Baseline diabetes as a way to predict CV outcomes in a lipid-modifying trial: a meta-analysis of 330,376 patients from 47 landmark studies

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Abstract

Background: Diabetes is a major cardiovascular risk factor. However, its influence on the rate of occurrence of cardiovascular (CV) events during a clinical trial that included a diabetes subgroup has not yet been quantified.

Aims: To establish equations relating baseline diabetes prevalence and incident CV events, based on comparator arms data of major lipid-modifying trials.

Methods: Meta-analysis of primary outcomes (PO) rates of key prospective trials, for which the baseline proportion of diabetics was reported, including studies having specifically reported CV outcomes within their diabetic subgroups.

Results: 47 studies, representing 330,376 patients (among whom 124,115 diabetics), were analyzed as regards the relationship between CV outcomes rates (including CHD) and the number of diabetics enrolled. Altogether, a total of 18,445 and 16,156 events occurred in the comparator and treatment arms, respectively. There were significant linear relationships between diabetes prevalence and both PO and CHD rates (%/year): y = 0.0299*x + 3.12 [PO] (p = 0.0128); and y = 0.0531*x + 1.54 [CHD] (p = 0.0094), baseline diabetes predicting PO rates between 3.12 %/year (no diabetic included) and 6.11 %/year (all patients diabetic); and CHD rates between 1.54 %/year (no diabetic) and 6.85 %/year (all patients diabetic). The slopes of the equations did not differ according to whether they were derived from primary or secondary prevention trials.

Conclusions: Absolute and relative CV risk associated with diabetes at inclusion can be readily predicted using linear equations relating diabetes prevalence to primary outcomes or CHD rates.

Keywords: Diabetes, Cardiovascular, Coronary heart disease, Clinical trial, Residual risk, Lipids

Introduction

Key prospective trials have demonstrated the effectiveness of long-term control of conventional risk factors (RFs) to prevent cardiovascular (CV) events. Next to decreasing tobacco use and physical inactivity, indisputable gains were achieved by targeting hypertension and hypercholesterolemia. Nevertheless, there remained a high residual risk of incident CV events in control and comparator arms of these trials, even in patients receiving appropriate standard of care [1–4]. This residual risk is driven by non-modifiable RFs (age; gender; familial or genetic features; and diabetes) and by modifiable conventional or emerging RFs (eg. atherogenic dyslipidemia; remnant lipoproteins; hyperglycaemia; hyperinsulinaemia; metabolic syndrome; subclinical inflammation; and chronic kidney disease).

Based on epidemiology and prospective studies, type 2 diabetes mellitus (T2DM) significantly increases the absolute risk of developing coronary heart disease (CHD), and confers a higher residual risk of large and small vessel damage. In the microcirculation, such risk is directly related to hyperglycaemia, whereas in large vessels, this residual risk is linked to hypertension, low-density lipoproteins (LDL); non-LDL dyslipidemias; and other metabolic comorbidities [5–10]. As a result, having T2DM, either individually or at
a sub-group level (within a cohort or population) increases residual CV risk to an extent that needs to be determined. Since residual risk varies considerably from one study to another, such an evaluation would require going beyond comparing CV outcomes rates in diabetic vs. non-diabetic subgroups of individual trials.

The aim of this work was to establish equations relating baseline diabetes prevalence and incident CV events, based on comparator arms data of major clinical trials having investigated the potential CV benefit of various pharmacological or dietary interventions targeting, in the vast majority, lipids and lipoproteins. We performed a systematic meta-analysis of CV outcomes rates of those key prospective studies, for which the baseline proportion of diabetics was reported and, where available, studies having reported CV outcomes of diabetic subgroups [11–90] (Table 1).

Patients and methods

To be selected for inclusion, major clinical trials with CV outcomes had to meet three requirements: (i) the main purpose of the trial was to study the effect on CHD of a pharmacological or dietary intervention targeting lipids or lipoproteins, with CHD rates as sole primary outcome (PO), or with a major adverse CV event (MACE) composite PO comprising CHD; (ii) to focus exclusively on diabetic patients, or (iii) to report data on a sufficient number of diabetic patients from pre-/post-hoc analyses of DM subgroups of the main trial. Among studies conducted non-exclusively in DM patients, eligible trials had to comply with ≥1 of the following criteria: (i) the main trial had a subgroup of patients already diagnosed with DM at baseline, whose proportion was deemed sufficiently representative (≥15 %); or (ii) the trial enrolled at least 100 DM patients, regardless of on-study new-onset diabetes.

For each study, the following items were analyzed: CV risk category at baseline (primary prevention [PP], secondary prevention [SP] or mixed [PP-SP]); number of patients included; number and proportion of patients with DM at baseline; number of patients in the active or comparator arms; duration of follow-up; age at inclusion; number of males; DM type and duration; HbA1c; total cholesterol (TC); low-density lipoprotein cholesterol (LDL-C); high-density lipoprotein cholesterol (HDL-C); non-HDL-cholesterol (non-HDL-C); apolipoprotein B (apoB); triglycerides (TG); type of pharmacological or dietary intervention; primary trial outcome; CHD outcomes (see Table 2 for CV outcomes categories); and CV events number and rates for each trial.

Results

Forty-seven studies were selected based on the criteria defined above [11–90]. They accounted for a total of 330,376 patients. The median year of publication for all studies was 2005. Table 1 describes, for each study, the acronym’s definition; the CV prevention category; the cohort size and the number or proportion of diabetic at baseline; the number of patients randomized in the active or comparator arms; the follow-up duration; and publication year. For all studies, mean age (ISD) was 61.7 (6.4) years, and the proportion of males was 74 (17 %). Regarding ethnicity, the majority of patients studied were Caucasian (median 86.5 % [between-study range (BSR 0 %)–99.2 %] Three studies [JELIS; MEGA; and PROFIT-J] included only Japanese patients [59, 66, 74]. Among studies, 8 of 47 (17 %; n = 42,279) enrolled patients in PP at baseline; 17 of 47 (36 %; n = 131,425) included populations whose CV risk was a mix of PP and SP; and 22 of 47 (47 %; n = 156,672) were SP trials. Lipid values at baseline were (mg/dL): 209 (34) [TC]; 126 (32) [LDL-C]; 44 (7) [HDL-C]; 161 (32) [non-HDL-C]; 99 (19) [apoB] and 162 (27) [TG]. In total, these studies have included 124,115 diabetic patients, representing 42.1 % [BSR 2.3 %–100 %] of the population studied. For studies that reported diabetes duration, it averaged 7.5 (4.9) years, whereas metabolic control assessed by Hba1c was 7.49 (0.68) % (Table 3). The trials investigated the following interventions over a mean (ISD) duration of 4.4 (1.9) years [BSR: 1.0–13.3 years]: statins (42 trials); fibrates (9 trials); n-3 fatty acids and/or traditional Mediterranean diet (5 trials); niacin (4 trials); CETP-inhibitor (2 trials); PPAR-γ agonist (2 trials); ezetimibe (1 trial); PPAR-α/γ agonist (1 trial); and Lp-PLA2 inhibitor (1 trial) (Table 4).

For all 47 studies, a total of 18,445 and 16,156 events occurred in the comparator and treatment arms, respectively. On an annual basis, this was equivalent to an average rate of occurrence for the primary CV outcome of 3.6 (2.4) %/year [BSR 0.5–11.8] (comparator) and 3.0 (1.9)%/year [BSR 0.3–9.1] (treatment), respectively (Table 4). The slopes of the equations relating PO rates (y) to diabetes prevalence (x) did not differ according to whether they were derived from PP or SP trials: thus, for PP trials y = 0.0208 x + 0.53 (R2 = 0.6369; p = 0.0058), whereas y = 0.0267 x +3.76 (R2 = 0.1436; p = 0.0464) for SP trials.

When comparing PO rates from the comparator arms of studies published prior to 2005 vs. those published ≥2005, average PO incidence decreased from 3.7 %/year [<2005] to 2.7 %/year [≥2005] for non-diabetic patients, ie. absolute and relative reductions of 1 % and 28 % (NS). For diabetic patients, the event rate decreased from 5.0 %/year [<2005] to 4.2 %/year [≥2005] (p = 0.007).
Table 1: Overview of 47 landmark prospective clinical trials with CV outcomes having included a substantial number and/or proportion of diabetic patients at baseline

| CV prevention Patients | Diabetes Patients | Diabetes proportion | Active arm Patients | Comparator arm Patients | Follow-up years | Publication year | Reference |
|------------------------|-------------------|---------------------|---------------------|-------------------------|-----------------|------------------|-----------|
| n                      | n                 | %                  | n                   | n                       |                 |                  |           |
| 4D PP-SP               | 1255              | 100                | 619                 | 636                     | 4.0             | 2005             | [11]      |
| 4S SP                  | 4444              | 2                  | 2221                | 2223                    | 5.4             | 1994             | [12–14]   |
| diabetes substudy SP   | 202               | 100                | 105                 | 97                      | 5.4             | 1997             | [14]      |
| ACCORD-Lipid PP-SP     | 5518              | 100                | 2766                | 2753                    | 4.7             | 2010             | [15, 16]  |
| ADDITION-Europe PP-SP  | 3055              | 100                | 1678                | 1377                    | 5.3             | 2011             | [17, 18]  |
| AFCAPS/TexCAPS PP      | 6605              | 5                  | 3304                | 3301                    | 5.2             | 1998             | [19, 20]  |
| AIM-HIGH SP            | 3414              | 34                 | 1718                | 1696                    | 3.0             | 2011             | [21, 22]  |
| AleCardio SP           | 7226              | 100                | 3616                | 3610                    | 2.0             | 2014             | [23, 24]  |
| ALERT PP-SP            | 2102              | 19                 | 1050                | 1052                    | 5.1             | 2003             | [25]      |
| ALLHAT-LLT PP-SP       | 10355             | 35                 | 5170                | 5185                    | 4.8             | 2002             | [26]      |
| Alpha-Omega SP         | 4837              | 36                 | 2404                | 2433                    | 3.4             | 2010             | [27]      |
| ASCOT-LLA PP           | 10305             | 25                 | 5168                | 5137                    | 3.3             | 2003             | [28, 29]  |
| diabetes substudy PP   | 2532              | 100                | 1258                | 1274                    | 3.3             | 2005             | [29]      |
| ASPEN SP               | 2410              | 1211               | 1199                | 4.0                     | 2006             | [30]             |           |
| AURORA PP-SP           | 2773              | 1389               | 1384                | 3.8                     | 2009             | [31, 32]         |           |
| diabetes substudy PP   | 731               | 388                | 343                 | 2.8                     | 2011             | [32]             |           |
| BIP SP                 | 3090              | 1548               | 1542                | 6.2                     | 2000             | [33, 34]         |           |
| CARDS PP               | 2838              | 1428               | 1410                | 3.9                     | 2004             | [35]             |           |
| CARE SP                | 4159              | 2081               | 2078                | 5.0                     | 1998             | [36–38]          |           |
| diabetes substudy SP   | 586               | 282                | 304                 | 5.0                     | 1998             | [38]             |           |
| CDP (clofibrate) SP    | 3892              | 1103               | 2789                | 6.2                     | 1975             | [39, 40]         |           |
| CDP (niacin) SP        | 3908              | 1119               | 2789                | 6.2                     | 1975             | [39, 40]         |           |
| dal-OUTCOMES SP        | 15871             | 7938               | 7933                | 2.6                     | 2012             | [41, 42]         |           |
| DIS PP                 | 761               | 379                | 382                 | 5.0                     | 1991             | [43]             |           |
| FIELD PP-SP            | 9795              | 4895               | 4900                | 5.0                     | 2005             | [44–46]          |           |
| GISSI-Prevenzione SP   | 4271              | 2138               | 2133                | 2.0                     | 2000             | [47]             |           |
| GREACE SP              | 1600              | 880                | 720                 | 3.0                     | 2002             | [48, 49]         |           |
| diabetes substudy SP   | 313               | 161                | 152                 | 3.0                     | 2003             | [49]             |           |
| HATS SP                | 107               | 73                 | 34                  | 3.0                     | 2001             | [50]             |           |
| HHS PP                 | 4081              | 2051               | 2030                | 5.0                     | 1987             | [51, 52]         |           |
| diabetes substudy PP   | 135               | 59                 | 76                  | 5.0                     | 1992             | [52]             |           |
| HPS - MRC/BHF PP-SP    | 20536             | 10269              | 10267               | 5.0                     | 2002             | [53, 54]         |           |
| diabetes substudy PP   | 5963              | 2978               | 2985                | 4.8                     | 2003             | [54]             |           |
| HPS2-THRIVE SP         | 25673             | 12835              | 12835               | 3.9                     | 2013             | [55]             |           |
| IDEAL SP               | 8888              | 4449               | 4449                | 4.8                     | 2005             | [56, 57]         |           |
| ILLUMINATE PP-SP       | 15067             | 7533               | 7534                | 1.0                     | 2007             | [58]             |           |
| JELIS PP-SP            | 18645             | 9326               | 9319                | 4.6                     | 2007             | [59]             |           |
| LEADER PP-SP           | 1568              | 783                | 785                 | 4.6                     | 2002             | [60, 61]         |           |
| LIPID SP               | 9014              | 4512               | 4502                | 6.1                     | 1998             | [62–64]          |           |
| LIPS SP                | 1677              | 844                | 833                 | 3.9                     | 2002             | [65]             |           |
| MEGA PP                | 7832              | 3866               | 3966                | 5.3                     | 2006             | [66]             |           |
Among these, 33 trials, totaling 259,151 patients, are described below as *predominantly non-diabetes studies* [12–14, 19–22, 25–29, 31–34, 36–42, 47–66, 68–70, 75, 78–80, 82–90] (Table 1). The mean age was 61.4 (5.5) years [BSR 47.0–75.0], and the proportion of males was 78.6 (17.8) % [BSR 31.4–100]. Among *predominantly non-diabetes studies*, 4 of 33 (12 %) enrolled patients who were in PP at baseline; 9 of 33 (27 %) included mixed populations whose CV risk was either PP or SP; and 20 of 33 (61 %) were clinical trials in SP only. Lipid values at baseline were (mg/dL): 212 (38) [TC]; 129 (36) [LDL-C]; 44 (7) [HDL-C]; 165 (36) [non-HDL-C]; 98 (21) [apoB] and 160 (25) [TG]. In total, these studies have included 63.189 diabetic patients, representing 21.3 % [BSR 2.3 %–44.2 %] of the population studied (Table 1; Table 3). These *predominantly non-diabetes studies* investigated the following interventions over a mean (1SD) duration of 4.3 (1.5) years [BSR: 1.0–7.5 years]: statins (19 trials); fibrates (6 trials); n-3 fatty acids (2 trials); niacin (4 trials); CETP-inhibitor (2 trials); ezetimibe (1 trial); and Lp-PLA2 inhibitor (1 trial) (Table 4).

### Table 1 Overview of 47 landmark prospective clinical trials with CV outcomes having included a substantial number and/or proportion of diabetic patients at baseline (Continued)

| Study | Type | Total (n) | Mean age | Mean (1SD) duration | Proportion of diabetic patients at baseline | Proportion of males at baseline | Mean (%a) | 10-year CV risk reduction | R | Mean difference in % | SD | 95% CI |
|-------|------|-----------|----------|---------------------|------------------------------------------|-------------------------------|----------|------------------------|---|----------------------|----|--------|
| ORIGIN | PP-SP | 12536 | 61.4     | 4.3 (1.5)           | 3.2                                      | 65.0                          | 3.2      | 10.4                   | 2.3 | -0.7                 | 1.7 | -2.7 to -0.2 |
| PERFORM | SP | 19120 | 61.4     | 4.3 (1.5)           | 3.2                                      | 65.0                          | 3.2      | 10.4                   | 2.3 | -0.7                 | 1.7 | -2.7 to -0.2 |
| Post-CABG | SP | 1501 | 61.4     | 4.3 (1.5)           | 3.2                                      | 65.0                          | 3.2      | 10.4                   | 2.3 | -0.7                 | 1.7 | -2.7 to -0.2 |

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CV: cardiovascular; PP and SP: primary and secondary prevention. Acronyms: 4D: Die Deutsche Diabetes Dialyse studie; 4S: Scandinavian Simvastatin Survival Study; ACCORD-Lipid: Action to Control Cardiovascular Risk in Diabetes - Lipid arm; ADDITION-Europe: Anglo-Danish-Dutch Study of Intensive Treatment in People with Screen Detected Diabetes in Primary Care; AFCAPS/TexCAPS: Air Force/Texas Coronary Atherosclerosis Prevention Study; AIM-HIGH: Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes; ALECardio: A Safety and Efficacy Study to Evaluate the Potential of Aleglitazar to Reduce CV Risk in CHD Patients with a Recent ACS and T2DM; ALERT: Assessment of Lescol in Renal Transplantation; ALLHAT-LLT: Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial; ASCOT-LLA: Anglo-Scandinavian Cardiac Outcomes Trial - Lipid Lowering Arm; ASPEN: Atorvastatin as Prevention of CHD Endpoints in Patients with Non-insulin dependent diabetes mellitus; AURORA: A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: an Assessment of Survival and Cardiovascular Events; BIP: Bezafibrate Infarction Prevention; CARDS: Collaborative Atorvastatin Diabetes Study; CARE: Cholesterol and Recurrent Events; CDP: Coronary Drug Project; dal-OUTCOMES: Efficacy and safety of dalcetrapib in patients with recent acute coronary syndrome; DEI: Diabetes Intervention Study; FIELD: Fenofibrate Intervention and Event Lowering in Diabetes; GISSI-Prevenzione: Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto miocardico - Prevenzione; GREACE: Greek Atorvastatin and Coronary-heart-disease Evaluation; HAT5: HDL-Atherosclerosis Treatment Study; HHS: Helsinki Heart Study; HPS: MRC/BHF: Medical Research Council and British Heart Foundation Heart Protection Study; HP52-THRIVE: Heart Protection Study - Treatment of HDL to Reduce the Incidence of Vascular Events; IDEAL: Incremental Decrease in End Points Through Aggressive Lipid Lowering Trial; ILLUMINATE: Investigation of Lipid Level Management to Understand its Impact in Atherosclerosis Events; JELIS: Japan EPA Lipid Intervention Study; LEADER: Lower Extremity Arterial Disease Event Reduction; LIPID: Long-term Intervention with Pravastatin in Ischaemic Disease; LIPS: Lescol Intervention Prevention Study; MEGA: Primary Prevention of Cardiovascular Disease with Pravastatin in Japan; ORIGIN: Outcome Reduction with an Initial Glargine Intervention; PERFORM: Prevention of cerebrovascular and cardiovascular Events of Ischaemic origin with telmisartan in patients with a history of ischaemic stroke or transient ischaemic attack; Post-CABG (FU): Post Coronary Artery Bypass Graft Trial (follow-up); PREDMED: Prevenzione con Dieta Mediterranea; PROACTIVE: PROspective pioglitAzone Clinical Trial In macrovascular Events; PROFIT-3: Primary Prevention on High risk Type 2 diabetes in Japan; PROSPER: Prospective Study of Pravastatin in the Elderly at Risk; RPS: Risk and Prevention Study; SHARP: Study of Heart and Renal Protection; STABILITY: STAbilization of Atherosclerotic plaque By Initiation of darapLadIb TherapY; STENO-2: STENO-2 Study; TNT: Treating to New Targets; VA C: Veterans Affairs Cooperators Study of Atherosclerosis; VA HIT: Veterans Affairs High-Density Lipoprotein Intervention Trial; VA-HIT: Veterans Affairs High-Density Lipoprotein Intervention Trial; VA Cooperative Study: VA Cooperative Study of Atherosclerosis, Neurology Section; VA-HIT: Veterans Affairs High-Density Lipoprotein Intervention Trial.
Within DSS, 2 of 9 (22%) enrolled patients who were in PP at baseline; 2 of 9 (22%) included mixed populations whose CV risk was either PP or SP; and 5 of 9 (56%) were clinical trials in SP only. Lipid values at baseline were (mg/dL): 200 (19) [TC]; 118 (16) [LDL-C]; 46 (6) [HDL-C]; 154 (19) [non-HDL-C]; and 165 (32) [TG] (Table 3). The DSS have investigated the following interventions over a mean (1SD) duration of 4.8 (2.7) years [BSR: 1.8–13.3 years]: statins (5 trials); fibrates (4 trials); n-3 fatty acids and/or traditional Mediterranean diet (3 trials); PPAR-γ agonist (2 trials) and PPAR-α/γ agonist (1 trial) (Table 4).

Among the 33 predominantly non-diabetic studies, a total of 14,732 and 12,604 events occurred in the comparator and treatment arms, respectively. On an annual basis, this was equivalent to an average rate of occurrence for the primary CV outcome of 3.8 (2.4) %/year [BSR 0.5–11.8] (comparator) and 3.1 (1.8) %/year [BSR 0.3–7.5] (treatment), respectively.

Amongst the 9 DSS, a total of 1,469 and 1,119 events occurred in the comparator and treatment arms, respectively. On an annual basis, this was equivalent to an average rate of occurrence for the primary CV outcome of 6.1 (3.0) %/year [BSR 2.1–10.8] (comparator) and 4.0 (2.1) %/year [BSR 0.7–7.8] (treatment), respectively.

Among the 14 studies focusing on diabetes, a total of 3,713 and 3,552 events occurred in the comparator and treatment arms, respectively. On an annual basis, this was equivalent to an average rate of occurrence for the primary CV outcome of 3.3 (2.5) %/year [BSR 1.1–9.6] (comparator) and 2.9 (2.4) %/year [BSR 0.8–9.1] (treatment), respectively.

In addition to PO rates, which include de facto CHD, we also examined CHD rate as a separate outcome [Table 4 and Fig. 1 left panels]. Rates of CHD were issued for 21 trials and DSS for comparator and treatment arms, and amounted to [%/year]: 11.1 and 7.2 [4S-DSS]; 1.3 and 0.9 [ACFAPPS/TexCAPS]; 1.5 and 1.0 [ASCOT-LLA]; 5.1 and 4.9 [AURORA]; 5.8 and 5.4 [BIP]; 12.0 and 9.3 [CARE-DSS]; 4.9 and 4.5 [CDP (clofibrate)]; 4.9 and 4.1 [CDP (niacin)]; 2.4 and 1.7 [HPS - MRC/BHF]; 2.6 and 2.0 [HPS - MRC/BHF-DSS]; 1.4 and 1.3 [HPS2-THRIVE]; 5.0 and 4.2 [IDEAL]; 2.0 and 2.4 [ILLUMINATE]; 0.8 and 0.6 [JELIS]; 3.1 and 2.5 [LEADER]; 0.5 and 0.3 [MEGA]; 1.0 and 0.9 [SHARP]; 4.3 and 4.0 [STABILITY]; 1.7 and 1.4 [TNT]; 2.6 and 2.1 [TNT-DSS]; and 1.9 and 1.7 [VA Cooperative Study] (Fig. 1; right panels).

The relationship between proportion of diabetic patients at inclusion and PO or CHD rates was inferred on
| Study                          | Age (years) | Males (%) | Diabetes type & duration (years) | HbA1c (%) | TC (mg/dL) | LDL-C (mg/dL) | HDL-C (mg/dL) | Non-HDL-C (mg/dL) | apoB (mg/dL) | TG (mg/dL) |
|-------------------------------|-------------|-----------|---------------------------------|-----------|------------|---------------|---------------|-----------------|-------------|-----------|
| 4D                            | 66          | 54        | T2DM                            | 18        | 6.7        | 218           | 125           | 36              | 182         | ~         | 261       |
| 4S                            | 59          | 81        | ~                               |           | 260        | 188           | 46            | 214             | ~           | 132       |
| diabetes substudy            | 60          | 78        | ~                               |           | 259        | 186           | 43            | 216             | ~           | 150       |
| ACCORD-Lipid                 | 62          | 69        | T2DM                            | 10        | 8.3        | 175           | 100           | 38              | 137         | ~         | 164       |
| ADDITION-Europe              | 60.3        | 58        | T2DM                            | 0         | 7          | 214           | 133           | 46              | 168         | ~         | 146       |
| AFCAPS/TexCAPS               | 58          | 85        | T1DM; T2DM                      |           |            | 221           | 150           | 37              | 184         | ~         | 158       |
| AIM-HIGH                      | 64          | 85        | ~                               |           | 6.7        | 146           | 74            | 35              | 111         | 83        | 168       |
| AleCardio                    | 60.8        | 73        | T2DM                            | 8.6       | 7.8        | 152           | 79            | 42              | 110         | ~         | 152       |
| ALERT                        | 50          | 66        | ~                               |           |            | 247           | 158           | 50              | 197         | ~         | 195       |
| ALLHAT-LLT                   | 66          | 51        | T2DM                            |           |            | 224           | 146           | 48              | 176         | ~         | 152       |
| Alpha-Omega                  | 69          | 78        | ~                               |           |            | 183           | 100           | 50              | 133         | ~         | 146       |
| ASCOT-LLA                    | 63          | 81        | ~                               |           |            | 212           | 131           | 50              | 162         | ~         | 150       |
| diabetes substudy            | 63.6        | 76        | T2DM                            |           |            | 205           | 128           | 46              | 159         | ~         | 168       |
| ASPEN                        | 61          | 66        | T2DM                            | 8         | 7.8        | 194           | 113           | 47              | 147         | ~         | 147       |
| AURORA                       | 64          | 62        | ~                               |           |            | 176           | 100           | 45              | 131         | 82        | 157       |
| diabetes substudy            | 65          | 66        | ~                               |           |            | 174           | 97            | 43              | 131         | ~         | 168       |
| BIP                          | 60          | 91        | T2DM                            |           |            | 212           | 148           | 35              | 177         | ~         | 145       |
| CARDS                        | 62          | 68        | T2DM                            | 8         | 7.9        | 207           | 117           | 54              | 153         | 117       | 173       |
| CARE                         | 59          | 86        | ~                               |           |            | 209           | 139           | 39              | 170         | ~         | 156       |
| diabetes substudy            | 61          | 80        | ~                               |           |            | 206           | 136           | 38              | 168         | ~         | 164       |
| CDP (clofibrate)             | 100         | ~         | ~                               |           | ~          | ~             | ~             | ~               | ~           | 183       |
| CDP (niacin)                 | 100         | ~         | ~                               |           | ~          | ~             | ~             | ~               | ~           | 183       |
| dal-OUTCOMES                 | 60.2        | 81        | ~                               |           |            | 145           | 76            | 42              | 103         | 81        | 134       |
| DIS                          | 46          | 56        | T2DM                            | 0         |            | 218           | ~             | ~               | ~           | ~         | 157       |
| FIELD                        | 62          | 63        | T2DM                            | 5         | 6.9        | 195           | 119           | 43              | 152         | 97        | 173       |
| GISSI-Prevenzione            | 60          | 86        | T2DM (79 %) T1DM (21 %)         |           |            | 229           | 152           | 46              | 183         | ~         | 166       |
| GREACE                       | 79          | ~         | ~                               |           |            | 264           | 193           | 39              | 225         | ~         | 159       |
| diabetes substudy            | 55          | 56        | T2DM (92 %) T1DM (8 %)          | 10.5      | 7.5        | 271           | 189           | 35              | 236         | ~         | 221       |
| HATS                         | 53          | 87        | ~                               |           |            | 200           | 128           | 30              | 170         | 119       | 219       |
| HHS                          | 47          | 100       | ~                               |           |            | 270           | 189           | 47              | 223         | ~         | 175       |
| diabetes substudy            | 49          | 100       | T2DM                            | 4.5       |            | 292           | 200           | 46              | 246         | ~         | 214       |
| HPS - MRC/BHF                | 75          | ~         | ~                               |           |            | 228           | 131           | 41              | 187         | 114       | 186       |
| diabetes substudy            | 62.1        | 70        | T2DM (90 %) T1DM (10 %)         | 27        | 7          | 220           | 124           | 41              | 179         | 110       | 204       |
| HPS2-THRIVE                  | 64.9        | 82.7      | ~                               |           |            | 128           | 63            | 44              | 84          | 68        | 127       |
| IDEAL                        | 62          | 81        | ~                               |           |            | 197           | 122           | 46              | 151         | 119       | 151       |
| ILLUMINATE                   | 61.3        | 77.8      | T2DM                            |           |            | 157           | 80            | 49              | 108         | 73        | 127       |
| JELIS                         | 61          | 31.4      | ~                               |           |            | 275           | 181           | 59              | 216         | ~         | 153       |
| LEADER                       | 68          | 100       | ~                               |           |            | 218           | 131           | 46              | 172         | ~         | 213       |
| LIPID                        | 62          | 83        | ~                               |           |            | 218           | 150           | 36              | 182         | 133       | 142       |
| LIPS                         | 60          | 84        | T2DM; T1DM                      |           |            | 200           | 131           | 38              | 162         | ~         | 160       |
| MEGA                         | 58.3        | 32        | ~                               |           |            | 242           | 157           | 58              | 184         | ~         | 128       |
the basis of the comparator and treatment arms data from the 33 predominantly non-diabetic studies, including where appropriate the rates for the corresponding DSS, i.e. 259,151 patients. Both for PO and CHD, there was a highly significant linear relationship between the proportion of diabetics enrolled and events rates, both in comparator arms (p = 0.0128 [PO] and p = 0.0094 [CHD]; Fig. 1; upper panels) and active arms (p = 0.0470 [PO] and p = 0.0272 [CHD]; Fig. 1; lower panels). When comparing the slopes of the equations between PO and the proportion of diabetes at baseline in the comparator arm of studies published < 2005 and from 2005 to 2014, they rose from 0.0129 to 0.0162, i.e. a relative increase of 26 % (not shown). Such relationships were more pronounced as regards CHD events, exhibiting steeper gradients than those of PO rates, with slope coefficients higher by a relative 78 % [comparator arms] and 110 % [treatment arms].

Vis-à-vis the comparator arms, the slopes of the relationships between proportions of diabetics and events rates in the treatment arms of the same studies were attenuated, by a relative 45 % [PO rates] and 34 % [CHD events] (Fig. 1; lower panels).

By relating incidence rates of PO and CHD in the treatment arms, it appears that the proportion of diabetics at inclusion predicts PO rates ranging from 2.65 %/year (no diabetic included) to 4.31 %/year (all patients diabetic). Predicted CHD rates based on diabetes prevalence ranged from 1.64 %/year (no diabetic included) to 5.13 %/year (all patients diabetic). It follows that a cohort exclusively composed of diabetic patients would present an on-treatment PO rate increased by an absolute 1.7 %/year solely due to the presence of DM at baseline. Such an absolute increase in events rate due to diabetes would further increase to 3.5 %/year for incident CHD risk (Fig. 1; lower panels).

The comparison of these equations linking the proportion of diabetics and outcome rates in comparator vs. treatment arms allows for determining whether being diabetic (apart from the observation that it increases the absolute rate of occurrence of CV events) is associated with an idiosyncratic on-treatment clinical response. As for PO and CHD, diabetic patients were characterized by a clinical response that was better than that calculated for a non-diabetic population that would have been subject to the same therapeutic interventions. Thus, residual CV risk
| Study                  | Intervention | Primary; secondary CV outcomes | Events (n) treatment | Events (%) treatment | Rate (%.year-1) treatment | Events (n) control | Events (%) control | Rate (%.year-1) control | HR 95 % CI for HR | P       |
|-----------------------|--------------|--------------------------------|----------------------|---------------------|---------------------------|---------------------|---------------------|---------------------------|-----------------|---------|
| 4D                    | statin C; D + J | 226 | 36.5 | 9.13 | 243 | 38.2 | 9.55 | 0.96 | 0.77-1.1 | 0.37 |
| 4S                    | statin A | 182 | 8.2 | 1.52 | 256 | 11.5 | 2.13 | 0.71 | 0.58-0.85 | 0.0003 |
| diabetes substudy     | statin A | 15 | 14.3 | 2.65 | 24 | 24.7 | 4.58 | 0.58 | NR | 0.087 |
| ACCORD-Lipid          | statin C; J + D | 291 | 10.5 | 2.24 | 310 | 11.3 | 2.40 | 0.93 | 0.79-1.08 | 0.32 |
| ADDITION-Europe       | statin/other B; D + J + M + Z | 121 | 7.2 | 1.36 | 117 | 8.5 | 1.60 | 0.85 | 0.65-1.05 | 0.12 |
| AFCAPS/TexCAPS        | statin C; E | 116 | 3.5 | 0.68 | 183 | 5.5 | 1.07 | 0.63 | 0.50-0.79 | <0.001 |
| AIM-HIGH              | niacin C; G + J + H + M | 282 | 16.4 | 5.47 | 274 | 16.2 | 5.39 | 1.02 | 0.87-1.21 | 0.8 |
| AleCardio             | PPAR-α/γ C; D + J | 344 | 9.5 | 4.76 | 360 | 10.0 | 4.99 | 0.95 | 0.83-1.11 | 0.57 |
| ALERT                 | statin C; G + J + M | 112 | 10.7 | 2.09 | 134 | 12.7 | 2.50 | 0.84 | 0.64-1.06 | 0.14 |
| ALLHAT-LLT            | statin A | 631 | 12.2 | 2.54 | 641 | 12.4 | 2.58 | 0.99 | 0.89-1.11 | 0.88 |
| Alpha-Omega n-3 fatty acids | B | 336 | 14.0 | 4.11 | 335 | 13.8 | 4.05 | 1.02 | 0.87-1.17 | 0.93 |
| ASCOT-LLA             | statin J + G | 100 | 1.9 | 0.59 | 154 | 3.0 | 0.91 | 0.65 | 0.50-0.83 | 0.0005 |
| diabetes substudy     | statin B | 116 | 9.2 | 2.79 | 151 | 11.9 | 3.59 | 0.78 | 0.61-0.98 | 0.04 |
| ASPEN                 | statin C; D + J + M + O + L | 166 | 13.7 | 3.43 | 180 | 15.0 | 3.75 | 0.91 | 0.73-1.12 | 0.34 |
| AURORA                | statin C; J + D | 396 | 28.5 | 7.50 | 408 | 29.5 | 7.76 | 0.97 | 0.84-1.11 | 0.59 |
| diabetes substudy     | statin C; G + J | 85 | 21.9 | 7.82 | 104 | 30.3 | 10.83 | 0.72 | 0.51-0.90 | 0.008 |
| BIP                   | fibrate C; K + J + P | 211 | 13.6 | 2.20 | 232 | 15.0 | 2.43 | 0.91 | NR | 0.26 |
| CARDS                 | statin C; H + M + T | 83 | 5.8 | 1.49 | 127 | 9.0 | 2.31 | 0.65 | 0.48-0.83 | 0.001 |
| CARE                  | statin G + J | 212 | 10.2 | 2.04 | 274 | 13.2 | 2.64 | 0.77 | 0.09-0.36 | 0.003 |
| diabetes substudy     | statin G + J + M | 81 | 28.7 | 5.74 | 112 | 36.8 | 7.37 | 0.78 | NR | <0.0001 |
| CDP (clofibrate)      | fibrate A | 281 | 25.5 | 4.11 | 709 | 25.4 | 4.10 | 1.00 | 0.89-1.0 | 0.09 |
| CDP (niacin)          | niacin A | 273 | 24.4 | 3.93 | 709 | 25.4 | 4.10 | 0.96 | 0.85-1.08 | 0.005 |
| dal-OUTCOMES CETP inhibitor | C; G + J + L + O | 656 | 8.3 | 3.20 | 633 | 8.0 | 3.09 | 1.04 | 0.93-1.16 | 0.52 |
| DIS                   | fibrate E | 32 | 8.4 | 1.69 | 31 | 8.1 | 1.62 | 1.04 | NR | NR |
| FIELD                 | fibrate C; B + D + I + M | 256 | 5.2 | 1.05 | 288 | 5.9 | 1.18 | 0.89 | 0.75-1.05 | 0.16 |
| GISSI-Prevenzione     | statin C; A + I | 120 | 5.6 | 2.77 | 136 | 6.4 | 3.15 | 0.88 | 0.71-1.15 | 0.41 |
| GREACE                | statin C; A + J + L + Q + M | 112 | 12.7 | 4.24 | 180 | 25.0 | 8.33 | 0.51 | <0.0001 |
| diabetes substudy     | statin C; A + J + L + Q + M | 20 | 12.4 | 4.14 | 46 | 30.3 | 10.09 | 0.41 | NR | <0.0001 |
| HATS                  | statin + niacin | 7 | 9.6 | 3.20 | 12 | 35.3 | 11.76 | 0.27 | NR | 0.02 |
| HHS                   | fibrate C; K + J + G | 56 | 2.7 | 0.55 | 84 | 4.1 | 0.83 | 0.66 | 0.08-0.53 | <0.02 |
| diabetes substudy     | fibrate C; K + J + G | 2 | 3.4 | 0.68 | 8 | 10.5 | 2.11 | 0.32 | NR | 0.19 |
| HPS - MRC/BHF         | statin C; A + G | 1328 | 12.9 | 2.59 | 1507 | 14.7 | 2.94 | 0.88 | 0.81-0.94 | 0.0003 |
| diabetes substudy     | statin E + B | 601 | 20.2 | 4.20 | 748 | 25.1 | 5.22 | 0.81 | 0.19-0.30 | <0.0001 |
| HPS2-THRIVE           | niacin C; G + M | 1696 | 13.2 | 3.39 | 1758 | 13.7 | 3.51 | 0.96 | 0.90-1.03 | 0.29 |
Persisting after treatment was further reduced in case of diabetes, in a relative proportion of 14.4% [PO] and 31.2% [CHD], respectively (Fig. 1; upper and lower panels).

Discussion
This meta-analysis shows that the presence of diabetics in a lipid-modifying trial is a determinant of CV events rate, the impact of which can be accurately assessed once known the proportion of diabetics enrolled, regardless of the CV risk category at baseline. Thus, the linear equations derived from this meta-analysis can be used to determine the absolute and relative enhancement of CV risk related to the inclusion of diabetics in a trial. Conversely, these algorithms can be used to estimate the proportion of diabetics to be included when designing a prospective study, in order to achieve a given number of CV events.

Major guidelines recognize a higher risk of CHD in DM patients, even in situations of primary prevention, as compared to non-diabetic subjects. The events rates in the comparator arms of randomized controlled trials and the meta-analyses of key statin trials show that CHD risk from hypercholesterolemia in non-diabetic

Table 4 Primary CV outcome rates in the active (treatment) and control (comparator/placebo) arms (Continued)

| Study | Intervention | Group | Total (n) | Mean | 95% CI | p-value |
|-------|--------------|-------|----------|------|--------|---------|
| IDEAL | statin       | C; G + J + O | 411      | 9.3  | 1.93   | 463     | 10.4    | 2.17  | 0.89 | 0.78-1.01 | 0.07 |
| ILLUMINATE | CETP inhibitor | C; G + J + L | 464      | 6.2  | 6.16   | 373     | 5.0    | 4.95  | 1.24 | 1.09-1.44 | 0.001 |
| JELIS | n-3 fatty acids | E; P; I; L; M; A | 262     | 2.8  | 0.61   | 324     | 3.5    | 0.76  | 0.81 | 0.69-0.95 | 0.01 |
| LEADER | fibrate      | E      | 150      | 19.2 | 4.95   | 160     | 20.4   | 5.20  | 0.95 | 0.76-1.21 | 0.72 |
| LIPID | statin       | G      | 287      | 6.4  | 1.04   | 373     | 8.3    | 1.36  | 0.77 | 0.12-0.35 | <0.001 |
| LIPS | statin       | C; G + J + M | 181     | 21.4 | 5.50   | 222     | 26.7   | 6.83  | 0.80 | 0.64-0.95 | 0.01 |
| MEGA | statin       | C; I + L + M + P | 66      | 1.7  | 0.32   | 101     | 2.5    | 0.48  | 0.67 | 0.49-0.91 | 0.01 |
| ORIGIN | n-3 fatty acids | D; D + J + U; A; T; M + W; Q; L; Z | 574     | 9.1  | 1.47   | 581     | 9.3    | 1.50  | 0.98 | 0.87-1.10 | 0.72 |
| PERFORM | antiplatelet | D; I   | 1091     | 11.4 | 4.83   | 1062    | 11.1   | 4.71  | 1.03 | 0.94-1.12 | NS  |
| Post-CABG | statin | C; D + J + M | 207      | 30.6 | 4.08   | 271     | 40.1   | 5.35  | 0.76 | NR         | 0.04 |
| PREDIMED | TMD     | C; D + I | 179      | 3.6  | 0.80   | 109     | 4.4    | 1.12  | 0.71 |
| PROACTIVE | glitazone | C; A + J + H + M | 514     | 19.7 | 6.80   | 572     | 21.7   | 7.49  | 0.91 | 0.80-1.02 | 0.1  |
| PROFIT-J | glitazone | C; A + J | 9       | 3.8  | 2.09   | 10      | 4.0    | 2.20  | 0.95 | 0.427-2.593 | 0.91 |
| PROSPER | statin       | C; G + J | 408      | 14.1 | 4.41   | 473     | 16.2   | 5.07  | 0.87 | 0.74-0.97 | 0.01 |
| RPS | n-3 fatty acids | D      | 733      | 11.7 | 2.35   | 745     | 11.9   | 2.38  | 0.99 | 0.88-1.08 | 0.64 |
| SHARP | statin/ezetimibe | C; J + G + M | 526     | 11.3 | 2.31   | 619     | 13.4   | 2.73  | 0.84 | 0.74-0.94 | 0.0021 |
| STABILITY | Lp-PLA2-inhibitor | C; D + J + U | 769     | 9.7  | 2.62   | 819     | 10.4   | 2.80  | 0.94 | 0.85-1.03 | 0.2  |
| STENO-2 | statin/fibrate | A      | 24       | 30.0 | 2.26   | 40      | 50.0   | 3.76  | 0.60 | 0.32-0.89 | 0.02 |
| TNT | statin       | C; G + J + O + T | 434     | 8.7  | 1.77   | 548     | 10.9   | 2.23  | 0.79 | 0.69-0.89 | <0.001 |
| diabetes substudy | statin | C; G + J + O + T | 103     | 13.7 | 2.79   | 135     | 18.0   | 3.68  | 0.76 | 0.58-0.97 | 0.026 |
| VA Cooperative Study | fibrate | A + B | 22       | 8.2  | 4.56   | 30      | 11.4   | 6.31  | 0.72 | 0.43-1.22 | NR  |
| VA-HIT | fibrate      | C; J + G | 219     | 17.3 | 3.40   | 275     | 21.7   | 4.26  | 0.80 | 0.07-0.35 | 0.006 |
| diabetes substudy | fibrate | C; J + G | 96      | 25.5 | 4.99   | 141     | 36.0   | 7.05  | 0.71 | 0.53-0.88 | 0.004 |
| Total (n) | 16156    | 18445 |          |      |        |        |        |      |      |        |      |
| Mean | 12.2      | 3.0    |          | 14.8  | 3.6    | 0.85   |

*: see legend to Table 1 for study acronyms definition; §§: see Table 2 for CV outcomes definition; §§§: ±antioxidants; CETP: cholesteryl ester transfer protein; CI: confidence interval; CV: cardiovascular; HR: hazard ratio; LpPLA2: lipoprotein-associated phospholipase A2; NR: not reported; NS: non significant; PPAR: peroxisome proliferator-activated receptor; TMD: traditional Mediterranean diet.
patients is proportional to baseline LDL-C level. This is also the case for type 2 DM patients, with the additional aggravating fact that this linear relationship was shifted upward compared to non-diabetics. This underlies current recommendations for effective lowering of LDL-C as the major modifiable lipid risk factor for CHD in diabetic patients.

It should be noted that mean PO rate in studies focusing on diabetes was considerably lower (~46%) than the risk that would be determined for diabetics if included,
as a subgroup, in a clinical trial not focusing on diabetes. This follows from the fact that studies focusing on diabetes had a lower CV risk at inclusion, as well as lesser PO or CHD events during the study. As a result, the impact of DM on CV events must be qualified according to whether it is evaluated from diabetic subgroups of cohorts followed in cardiology (mostly in a macrovascular setting), or whether it is obtained in patients from clinical trials focusing on nutrition or diabetes (usually dealing with glycemic control or microvascular risk reduction). In addition, variation in residual risk related to T2DM in key trials may result from inhomogeneity in inclusion criteria; varying baseline CV risk; individual differences in diabetes duration or severity; and heterogeneous RFs exposure among diabetics.

As opposed to what occurs in microvessels, and unlike a widely held view about it, residual risk targeting large vessels is related to a limited extent only by hyperglycaemia in (pre)diabetes states. Rather, the accrued macrovascular risk is associated with the common form of T2DM (that is to say the one that expresses a MetS phenotype, including insulin resistance and hyperinsulinemia). The common pathogenic factors underlying the observed association between hyperglycaemia and CHD are involved either (i) at the onset of diabetes (promoting B-cell decompensation or altering one or two variable(s) of the hyperbolic product between insulin secretion and insulin sensitivity), and/or (ii) because they embody cardiometabolic comorbidities that increase the macrovascular risk regardless of glucose levels.

It should be noted that the slopes of the relationships between CV events and percentage of included diabetics were less marked when it came to comparing PO vs. CHD events rates, both in comparator and treatment arms, on one hand, or when it came to comparing PO or CHD events rates in treated arms vs. comparator arms, on the other hand. These observations suggest (i) that the presence of diabetes at baseline has less adverse effect on the occurrence of certain constituents of the PO, such as all-cause deaths or coronary revascularization; and (ii) that diabetic patients derive more benefits from the different treatment approaches studied than non-diabetic patients as regards the occurrence of macrovascular events [91]. In this meta-analysis, we have not distinguished between studies on the basis of pharmacological or nutritional interventions, since we based our findings on patients from comparator arms, usually receiving a placebo or standard care. When comparing less recent (published <2005) and more contemporary studies (published ≥2005), a decrease in absolute and relative events rates was observed (~28 % and -1 % respectively), suggestive of a reduction in exposure to CV RFs over time and/or of improved overall CV management. Such changes were however not significant and further, diabetic patients benefited less from this trend, reducing the absolute and relative rates by only -14 % and -0.7 %. It seemed therefore appropriate to include all studies in this analysis regardless of publication year.

It is noteworthy that the increased risk of CV events due to the presence of a subgroup of diabetics had a pretty similar slope, whatever the CV risk category at baseline. It follows that the excess CV risk associated with the inclusion of people with diabetes in a lipid-modifying trial is relatively independent of study design, expanding the applicability of equations derived from this meta-analysis. There exists a positive relationship between biomarkers and occurrence of CV events [92]; our meta-analysis suggests that documenting the frequency of enlisted T2DM patients can also be used as surrogate biomarker predicting a non-modifiable component of residual CV risk. Considering that our analysis focused on populations enrolled in the comparator arms of mostly LMT studies, it would be interesting to determine the impact on residual risk arising from enlistment of diabetics in clinical trials testing several interventions in primary care [93].

This study has several limitations. Firstly, the risk estimates attributed to DM were not adjusted for age or other CV RFs comorbid to T2DM and, as in all systematic collection of published data, there is always a potential bias related to publications [94]. Secondly, the adequacy of these equations to predict CV outcomes has not been independently validated in a prospective context. Thirdly, for reasons related to the design and reporting of individual studies, it was not feasible to derive specific equations applicable to T1DM vs. T2DM subgroups, or to newly-diagnosed vs. long-standing T2DM patients [95]. We were not able to analyze the potential influence of glycaemic control in diabetic subgroups at baseline, due to the low reporting rate of HbA1c values [96]. Finally, we did not examine, for reasons of brevity, the relationship between diabetes prevalence and non-CHD outcomes, such as HF, which will require dedicated meta-analyses [97].

Conclusion
This study attempted to quantify the impact of diabetes on the occurrence of CV events during a lipid-modifying trial, based on the proportion of known diabetics included. The component of absolute and relative residual CV risk associated with diabetes can be measured from linear equations relating diabetes prevalence to primary outcomes or CHD rates. Such calculations may help clinical study designers when selecting inclusion criteria; cohort size; and planned diabetics’ enrollment, so as to achieve sufficient CV events over time.

Abbreviations
apoB: apolipoprotein B100; BSR: Between-study range; CETP: Cholesteryl ester transfer protein; CHD: Coronary heart disease; CV: Cardiovascular; DM: Diabetes mellitus; DSS: Diabetes substudy; HbA1c: glycated hemoglobin;
HDLC: High-density lipoprotein; HDL-C: High-density lipoprotein cholesterol; LDL-L: Low-density lipoproteins; LDL-C: Low-density lipoprotein cholesterol; Lp-PLA2: Lipoprotein-associated phospholipase A2; non-HDL-C: non-high-density lipoprotein cholesterol; NS: Non-significant; PO: Primary outcome; PP: Primary prevention; PPAR: Peroxisome proliferator-activated receptor; RF: Risk factor; SD: Standard deviation; SP: Secondary prevention; T1DM: Type 1 diabetes mellitus; T2DM: Type 2 diabetes mellitus; TG: Triglycerides (triacylglycerols).

Competing interests
The authors declare that they have no competing interests.

Authors’ contributions
All authors contributed equally to the manuscript. M.P.H., S.A.A. and M.F.R. designed the study, set up and manage the database, and performed the statistical analyses. E.B. and K.D.A. participated in study design development and helped to draft the manuscript. All authors read and approved the final manuscript.

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