

as nephropathy, retinopathy, and, possibly, neuropathy are present. Conversely, in patients whose only risk factor is diabetes, the population attributable risk of death may not be very high.⁶

In contrast to epidemiologic studies, which provide the most accurate assessment of disease burden in population, randomized controlled trials (RCTs) use inclusion and exclusion criteria to target a specific subpopulation and provide an insight to contributions of comorbidities on mortality in a selected population. Although the specific selection criteria distort the disease proportion in the population, including patients who fulfill specific selection criteria can augment the overall morbidity and mortality risk. Across trials, the selection or exclusion of a specific risk profile offers a diverse sample that extends from low mortality to those with the extreme hazard.

In RCTs of T2DM patients, while any cardiovascular or renal diseases increase mortality in diabetes, patients without evidence of such would be expected to experience fewer complications.⁷ Furthermore, annualized death rates can characterize the risk in diabetes populations across trials. We used data from recent RCTs in T2DM to further examine the relationship between cardiovascular risk factors and renal disease and its complications and how this interplay augments the risk of death.

From the Cardiovascular Division (E.B., H.S., S.D.S., M.A.P.); General Medicine Division, Brigham and Women's Hospital (E.B.); and; Department of Biostatistics and Computational Biology (H.U.), Dana Farber Cancer Institute, Boston, MA.

Correspondence to: Marc A. Pfeffer, MD, PhD, Cardiovascular Division, Brigham and Women's Hospital, 75 Francis St, Boston, MA 02115. E-mail mpfeffer@rics.bwh.harvard.edu

Received November 21, 2011; accepted January 3, 2011.

© 2012. The Authors. Published on behalf of the American Heart Association, Inc., by Wiley-Blackwell. This is an Open Access article under the terms of the Creative Commons Attribution Noncommercial License, which permits use, distribution, and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

Methods

Study Selection and Search Strategy

The selection criteria included RCTs of adults with T2DM of at least 1000 patients, reporting all-cause mortality results, and with a minimum follow-up duration of 1 year. We excluded trials that selected patients with acute coronary syndrome or end-stage renal disease.

The search included the following terms: MeSH major topic: diabetes mellitus type 2 treatment; Limits: Humans, RCT, English, and 19+ years adult. The MEDLINE database was searched for studies using these eligibility criteria between August 1980 and March 2011. All references were examined to attempt identify additional trials. The initial search generated 4191 publications. After reviewing titles and abstracts (Figure 1), and applying prespecified criteria, 22 studies⁸⁻²⁹ were eligible (Table 1).

Data Extraction, Synthesis, and Analysis

In RCTs that met our criteria, we calculated the all-cause mortality rate for the overall population, regardless of treatment allocation. Patient-years were estimated in each trial by multiplying the sample size by the average follow-up time (median was used when mean was not reported). Annualized mortality incidence rates were derived accordingly by dividing the total number of deaths by total patient-years, from all treatment arms, and expressed per 100 patient-years. Because most of these trials were not designed or powered to study the effect on all-cause mortality, we used the overall mortality rate regardless from intervention allocation.

Inclusion and exclusion criteria were obtained for each trial. When available, the selection—or exclusion—for hypertension, CVD, elevated serum creatinine or estimated glomerular filtration rate < 60 mL/min/1.73 m², or the presence of proteinuria were tabulated. When a specific inclusion/exclusion criterion was not specified, we considered it a permitted condition. RCTs were sorted by ascending mortality rates and then categorized in 4 groups: < 1, ≥ 1 to < 2, ≥ 2 to < 4, and ≥ 4 deaths per 100 patient-years. Within each mortality group, annualized mortality rates were derived by dividing the sum of deaths by total patient-years of group's trials and express the product by 100 patient-years.

Within each category, every trial was attributed a weight according to its sample size. Weighted values (ie, weighted means and corresponding 95% confidence intervals) for baseline characteristics were calculated accordingly.³⁰ When available, we obtained the mean or median of the descriptive characteristics of the population: age, sex, body mass index, duration of diabetes, total cholesterol, low-density lipoprotein cholesterol, systolic blood pressure, serum creatinine, smoking status along with the rates of retinopa-

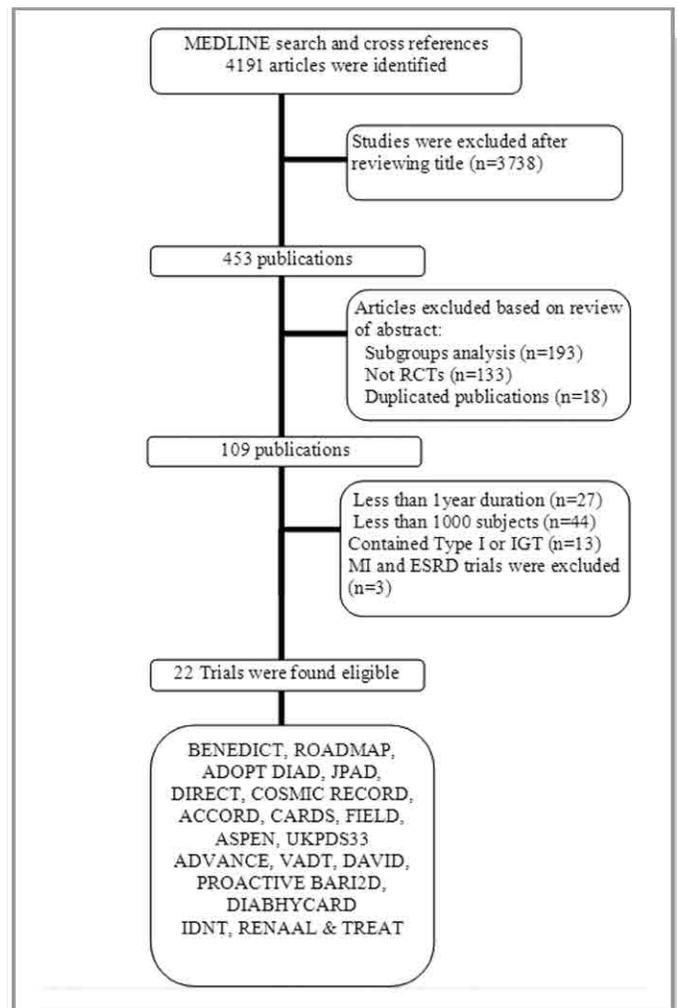


Figure 1. Literature flow.

thy, hypertension, history of CVD, and the presence of proteinuria defined by any abnormal excretion of albumin or protein.

Results

Our analysis included 91 742 patients and 6837 deaths (7.5%). The overall mortality rate in the entire population was 1.83 deaths per 100 patient-years and varied widely from 0.28 to 8.24 deaths per 100 patient-years across the selected trials (Figure 2 and Table 2).

All RCTs included additional risk factors other than diabetes in their inclusion criteria. Hypertension was a common inclusion criterion for low- and high-mortality trials. Mortality rates were the lowest in primary prevention trials and those for which hypertension was the only additional inclusion criterion (BENIDICT, DIRECT, JPAD, and ROADMAP). These trials, excluding JPAD, shared an exclusion criterion of proteinuria at baseline. Studies selecting for the presence of CVD other than

Table 1. Eligible Studies Sorted by Publication Date

Acronyms	Trial	Publication
UKPDS33	UK Prospective Diabetes Study ⁸	<i>Lancet</i> . 1998;352:837–853.
IDNT	Irbesartan in Patients with Nephropathy due to Type 2 Diabetes ⁹	<i>N Engl J Med</i> . 2001;345:851–860.
RENAAL	Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan ¹⁰	<i>N Engl J Med</i> . 2001;345:861–869.
DIABHYCAR	Non–insulin-dependent DIABetes, Hypertension, microalbuminuria or proteinuria, CARdiovascular events, and Ramipril ¹¹	<i>BMJ</i> . 2004;328:495–500.
DAVID	Atherosclerotic Vascular Disease in Diabetics ¹²	<i>Eur Heart J</i> . 2004; 25:1845–1852.
CARDS	Collaborative Atorvastatin Diabetes Study ¹³	<i>Lancet</i> . 2004;364:685–696.
BENEDICT	Bergamo Nephrologic Diabetes Complications Trial ¹⁴	<i>N Engl J Med</i> . 2004;351:1941–1951.
COSMIC	Comparative Outcomes Study of Metformin Intervention versus Conventional ¹⁵	<i>Diabetes Care</i> . 2005;28:539–543.
PROactive	PROspective pioglitAzone Clinical Trial In macroVascular Events ¹⁶	<i>Lancet</i> . 2005;366:1279–1289.
FIELD	Fenofibrate Intervention and Event Lowering in Diabetes ¹⁷	<i>Lancet</i> . 2005;366:1849–1861.
ASPEN	The Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-Insulin-Dependent Diabetes Mellitus ¹⁸	<i>Diabetes Care</i> . 2006;29:1478–1485.
ADOPT	A Diabetes Outcome Progression Trial ¹⁹	<i>N Engl J Med</i> . 2006;355:2427–2443.
ACCORD	Action to Control Cardiovascular Risk in Diabetes ²⁰	<i>N Engl J Med</i> . 2008;358:2545–2559.
ADVANCE	Action in Diabetes and Vascular Disease ²¹	<i>N Engl J Med</i> . 2008;358:2560–2572.
DIRECT-2	Diabetic REtinopathy Candesartan Trial ²²	<i>Lancet</i> . 2008;372:1385–1393.
JPAD	Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes ²³	<i>JAMA</i> . 2008;300:2134–2141.
VADT	Veterans Affairs Diabetes Trial ²⁴	<i>N Engl J Med</i> . 2009;360:129–139.
DIAD	Detection of Ischemia in Asymptomatic Diabetics ²⁵	<i>JAMA</i> . 2009;301:1547–1555.
RECORD	Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes ²⁶	<i>Lancet</i> . 2009;373:2125–2135.
BARI2D	Bypass Angioplasty Revascularization Investigation 2 Diabetes ²⁷	<i>N Engl J Med</i> . 2009;360:2503–2515.
TREAT	Trial to Reduce Cardiovascular Events With Aranesp Therapy ²⁸	<i>N Engl J Med</i> . 2009;361:2019–2032.
ROADMAP	The Randomized Olmesartan and Diabetes Microalbuminuria Prevention ²⁹	<i>N Engl J Med</i> . 2011;364:907–917.

hypertension (DAVID, PROACTIVE, and BARI2D) had higher mortality than those permitting CVD in their inclusion criteria (RECORD, ACCORD, FIELD, UKPDS, ADVANCE, and VADT). Moreover, trials in which inclusion required elevated serum creatinine values (mostly > 1.5 mg/dL) or estimated glomerular filtration rate < 60, or/and evident proteinuria (DIABHYCAR, IDNT, RENAAL, and TREAT) showed the highest mortality rates.

Mortality, across trials, was associated with certain characteristics: serum creatinine, proteinuria prevalence, age, diabetes duration, and systolic blood pressure averages (Table 3). Furthermore, subjects in the lower mortality category were younger (59 years), had lower serum creatinine averages (0.9 mg/dL), and proteinuria prevalence (9%). Conversely, subjects enrolled in the highest mortality trials were more likely to be older (64.2 years); have longer diabetes duration (15.2 years); and have higher systolic blood pressure (145 mmHg), serum creatinine averages (1.8 mg/dL), and proteinuria prevalence (100%).

Lower low-density lipoprotein averages and current smoking status were observed with higher mortality rates (126, 117,

107, 99 mg/dL and 16%, 15%, 14%, and 9%, respectively, along the categories). In addition, we observed variation in body mass index and glycated hemoglobin averages across mortality and were highest in the trials with CVD trials. Moreover, hypertension prevalence was highest in the highest mortality trials category (97%) and ranged 69% to 73% across all other mortality categories. Similarly, reporting retinopathy varied in consistency across mortality groups with higher presence in the highest mortality category. Gender type was not associated with mortality in our analysis.

Discussion

Patients with diabetes mellitus enrolled in RCTs do not represent a homogenous population.³¹ Different inclusion criteria, according to study aim, influence baseline characteristics of the enrolled subjects and subsequently the risk profile and observed outcomes. As a result, the heterogeneity of this population is translated into a wide range of death rates. The term

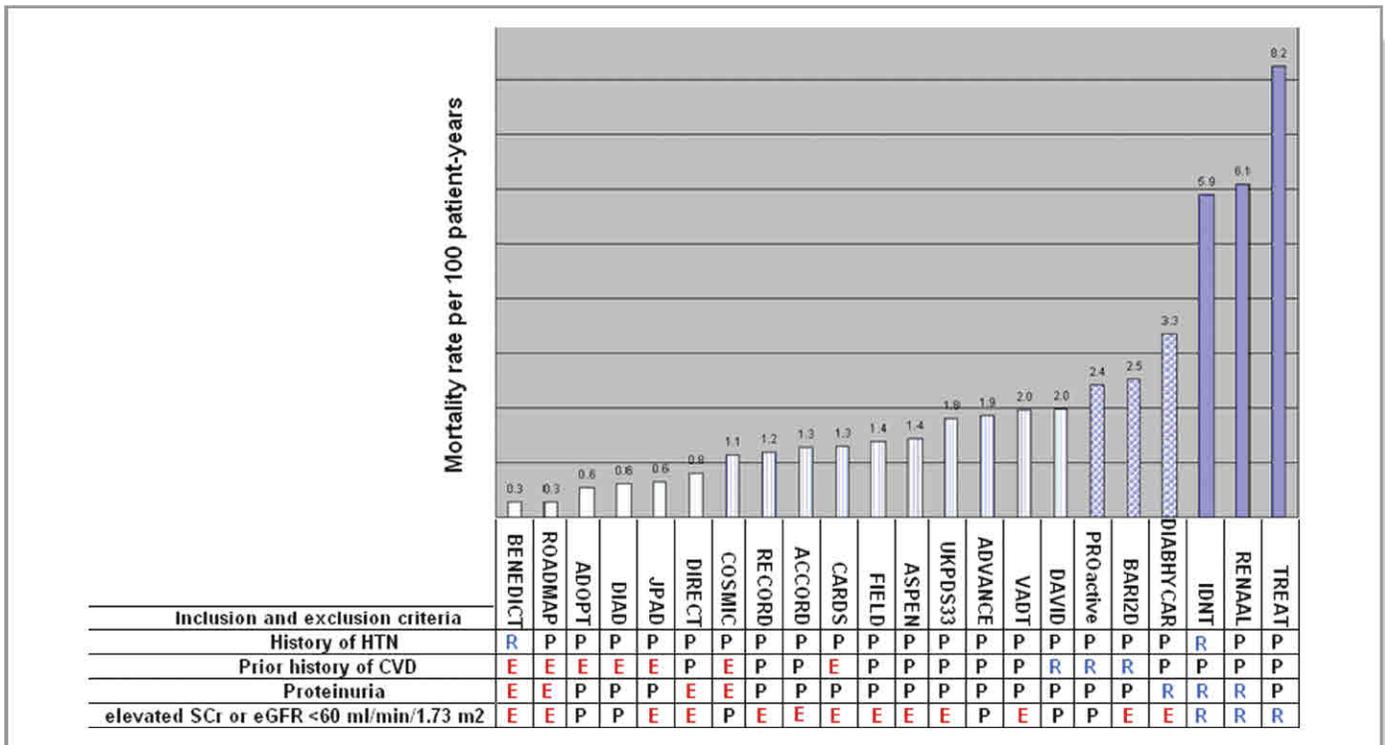


Figure 2. All eligible trials according to ascending death rate. R: condition required; P: condition permitted; E: condition excluded; E: excluded as directly stated or no mention of baseline MI, HF, or Stroke for prior history of CVD. Also excluded for serum creatinine > 1.5 or > 1.7 per trial’s protocol.

“diabetes risk” in and of itself does not differentiate those with the highest death risk in the spectrum.

Our report highlights the risk of death in subjects with diabetes, with an approximately 30-fold difference in annualized mortality rate across the range of trials we examined. Hypertension was not associated with higher mortality rate and selection for hypertension specifically did not discriminate those at higher risk of death. Furthermore, in RCTs of subjects with diabetes, the selection for increased urinary protein excretion or/and elevated serum creatinine was particularly and closely associated with increased risk of death.

Our study is consistent with prior reports describing the risk associated with nephropathy in diabetes. UKPDS 64 data described mortality rates similar to our data with a stepwise increase in death rate on the progression from normoalbuminuria to albuminuria to decline in kidney function.³² Although multiple studies demonstrated that baseline characteristics affect mortality in diabetic subjects^{33,34}, our descriptive report shows that chronic kidney disease (CKD) in diabetes is associated with major mortality risk.

In addition to diabetes and CKD, TREAT also required hemoglobin level ≤11.0 g/dL as an inclusion criterion. This additional eligibility requirement would be expected to be associated with a greater risk of death.³⁵ Additionally, other de-

tectable serum cardiac biomarkers were shown to be associated with even higher risk of death³⁶ and could potentially be used for further risk stratification and/or selection of specific populations for clinical trials.³⁷

The Emerging Risk Factors Collaboration showed that diabetes increases the risk of vascular and nonvascular mortality causes.³⁸ The report also demonstrated that the risk of death increased with estimated glomerular filtration rate decline. Our study illustrates that any degree of proteinuria in diabetes is associated with a higher death rate. Risk stratification by evidence of kidney disease, determined by renal function or proteinuria, should be emphasized in diabetic subjects given its major impact on morbidity and mortality.³⁹

Most clinical trials, by design, augment the studied risk in clinical trials and eventually increase endpoint rates. In our cohort of all subjects with type 2 diabetes, each trial contains an attributed risk in its inclusion. Although hypertension is an element of the cardiovascular continuum risk profile in diabetes, its mortality augmentation was not evident in our cohort especially in the absence of proteinuria and did not provide further risk discrimination. Recent analysis concluded the similar finding.⁴⁰ Although the diagnosis of hypertension was common across all mortality categories, the actual weighted systolic blood pressure average was greater in the highest mortality trials.

Within our cohort of subjects with T2DM participants in RCTs, we did not observe an increase of other “traditional” risk factors along with increasing mortality.⁴¹ Moreover, variation of certain characteristic risk factors was seen across the selected trials; for example, body mass index and glycosylated hemoglobin weighted average values showed a disparity across the arbitrary categories and likely due to the selection processes in these trials. Notably, current smoking and low-density lipoprotein weighted averages were lower in higher mortality categories. Although the lower prevalence of smoking is probably related to the inclusion criteria, reports from cohorts of CKD and heart failure demonstrated that lower cholesterol correlates with higher mortality what is described as “reverse epidemiology” in other population of patients with advanced disease.⁴² Moreover, the presence of CKD matched higher presence of hypertension and retinopathy. This matching increase is probably explained by the bidirectional influence between the vasculature and the kidney along with the end-organ damage of both systems simultaneously.⁴³

Our report was limited by the lack of individual patient data to allow detailed analyses of baseline characteristics and risk of death. Baseline characteristics were obtained from the publication as averages; not all baseline characteristics were reported in every trial; we also used overall prevalence of CVDs in our analysis and not its subtypes. Furthermore, we did not account for the medications and therapeutic interventions during trials. We examined overall mortality in the analyzed trials and did not take into account randomized treatment arms and treatment effects on mortality, albeit these were generally neutral. Although we also did not account for potential secular decline in mortality rates over time, 21 of our 22 trials in our analysis were published in the past 10 years. The strength of this report includes the review of numerous baseline demographics and examination of a large cohort. Moreover, the extensive literature search that was performed makes publication selection bias less likely. Our report focuses on comparing the exclusion and inclusion criteria and demonstrating the contrast in the clinical trials population as selective cohort to supplement for epidemiologic studies, which have critical estimates of demographics. Furthermore, the truncated distribution of the population demographics was dictated by the trials selection criteria and probably resulted in a less pronounced relationship between demographics and outcomes.

Mortality has a broad range of representation in trials of type 2 diabetes subjects. Moreover, diabetes trials with nephropathy selection had the highest death rates. We conclude that the selection for CKD, defined by either decline in renal function or presence of proteinuria, augmented the death risk in diabetes.

Acknowledgments

We thank Dr John JV McMurray of British Heart Foundation Glasgow Cardiovascular Research Centre, University of Glasgow and the Cardiovascular Division, Department of Medicine, Brigham and Women’s Hospital and Harvard Medical School for his invaluable comments.

Disclosures

Dr. Pfeffer reports receiving grant support from Amgen, Novartis, and Sanofi-aventis, as well as consulting fees from Amgen, Anthera, Boehringer Ingelheim, Boston Scientific, Bristol-Myers Squibb, Cerenis, Eleven Biotherapeutics, GlaxoSmithKline, Hamilton Health Sciences, Karo Bio, Novartis, Roche, Saltria, Sanofi Aventis, Servier, University of Oxford. Dr Pfeffer is a coinventor on a patent that Brigham and Women’s Hospital has for the use of inhibitors of the renin-angiotensin system in selected survivors of MI. His share of the licensing agreements with Novartis and Boehringer, which are irrevocably transferred to charity, are not linked to sales. Dr. Solomon reports receiving research support from Sanofi-Aventis paid through Brigham and Women’s Hospital. Drs. Barkoudah, Skali, and Uno report none.

References

- Roglic G, Unwin N, Bennett PH, Mathers C, Tuomilehto J, Nag S, Connolly V, King H. The burden of mortality attributable to diabetes: realistic estimates for the year 2000. *Diabetes Care*. 2005;28:2130–2135.
- Sowers JR, Lester MA. Diabetes and cardiovascular disease. *Diabetes Care*. 1999;22:14–20.
- Huang ES, Basu A, O’Grady M, Capretta JC. Projecting the future diabetes population size and related costs for the U.S. *Diabetes Care*. 2009;32:2225–2229.
- Panzram G. Mortality and survival in type 2 (non-insulin-dependent) diabetes mellitus. *Diabetologia*. 1987;30:123–131.
- Buse JB, Ginsberg HN, Bakris GL, Clark NG, Costa F, Eckel R, Fonseca V, Gerstein HC, Grundy S, Nesto RW, Pignone MP, Plutzky J, Porte D, Redberg R, Stitzel KF, Stone NJ. Primary prevention of cardiovascular diseases in people with diabetes mellitus: a scientific statement from the American Heart Association and the American Diabetes Association. *Circulation*. 2007;115:114–126.
- Boyko EJ, Meigs JB. Does diabetes always confer coronary heart disease risk equivalent to a prior myocardial infarction?: implications for prevention. *Diabetes Care*. 2011;34:782–784.
- Ingelfinger JR. Preemptive olmesartan for the delay or prevention of microalbuminuria in diabetes. *N Engl J Med*. 2011;364:970–971.
- UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet*. 1998;352:837–853.
- Lewis EJ, Hunsicker LG, Clarke WR, Berl T, Pohl MA, Lewis JB, Ritz E, Atkins RC, Rohde R, Raz I, Collaborative Study Group. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med*. 2001;345:861–869.
- Brenner BM, Cooper ME, de Zeeuw D, Keane WF, Mitch WE, Parving HH, Remuzzi G, Snapinn SM, Zhang Z, Shahinfar S. Effects of Losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med*. 2001;345:861–869.
- Marre M, Lievre M, Chatellier G, Mann JF, Passa P, Ménard J. Effects of low dose ramipril on cardiovascular and renal outcomes in patients with type 2 diabetes and raised excretion of urinary albumin: randomised, double blind, placebo controlled trial (the DIABHYCAR study). *BMJ*. 2004;328:495–500.