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All-cause mortality in patients with diabetes under treatment with dapagliflozin: a population-based, open-cohort study in THIN database.

Konstantinos A. Toulis PhD, Brian H. Willis PhD, Tom Marshall PhD, Balachadran Kumarendran MD, Krishna Gokhale MSc, Sandip Ghosh FRCP, G Neil Thomas PhD, Kar Keung Cheng PhD, Parth Narendran PhD, Wasim Hanif PhD, Krishnarajah Nirantharakumar MD

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All-cause mortality and dapagliflozin

All-cause mortality in patients with diabetes under treatment with dapagliflozin: a population-based, open-cohort study in THIN database.

Konstantinos A. Toulis^{1,2} PhD, Brian H. Willis¹ PhD, Tom Marshall¹ PhD, Balachadran Kumarendran¹ MD, Krishna Gokhale¹ MSc, Sandip Ghosh³ FRCP, G Neil Thomas¹ PhD, Kar Keung Cheng¹ PhD, Parth Narendran^{3,4} PhD, Wasim Hanif³ PhD, Krishnarajah Nirantharakumar^{1,3*} MD

1. *Institute of Applied Health Research, University of Birmingham, UK*

2. *424 General Military Hospital, Thessaloniki, Greece*

3. *Diabetes Department, University Hospitals Birmingham NHS Foundation Trust, UK*

4. *Institute of Metabolism and Systems Research, University of Birmingham, UK*

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Context: Empagliflozin was found to decrease mortality in patients with type 2 diabetes (T2DM) and a prior cardiovascular (CVD) event.

Objectives: To establish whether these benefits can be replicated in a real-world setting, should be expected with the use of dapagliflozin, and apply to T2DM patients at low risk of CVD.

Design: General Practice, population-based, retrospective cohort study (January 2013-September 2015).

Setting: The Health Improvement Network Database (THIN).

Participants: A total of 22,124 patients (4,444 exposed to dapagliflozin, 17,680 unexposed T2DM patients), matched for age, sex, body mass index, T2DM duration and smoking.

Main outcome measures: The primary outcome was all-cause mortality in the total study (high and low risk for CVD) population expressed as the adjusted incidence rate ratio (aIRR) with 95% confidence intervals (CI). As a secondary analysis in the low risk population, all-cause mortality and incident cardiovascular disease (CVD) were considered.

Results: Patients with T2DM exposed to dapagliflozin were significantly less likely to die from any cause (0.50, 95% CI: 0.33-0.75, p -value = 0.001). Similarly, in low-risk patients, death from any cause was significantly lower in the exposed to dapagliflozin cohort (aIRR: 0.44, 95% CI: 0.25-0.78, p -value = 0.002). The difference in the risk of incident CVD did not reach statistical significance between groups in low-risk patients (aIRR: 0.89, 95% CI: 0.61-1.31, p -value = 0.546).

Conclusions: Patients with T2DM exposed to dapagliflozin were at a lower risk of death from any cause irrespective of baseline CVD status.

In a population-based, open cohort study, patients with T2DM exposed to dapagliflozin were at a lower risk of death from any cause irrespective of their baseline CVD risk.

Introduction

Patients with diabetes mellitus type 2 (T2DM) have a two-fold increased risk of all-cause mortality and a threefold increased risk of cardiovascular mortality (1). Despite this, evidence of a significant mortality benefit with intensive glucose-lowering treatment remains debatable (2). Additionally, commonly prescribed glucose-

lowering medications, such as sulphonylureas and dipeptidyl peptidase 4 inhibitors (DPP4i) might not be associated with a favorable cardiovascular risk profile (3,4).

The findings of the EMPA-REG OUTCOME trial (5), reporting substantial CVD and mortality benefits in patients with T2DM receiving empagliflozin, have received intense attention and scrutiny (6-11). In this trial, it was reported that high-CVD risk patients with T2DM had a significant relative risk reduction in the risk of cardiovascular mortality (38%), all-cause mortality (32%), and hospital admission for heart failure (35%) when sodium-glucose cotransporter 2 inhibitor (SGLT2i) was added to their background therapy. Importantly, the magnitude of effect and the rapid onset of action (within 3 months) instigated an ongoing discussion about the potential underlying cardioprotective mechanism(s). The haemodynamic effect, resulting from osmotic diuresis, the subsequent activation of renin–angiotensin–aldosterone system (RAAS) pathways, and/or the modification of glucagon concentrations have all been proposed as effectors of the additive cardiovascular benefits (6-10). Synergy with RAAS blockade medications (10) and a favorable SGLT2i-induced metabolic substrate shift (12) are also interesting theories warranting further investigation. On top of this ongoing discussion, a series of additional, clinically relevant questions promptly arises and needs to be addressed in a timely fashion.

Firstly, it is important to clarify whether the reported CVD benefits are intrinsic to empagliflozin or should be anticipated with the use of other approved SGLT2i, such as dapagliflozin. Such trials are currently ongoing, but their results are not expected soon. Secondly, the relevance of any beneficial CVD effects of SGLT2i in low-risk patients with T2DM is still unknown, since only patients with a prior CVD event were included in the EMPA-REG OUTCOME trial. Of note, the same partly applies for younger patients with a relatively short duration of diabetes, since published data refer to predominantly older patients with long-standing diabetes (7). Finally, replicating the beneficial CVD results in a pragmatic setting, other than the strict RCT setting, would certainly add to both external validity and generalisability of any cardioprotective effects.

To these ends, we conducted a population-based, retrospective open cohort study in which patients with T2DM exposed to any dapagliflozin were compared to appropriately matched controls with T2DM, unexposed to dapagliflozin, but receiving standard, background antidiabetic medication.

Research Design and Methods

Study design

Population-based, retrospective open cohort study in which patients with T2DM exposed to SGLT2i were compared to appropriately matched patients with T2DM unexposed to SGLT2i. Age, sex, body mass index (BMI), documented duration of T2DM and smoking status were used as the matching parameters. Considering that the great majority (almost 90%) of the exposed cohort was treated with dapagliflozin, analysis and inferences were restricted to those treated with dapagliflozin and their respective controls to promote homogeneity and thus, consolidate the findings.

Source of data

Data were derived from The Health Improvement Network database (THIN). This is a database of anonymised electronic patient records contributed by general practices (GP) using the Vision computer system. It includes records from over 640 UK GPs (approximately 12 million patients, of which 3.5 million are actively registered with their practices).

Study cohort

The study period was set from 1st January 2013 (study start) to 1st September 2015 (study end, date of the last data collection). All individuals in the study cohort were required to be registered at their practice at least a year before entry into the study. The decision to use a one year registration period was made to ensure these are new (incident prescriptions) rather than a patient being continued on a prescription that was initiated in another practice. Their practice was also required to have been using their computer system (Vision) for at least a year prior to their index date and have an AMR date (an indicator of practice data quality) prior to their index date in order to ensure that the practice was making full use of their system and not under-recording important outcomes [13].

Exposure

Any subject administered dapagliflozin at any time point during the observation period was identified and recorded first. Individuals were included in the exposed cohort if they (i) were aged 18+ years at the index date, (ii) had a diagnosis of diabetes mellitus any time before their index date, (iii) had been initiated treatment with dapagliflozin, (iv) remained at their practice at least three months after treatment initiation. This date (3 months after dapagliflozin prescription) was assigned as the index date for each exposed patient. An intention-to-treat approach was followed and exposure was assumed to remain unchanged during the observation period. A description of the observed treatment patterns is provided in the [Appendix](#).

Selection of the unexposed cohort (controls)

After the completion of the exposed cohort, the identification of the unexposed patients (controls) and matching procedure were applied and by definition, no “control” was exposed to SGLT2i. For each exposed patient up to four unexposed controls were selected. Unexposed patients (controls) (i) were individually matched to cases on sex, age at index date (to within one year), BMI (to within 2 kg/m²), duration of diabetes (to within two years) and smoking status (ii) should have a diagnosis of diabetes any time before their index date, (iii) were (by definition) unexposed to SGLT2i. No additional matching variables were used to ensure a balanced selection of the unexposed group. The diagnosis of diabetes naturally had to be made any time before the index date for all study participants. To avoid immortal time bias, the unexposed cohort were matched at the index date of their respective exposed patients and are assigned the same index as their respective exposed patients.

Follow-up

Exposed and unexposed patients with T2DM were followed up (observation period) from the index date until the first of the following events (exit date): patient died; patient left practice; last data collection from practice; patient diagnosed with any of the following cardiovascular outcomes [myocardial infarction or ischaemic heart disease, stroke or transient ischaemic attack (TIA), heart failure or left ventricular dysfunction). When cardiovascular events were followed by death the observation period was calculated according to the outcome under study.

Outcomes

The primary outcome was all-cause mortality (death from any cause during the observation period). A composite end-point of CVD outcomes (myocardial infarction and ischaemic heart disease, stroke or TIA and heart failure or left ventricular dysfunction) served as secondary outcomes in an analysis restricted to low-risk population. The low-risk population was defined as the absence of all-CVD outcomes (myocardial infarction and ischaemic heart disease, stroke and TIA and heart failure)

at baseline. CVD end-points were used as an outcome only in the low-risk subset of the study population. This decision was made in order to avoid any bias arising from miscoding between incident and prevalent CVD outcomes. Medication-specific effects were also considered in the analysis. The validity of the definition of the primary outcome in THIN database has been previously documented (14).

Diagnosis of diabetes mellitus, myocardial infarction and ischaemic heart disease, stroke and TIA, and heart failure (inclusive of codes suggestive of left ventricular dysfunction) was determined by Read codes (<http://systems.hscic.gov.uk/data/uktc/readcodes>).

Covariates

Potential confounders were used as model covariates (on top of matching parameters age, sex, BMI, smoking status and duration of diabetes) and were selected on the basis of biological plausibility. These covariates were glycated haemoglobin, renal function (on the basis of estimated glomerular filtration rate), systolic blood pressure, insulin use, the use of lipid-lowering medications, diagnosis of hypertension at baseline, diagnosis of peripheral vascular disease at baseline and Townsend deprivation index. The latter is a measure of socioeconomic and material deprivation with five categories starting from the least to the most deprived, and has been validated in THIN database (15). When all-cause mortality was the outcome, Charlson's comorbidity index was also used as a model covariate (16). The index encompasses 22 medical conditions weighted 1–6 with total scores ranging from 0–37, shows marked predictive power for mortality (17) and validated for used in primary care setting (18).

Statistical analysis

The cohort covariates and matching characteristics were summarised for those exposed and unexposed to dapagliflozin using appropriate descriptive statistics. Differences between exposed and unexposed groups were investigated using chi-squared tests (for categorical variables) and t-tests or Mann-Whitney U test for continuous variables. Missing data (the extent of which was minimal as shown in the [Appendix](#)) were handled by multiple imputation techniques (chained equations with predicted mean matching). Incidence Rate Ratios (IRR) were calculated using Poisson regression. Both crude and adjusted estimates were presented. Statistical significance level was set at 0.05 (two-sided) and 95% confidence intervals (CI) were presented. All analyses were performed in Stata MP 14.0. This study was approved by the relevant Scientific Review Committee (SRC Reference Number: 16THIN032A1).

Sensitivity, subgroup and supplementary analyses

Although it was reasonable to assume that dapagliflozin were prescribed exclusively to patients with T2DM and Read Codes specific for type 1 diabetes mellitus (T1DM) were not included, a supplementary effort to avoid any possibility of sample “contamination” with T1DM cases was also made. Therefore, we performed a sensitivity analysis by excluding those patients who fulfilled eligibility criteria at baseline, but subsequently had a Read Code suggestive of T1DM.

To detect any source of spurious causal inference, a supplementary analysis was undertaken using the “negative control” methodology as detailed in Lipsitch *et al* (19) and implemented in a similar study design (20). We used dipeptidyl peptidase-4 inhibitors (DPP4i) as the negative controls, since it has been shown that no significant effect on all-cause mortality should be expected (3), at least in the short term. Finally, a subgroup analysis was undertaken to explore the risk of death from any cause in the high-risk subset of the population.

Results

Cohort characteristics

A total of 22,124 patients (4,444 exposed to dapagliflozin and 17,680 unexposed patients with T2DM) constituted the final study population. The mean age and BMI were 58.4 years and 34.8 kg/m² respectively, whereas the mean duration of diabetes was approximately nine years. Approximately one fifth of the study population (n=4,350) have had a previous CVD event (ischaemic heart disease, stroke and/or heart failure). The mean HbA1c in the total study population was 7.7% (61.3 mmol/mol). A table summarizing key study characteristics on the basis of exposure to dapagliflozin is presented in [Table 1](#).

All-cause mortality

Patients with diabetes who were administered dapagliflozin were significantly less likely to die from any cause compared to matched controls with diabetes under standard treatment (Crude IRR: 0.49, 95% CI: 0.33-0.72, *p*-value = 0.0001, [Table 2](#)). This finding remained robust after adjusting for key covariates (Adjusted IRR: 0.50, 95% CI: 0.33-0.75, *p*-value = 0.001, [Table 2](#) and [Figure 1](#)).

All-cause mortality in the low-risk population

In the low-risk subset of the study population, patients with diabetes who were administered dapagliflozin were significantly less likely to die from any cause compared to matched controls with diabetes receiving standard treatment (Crude IRR: 0.43, 95% CI: 0.25-0.74, *p*-value = 0.002, [Table 2](#)). This finding remained unchanged after adjusting for key covariates (aIRR: 0.44, 95% CI: 0.25-0.78, *p*-value = 0.005, [Table 2](#)).

Risk of incident cardiovascular event in the low-risk population

In the low-risk subset of the study population, no difference in the risk of incident CVD was detected between patients with diabetes who were administered dapagliflozin and matched controls with diabetes receiving standard treatment (Crude IRR: 1.00, 95% CI: 0.70-1.42, *p*-value = 0.981; aIRR: 0.89, 95% CI: 0.61-1.30, *p*-value = 0.55, [Table 2](#)).

Sensitivity, subgroup and supplementary analyses

Both magnitude and direction of effects remain unchanged in sensitivity analyses excluding a subset of participants with a Read Code suggestive of T1DM ([Appendix](#)). Crude and adjusted risk of death from any cause in the high-risk subset of the population was similar in effect size with the one observed in the low-risk subset and presented in the [Appendix](#). The findings of the “negative control” analysis were supportive of the validity of the study design and no evidence of systemic bias was detected.

Discussion

In this observational, population-based analysis involving a total of 22,124 individuals with T2DM and approximately 16,500 person-years of follow-up, our data suggest that patients exposed to dapagliflozin were found to be significantly less likely to die from any cause compared to appropriately matched controls receiving standard, background antidiabetic medication. This data extends the observations from the patients included through the narrowly specified inclusion criteria of the trials to the general diabetic population, and shows such patients may similarly benefit. Similarly, our data support the contention that treatment with dapagliflozin was associated with a reduced risk of death from any cause even in the low-risk

population. In contrast, although showing a similar trend, the risk of any CVD event was not found to be significantly different between the low-risk exposed cohort and unexposed cohort.

The above results can be interpreted as both confirmatory and novel. They are confirmatory and reassuring since both the direction and magnitude of effect observed in the total study population are similar to the findings reported in the EMPA-REG OUTCOME trial (5) and a relevant meta-analysis of RCTs (21). Importantly, they are novel since the favourable findings now relate to dapagliflozin, which might be equally effective not only in patients at high-risk for CVD, but in the low-risk population as well. Both these end-points have significant clinical and research ramifications. Furthermore establishing whether reductions in mortality with SGLT2i represent a class effect across all SGLT2i could be a relevant end-point. As all patients included in the analysis were treated with dapagliflozin we cannot provide evidence of a class effect, but do show the observations extend to dapagliflozin.

The findings of the present study should be considered in light of its limitations. First, this is retrospective evidence and the possibility of bias inherent to this study design should be noted. Furthermore, the actual number of events was low, which is reflected in the wide 95% CIs. Therefore, the accuracy of the reported effect size may be undermined and the 95% CIs would provide a rather more solid basis for interpretation. Furthermore, the observation period (median of almost a year) may be short for CVD outcomes to manifest. Collectively, these shortcomings may have resulted in an underpowered analysis, especially with respect to the low-risk population that showed a lack of significance for all-CVD. However, both number of events and total person-years of follow-up in the present study were above relevant minimum requirements (22). The possibility that a bias may exist due to preferential prescription of SGLT2i to a specific subgroup of patients with diabetes who had a survival benefit may be present but negated by appropriate matching and controlling, for example controlling for renal function. However, we cannot completely rule out prescription by indication bias. Additionally, no information on education and income was available at an individual level. Therefore, we used Townsend score, based on postcode, as a proxy for measure of deprivation. Of note, Charlson Comorbidity Index does not include all comorbidities such as debilitating neurological conditions (multiple sclerosis) and non-malignant hematological diseases (anemia), and therefore, it might be an imperfect measure of comorbidity index on mortality. Finally, it was not feasible to explore any difference in cardiovascular mortality between groups, since it was not possible to adjudicate on the specific cause of death in the present study design. The latter might also be a methodological concern in the notion that there is no documentation that risk of death was actually comparable between groups at baseline. On the other hand, any major, established risk factor for CVD and death was taken into account in the matching process (age, sex, BMI, disease duration, smoking) and covariate selection (Charlson's comorbidity index, glycaemic control, hypertension, hyperlipidaemia, renal function, baseline peripheral vascular disease, treatment with insulin and socioeconomic status).

The (clinical and research) implications of the findings are of great interest. Our data indicate the benefits from treatment with SGLT2i observed in high-risk diabetic patients are not only reproducible in the general diabetic population, but might also be extended to the low-risk population when dapagliflozin is concerned. This observation should be further pursued in a trial setting. In case an incremental mortality benefit is confirmed in subsequent studies, then treatment with dapagliflozin

might then be considered a reasonable option to a broad range of patients with type 2 diabetes.

In conclusion, our findings suggest that dapagliflozin might be associated with a decrease in all-cause mortality irrespective of the baseline CVD status.

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None

Joint Corresponding Authors: Professor Wasim Hanif, Diabetes - University Hospitals Birmingham NHS Foundation Trust, Birmingham, B15 2TH, United Kingdom, Tel: +44 (0) 121 3714404 Fax +44(0) 1213714405, Email: Wasim.Hanif@uhb.nhs.uk, Dr. Krishnarajah Nirantharakumar, Institute of Applied Health Research, University of Birmingham, B15 2TT, United Kingdom, Tel: +44 (0) 121 4148344, Email: k.nirantharan@bham.ac.uk

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Disclosure statement

Dr Narendran has participated in advisory board meetings for Astra Zeneca. Dr Ghosh has received honoraria for lectures from different pharmaceutical companies including Boehringer Ingelhiem, MSD, Takeda, Novo Nordisk, Eli Lilly, Pfizer. Professor Cheng is affiliated to the Department of General Practice, Peking University Health Science Center in China, which receives financial support from Pfizer China for primary care development. Professor Hanif has received honoraria and consulting fees from different pharmaceutical companies including Boehringer Ingelhiem, MSD, Takeda, Novo Nordisk, Eli Lilly, Pfizer. Professor Marshall is partly funded by the NIHR through the Collaborations for Leadership in Applied Health Research and Care for West Midlands (CLAHRC-WM). The views expressed in this publication are not necessarily those of the NIHR, the Department of Health, NHS Partner Trusts, University of Birmingham or the CLAHRC-WM Management Group. All other co-authors have nothing to declare.

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Figure 1. All-cause mortality in patients with diabetes under treatment with dapagliflozin and controls (cumulative hazards estimates).

Table 1: Baseline characteristics of the study population on the basis of exposure to dapagliflozin.

| | Exposed to dapagliflozin | Unexposed cohort |
|---|--------------------------|------------------|
| N | 4,444 | 17,680 |
| Age (years) | 58.3 (10.4) | 58.5 (10.4) |
| Male | 2,605 (58.6) | 10,364 (58.6) |
| Body Mass Index | 35.0 (6.9) | 34.7 (6.6)* |
| Systolic blood pressure (mmHg) | 131.6 (12.9) | 132.2 (14.1)* |
| Smoking | 600 (13.5) | 2,373 (13.4)* |
| Use of lipid-lowering medications | 3,931 (88.4) | 14,966 (84.7) |
| Estimated Glomerular Filtration Rate | 91.7 (22.0) | 88.6 (24.8)* |
| Townsend | | * |
| 1 | 903 (20.3) | 3,134 (17.7) |
| 2 | 825 (18.6) | 3,214 (18.3) |
| 3 | 1,016 (22.9) | 3,744 (21.2) |
| 4 | 885 (19.9) | 3,886 (22.0) |
| 5 | 642 (14.5) | 2,966 (16.8) |
| Not available | 173 (3.9) | 709 (4.0) |
| Follow-up (months) | 9.3 (6.5) | 8.9 (6.3)* |
| Diabetes-specific characteristics | | |
| Duration (years) | 9.8 (6.0) | 8.5 (5.5)* |
| Glycated Hemoglobin A1c (% -mmol/mol) | 9.1 (3.8) | 7.5 (3.8) |
| | 76.1 (17.7) | 60.0 (18.8)* |
| Insulin use | 1,325 (29.8) | 3,647 (20.6)* |
| Key co-morbidities at baseline | | |
| Ischaemic Heart Disease | 586 (13.2) | 2,613 (14.8)* |
| Stroke or transient ischaemic attack | 216 (4.9) | 1,043 (5.9)* |
| Heart Failure or Left Ventricular Dysfunction | 95 (2.1) | 590 (3.3)* |
| Peripheral Vascular Disease | 142 (3.2) | 626 (3.5) |
| Hypertension | 2,449 (55.1) | 10,315 (58.3)* |
| Low risk n (%) | 3,656 (82.3) | 14,118 (79.9)* |
| Charlson's Comorbidity Index | | * |
| 1 | 1,941 (43.7) | 7,526 (42.6) |
| 2 | 889 (20.0) | 3,582 (20.3) |
| 3 | 959 (21.6) | 3,558 (20.1) |
| 4 | 395 (8.9) | 1,624 (9.2) |
| 5 or more | 260 (5.9) | 1,390 (8.0) |

CVD: Cardiovascular disease. Low risk for CVD defined as the absence of ischaemic heart disease, stroke/transient ischaemic attack and heart failure/left ventricular dysfunction. Continuous data presented as mean (standard deviation) unless otherwise specified. Dichotomous and ordinal data presented as N (%). Townsend index is a measure of material deprivation (1 denotes the least deprived and 5 the most deprived individuals) *Statistically significant at the level of 0.05

Table 2: Risk of death from any cause and incident cardiovascular disease in dapagliflozin cohort compared to standard treatment cohort

| | Exposed to dapagliflozin | Unexposed | Crude IRR (95%CI) | P-value | Adjusted IRR* (95%CI) | P-value |
|--|--------------------------|-----------|-------------------|---------|-----------------------|---------|
| Total population | | | | | | |
| Person-years | 3,456 | 13,129 | | | | |
| Death from any cause | 29 | 226 | | | | |
| Incidence rate (deaths per 1000 person-years) | 8.39 | 17.2 | 0.49 (0.33-0.72) | 0.0001 | 0.50 (0.33-0.75) | 0.001 |
| Low-risk population | | | | | | |
| Person-years | 2,842 | 10,514 | | | | |
| Death from any cause | 15 | 128 | | | | |
| Incidence rate (deaths per 1000 person-years) | 5.27 | 12.17 | 0.43 (0.25-0.74) | 0.002 | 0.44 (0.25-0.78) | 0.005 |
| Person-years (CVD) | 2,839 | 10488 | | | | |
| Incident CVD | 38 | 141 | | | | |
| Incidence rate (CVD per 1000 person-years) | 13.38 | 13.43 | 1.00 (0.70-1.42) | 0.981 | 0.89 (0.61-1.30) | 0.546 |

CI: Confidence Interval, CVD: Cardiovascular Disease, IRR: Incidence Rate Ratio, *Adjusted for age, gender, body mass index, smoking, glycated haemoglobin A1c, duration of diabetes, systolic blood pressure, lipid lowering medication, insulin use, estimated glomerular filtration rate, social deprivation index, presence of hypertension and Charlson's comorbidity index || Charlson's comorbidity index was not used as a covariate in incident CVD outcomes | P-values derived from poisson regression | Incident CVD was defined as the new diagnosis of either ischaemic heart disease, stroke or transient ischaemic attack or heart failure or left ventricular dysfunction in the low risk subset of the population

