Nicholas, J; Charlton, J; Dregan, A; Gulliford, MC; (2013) Recent HbA1c Values and Mortality Risk in Type 2 Diabetes. Population-Based Case-Control Study. PloS one, 8 (7). ISSN 1932-6203 DOI: https://doi.org/10.1371/journal.pone.0068008

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Introduction

Diabetes represents a major public health concern and efforts to control hyperglycaemia are an important element of the management of patients with type 2 diabetes [1]. Hyperglycaemia is measured using haemoglobin A1c (HbA1c) test which assesses the average level of blood glucose in the preceding 60–120 days. For diabetes patients an HbA1c target of 6.5% (<8 mmol/mol) is recommended [2,3] on the basis that lowers the risk of developing diabetic complications (i.e. kidney disease, heart disease). The UK Prospective Diabetes Study (UKPDS) established that intensive control of blood glucose in type 2 diabetes reduced the risk of microvascular complications, especially diabetic retinopathy, in patients with type 2 diabetes [4]. While the UKPDS did not find any effect of intensive blood glucose lowering on cardiovascular events, these were also found to be reduced during post-trial follow-up [5]. A systematic review of five trials confirmed that cardiovascular events were reduced through intensive control [6]. However, hypoglycaemia is recognized as a hazard of intensive therapy, being more frequent in intensively treated patients [7]. Recent evidence suggests that hypoglycaemia may also be associated with adverse vascular events and all-cause mortality [7,8]. The ACCORD study [9] found that intensive lowering of blood glucose (HbA1c target of 6.0%) was not associated with reduced cardiovascular events, but there was an increase in all-cause mortality in type 2 diabetic subjects at high risk of cardiovascular disease (CVD). A subsequent analysis of data from the ADVANCE study [10] suggested that there might be a threshold for the beneficial effect of glucose lowering with no benefit observed from reducing HbA1c below 7% for macro-vascular events and mortality or below 6.5% for microvascular events [11].

Recently, Currie et al. [12] reported that either very high or very low HbA1c increased the risk of all-cause mortality in a large cohort of patients routinely treated in UK primary care. Their primary analysis did not allow for changes in HbA1c over time and instead used the mean of all HbA1c values subsequent to the index date. Although further time dependent analysis were carried out using yearly mean HbA1c, missing data was dealt with using multiple imputation of missing HbA1c values the AOR was 1.20 (CI: 1.12,1.28). The complete case analysis gave an AOR for HbA1c >9.0% of 1.51 (CI: 1.33, 1.70), in the multiple imputation analysis this was 1.29 (1.17,1.41). The risk associated with HbA1c <6.5% was age dependent. In the multiple imputation analysis the AOR was 1.53 (CI: 0.84 to 2.79) at age <55 years but 1.04 (CI: 0.92, 1.17) at age 85 years and over. In non-randomised data, values of HbA1c that are either <6.5% or >9.0% may be associated with increased mortality within one year in clinical type 2 diabetes. Relative risks may be higher at younger ages.

Abstract

This study aimed to evaluate mortality within 365 days of HbA1c values of <6.5% or >9.0% in participants with clinical type 2 diabetes mellitus. A matched nested case-control study was implemented, within a cohort of participants with type 2 diabetes from 2000 to 2008. Conditional logistic regression was used to model the odds ratio for mortality adjusting for comorbidity and drug utilisation. There were 97,450 participants with type 2 diabetes; 16,585 cases that died during follow up were matched to 16,585 controls. The most recent HbA1c value was <6.5% (48 mmol/mol) for 22.2% of cases and 24.2% of controls, the HbA1c was >9.0% for 9.0% of cases and 7.7% of controls. In a complete case analysis, the adjusted odds ratio (AOR) for mortality associated with most recent HbA1c <6.5% was 1.31 (95% confidence interval (CI): 1.21,1.42). After multiple imputation of missing HbA1c values the AOR was 1.20 (CI: 1.12,1.28). The complete case analysis gave an AOR for HbA1c >9.0% of 1.51 (CI: 1.33, 1.70), in the multiple imputation analysis this was 1.29 (1.17,1.41). The risk associated with HbA1c <6.5% was age dependent. In the multiple imputation analysis the AOR was 1.53 (CI: 0.84 to 2.79) at age <55 years but 1.04 (CI: 0.92, 1.17) at age 85 years and over. In non-randomised data, values of HbA1c that are either <6.5% or >9.0% may be associated with increased mortality within one year in clinical type 2 diabetes. Relative risks may be higher at younger ages.

Citation: Nicholas J, Charlton J, Dregan A, Gulliford MC (2013) Recent HbA1c Values and Mortality Risk in Type 2 Diabetes. Population-Based Case-Control Study. PLoS ONE 8(7): e68008. doi:10.1371/journal.pone.0068008

Editor: Heiner K. Berthold, Charité University Medicine Berlin, Germany

Received February 14, 2013; Accepted May 24, 2013; Published July 5, 2013

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Funding: This research was supported by the National Institute for Health Research (NIHR) Biomedical Research Centre at Guy’s and St Thomas’ NHS Foundation Trust and King’s College London. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health. Access to the GPRD database was funded through the Medical Research Council’s license agreement with MHRA. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: The authors have declared that no competing interests exist.

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underlined the importance of establishing whether age-specific treatment criteria would be appropriate. This study aimed to evaluate short-term associations between HbA1c values recorded in clinical practice in primary care and subsequent risk of mortality in a post-UKPDS population. A case control study was implemented to establish an explicit temporal link between HbA1c values recorded in the previous 365 days and mortality risk, rather than utilizing HbA1c records that might cover a considerable length of time, as has been done previously [12]. We aimed to determine whether the risk of mortality was higher when the most recent HbA1c value in the preceding 365 days was either <6.5% or >9.0% compared to HbA1c values that were between 6.5% and 9%. Considering the scarce evidence for a possible age-depended influence of HbA1C levels on mortality [14], an additional aim of the present study was to explore potential age-associated differences in mortality rates for both low and high HbA1C levels.

Methods

A nested case-control study was implemented using data from family practices contributing to the Clinical Practice Research Datalink (CPRD, formerly known as the General Practice Research Database) between 1 July 2000 and 30 April 2008. The CPRD contains comprehensive information on patients’ medical diagnoses, drug prescriptions, lifestyle advice, specialist referrals, laboratory tests, hospital admissions, and clinical findings (i.e. BMI, smoking, and blood pressure). For entry into the GPRD, practice data must be up to standard (UTS) for research as set out by the GPRD group. The validity of CPRD data for diagnoses and prescribing has been documented in several studies [15,16]. Data for the present study was based on a research project developed in 2009 and thus the latest available data for analysis was to the end of December, 2008.

The case-control study was nested in a cohort of people with type 2 diabetes. A case-control design was preferred because it is more efficient than a cohort design for a rare outcome such as mortality. The study also intended to validate Currie et al.'s [12] findings by using a different approach to design. Participants were included in the cohort if they had ever been diagnosed with diabetes mellitus, or prescribed oral hypoglycemic drugs or insulin. Date of diabetes onset was defined as the earlier of first recorded medical or referral code for diabetes or first date of prescription of oral hypoglycemic drugs or insulin. Participants were excluded if they had ever been diagnosed with type 1 diabetes mellitus; were aged less than 30 years at diabetes onset; or were prescribed insulin within 180 days of diabetes onset. Participant follow-up started from the later of: date of onset of diabetes, date of registration with a CPRD practice, date at which the practice began contributing practice data must be up to standard (UTS) for research as set out by the GPRD group. The validity of CPRD data for diagnoses and prescribing has been documented in several studies [15,16]. Data for the present study was based on a research project developed in 2009 and thus the latest available data for analysis was to the end of December, 2008.

Cases were participants who died while on follow-up in the cohort. For each eligible case, one control was randomly selected from the study cohort matched by gender, age category (<35, 35 to 44, 45 to 54, 55 to 64, 65 to 74, 75 to 84, 85+ years), and time since cohort entry (<90; 90 to 179; 180 to 364, 365+ days). Additional matching variables were considered unnecessary and might have resulted in overmatching. In addition, the study was sufficiently large to allow regression adjustment for multiple confounding variables [17]. One control per case was preferred as with large sample sizes as in the present study there is little gain in statistical power by including more than one control per case [18]. Each control was assigned the index date of their matched case.

Statistical Analysis

Data were analyzed using conditional logistic regression in Stata MP version 11.2 (Stata corporation, College Station, Texas, USA) to estimate the association of mortality with low and high HbA1c levels using normal HbA1c level as the reference category. The initial model included adjustment only through matching (gender, age, time since cohort entry). The final model adjusted for all confounders listed above. The confounders were entered into the model as categorical explanatory variables. In order to evaluate effect modification, analyses were also carried out stratified by age group (age at index date: <55, 55–64, 65–74, 75–84, 85+ years). As with the primary analysis, conditional logistic regression models were fitted with and without adjustment for possible confounders of the relationship between HbA1c and mortality.
Missing Data

Initial models used complete case analysis and included only matched sets where both the case and control had a valid HbA1c test result within the 365 days prior to the index date. For models examining change in HbA1c values, the complete case analysis included only matched sets where both the case and control had two valid HbA1c test results within the 365 days prior to the index date.

To evaluate the impact of missing data, multiple imputation was used to replace any missing values for the most recent two HbA1c tests. Multiple imputation was used to replace missing values for smoking status and BMI for patients without a record of these data in the previous 365 days. Multiple imputation was preferred because it is superior to other missing data approaches (i.e. mean replacement, last observation) even in situations where a large proportion of the data is missing [22]. Also, removing patients with missing data from the study (i.e. listwise) would result in a significant loss of the study sample, raising concerns about the validity of the results [23]. Data were imputed using multiple imputation by chained equations, which allows an appropriate imputation model to be defined for each variable. The “mi impute chained” command in Stata was used to implement predictive mean matching for HbA1c tests, and multinomial logistic regression for smoking and BMI category. Ten imputed datasets were generated. Predictive mean matching replaces each missing value by the observed value with the closest match on predicted value from the imputation regression model. Predictive mean matching was used as it is considered more robust to violation of the normality assumption of the regression model underlying the multiple imputation procedure and ensures that imputed values will be within the range of observed values [24]. Multinomial logistic regression was selected for imputing missing values for smoking and BMI category because these were constructed as a multinomial categorical variable (e.g. never smoked, ex-smoker, current smoker).

Results

The cohort of participants included 97,450 participants from 226 family practices, who were followed up for a total of 386,738 person years (median 3.7 years per participant). All 16,585 cases that died during follow-up were matched to a suitable control and were included in the analyses. Participant characteristics for cases and controls are presented in Table 1. Cases tended to have marginally longer duration of diabetes relative to controls. Also a greater proportion of cases than controls were treated with insulin or sulphonylureas and a lower proportion were treated with biguanides, pioglitazone or rosiglitazone. A greater proportion of cases than controls had diagnosis of hypertension or treatment with lipid lowering medications. In addition, cases were more likely to be recorded as smokers and weigh less than controls.

At least one valid value of HbA1c was recorded in the 365 days before the index date for 79.9% of controls and 67.5% of cases (Table 2). Change in the last 365 days could be calculated for the 43.1% of controls and 33.0% of cases. Although mean HbA1c was higher for cases than controls, the average change in HbA1c was similar (0.14).

The complete case analysis revealed that higher HbA1c (>9% or 75 mmol/mol) values were associated with increased odds (OR 1.58, Cl: 1.37,1.82) of all-cause mortality. Low HbA1c (<6.5%) values were also associated with increased odds of all-cause mortality (OR = 1.22, Cl: 1.11,1.34) in comparison to normal HbA1c levels after adjustment for study confounders (Table 3). Since not all cases and controls had a valid HbA1c test result in the last 365 days, only 9,241 of the total of 16,585 pairs of matched case and controls were available for the complete case analysis. Participants with missing HbA1c values were more likely to be cases and were also younger, less intensively treated with lipid lowering medications and diabetes medications, less likely to have diagnosis of CHD, heart failure, renal disease or hypertension and had shorter length of follow-up time at their index date. Therefore, it appears unlikely that data were missing completely at random so it is possible that bias may be present in the complete case analysis. Multiple imputation analyses results also suggested that both low and high HbA1c levels were associated with increased risk of mortality in comparison to normal HbA1c levels (Table 3), but the effect sizes were somewhat smaller relative to the complete case analysis.

From the complete case model and multiple imputation model, changes in HbA1c within the last 365 days also appeared to be associated with increased mortality risk. Adjusting for study confounders, decreasing HbA1c levels prior to death were associated with 1.50 (Cl: 1.11, 2.02) greater odds of all-cause mortality compared to no HbA1c level change. A lower and effect size was observed with respect to increasing HbA1c levels (OR = 1.39, Cl: 1.10,1.75). Fully specified models are detailed in the Supplementary material (Table S1 in File S1).

When the association between HbA1c and mortality was examined separately by age group, both the complete case analysis and multiple imputation models indicated that both low and high HbA1c was significantly associated with increased risk of mortality among participants aged 55 to 74 (Table 4). In addition, multiple imputation results indicated that high HbA1c (>9%) were significantly associated with increased risk of all-cause mortality (OR = 1.29, Cl: 1.08,1.53) among the 75 to 84 age groups compared to normal HbA1c (6.5% to 9%). Both complete case analysis and multiple imputation models indicated that the odds ratio for low HbA1c (<6.5%) was greatest in participants aged less than 55 years old (2.05 (Cl: 0.83,5.06) for complete case analysis and 1.53 (Cl:0.84,2.79) for multiple imputation), and declined steadily with older age to become close to one for participants aged 85 and older (1.05 (Cl:0.87,1.26) for complete case analysis and 1.04 (Cl:0.92,1.17) for multiple imputation). A similar declining trend with age was observed with respect to high HbA1c levels (apart from the youngest age group). Fully specified models are detailed in the Supplementary material (Table S2 in File S1).

Discussion

In a population-based study it was revealed that both low and high HbA1c values are associated with increased short-term risk of all-cause mortality. In adults diagnosed with diabetes in primary care there was a 60% increase in the odds of all-cause mortality associated with high HbA1c levels and a 40% increase in the odds of all-cause mortality associated with low HbA1c levels. Employing a post-UKPDS population, the study also demonstrates that both increases and decreases in HbA1c values prior to death are associated with increased risk of mortality.

A possible age-associated effect for the relationship between HbA1c and mortality risk was observed. In particular, the strength of the association between HbA1c levels and all-cause mortality showed a consistent decline from younger age group (<55 years of age) to the older age group (>85 years of age) suggesting a possible
Table 1. Participant characteristics for cases and controls.

| Variable                              | Controls (n = 16585) | Cases (n = 16585) |
|---------------------------------------|----------------------|-------------------|
| **Male**                              |                      |                   |
| 8569 (51.7)                           | 8569 (51.7)          |
| **Age at index date, years**          |                      |                   |
| <45                                   | 79 (0.5)             | 79 (0.5)          |
| 45 to 54                              | 353 (2.1)            | 353 (2.1)         |
| 55 to 64                              | 1378 (8.3)           | 1378 (8.3)        |
| 65 to 74                              | 3842 (23.2)          | 3842 (23.2)       |
| 75 to 85                              | 6496 (39.2)          | 6496 (39.2)       |
| 85+                                   | 4437 (26.8)          | 4437 (26.8)       |
| **Duration diabetes (years)**         |                      |                   |
| 5.5 (2.25, 10.63)                     | 6.3 (2.55, 11.99)    |
| **Duration of follow-up (years)**     |                      |                   |
| 2.4 (1.00, 4.33)                      | 2.5 (1.00, 4.44)     |
| **Year of death**                     |                      |                   |
| 2000                                  | 847 (5.1)            | 847 (5.1)         |
| 2001                                  | 1858 (11.2)          | 1858 (11.2)       |
| 2002                                  | 2057 (12.4)          | 2057 (12.4)       |
| 2003                                  | 2154 (13.0)          | 2154 (13.0)       |
| 2004                                  | 2184 (13.2)          | 2184 (13.2)       |
| 2005                                  | 2315 (14.0)          | 2315 (14.0)       |
| 2006                                  | 2447 (14.8)          | 2447 (14.8)       |
| 2007                                  | 2478 (14.9)          | 2478 (14.9)       |
| 2008                                  | 245 (1.5)            | 245 (1.5)         |
| **Smoking status**                    |                      |                   |
| Non-smoker                            | 7348 (44.3)          | 6312 (38.1)       |
| Ex-smoker                             | 6795 (41.0)          | 6451 (38.9)       |
| Current-smoker                        | 1657 (10.0)          | 2382 (14.4)       |
| Missing                               | 785 (4.7)            | 1440 (8.7)        |
| **BMI category**                      |                      |                   |
| Normal/underweight (BMI <25)          | 4297 (25.9)          | 5218 (31.5)       |
| Overweight (25≤BMI <30)               | 6124 (36.9)          | 4736 (28.6)       |
| Obese (BMI≥30)                        | 4802 (29.0)          | 3771 (22.7)       |
| Missing                               | 1362 (8.2)           | 2860 (17.2)       |
| **Glucose-lowering therapy in 180 days before index date:** | | |
| Insulins                              | 1328 (8.0)           | 2077 (12.5)       |
| Sulphonylureas                         | 6619 (39.9)          | 7254 (43.7)       |
| Biguanides                             | 6484 (39.1)          | 5531 (33.3)       |
| Pioglitazone                           | 270 (1.6)            | 167 (1.0)         |
| Rosiglitazone                          | 694 (4.2)            | 544 (3.3)         |
| Other glucose lowering medications    | 253 (1.5)            | 234 (1.4)         |
| Dietary advice onlyb                   | 946 (5.7)            | 797 (4.8)         |
| **Diagnoses & treatments 365 days before index date** | | |
| Coronary heart disease                 | 1099 (6.6)           | 2799 (16.9)       |
| Arrhythmia                             | 258 (1.6)            | 322 (1.9)         |
| Heart failure                          | 469 (2.8)            | 2176 (13.1)       |
| Stroke or transient ischemic attack    | 350 (2.1)            | 1410 (8.5)        |
| Hypertension                           | 2820 (17.0)          | 1802 (10.9)       |
| Cancer                                 | 818 (4.9)            | 3610 (21.8)       |
| Malnutrition or malabsorption          | 97 (0.6)             | 204 (1.2)         |
| Renal failure                          | 297 (1.8)            | 1177 (7.1)        |
| Liver disease                          | 32 (0.2)             | 345 (2.1)         |
| Treatment with lipid lowering medications | 8064 (48.6)       | 6448 (38.9)       |

Values are frequency (percent) unless otherwise stated.

*Figures are medians (interquartile range).

*No glucose lowering drugs were prescribed for these diabetes patients and most these patients were possible referred to dietary and exercise support.

doi:10.1371/journal.pone.0068008.0001
The finding that high HbA1c levels are associated with increased risk of mortality across the age continuum, but also that the greater relative risk was observed in younger (<55 years of age) diabetes patients. The findings of the present study also appear to be consistent with those found in the ACCORD and VADT trials [29,50]. In an earlier study, Gerstein et al. [25] suggested that stringent HbA1c levels might cause an excess risk of all-cause mortality. By contrast, Ray et al. [31] in a recent meta-analysis of five RCTs concluded that a decrease in HbA1c levels were not associated with reducing risk of all-cause mortality. More recently, Boussageon et al. [32] and Hemmingen et al. [33] reached a similar conclusion in two meta-analyses of RCTs. The present study raises questions concerning the application of trial evidence to a wider primary care. By addressing some of the previous studies methodological problems, the present study helps clarify the current debate and established that both high and low HbA1c levels can be associated with an increased risk for all-cause mortality.

This study has notable strengths including the consideration of different HbA1c levels and short-term changes in HbA1c values with use of multiple imputation to explore potential bias from missing values, to provide evidence about the impact of HbA1c on mortality risk across the age spectrum.
mortality in a nationally representative cohort of diabetic patients. However, several limitations are worth mentioning. The study did not include information on patients’ exercise or dietary habits which may modify medication effects and might partially explain associations with mortality. We did not explore whether stable or changing HbA1c levels with mortality could mask rather unstable HbA1c levels over time. The findings that both increased and decreased HbA1c levels were associated with higher mortality likelihood point towards such possibility. Causes of death were not available for analysis limiting our ability to explore whether disorders of blood glucose were immediately related to patient death or whether other conditions including comorbid disorders or fatal accidents may be responsible for greater mortality rates in this population. Adjusting for comorbid disorders ensured however that comorbidity might not be the sole explanations for the findings.

The small proportion of patients who experienced a decrease or increase in HbA1c values between the last two measurements limited our ability to conduct more detailed analyses such the effect of decrease or increase in HbA1c values within the low (<6.5%) and high (>9.0%) categories. The study cannot rule out possibilities of residual confounding which may explain the observed association between Hb1A1c and mortality. Additionally, because of the inconsistent recording of dietary data in CPRD it was not possible to compare the reduction in HbA1c levels due to diet or medication. However, most patients on diabetes medication will also be offered dietary advice, making difficult any definite distinction about differential reduction in HbA1c levels between diet and medication in observational studies.

It is likely that mortality risks may differ for different drugs and drug combinations and several studies [34,35] have linked sulphonylurea drugs with increased mortality and glitazone therapy with increased risk of cardiovascular events [36,37]. These are important hypotheses that deserve to be evaluated as primary hypotheses of interest in purposely designed studies, rather than as secondary analyses in studies implemented for other purposes such as the present study.

Conclusion

The present findings suggest that an HbA1c target of less than 6.5% or 48 mmol/mol might be too low for some patients and large reductions, or increases, in HbA1c levels should be approached cautiously. The findings also point to potential age-related differences in HbA1c levels and mortality rates with younger diabetes patients being at relatively greater risk of mortality associated with low HbA1c levels even though absolute risks are smaller at young ages. However, this finding needs replication in future studies before making any definitive recommendations regarding the development of different HbA1c treatment targets for younger and older age diabetes patients.

Supporting Information

File S1 Table S1. Association between mortality and HbA1c. Table S2. Association between mortality and HbA1c, stratified by age group. (PDF)

Acknowledgments

This study is based in part on data from the Full Feature General Practice Research Database obtained under licence from the UK Medicines and Healthcare Products Regulatory Agency. However, the interpretation and conclusions contained in this study are those of the authors alone. Access to the GPRD database was funded through the Medical Research Council's licence agreement with MHRA.

Table 4. Association between mortality and HbA1c, stratified by age group.

| Model       | Age group (years) |
|-------------|-------------------|
|             | <55   | 55–64 | 65–74 | 75–84 | 85+   |
| COMPLETE CASE |       |       |       |       |       |
| Matched OR  |       |       |       |       |       |
| Number of matched pairs | 179   | 793   | 2353  | 3818  | 2098  |
| <6.5%       | 2.16 (1.31, 3.56) | 1.51 (1.20, 1.91) | 1.31 (1.15, 1.50) | 1.19 (1.08, 1.31) | 1.03 (0.91, 1.18) |
| >9.0%       | 1.59 (0.91, 2.76) | 1.65 (1.26, 2.15) | 1.93 (1.59, 2.33) | 1.62 (1.37, 1.91) | 1.28 (1.02, 1.62) |
| Adjusted OR |       |       |       |       |       |
| Number of matched pairs | 164   | 737   | 2149  | 3307  | 1545  |
| <6.5%       | 2.05 (0.83, 5.06) | 1.67 (1.14, 2.46) | 1.37 (1.12, 1.67) | 1.19 (1.03, 1.37) | 1.05 (0.87, 1.26) |
| >9.0%       | 1.72 (0.76, 3.90) | 1.84 (1.19, 2.84) | 1.89 (1.43, 2.50) | 1.60 (1.27, 2.02) | 1.28 (0.92, 1.77) |
| MULTIPLE IMPUTATION |       |       |       |       |       |
| Number of matched pairs | 432   | 1378  | 3842  | 6496  | 4437  |
| Matched OR  |       |       |       |       |       |
| <6.5%       | 1.70 (1.19, 2.43) | 1.32 (1.09, 1.60) | 1.16 (1.04, 1.30) | 1.11 (1.03, 1.21) | 1.08 (0.98, 1.19) |
| >9.0%       | 1.34 (0.89, 2.00) | 1.49 (1.18, 1.87) | 1.60 (1.37, 1.87) | 1.41 (1.23, 1.62) | 1.20 (1.01, 1.42) |
| Adjusted OR |       |       |       |       |       |
| <6.5%       | 1.53 (0.84, 2.79) | 1.42 (1.04, 1.92) | 1.19 (1.01, 1.41) | 1.08 (0.96, 1.21) | 1.04 (0.92, 1.17) |
| >9.0%       | 1.20 (0.70, 2.07) | 1.64 (1.13, 2.38) | 1.46 (1.19, 1.80) | 1.29 (1.08, 1.53) | 1.15 (0.94, 1.41) |

Figures are odds ratios (95% confidence intervals).

*6.5% to 9.0% as reference category;
*Adjusted for comorbidity, lipid lowering medication, smoking, BMI and diabetes drug utilisation.

doi:10.1371/journal.pone.0068008.t004
Author Contributions
Conceived and designed the experiments: JN JC AD MG. Analyzed the data: JN JC AD MG. Contributed reagents/materials/analysis tools: MG.

References
1. American Diabetes Association (2011) Summary of revisions to the 2011 clinical practice recommendations. Diabetes Care (Suppl 1): S3.
2. National Institute for Health and Clinical Excellence (2008) Type 2 diabetes: The management of Type 2 diabetes. London, NICE clinical guidelines 66.
3. International Diabetes Federation (2013) Global Guidelines for Type 2 Diabetes: Brussels, Belgium: IDF.
4. UK Prospective Diabetes Study (UKPDS) Group (1998) Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes. Lancet 352: 837–853.
5. Holman RR, Paul SK, Bethel MA, Matthews DR, Neilly HA (2008) 10-Year Follow-up of Intensive Glucose Control in Type 2 Diabetes. N Engl J Med 359: 1577–1586.
6. Kelly TN, Bazzano LA, Fonseca VA, Thethi TK, Reynolds K, et al (2009) Systematic Review: Glucose Control and Cardiovascular Disease in Type 2 Diabetes. Ann Intern Med 151: 394–403.
7. Kowall B, Rathmann W, Heier M, Giani G, Peters A, et al (2011) Categories of glycaemia and continuous glycemic measures and mortality. Eur J Epidemiol 26: 637–645.
8. Zoungas S, Patel A, Chalmers J, de Galan BE, Li Q, et al (2008) Severe Hypoglycaemia and Risk of Vascular Events and Death. New Engl J Med 363: 1410–1418.
9. Gerstein HC, Miller ME, Byington RP, Goff DC Jr, Bigger JT, et al (2008) Association of hemoglobin A1c and risk of all-cause mortality among US adults without diabetes. Circ Cardiovasc Qual Outcomes 3: 661–667.
10. The ADVANCE Collaborative Group (2008) Intensive Blood Glucose Control and Vascular Outcomes in Patients with Type 2 Diabetes. N Engl J Med 358: 2560–2572.
11. Zoungas S, Chalmers J, Nisoniyi T, Li Q, Cooper ME, et al (2012) Association of HbA1c levels with vascular complications and death in patients with type 2 diabetes: evidence of glycaemic thresholds. Diabetologia 55: 636–643.
12. Currie CJ, Peters JR, Tynan A, Evans M, Heine RJ, et al (2010) Survival as a function of HbA1c in people with type 2 diabetes: a retrospective cohort study. Lancet 375: 481–489.
13. Riveline JP, Roussel R, Mohammel K (2010) Survival as a function of HbA1c in people with type 2 diabetes. Lancet 375: 1433.
14. Pani LN, Koolenda I, Meigs JB, Driver C, Chramay S, et al (2008) Effect of aging on A1C levels in individuals without diabetes: evidence from the Framingham Offspring Study and the National Health and Examination Survey 2001–2004. Diabetes Care 31: 1991–1996.
15. Herrett E, Thomas SL, Schoonen WM, Smith L, Hall AJ (2010) Validation and validity of diagnoses in the General Practice Research Database: a systematic review. Br J Clin Pharmacol 69: 4–14.
16. Khan NF, Harrison SE, Rose PW (2010) Validity of diagnostic coding within the General Practice Research Database: a systematic review. Br J Gen Pract 60: e128–e136.
17. Bland JM, Altman DG (1994) Matching. BMJ 309: 1128.
18. Grimes DA, Schulz KF (2003) Compared to what: finding controls for case-control studies. Lancet 362: 1429–1433.
19. Monami M, Lamanna C, Desideri GM, Mannucci E (2012) DPP-4 inhibitors and lipid. Systematic review and meta-analysis. Adv Ther 29: 14–21.
20. Zoungas S, Patel A, Chalmers J, de Galan BE, Li Q, et al (2012) Severe hypoglycaemia and risk of vascular events and death. NEJM 363: 1410–1418.
21. Iqbal N, Morgan C, Maksoud H, Idris I (2008) Improving patients’ knowledge on the relationship between HbA1c and mean plasma glucose improves glycemic control among persons with poorly controlled diabetes. Ann Chem Biochem 45: 504–507.
22. He Y (2010) Missing data analysis using multiple imputation: getting to the heart of the matter. Circ Cardiovasc Qual Outcomes 3: 98–105.
23. Sterne JA, White IR, Carlin JB, Spratt M, Royston P, et al (2009) Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. BMJ 338: b2592.
24. Rubin DB (1987) Multiple Imputation for Non-Response in Surveys. New York: John Wiley and Sons.
25. Gerstein HC, Swedberg K, Carlson J, McMurray JJV, Michelson EL, et al (2008) The hemoglobin A1c level as a progressive risk factor for cardiovascular death, hospitalization for heart failure, or death in patients with heart failure. Arch Int Med 168: 1699–1704.
26. Khaw KT, Wareham N, Bingham S, Lahen R, Welch A, et al (2004) Preliminary communication: glycated hemoglobin, diabetes, and incident colorectal cancer in men and women: a prospective analysis from the European prospective investigation into cancer-Norfolk study. Cancer Epidemiol Biomarkers Prev 13: 915–919.
27. Carson AP, Fox CS, McGuire DK, Levitan EB, LaCassandra M, et al (2010) Low hemoglobin A1c and risk of all-cause mortality among US adults without diabetes. Circ Cardiovasc Qual Outcomes 3: 661–667.
28. Christman AL, Selvin E, Margolis DJ, Lazarus GS, Garza LA (2011) Hemoglobin A1C predicts healing rate in diabetic wounds. J Invest Dermatol 131: 2121–2127.
29. Duckworth W, Abraira C, Moritz T, Reda D, Emanuelle N, et al (2009) Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med 360: 129–139.
30. Riddle MC, Ambrosius WT, Brilllon DJ, Buse JB, Byington RP, et al (2010) Epidemiologic relationships between A1C and all-cause mortality during a median 3.4 year follow up of glycemic treatment in the ACCORD trial. Diabetes Care 33: 983–990.
31. Ray KK, Sesso SRK, Wijesuriya S, Sivakumar R, Nethercot S, et al (2009) Effect of intensive control of glucose on cardiovascular outcomes and death in patients with diabetes mellitus: a meta-analysis of randomized controlled trials. Lancet 373: 1763–1772.
32. Boussagone R, Bejan-Angoulvant T, Saadatian-Eliahi M, Lafont S, Bergeonneau C, et al (2011) Effect of intensive glucose lowering therapy on all cause mortality, cardiovascular death, and microvascular events in type 2 diabetes: meta-analysis of randomised controlled trials. BMJ 343: d4169.
33. Hemmingsson B, Lund SS, Gluud C, Vaag A, Almdal T, et al (2011) Intensive glycaemic control for patients with type 2 diabetes: systematic review with meta-analysis and trial sequential analysis of randomised clinical trials. BMJ 343: d8098.
34. Gazzarr KN, Brayda B, Hassinger NL, Grill DE, Terzic A, et al (1999) Sulphonylurea drugs increase early mortality in patients with diabetes mellitus after direct angioplasty for acute myocardial infarction. J Am Coll Cardiol 33: 119–124.
35. Simpson SH, Majumdar SR, Tsuyuki RT, Urchst DJ, Johnson JA (2006) Dose-response relation between sulphonylurea drugs and mortality in type 2 diabetes mellitus: a population-based cohort study. CMAJ 174: 169–174.
36. Currie CJ, Poole CD, Evans M, Peters JR, Morgan CL (2013) Mortality and other important diabetes-related outcomes with insulin vs other antihyperglycemic therapies in type 2 diabetes. J Clin Endocrinol Metab 98: 660–677.
37. Forst T, Hanefeld M, Jacob S, Moeser G, Schwenger G, et al (2013) Association of sulphonylurea treatment with all-cause and cardiovascular mortality: A systematic review and meta-analysis of observational studies. Diab Vasc Dis Res [Epub ahead of print] PMID: 23291340.

Wrote the paper: JN JC AD MG. Obtained the data: MG. Read and approved the final draft and submission of the manuscript: JN JC AD MG.