Nutrition, Metabolism & Cardiovascular Diseases (2013) 23, 1101–1106

Available online at www.sciencedirect.com

SciVerse ScienceDirect

journal homepage: www.elsevier.com/locate/nmcd

Nutrition, Metabolism & Cardiovascular Diseases

Primary prevention with statins and incident diabetes in hypertensive patients at high cardiovascular risk☆

R. Izzo [a], G. de Simone [a,*], V. Trimarco [b], R. Giudice [a], M. De Marco [a], G. Di Renzo [b], N. De Luca [a], B. Trimarco [c]

[a] Department of Translational Medical Sciences, Federico II University, Naples, Italy
[b] Department of Neurosciences, Federico II University, Naples, Italy
[c] Department of Advanced Biomedical Sciences, Federico II University, Naples, Italy

Received 4 June 2012; received in revised form 25 October 2012; accepted 1 November 2012
Available online 15 February 2013

KEYWORDS
Statins;
Diabetes;
CV risk

Abstract *Background and aims:* The ESC/ESH guidelines for arterial hypertension recommend using statins for patients with high cardiovascular (CV) risk for both secondary and primary prevention. A recent meta-analysis, combining previous studies on statins, concluded that they are associated with a 9% increased risk of incident type 2 diabetes mellitus (DM). There is no information on whether statins increase incidence of DM in primary prevention.
Method and results: We evaluated risk of incident DM in relation to statin prescription in 4750 hypertensive, non-diabetic outpatients (age 58.57 ± 9.0 yrs, 42.3% women), from the CampaniaSalute Network, without chronic kidney disease more than grade 3, free of prevalent CV disease and with at least 12 months of follow-up. DM was defined according to ADA criteria. At the end of follow-up period (55.78 ± 42.5 months), 676 patients (14%) were on statins. These patients were older (62.54 ± 7.3 vs 57.91 ± 9.1 yrs; $p < 0.0001$), more often female (49% vs 41.2%; $p = 0.0001$), with higher initial total cholesterol (217.93 ± 44.3 vs 205.29 ± 36.6 mg/dl), non-HDL cholesterol (167.16 ± 44.5 vs 155.18 ± 36.7 mg/dl) and triglycerides (150.69 ± 85.2 vs 130.98 ± 72.0 mg/dl; all $p < 0.0001$) than patients no taking statins, without other differences in clinical and laboratory characteristics. At the end of follow-up, prevalence of DM was 18.1% among patients on statins and 7.2% among those without lipid-lowering therapy ($p < 0.0001$). However, incident DM was 10.2% in patients on statins and 8.7% in those free of statin therapy (NS).

☆ This work has been supported in part by grant AIFA: Italian agency of drugs. Supported in part by grant: AIFA/FARM5STRH9.
* Corresponding author. Department of Clinical and Experimental Medicine, Federico II University Hospital, via S. Pansini 5 bld 1, 80131 Naples, Italy. Tel.: +39 081 7462025.
E-mail address: simogi@unina.it (G. de Simone).

0939-4753/$ - see front matter
http://dx.doi.org/10.1016/j.numecd.2012.11.002

Conclusion: In real-life outpatient environment, statin prescription for primary prevention is not associated with increased risk of incident DM.

Clinical trial registration identifier: NCT01077037.

Introduction

Incidence of type 2 diabetes mellitus (DM) is increasing rapidly [1] and even high fasting glucose is associated with increased cardiovascular (CV) risk [2]. High blood pressure is also one of major causes of CV disease [3] and arterial hypertension is common in patients with DM. The relationship between hypertension and DM is complex; DM is a predictor of hypertension [4] and also occurs more frequently in patients with arterial hypertension [4], particularly in patients in whom antihypertensive therapy does not control blood pressure [5]. Because the frequent occurrence of hypertension combined with DM further increases the absolute risk of CV death [6], particular attention should be paid to the occurrence of DM in hypertensive patients in order to prevent rising CV risk.

Current guidelines for the management of arterial hypertension recommend that treatment with HMG-CoA reductase inhibitors (statins) be prescribed in all hypertensive subjects with diabetes or with high or very high CV risk, for both primary and secondary prevention [7]. Opposing to this recommendation, a meta-analysis has reported that statin therapy might be associated with 9% increase in incident DM [8], a finding that raised alarm. In this meta-analysis there was a substantial proportion of patients with coronary heart disease likely taking high doses of statins, according to recent guidelines and it is now becoming more evident that treatment with intensive doses of statins is associated with higher incidence of new-onset DM than low-to- moderate dose as prescribed for primary prevention [9].

It is still unclear whether statin therapy is associated with a generalized tendency to an increase in diabetes risk in a real-life clinical context and, specifically, there is no direct information about the problem whether statins can still be safely prescribed for primary CV prevention, especially in hypertensive patients who are at risk of developing DM.

Accordingly, this study has been designed to verify whether in a large cohort of hypertensive, non-diabetic patients, followed up in a tertiary care setting and subjected to a program of primary prevention, statin therapy is independently associated with an increased probability of new-onset DM.

Methods

Participants

The cohort of the CampaniaSalute Network was analyzed. Details on this cohort have been previously reported [10]. Briefly, beginning 1997, a network has been generated among the Hypertension Center of the Federico II University Hospital (Naples, Italy), 23 Community Hospital-based Hypertension Clinics and 60 General Practitioners from the Campania district in Southern Italy (CampaniaSalute Network) including over 12,000 cardiovascular (CV) patients, of whom 10,254 had arterial hypertension. Among hypertensive subjects at the time of the first examination in the outpatient clinic, 7097 were free of prevalent CV disease [10] (previous myocardial infarction or angina or procedures of coronary revascularization, stroke or transitory ischemic attack, congestive heart failure or chronic kidney disease more than grade 3 (glomerular filtration rate [GFR] $<$ 30 ml/min/1.73 m^2) [11]). Prevalent CV disease was excluded by an ad-hoc committee in the Hypertension Center, and based on patient's history and clinical exam, contact with the referring general practitioner or community hospital center and clinical records documenting the occurrence of disease [12].

Criteria for selection in the present study included the availability of at least 12 months of follow-up and the absence of diabetes at the time of the first visit in the Hypertension Clinic. From the initial population, 2347 patients were excluded: 1237 had a follow-up period or duration of statin therapy shorter than 1 year, 724 (i.e. 10%) were lost to follow-up, 386 had prevalent diabetes mellitus. Thus, 4750 Caucasian, non-diabetic hypertensive patients, (42.3% women, age 58.6 $\pm$ 9.0 years) free of prevalent CV disease were analyzed, who had been followed up over 55.8 $\pm$ 42.5 months.

All patients on statins had received the medication over at least one year without any suspension for the entire year before the end of follow-up. Statin therapy was censored at the time of the last visit before diagnosis of diabetes for patients with incident diabetes and at the time of the last available visit for patients without incident diabetes. Prescribed statins were: simvastatin 20 or 40 mg/die, atorvastatin 10 or 20 mg/die, rosuvastatin 10 mg/die.

The data-base generation of the CampaniaSalute Network was approved by the Federico II University Hospital Ethic Committee. Signed informed consent for the use of data for scientific purposes was obtained from all the participants.

Laboratory tests and definitions

Fasting plasma glucose and lipid profiles were measured by standard methods. Non-HDL cholesterol was also calculated as the difference between total and HDL cholesterol. Reported medical diagnostic codes for diabetes and prescriptions of oral hypoglycaemic drugs or insulin were used to identify prevalent cases of diabetes. Diagnosis of prevalent and incident diabetes was also confirmed by fasting plasma glucose $\geq$ 126 mg/dl, according to ADA guidelines [13].

GFR was estimated from serum creatinine by the modified MDRD equation [11]. Systolic and diastolic blood pressure (BP) were measured at each visit by standard sphygmomanometer after 5 min in the sitting position, according to European Society of Hypertension/European Society of Cardiology guidelines [7]. Body mass index (BMI) was calculated at each visit. Number and type of prescribed antihypertensive medications were recorded for all participants. Classes of medications were categorized as follows: anti-Renin–Angiotensin System (Anti-RAS: including ACE inhibitors and/or Angiotensin AT1 receptor antagonists), calcium-channel blockers (CCB), β-blockers, diuretics, according to their overall use during the individual follow-up, based on the frequency of prescription during the various control visits. At each control visit, prescription of statins was also recorded.

Statistical analysis

Data were analyzed using SPSS (version 17.0; SPSS, Chicago, IL) and expressed as mean ± 1 standard deviation. All variables deviating from normal distribution were log-transformed before parametric statistics. Patients with or without at least one year of statin therapy were initially compared using *t*-tests. Categorical variables were compared using chi-square statistics.

Hazard functions for incident DM were generated by Cox regression analysis comparing participants taking or not taking statins, adjusting for covariates, including BMI and all variables that significantly differed between the subgroups in exploratory statistics. These variables included: age, sex, BMI, fasting plasma glucose, duration of hypertension, BP, heart rate, non-HDL cholesterol and triglycerides at the time of the first visit. Cox regression was also repeated by including classes of antihypertensive medications and number of prescribed antihypertensive medications. To account for therapy, single classes of antihypertensive medications were dichotomized according to their overall use during the individual follow-up. Thus, as previously reported [5], antihypertensive *medications* that were prescribed for more than 50% of the total number of control visits were censored in the analysis. Two-tailed $p < 0.05$ was considered statistically significant. A post-hoc "compromise power analyses" (by GPower 3.0.10), based on the 9% difference in incidence found in the Sattar meta-analysis, the size of the two subpopulations and an optimized β/α ratio (i.e. $\beta = 0.80$ and $\alpha = 0.05$) was run, confirming a one-tail $\alpha = 0.052803$ and a $\beta = 0.847124$.

Results

Among the 4750 hypertensive outpatients included in the analysis, 42.3% were women; 39.7% were obese and 14.2% ($n = 676$) were on statin treatment.

Patients on statins were older, more often women, with longer duration of hypertension and follow-up period. At the time of initial visit, they had lower diastolic BP and heart rate, higher plasma levels of fasting glucose, total, non-HDL cholesterol and triglycerides (Table 1, all $0.005 < p < 0.0001$). No difference was found in BMI, creatinine, GFR and HDL cholesterol.

At the time of the last visit before diagnosis of DM, patients on statins had lower systolic and diastolic BP, heart rate, GFR, total and non-HDL cholesterol, and higher levels of fasting glucose, HDL cholesterol and triglycerides than patients not on statin therapy (Table 2, $0.05 < p < 0.0001$).

Table 3 shows that, before of diagnosis of DM, the number of prescribed antihypertensive *medications* was higher, and the single prescriptions of anti-RAS, diuretics and CCB more frequent in patients on statins than in those not taking statins ($0.03 < p < 0.0001$), whereas no difference was found for β-blockers.

Table 1 Initial characteristics of the study population (by statin prescription during the follow-up).

	No statins $N = 4074$	Statins $N = 676$	$p \leq$
Age (years)	57.91 ± 9.1	62.54 ± 7.3	0·0001
Gender (% women)	41.2%	49%	0.0001
BMI (kg/m^2)	27.74 ± 4.2	27.47 ± 3.9	NS
Duration of hypertension (years)	5.44 ± 6.3	7.20 ± 6.9	0.0001
Family history of diabetes	29.3	29.1	NS
Follow-up time (months)	54.99 ± 42.0	60.49 ± 45.1	0.002
Systolic BP (mmHg)	141.76 ± 17.1	141.85 ± 17.3	NS
Diastolic BP (mmHg)	90.21 ± 10.3	88.78 ± 10.1	0.001
Heart rate (bpm)	74.89 ± 11.5	73.56 ± 11.3	0.005
Fasting plasma glucose (mg/dl)	95.47 ± 12.4	96.62 ± 12.3	0.026
Creatinine (mg/dl)	0.96 ± 0.2	0.94 ± 0.2	NS
GFR_{MDRD} (ml/min/1.73 m^2)	79.99 ± 17.3	78.35 ± 17.0	NS
Cholesterol (mg/dl)	205.29 ± 36.6	217.93 ± 44.3	0.0001
HDL cholesterol (mg/dl)	50.07 ± 12.6	50.7 ± 12.6	NS
Non-HDL cholesterol (mg/dl)	155.18 ± 36.7	167.16 ± 44.5	0.0001
Triglycerides (mg/dl)	130.98 ± 72.0	150.69 ± 85.2	0.0001

Abbreviations: BMI: body max index, BP: blood pressure, GFR: glomerular filtration rate, MDRD: modification of diet in renal disease, HDL: high-density lipoprotein.

Table 2 Characteristics of the study population at the time of last visit in the absence of diabetes.

	No statins $N = 4074$	Statins $N = 676$	$p\leq$
BMI (kg/m^2)	27.85 ± 4.1	27.80 ± 4.0	NS
Systolic BP (mmHg)	132.65 ± 18.3	131.16 ± 15.9	0.046
Diastolic BP (mmHg)	82.59 ± 14.0	79.22 ± 8.9	0.0001
Heart rate (bpm)	72.71 ± 18.3	70.47 ± 10.5	0.002
Fasting plasma glucose (mg/dl)	95.47 ± 12.4	96.62 ± 12.3	0.026
Creatinine (mg/dl)	0.96 ± 0.3	0.94 ± 0.2	NS
GFR_{MDRD} (ml/min/1.73 m^2)	79.99 ± 17.3	78.35 ± 17.0	0.024
Cholesterol (mg/dl)	200.90 ± 4.5	192.38 ± 39.9	0.0001
HDL cholesterol (mg/dl)	50.34 ± 12.8	52.06 ± 13.4	0.001
Non-HDL cholesterol (mg/dl)	150.55 ± 44.1	140.31 ± 38.6	0.0001
Triglycerides (mg/dl)	129.41 ± 67.2	137.77 ± 65.7	0.003

Abbreviations: BMI: body max index, BP: blood pressure, GFR: glomerular filtration rate, MDRD: modification of diet in renal disease, HDL: high-density lipoprotein.

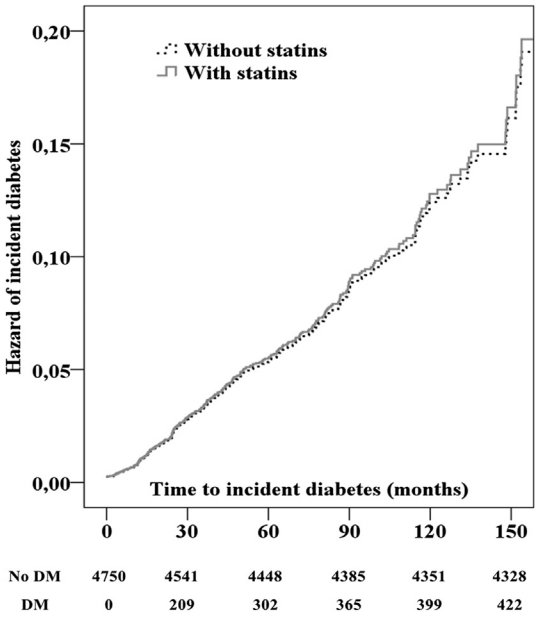

Figure 1 Incidence of type 2 diabetes in relation to statin therapy prescribed before diagnosis, adjusted for age, gender, duration of hypertension and baseline parameters (see Table 4).

At the end of follow-up, prevalence of diabetes was 18.1% in patients under statin therapy, compared to 7.2% in those without statin therapy (RR = 2.85; 95% CI = 2.28−3.56; $p < 0.0001$), but the unadjusted risk of incident diabetes in relation of prescribed statin therapy before diagnosis of diabetes was not significantly different, with 10.2% incidence among patients taking statins and 8.7% in patients free of the medication (RR = 1.02, $p = 0.192$).

In a Cox model, adjusted for gender, duration of hypertension, initial diastolic BP, heart rate, plasma glucose, total and non-HDL cholesterol and triglycerides, statin prescription was confirmed to be not associated with incident DM (Fig. 1). In this Cox model, predictors of incident diabetes during follow-up were older age, higher BMI, higher initial plasma glucose, total cholesterol and triglycerides, and duration of hypertension (Table 4). The Cox model was repeated after addition of classes of antihypertensive medications and number of prescribed antihypertensive medications confirmed exactly the model displayed in Table 4 with negligible variations of coefficients of regression (not shown).

Table 3 Frequency of antihypertensive prescription in >50% of visit.

	No statins $N = 4074$	Statins $N = 676$	$p\leq$
Thiazides (%)	39.3	49.6	0.032
β-Blockers (%)	30.7	30.9	NS
ANTI-RAS (%)	63.2	78	0.001
CCB (%)	24.9	32.1	0.001
Mean number of medications	1.58	1.87	0.0001

Discussion

In contrast to what has been suggested in a metanalysis [8], this study demonstrates that statin therapy, at least performed at the doses used for primary prevention, is not associated with incident DM. We analyzed a representative and relatively unselected large cohort of hypertensive patients free of prevalent CV disease and followed in our

Table 4 Cox model showing baseline predictors of new-onset type 2 diabetes in hypertensive, non-diabetic patients. The model includes age, gender, use of statins before diagnosis of diabetes, duration of hypertension and baseline parameters.

	$p\leq$	HR	95% CI
Statin before diagnosis of DM (y/n)	0.832	1.03	0.79−1.35
Age (years)	0.002	1.02	1.01−1.04
Initial triglycerides (×10 mg/dl)	0.000	1.02	1.01−1.03
Initial diastolic BP (×5 mmHg)	0.290	1.03	0.98−1.07
Gender (m/f)	0.108	1.19	0.96−1.48
Initial BMI (kg/m^2)	0.000	1.054	1.03−1.08
Duration of hypertension (×5 years)	0.020	1.10	1.02−1.16
Initial HR (bpm)	0.659	1.00	0.99−1.07
Initial fasting glucose (mg/dl)	0.0001	1.46	1.41−1.55
Initial cholesterol (×5 mg/dl)	0.025	0.95	0.93−0.99
Initial non-HDL cholesterol (mg/dl)	0.284	1.01	1.00−1.01

Abbreviations: DM: type 2 diabetes mellitus, BMI: body max index, BP: blood pressure, HR: heart rate, HDL: high-density lipoprotein.

tertiary care unit. This finding is consistent with another meta-analysis showing that the risk of incident DM is associated with high-dose statin therapy (usually given for secondary prevention programs) rather than low—moderate dose [9].

As largely expected, in cross-sectional analyses, statins were more often prescribed in patients with prevalent DM and high CV risk. The strength of this analysis is the examined context, which reflects the physician behavior in real life. Because all patients of the CampaniaSalute network are referred to our Center, the risk of a selection bias is minimized. Despite the improvement in CV prevention and the reduction of mortality and morbidity for CV events during the past decades, public health burden due to CV risk remains high. Statin therapy is generally considered to be effective and safe in reducing CV events [14,15].

Despite the consolidated evidence of lack of serious major side effects [9,16—18], several large trials [19—22] have reported an association between statin therapy and development of diabetes, thus raising doubts on this particular metabolic aspect of statin safety. However, this association was not confirmed in other intervention studies [23,24]. In addition, in a relatively tiny sample of hyperlipidemic patients, including patients on high-dose statins, with or without coronary heart disease, a significant, though modest, increase in circulating insulin levels was seen after 6 weeks of treatment in the absence of deterioration of glucose control [25].

The relevance of the problem and the contradictory findings led to calls for a systematic exploration of the possible effect of statin therapy on incident diabetes [26].

To contribute clarifying the uncertainty produced by those contrasting results, a meta-analysis was performed taking into account published and unpublished data from large placebo-controlled and standard-care-controlled statin trials. Results from this meta-analysis suggested that statin therapy could be in fact associated with an overall tiny 9% increased risk for incident diabetes [8] in a context, however, in which all the other potential confounders could not be considered, including prevalence of CV disease, different med dose, and co-morbidities.

In contrast, in our cohort all patients were free of prevalent CV disease and received statins at low—moderate doses, as suggested by the usual clinical practice, and all potential confounders were taken into account. Therefore, our study is the first direct evidence that in a large, relatively unselected clinical sample of hypertensive, non-diabetic outpatients, free of prevalent CV disease and subjected to a primary prevention program, therapy with statins is not associated with increased risk of new-onset DM, also when major risk factors and confounders are considered over a follow-up of 1—10 years. The strength of this analysis is in the clinical characteristics of this outpatient population, which can be easily generalized in similar contexts.

The different prevalence in diabetes rates recorded cross-sectionally at the end of follow-up between the two subpopulations confirms that statin was given mostly to patients with more severe and long-standing hypertension and worse metabolic profile, thus at higher risk of diabetes [5] and, it is, therefore, relevant that despite the increased risk of diabetes and after accounting for the different initial risk-profile, statins do not exhibit independent effect on incident diabetes, at least at the doses we used for our primary prevention program.

The information, is, therefore, *mostly* applicable *to hypertensive population*. This type of analysis, in this context reflecting real behavior of doctors, is increasingly valorized by the widely emerging position of medical researchers and even political leaders, highlighting the unsuccessful translation of a number of findings from research papers into medical practice and personal physician's behavior [27].

The second strength of our study is that our design is prospective, and therefore scarcely affected by selection bias. Rather, a potential bias, favoring the possible rejection of our null hypothesis was the tendency to prescribe statin therapy in patients who have a greater risk of developing diabetes, as evident in our cross-sectional analysis.

Sometimes meta-analysis reports are contradicted by large population studies [28], due to the known limitations [29—32]. Focusing the attention on the reported meta-analysis [8], it is even important to highlight that only two of the 13 analyzed studies reported a statistical association between statin therapy and incident DM, and one of the two was also the largest. Secondly, many trials reported opposite results even using the same type of statin [8,23]. Thirdly, in the Sattar's meta-analysis, the 95% confidence interval of odds ratios has been used, whereas the 99% confidence interval could be preferentially estimated, as it has been suggested [33]. Thus, the small difference (9%) in the incidence of DM could have been occurred by chance. Lastly, most trials in this meta-analysis analyzed clinical situation requiring use of high-dose statins, in contrast with our study performed in a clinical context of primary prevention program.

Our study offsets, at least in part, the lack of trials specifically addressed to evaluate the effect of long-term use of low—moderate dose statin on incident diabetes in primary prevention programs.

In our hypertensive cohort, a number of risk factors confirmed to be predictors of incident DM [5], including older age, initial impaired fasting glucose and lipid profile, and duration of hypertension. Furthermore the results of the present study suggest that statin therapy, at the doses used for primary prevention programs, is safe and does not increase the risk of incident DM. Our results also indicate that in a real-life context, prescriptions are more frequent in patients after development of diabetes and in those at high risk of diabetes. Our findings are mostly applicable to hypertensive population, in a real-life context reflecting real behavior of doctors. This context is increasingly valorized by the widely emerging position of medical researchers and even political leaders, highlighting the unsuccessful translation of a number of findings from research papers into medical practice and personal physician's behavior [27].

Limitations

A potential limitation of the study, common in studies performed using registries in real-life contexts, is that

diagnosis of diabetes was based on fasting glucose levels only, as we do not have oral glucose tolerance test as a primary work-up test in all patients. However, because our purpose was to select patients with normal glucose metabolism, probably selection based on impaired fasting glucose is more conservative than selection based on glucose tolerance test, which appears to be a higher level of metabolic abnormality [34].

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.numecd.2012.11.002.

References

[1] Zimmet P, Alberti KG, Shaw J. Global and societal implications of the diabetes epidemic. Nature 2001;414:782—7.

[2] Danaei G, Lawes CM, Vander Hoorn S, Murray CJ, Ezzati M. Global and regional mortality from ischaemic heart disease and stroke attributable to higher-than-optimum blood glucose concentration: comparative risk assessment. Lancet 2006;368:1651—9.

[3] Ezzati M, Lopez AD, Rodgers A, Vander Hoorn S, Murray CJ. Selected major risk factors and global and regional burden of disease. Lancet 2002;360:1347—60.

[4] Brancati FL, Kao WH, Folsom AR, Watson RL, Szklo M. Incident type 2 diabetes mellitus in African American and white adults: the atherosclerosis risk in communities study. JAMA 2000;283:2253—9.

[5] Izzo R, de Simone G, Chinali M, Iaccarino G, Trimarco V, Rozza F, et al. Insufficient control of blood pressure and incident diabetes. Diabetes Care 2009;32:845—50.

[6] Stamler J, Vaccaro O, Neaton JD, Wentworth D. Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the multiple risk factor intervention trial. Diabetes Care 1993;16:434—44.

[7] Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G, et al. Guidelines for the management of arterial hypertension: the task force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens 2007;25:1105—87.

[8] Sattar N, Preiss D, Murray HM, Welsh P, Buckley BM, de Craen AJ, et al. Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. Lancet 2010;375:735—42.

[9] Preiss D, Seshasai SR, Welsh P, Murphy SA, Ho JE, Waters DD, et al. Risk of incident diabetes with intensive-dose compared with moderate-dose statin therapy: a meta-analysis. JAMA 2011;305:2556—64.

[10] De Luca N, Izzo R, Iaccarino G, Malini PL, Morisco C, Rozza F, et al. The use of a telematic connection for the follow-up of hypertensive patients improves the cardiovascular prognosis. J Hypertens 2005;23:1417—23.

[11] Hallan S, Asberg A, Lindberg M, Johnsen H. Validation of the modification of diet in renal disease formula for estimating GFR with special emphasis on calibration of the serum creatinine assay. Am J Kidney Dis 2004;44:84—93.

[12] de Simone G, Izzo R, Chinali M, De Marco M, Casalnuovo G, Rozza F, et al. Does information on systolic and diastolic function improve prediction of a cardiovascular event by left ventricular hypertrophy in arterial hypertension? Hypertension 2010;56:99—104.

[13] Report of the expert committee on the diagnosis and classification of diabetes mellitus. Diabetes Care 1997;20:1183—97.

[14] Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet 2005;366:1267—78.

[15] Kearney PM, Blackwell L, Collins R, Keech A, Simes J, Peto R, et al. Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: a meta-analysis. Lancet 2008;371:117—25.

[16] Cannon CP, Braunwald E, McCabe CH, Rader DJ, Rouleau JL, Belder R, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. N Engl J Med 2004;350:1495—504.

[17] LaRosa JC, Grundy SM, Waters DD, Shear C, Barter P, Fruchart JC, et al. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. N Engl J Med 2005;352:1425—35.

[18] Armitage J. The safety of statins in clinical practice. Lancet 2007;370:1781—90.

[19] Collins R, Armitage J, Parish S, Sleigh P, Peto R. MRC/BHF heart protection study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. Lancet 2003;361:2005—16.

[20] Kjekshus J, Apetrei E, Barrios V, Bohm M, Cleland JG, Cornel JH, et al. Rosuvastatin in older patients with systolic heart failure. N Engl J Med 2007;357:2248—61.

[21] Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto Jr AM, Kastelein JJ, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med 2008;359:2195—207.

[22] Sever PS, Dahlof B, Poulter NR, Wedel H, Beevers G, Caulfield M, et al. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian cardiac outcomes trial—lipid lowering arm (ASCOT-LLA): a multicentre randomised controlled trial. Lancet 2003;361:1149—58.

[23] Freeman DJ, Norrie J, Sattar N, Neely RD, Cobbe SM, Ford I, et al. Pravastatin and the development of diabetes mellitus: evidence for a protective treatment effect in the West of Scotland coronary prevention study. Circulation 2001;103:357—62.

[24] Keech A, Colquhoun D, Best J, Kirby A, Simes RJ, Hunt D, et al. Secondary prevention of cardiovascular events with long-term pravastatin in patients with diabetes or impaired fasting glucose: results from the LIPID trial. Diabetes Care 2003;26:2713—21.

[25] Thongtang N, Ai M, Otokozawa S, Himbergen TV, Asztalos BF, Nakajima K, et al. Effects of maximal atorvastatin and rosuvastatin treatment on markers of glucose homeostasis and inflammation. Am J Cardiol 2011;107:387—92.

[26] Yusuf S, Lonn E, Bosch J. Lipid lowering for primary prevention. Lancet 2009;373:1152—5.

[27] Lenfant C. Shattuck lecture — clinical research to clinical practice — lost in translation? N Engl J Med 2003;349:868—74.

[28] Egger M, Smith GD. Misleading meta-analysis. BMJ 1995;311:753—4.

[29] Easterbrook PJ, Berlin JA, Gopalan R, Matthews DR. Publication bias in clinical research. Lancet 1991;337:867—72.

[30] Egger M, Smith GD. Bias in location and selection of studies. BMJ 1998;316:61—6.

[31] Egger M, Zellweger-Zahner T, Schneider M, Junker C, Lengeler C, Antes G. Language bias in randomised controlled trials published in English and German. Lancet 1997;350:326—9.

[32] Gotzsche PC. Reference bias in reports of drug trials. Br Med J (Clin Res Ed) 1987;295:654—6.

[33] Sheikh K. Statins and risk of incident diabetes. Lancet 2010;375:2139—40. author reply 41—2.

[34] Tooke JE. Microvascular function in human diabetes. A physiological perspective. Diabetes 1995;44:721—6.