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Prescribing paradigm shift? Applying the 2019 European Society of Cardiology-led guidelines on 'diabetes, pre-diabetes, and cardiovascular disease' to assess eligibility for sodium-glucose co-transporter-2 inhibitors or glucagon-like peptide-1 receptor agonists as first-line monotherapy (or add-on to metformin monotherapy) in type 2 diabetes in Scotland

Caparrotta, Thomas M.; Blackbourn, Luke A. K.; McGurnaghan, Stuart J.; Chalmers, John; Lindsay, Robert; McCrimmon, Rory

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Prescribing paradigm shift? Applying the 2019 European Society of Cardiology-led guidelines on 'diabetes, pre-diabetes, and cardiovascular disease' to assess eligibility for sodium-glucose co-transporter-2 inhibitors or glucagon-like peptide-1 receptor agonists as first-line monotherapy (or add-on to metformin monotherapy) in type 2 diabetes in Scotland

Running title: New diabetes guidelines prescribing shift?

Caparrotta Thomas M[1], Blackbourn Luke AK[1], McGurnaghan Stuart J[1], Chalmers John[2], Lindsay Robert[3], McCrimmon Rory[4], McKnight John[5], Wild Sarah[6], Petrie John R[3], Philip Sam[7], McKeigue Paul M,[6] Webb David J[8], Sattar Naveed[3], Colhoun Helen M[1,9] on behalf of Scottish Diabetes Research Network - Epidemiology Group

[1]MRC Institute of Genetic and Molecular Medicine, University of Edinburgh, Edinburgh United Kingdom

[2]Diabetes Centre, Victoria Hospital, Kirkcaldy, United Kingdom

[3]Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, United Kingdom

[4]Division of Molecular and Clinical Medicine, University of Dundee, Dundee, United Kingdom.

[5]Western General Hospital, NHS Lothian, Edinburgh, United Kingdom

[6]Usher Institute of Population Health Sciences and Informatics, Centre for Population Health Sciences, School of Molecular, Genetic and Population Health Sciences, University of Edinburgh, Edinburgh, United Kingdom

[7]Grampian Diabetes Research Unit, Diabetes Centre, Aberdeen Royal Infirmary, Aberdeen, United Kingdom

[8]University/BHF Centre for Cardiovascular Science, Queen's Medical Research Institute, University of Edinburgh, Edinburgh, United Kingdom

[9]Public Health, NHS Fife, Kirkcaldy, United Kingdom

Corresponding Author:
Helen M. Colhoun - helen.colhoun@igmm.ed.ac.uk,
Institute of Genetics and Molecular Medicine

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Western General Hospital
Crewe Road
Edinburgh, UK EH4 2XUT
Tel : +44 (0) 131 651 8770

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Author contributions

TMC, LAKB and SJM conceived, planned and executed the analysis; TMC authored the draft manuscript, subsequent revisions and took the decision to submit. SW contributed to data procurement and commented critically on the analysis and manuscript. JP commented on an initial draft and stimulated additional analyses. DJW reviewed, commented on and edited all

drafts of the manuscript, providing expert academic and clinical advice on the modern management cardiovascular risk. NS contributed to all drafts of the paper, was involved in discussions around clinical cut-offs, sensitivity analyses and provided expert opinion on the broader clinical context of the article with regards to evidence-based care of type 2 diabetes. SP helped with acquisition of data, data interpretation, revision and edited the manuscript. JM has contributed to developing the dataset used in this analysis. He has reviewed edited and approved the manuscript. RL has contributed to data collection and commented on the manuscript. JC contributed to the interpretation of the results and the final paper. RM contributed to writing the manuscript. PMM wrote code underlying the database structure. HMC provided guidance, reviewed all drafts, is the corresponding author and guarantor of the paper.

Conflict of interest

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Abstract

Objective: In 2019, the European Society of Cardiology led and released new guidelines for diabetes' cardiovascular risk management, reflecting recent evidence of cardiovascular disease (CVD) reduction with sodium-glucose co-transporter-2 inhibitors (SGLT-2i) and some glucagon-like peptide-1 receptor agonists (GLP1RA) in type 2 diabetes (T2D). A key recommendation is that all those with T2D who are (anti-hyperglycaemic) drug-naïve or on metformin monotherapy should be CVD-risk-stratified and an SGLT-2i or GLP1RA initiated in all those at high or very high risk, irrespective of glycated haemoglobin. We assessed the impact of these guidelines in Scotland were they introduced as is.

Research Design and Methods: Using a nationwide diabetes register in Scotland, we did a cross-sectional analysis, employing variables in our register for risk stratification at 1 January 2019. We were conservative in our definitions, assuming the absence of a risk factor where data were not available. The risk classifications were applied to those drug-naïve or metformin monotherapy people and the anticipated prescribing change calculated.

Results: Of the 265,774 people with T2D in Scotland, 53,194 (20.0% of T2D) were drug-naïve and 56,906 (21.4%) were on metformin monotherapy. Of these, 74.5% and 72.4% respectively were estimated as at least high risk given the guideline risk definitions.

Conclusion: Thus, 80,830 (30.4%) of *all* those with T2D (n=265,774) would start one of these drug classes according to table 7 and figure 3 of the guideline. The sizeable impact on drug budgets, enhanced clinical monitoring and the trade-off with reduced CVD-related healthcare costs will need careful consideration.

[247/250 words max]

Introduction

Diabetes is a significant risk factor for cardiovascular disease (CVD).[1] In recent years, new medicines have been licensed for the treatment of type 2 diabetes (T2D). In the case of sodium-glucose co-transporter 2 inhibitors (SGLT-2i) and specific glucagon-like peptide-1 receptor agonists (GLP1RA), large cardiovascular and renal outcomes' trials have variously demonstrated a lowering of the risk of future cardiovascular events, admissions due to heart failure (HF) and chronic kidney disease (CKD) progression as well as mortality postponement in people with T2D at elevated cardiovascular risk.[2–8]

In August 2019, the European Society of Cardiology (ESC) in collaboration with the European Association for the Study of Diabetes (EASD) published new guidelines on 'diabetes, pre-diabetes and CVD'.[9] These aimed to incorporate the beneficial effect on CVD of SGLT-2i and some GLP1RA in those with T2D into evidence-based guidelines but also align the management recommendations for T2D to a cardiovascular (CV) risk-stratified approach to initial treatment selection, rather like the modern management of other aspects of CV risk, particularly statins for hypercholesterolaemia.

The ESC-led guideline (table 7 and figure 3[9]) first divides people living with T2D into whether they are (anti-hyperglycaemic) drug-naïve or on metformin monotherapy, and then to one of three risk categories for CVD, depending on the presence or absence of features: very high, high and moderate risk (see table 1 for abbreviated description of these risk categories). Once assigned to being at high or very high risk, anyone currently drug-naïve or on metformin monotherapy is recommended to have a GLP1RA or an SGLT-2i with proven CV benefit[2–8] initiated, irrespective of baseline HbA1c or age (see table 2 for initial treatment algorithm modified from the guidelines)[9].

Although not currently adopted or endorsed in the United Kingdom (UK), Scotland or other countries, these guidelines are likely to influence clinical practice in many parts of Europe. In spite of the commendable aim of the ESC-led guidelines to reduce CVD in DM there is a

departure from convention in some aspects of the risk stratification and initial treatment selection for T2D. First, the disregarding of baseline HbA1c for initial treatment selection, when the trials had a minimum HbA1c in their inclusion criteria. Second, offering the agents to drug-naïve people, when those included in the trials were on background treatment. Third, and finally, issues around the tolerability and side effect profiles of these medicines such that they may be inappropriate for some or not adhered to.[2–8]

In this study we explore the potential impact of strict adherence to specific sections (figure 3 and table 7) of the guideline on new prescribing rates in the Scottish population of people with T2D through a main analysis and through a number of sensitivity analyses.

Method

We did a cross-sectional analysis, applying table 7 and figure 3 of the ESC-led guideline[9], using the Scottish Care Information (SCI)-Diabetes clinical information system. This includes >99% of those with a diagnosis of diabetes living in Scotland and records demographic information, prescriptions, routine clinical assessment (including retinal photographs), relevant laboratory measurements and, through linkage to routine administrative healthcare data (Scottish Morbidity Record 01(SMR01)), all hospital discharges. SCI-Diabetes has previously been described in detail.[10,11]

We assessed eligibility for GLP1RA and SGLT-2i in all those alive and observable (an active patient, based on recent evidence of laboratory results, prescribing, screening or hospital admission data) with T2D and either drug-naïve or on metformin monotherapy as of 1 January 2019 (our latest data extract).

CV risk, in accordance with the ESC-led guideline, was evaluated from clinical history and laboratory data in SCI-Diabetes, linked to prior hospitalisations for CVD in SMR01. We were conservative in our allocation of definitions, assuming the absence of risk factor where data were not available. We used the following definitions: we defined "established atherosclerotic CVD" (ASCVD) as prior hospital discharge that included any cardiovascular, cerebrovascular or peripheral vascular ICD-10 code (see supplementary table S1). For target organ damage, the definitions in the ESC-led guidelines are: proteinuria, renal impairment (estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2), left ventricular hypertrophy (LVH) or retinopathy. The guideline does not give a precise definition of proteinuria, so we counted all people with micro- and macroalbuminuria (albumin-creatinine ratio >3.39 mg/mmol (>30 mg/g)) as proteinuric, as would be conventional.[12] Other than 'LVH hospital discharges', which met the criterion for established ASCVD, LVH could not be captured (so our definition of target organ damage is potentially conservative in this respect). The guideline does not define retinopathy, so we used a conservative definition of having a retinopathy screening grade of moderate non-

proliferative/moderate pre-proliferative or worse retinopathy or referable maculopathy (the criterion for referral to an eye clinic in our screening programme).

The guideline specifies that the risk factors that should be considered are: age, hypertension, dyslipidaemia, smoking and obesity, but does not actually define what thresholds of these to use. Therefore we used the following cut-offs to define presence of the risk factor: age ≥65 years; a systolic blood pressure (SBP) ≥135 mmHg or treated hypertension; a low-density lipoprotein – cholesterol (LDL-C) ≥2.5mmol/L or total cholesterol (TC) ≥4.5mmol/L; current smoking; or a body mass index ≥30kg/m^2. Diabetes duration was based on date of diagnosis and verified against prescribing data, presence of diabetes codes on hospital discharge data and HbA1c data. Drug prescribing records were then utilised to define whether individuals were T2D drug-naïve or on metformin monotherapy and to define the current level of exposure to SGLT-2i and GLP1RA. Like the algorithm used in the guidelines, we treated drug-naïve and metformin monotherapy individuals separately (but also calculated the risk strata in the whole population for reference) and then assigned people to having i) moderate, ii) high or iii) very high risk of CVD. Table 3 describes the distribution of the various characteristics in the whole Scottish population with T2D and also in drug-naïve and metformin monotherapy people.

In light of the definitions of i) some forms of target organ damage and ii) the cut-offs for risk factor definitions being arbitrarily defined, we did sensitivity analyses by modifying our definitions of these to see how this changed the classification of people to risk categories and hence eligibility. We also did sensitivity analyses using different minimum thresholds of HbA1c for prescribing to examine how this changed eligibility for these medicines, as although ESC-led guidelines do not recommend consideration of these for eligibility, current prescribing guidelines in the UK and Scotland do. We also investigated the effect of setting an upper age limit for eligibility to see how this affects numbers eligible. Of note the risk algorithm in the guidelines is based on the presence or absence of ASCVD, organ damage and risk factors but not

HbA1c and age (which is considered a risk factor as a binary variable ≥65y but not an eligibility criteria) (all sensitivity analyses in table S2).

We deliberately did not undertake a cost-effectiveness analysis of this guideline given the multiple agents with different risk/benefit profiles being examined, as well as varying costs between countries. Our focus was the first component of the treatment algorithm (figure 3, page 31 of the guidelines), as the other downstream components are conditional statements based on initial treatment response, assessed by HbA1c, which cannot be known.[9]

Results

265,774 people were alive and observable with T2D in Scotland on 1 January 2019. Of these, 53,194 (20.0%) were drug-naïve and 56,906 (21.4%) were on metformin monotherapy.

Applying even our conservative risk stratification criteria to the *whole population with T2D*, 188,367 (70.9%) people were identified as being at very high risk of CVD and a further 25,957 (9.8%) were identified as being at high risk. The guideline states that simply having a diagnosis of T2D puts people at moderate CVD risk, so the remainder were classified as such (n=51,450, 19.4%).[9] In this population of people with T2D in Scotland, of those classified as very high risk, 90,396 (48.0%) had established ASCVD; 72,765 (38.6%) had target organ damage; and 138,010 (73.3%) had ≥3 major risk factors. Presence of any one of these features was sufficient to be classified as very high risk (see table 2) and some people have >1 of these. 115,756 (43.6% of all people with T2D) people had "diabetes duration >10 years (y) and least one additional risk factor", the criteria for high risk. Of these, 89,799 also met the very high risk criteria such that 25,957 were classified as high risk only.

Table 3 describes the differences between the entire population with T2D and those who are drug-naïve and on metformin monotherapy. Compared to the *whole T2D population*, the drug-naïve or on metformin monotherapy groups had fewer people with prevalent ASCVD, fewer people with organ damage and fewer people with a diabetes duration >10y. The drug-naïve and metformin monotherapy groups had similar levels of hypertension and smoking prevalence but the drug-naïve group was older (71.0y (interquartile range (IQR) 61.8, 79.3) vs 66.4y (IQR 57.1, 74.7), with fewer obese people (50.2% vs. 56.0%) and had more dyslipidaemia (47.9% vs 40.3%). The median HbA1c was lower in the drug-naïve than the metformin monotherapy group, 47mmol/mol ((IQR 42, 52) (6.5% (IQR 6.0%, 6.9%)) vs 53mmol/mol (IQR 47, 61) (7.0% (IQR 6.5%, 7.7%)), and also a lower prevalence of those with an HbA1c ≥53 mmol/mol (≥7%) (23.3% vs 51.5%).[13,14] In table 3, we also show the levels of exposure to drugs which affect CVD risk (all cardiovascular drugs, anti-hypertensives, anti-platelets, anti-coagulants and cholesterol

lowering drugs) in the groups. Most drug-naïve and metformin monotherapy people already have high levels of exposure to drugs that prevent CVD.

Of the 53,194 people who were *drug-naïve*, 4.0% were considered high risk and 70.5% very high risk. Of the 56,906 people on *metformin monotherapy* 6.5% were considered high risk and 65.9% very high risk. Drug-naïve people also had a higher prevalence of ASCVD (33.2% vs. 30.3) and ≥3 major risk factors (57.1% vs. 51.2%) which accounts for the differences in high risk and very high-risk proportions (see figure 1 for risk-stratification break down).

Thus 74.5% (n=39,630/53,194) of drug-naïve individuals and 72.4% (n=41,200/56,906) of people on metformin monotherapy (see figure 2) would be eligible to receive an SGLT-2i or GLP1RA (n= 80,830 beyond current prescribing levels of n=31,228 of people currently exposed to SGLT-2i and/or GLP1RA in Scotland). In other words, this would mean initiation of either an SGLT-2i or a GLP1RA in almost *one third* (30.4% 80,830/265,774) of people with T2D *were this guideline implemented as is*. Whilst during 2019 number of people exposed will likely have increased, most of this increase is expected to have occurred in those with T2D previously on ≥1 drug, given the current guideline recommendations.[13,14]

In our sensitivity analyses we examined lowering or raising, where appropriate, the threshold for classification of a variable not precisely defined by the guidelines, while holding the remaining variable thresholds as described above. None of the sensitivity analyses changed the total eligible population by >±6%. The greatest decrease in eligibility occurred by increasing the limit of the age risk factor to ≥70y (c.f. ≥65y), resulting in 4,108 (-5.1%) fewer people being eligible for an SGLT-2i or GLP1RA. The greatest increase in eligibility came by lowering the threshold of the dyslipidaemia risk factor total cholesterol component to ≥4.0mmol/L (c.f. ≥4.5mmol/L), leading to 4,794 (+5.9%) more people being eligible for drug therapy.

We did further sensitivity analysis exploring the effect of setting an HbA1c threshold for prescribing eligibility. In this instance, those eligible for treatment fell with an increasing HbA1c threshold for prescribing (-45.1% (n=-38,602) from baseline analysis at >48mmol/mol (>6.5%)

threshold to -80.0% (n=-66,813) at >58mmol/mol (>7.5%) threshold). We also examined the effect of setting an upper age limit for prescribing eligibility to the baseline analysis where eligibility increased with an increasing age threshold (-21.1% (n=-19,255) from baseline at ≥80y to -3.06% (n=-4,644) from baseline at ≥90y). Neither the HbA1c or age threshold are part of the risk stratification or initial therapy selection criteria in the guideline.

All sensitivity analyses are reported in table S2.

Discussion

In this conservative analysis of strict application of the ESC-led risk stratification tool to people with T2D who were drug-naïve or on metformin monotherapy, >30% of the *entire population* of those with T2D would immediately become eligible to receive an SGLT-2i or GLP1RA on the basis of CV risk stratification in our baseline analysis. Current guidelines in the UK and Scotland recommend SGLT-2i as second or subsequent-line therapy and GLP1RA as third or subsequent-line therapy on the basis of failure to achieve pre-specified HbA1c targets (although the guidelines do make allowance for earlier introduction in contemplation of pre-existing CVD).[13,14]

74.5% of drug-naïve and 72.4% of people on metformin monotherapy would be eligible to receive these new classes of drugs straight away on the basis of the guidelines (where 4.0% and 6.5% were considered high risk and 70.5% and 65.9% were considered at very high risk, respectively), a large majority. This pattern of risk classification holds in the overall Scottish population of people living with T2D (including those who are not drug-naïve or on metformin monotherapy) where the majority of people (70.9%) would be considered very high risk with a smaller proportion considered high risk (9.8%).

Our findings remained stable in sensitivity analysis (<±6% shift in eligibility for drug-naïve people and those on metformin monotherapy for every not-precisely-defined variable changed), mainly because this exercise resulted in people shifting between high risk and very high risk categories, with both groups being eligible for the new classes of medicines, and not between very high/high risk and moderate risk, which would have reduced eligibility. However, were a minimum target HbA1c threshold for prescribing introduced this would lead to a *significant decrease in eligibility for these drugs from baseline* from -45.1% to -77.8% from baseline analysis (at >48mmol/mol (>6.5%) vs. >58mmol/mol (>7.5%)). If an age-related prescribing threshold were set, this would also reduce eligibility from baseline more modestly than an HbA1c threshold, from -21.0% to -3.06% from baseline (at age >80 vs. age >90), with the reduction attenuating with increasing age.

Whether our findings of an overwhelming increase in immediate eligibility of SGLT-2i and GLP1RA prescribing by applying the ESC-led guidelines generalise to other countries remains to be seen. In Scotland we found 38.0% of the population living with T2D have prevalent ASCVD and a recent (2017) systematic review of the literature reported a prevalence of ASCVD in T2D of 32.2% worldwide (Europe = 30.0%, North America and Caribbean = 46.0%, South East Asia = 42.5%, South and Central America = 27.5%, Western Pacific (including China) = 33.6 and Middle East and North Africa = 26.9%).[15] Thus our analysis may over- or underestimate the level of eligibility to these newer classes of drugs depending on region. The proportion of drug-naïve people with T2D in Sweden was found to be 37.9% (2015)[16] and 38.5% for those on metformin monotherapy (2012)[17] (compared with 20.0% and 21.4% in Scotland respectively). Although these proportions are likely to have decreased somewhat in the intervening years, given the increased push for earlier and more intense treatment for T2D in guidelines, these numbers suggest that the proportion of people eligible for immediate initiation of an SGLT-2i or GLP1RA under the 2019 ESC-led guidelines are likely to be broadly similar in most other European countries. As a rough calculation, taking the NICE per person *per annum* (*p.a.*) costings for the cheapest SGLT-2i (canagliflozin at £477.26 *p.a.*) given to all 80,830 people eligible, this would cost ~£38.6 million in Scotland.[18]

The strengths of this study include extensive data we hold for an entire population with T2D and a large sample size with almost complete capture of variables (with the exception of echocardiographic values for LVH).

The limitations are that some of the definitions of risk factors are arbitrary (although we have attempted to use conservative working definitions). It is also unclear whether the discriminatory ability of the ESC-led risk stratification system has been validated and whether it truly identifies those who benefit most from treatment with an SGLT-2i or a GLP1RA or results in over estimation of CV risk and consequently overprescribing, particularly in light of more complex risk assessment tools recently being shown to over-estimate CV risk in T2D.[19,20] The

guidelines' algorithm for risk stratification might, indeed, be considered crude in light of more refined cardiovascular risk engines for T2D becoming available.[20] Whether it is possible to have specific risk scores that includes risk for major adverse cardiovascular events, and HF, should also be urgently investigated.

We did not perform a cost-effectiveness analysis due to the number of agents considered by the guidelines (at least 4) and thus do not provide the estimated cost benefit of CVD/CKD risk reduction, mortality postponement and reduced hospitalisation, another limitation to the study. This is because our paper's main focus is the magnitude of prescribing change however a formal cost-benefit analysis should be undertaken in due course and we hope that our data will inform this. Also this analysis would have to take into consideration modelling accounting the prescribing of SGLT-2i/GLP1RA which would occur beyond initial treatment selection in the algorithm based on the conditional statements of not achieving an HbA1c target, which we did not attempt to do. However the order of magnitude of the expected reduction in major adverse cardiovascular events can be gleaned from the hazard ratios of the cardiovascular outcomes' trials: liraglutide, 0.87 (95% confidence interval (CI) 0.78, 0.97)[5], semaglutide 0.74 (95% CI 0.58, 0.95)[6], empagliflozin 0.86 (95% CI 0.74, 0.99)[4] and canagliflozin 0.86, (95% CI 0.75, 0.97)[3].

In addition, it remains to be seen if ignoring glycaemic control for initial therapy selection is advised in future national guidelines. This is because those with acceptable glycaemic control (typically HbA1c ≤53mmol/mol (≤7%)) were not eligible for outcomes' trial participation. Thus it is unclear whether the benefits observed extend to these people.[2–8] However given recent trial evidence, the American Diabetes Association (ADA) and the EASD have recently issued a brief update to their 'management of hyperglycaemia in [T2D], 2018' guidelines.[21] This states "in appropriate high risk individuals with established [T2D], the decision to treat with a [GLP1RA] or an [SGLT-2i] to reduce [CV and CKD] outcomes should be considered independently of baseline HbA1c or individualised HbA1c target".[22] In brief, recently published outcomes' trials for i) dulaglutide showed equivalent efficacy both above and below the median

HbA1c of 56 mmol/mol (7.3%) and had no lower minimum HbA1c for enrolment[7] and ii) dapagliflozin in HF showed a reduction in HF and CV mortality outcomes in people both with and *without* diabetes.[23] On this basis, it appears that the beneficial effects of these medicines may indeed be independent of glycaemia, so disregarding baseline HbA1c for eligibility for these classes of drugs is likely to become more commonplace in the future. It will be interesting to see if the step change is incorporated into ADA Standards of Medical Care in Diabetes. However, since the main focus of the *current* ADA/EASD consensus statement remains achieving an individualised HbA1c target rather than choosing initial therapy based on CVD risk (which is the major difference in the ESC-led guidelines), our sensitivity analysis of HbA1c thresholds implies that there would be much less new prescribing under the current ADA/EASD consensus than under the ESC-led guidelines.[21] Furthermore, the outcomes' trials included people who were already on background anti-hyperglycaemic therapy (usually at least metformin), so whether the same CV advantage is seen in drug-naïve people is unclear. The guideline justifies this by stating "The results obtained from these trials, using both GLP1RAs… and SGLT2 inhibitors…, strongly suggest that these drugs should be recommended in patients with T2D with prevalent CVD or very high/high CV risk, such as those with target-organ damage or several [cardiovascular risk factors], whether they are treatment-naïve or already on metformin." It also suggests than an SGLT-2i is of particular benefit in people who exhibit "a high risk for HF", although the guideline's risk stratification tool does not appear to discriminate for this.[9]

There are known harms associated with these medicines, such as genitourinary infections and diabetic ketoacidosis with SGLT-2i, and gastrointestinal adverse effects and potential worsening of retinopathy with GLP1RA.[2–8] It is unclear whether it is possible to identify those at greatest risk of harm and, indeed, whether the adverse effect profiles of these medicines are tolerable such that those eligible would adhere with treatment, if offered. Also, the acceptability of injectable therapies (i.e. GLP-1RA), given the training, discomfort and inconvenience, is uncertain. There are also questions about whether these therapies are appropriate for the very

old or the frail, especially if added to an already extensive medication burden, although setting an age limit of 80y for prescribing only reduced eligibility by ~20% from baseline.

For the first time in the management of T2D, drug therapies that not only improve glycaemic control but reduce risk of CVD, HF and CKD, and improve survival, are available. These new ESC-led guidelines for the management of diabetes are clearly a step change in prescribing recommendations for the management of T2D incorporating, as they do, the evidence of cardiovascular benefit of SGLT-2i and GLP1RA. Such benefits are independent of glycaemia change. However, there are also controversial aspects to the guideline, which brings the management of T2D in line with others that incorporate a risk-stratified approach to the selection of initial therapy (like the risk-stratified approach recommended for the offering of statin therapy in some guidelines).

Nevertheless, a detailed health economic assessment needs to be made, balancing the costs of offering these new medicines compared to cost-savings brought about by the expected reduction in CV/HF/CKD events. Furthermore, there could be shorter-term benefits on blood pressure and weight so that it is currently difficult to establish the cost-effectiveness of these new guidelines. The costs related to the known harms associated with these medicines would also need to be taken into account, as would the monitoring for harms or training for injectable therapy.

In short, evidence exists for the benefits of SGLT-2i and GLP1RA with proven CV benefit in T2D, especially in those at elevated cardiovascular, renovascular or HF risk. We believe that policy makers will find our analysis useful when considering whether, or how, to apply the recommendations in the ESC-led 2019 guidelines on ‘diabetes, pre-diabetes and CVD’. More importantly, we hope our work can help improve future iterations of such guidelines.

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Table 1. Risk category definition modified from table 7 in the guideline[9], references to type 1 diabetes removed.

Risk category	**Characteristics**
Very high risk	Patients with diabetes mellitus (DM) and established CVD or other target organ damage; or three or more major risk factors
High risk	Patients with DM duration ≥10 years without target organ damage plus any other additional risk factor
Moderate risk	Young patients (T2D) aged <50 years) with DM duration <10 years, without other risk factors [everyone with T2D considered at moderate risk]
Definitions	
Target organ damage	Proteinuria, renal impairment defined as eGFR <30 mL/min/1.73 m^2, left ventricular hypertrophy, or retinopathy
Major risk factors	Age, hypertension, dyslipidaemia, smoking, obesity

Table 2. Initial therapy selection only, modified from figure 3 of the guideline[9]

T2D – Anti-hyperglycaemic drug-naïve		**T2D - On metformin monotherapy**	
↓		↓	
Atherosclerotic cardiovascular disease or high / very high CV risk (target organ damage or multiple risk factors)		Atherosclerotic cardiovascular disease or high / very high CV risk (target organ damage or multiple risk factors)	
Present	Absent	Present	Absent
↓	↓	↓	↓
SGLT-2i or GLP1RA monotherapy	Metformin monotherapy	Add SGLT-2i. or GLP1RA	Continue Metformin Monotherapy

Table 3, overall distribution of population characteristics contributing to risk stratification

Characteristics *contributing to risk stratification*	**Total T2D population N (%)**	**Drug-naïve population N (%)**	**Metformin monotherapy population N (%)**
T2D (denominator)	265,774 (100.0)	53,194 (100.0)	56,906 (100.0)
ASCVD	100,888 (38.0)	17,667 (33.2)	17,218 (30.3)
Target organ damage (any)	72,765 (27.4)	8,802 (16.6)	10,645 (18.7)
Proteinuria	60,660 (22.8)	7,892 (14.8)	9,548 (16.8)
Renal impairment (eGFR < 30 mL/min/1.73 m^2)	8,395 (3.16)	1,015 (1.91)	300 (0.53)
LVH	NA (NA)	NA (NA)	NA (NA)
Retinopathy	16,018 (6.03)	578 (1.09)	1,221 (2.15)
Diabetes duration >10 years	117,054 (44.0)	8,947 (16.8)	13,404 (23.6)
Major risk factor			
Age ≥65y	156,294 (58.8)	35,786 (67.3)	30,691 (53.9)
Hypertension	222,738 (83.8)	44,799 (84.2)	47,371 (83.2)
Dyslipidaemia	106,391 (40.0)	25,498 (47.9)	22,956 (40.3)
Smoking	41,107 (15.5)	7,566 (14.2)	9,920 (17.4)
Obesity	144,171 (54.3)	26,708 (50.2)	31,843 (56.0)
≥3 major risk factors[a]	138,010 (51.9)	30,392 (57.1)	29,109 (51.2)
Diabetes duration >10 years + any other additional risk factor[b]	115,756 (43.6)	8,912 (16.8)	13,275 (23.3)
Characteristics *not contributing to risk stratification*			
Age years median (IQR)[c]	68.1 (58.7, 76.5)	71.0 (61.8, 79.3)	66.4 (57.1, 74.7)
HbA1c mmol/mol median (IQR) (HbA1c % (IQR))[c]	55 (47, 67) (7.2 (6.4, 8.3))	47 (42, 52) (6.5 (6.0, 6.9))	53 (47, 61) (7.0 (6.5, 7.7))
HbA1c ≥53 mmol/mol (≥7%)[c]	151,708 (57.1)	12,373 (23.26)	29,314 (51.5)
All cardiovascular drugs [c, d]	232,623 (87.5)	45,109 (84.8)	50,669 (89.0)
Lipid modifying agents [c, d]	185,241 (69.7)	32,887 (61.8)	41,370 (72.7)
Anti-platelet agents [c, d]	83,230 (31.3)	15,044 (28.3)	16,042 (28.1)
Anti-hypertensives [c, d]	195,291 (73.5)	39,082 (73.5)	41,451 (72.8)
Anti-coagulants [c, d]	23,665 (8.90)	5,500 (10.3)	4,328 (7.61)

[a] = all classified as 'very high risk'.

[b] = criteria for 'high risk', note that some people counted here may be classified as very high risk due to the presence of additional risk factors, target organ damage or presence of ASCVD see table 1 for each risk band.

[c] = not used in risk stratification but given for reference.

[d] = see supplementary table S3 for ATC codes of drugs in these classes

Figure 1, risk stratification of drug-naïve and metformin monotherapy population

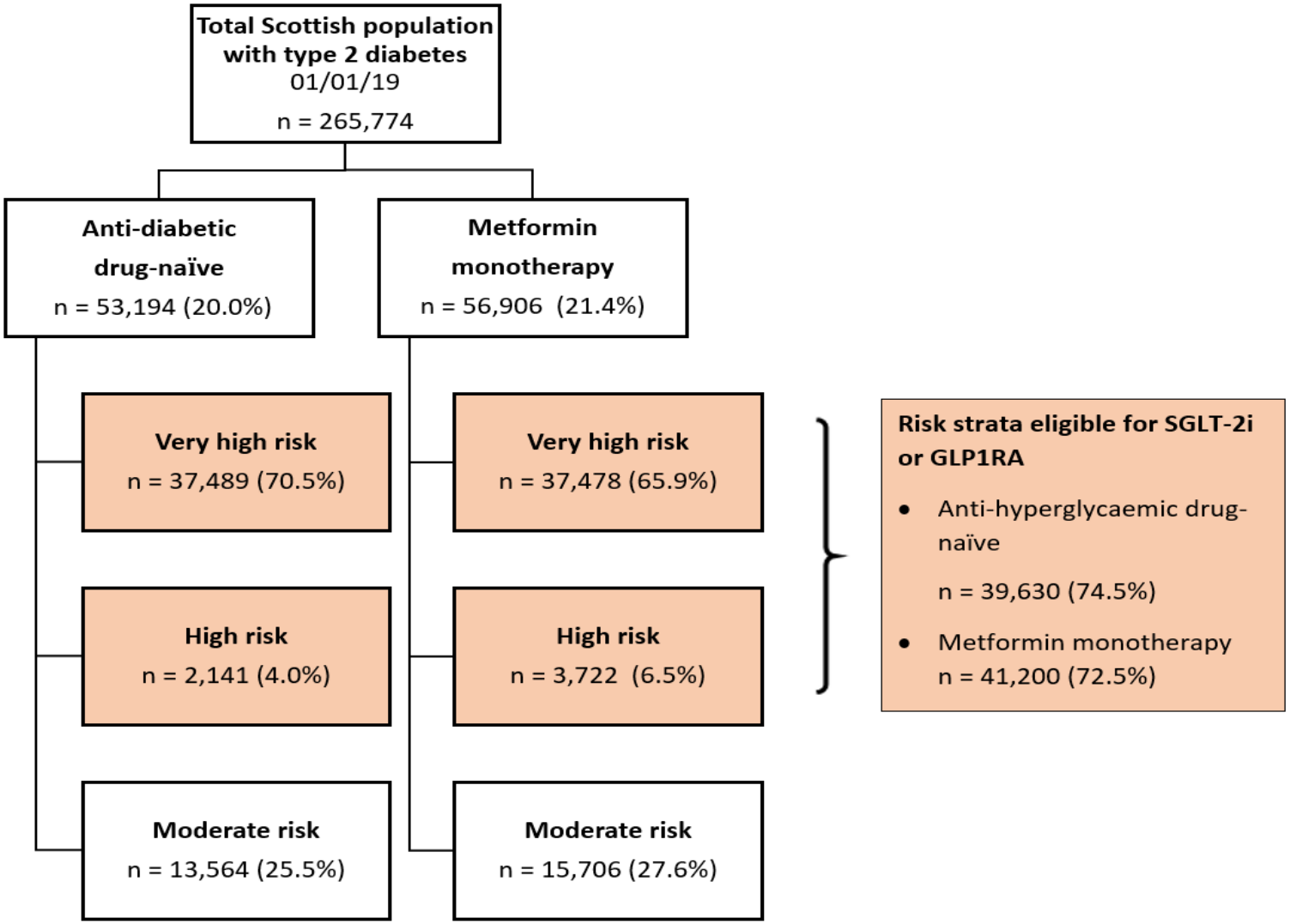
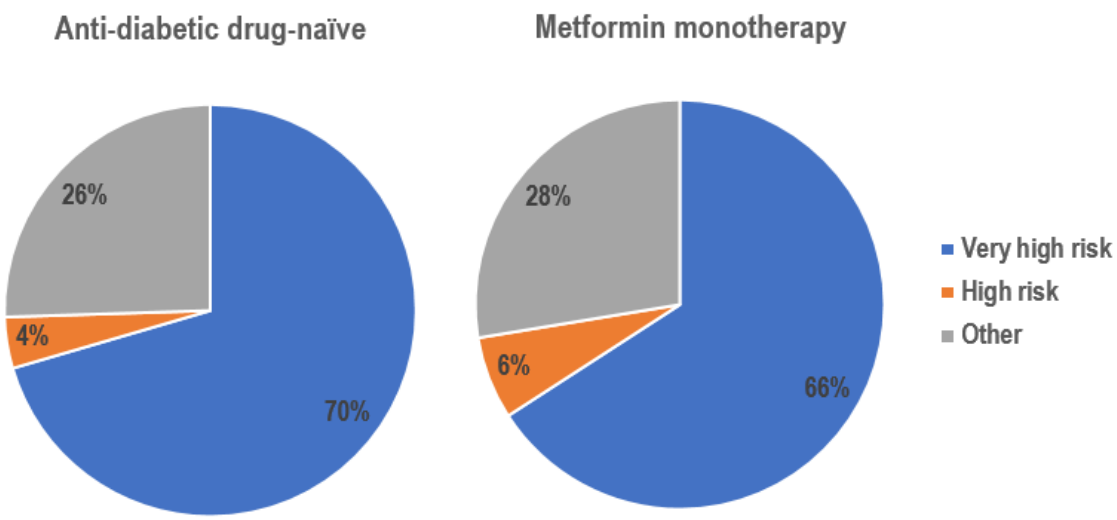


Figure 2, risk stratification of only drug-naïve and metformin monotherapy population with type 2 diabetes



Supplementary Table S1 ICD codes for ASCVD and N people

icd.code	N	description
G45.0	86	Vertebro-basilar artery syndrome
G45.1	85	Carotid artery syndrome (hemispheric)
G45.2	2	Multiple and bilateral precerebral artery syndromes
G45.3	219	Amaurosis fugax
G45.4	104	Transient global amnesia
G45.8	226	Other transient cerebral ischaemic attacks and related syndromes
G45.9	6651	Transient cerebral ischaemic attack, unspecified
G46.0	20	Middle cerebral artery syndrome
G46.1	63	Anterior cerebral artery syndrome
G46.2	67	Posterior cerebral artery syndrome
G46.3	21	Brain stem stroke syndrome
G46.4	29	Cerebellar stroke syndrome
G46.5	25	Pure motor lacunar syndrome
G46.7	264	Other lacunar syndromes
G46.8	9	Other vascular syndromes of brain in cerebrovascular diseases
I11.0	215	Hypertensive heart disease with (congestive) heart failure
I11.00	27	Hypertensive heart disease with (congestive) heart failure -- Reduced Left Ventricular Ejection Fraction (ISD Extension)
I11.01	16	Hypertensive heart disease with (congestive) heart failure -- Preserved Left Ventricular Ejection Fraction (ISD Extension)
I11.09	41	Hypertensive heart disease with (congestive) heart failure -- No information on Left Ventricular Ejection Fraction (ISD Extension)
I11.9	375	Hypertensive heart disease without (congestive) heart failure
I13.0	6	Hypertensive heart and renal disease with (congestive) heart failure
I13.00	1	Hypertensive heart and renal disease with (congestive) heart failure -- Reduced Left Ventricular Ejection Fraction (ISD Extension)
I13.09	1	Hypertensive heart and renal disease with (congestive) heart failure -- No information on Left Ventricular Ejection Fraction (ISD Extension)
I13.1	10	Hypertensive heart and renal disease with renal failure
I13.2	11	Hypertensive heart and renal disease with both (congestive) heart failure and renal failure
I13.21	3	Hypertensive heart and renal disease with both (congestive) heart failure and renal failure -- Preserved Left Ventricular Ejection Fraction (ISD Extension)
I13.9	28	Hypertensive heart and renal disease, unspecified
I20.0	14034	Unstable angina
I20.00	889	Unstable angina -- Clinical statement - 'troponin positive' - (THIS EXTENSION NOW OBSOLETE) (ISD Extension)
I20.01	1391	Unstable angina -- Clinical statement - 'troponin negative' - (THIS EXTENSION NOW OBSOLETE) (ISD Extension)
I20.02	365	Unstable angina -- Coder knows troponin was measured but has no clinical statement of 'troponin positive' or 'troponin negative - (THIS EXTENSION NOW OBSOLETE) (ISD Extension)

I20.09	775	Unstable angina -- Coder does not know if troponin was measure OR coder knows troponin not measured - (THIS EXTENSION NOW OBSOLETE) (ISD Extension)
I20.1	418	Angina pectoris with documented spasm
I20.8	2814	Other forms of angina pectoris
I20.9	67164	Angina pectoris, unspecified
I21.0	3879	Acute transmural myocardial infarction of anterior wall
I21.00	1236	Acute transmural myocardial infarction of anterior wall -- Non-ST Elevated Myocardial Infarction (NSTEMI) (ISD Extension)
I21.01	2382	Acute transmural myocardial infarction of anterior wall -- ST Elevated Myocardial Infarction (STEMI) (ISD Extension)
I21.09	265	Acute transmural myocardial infarction of anterior wall -- MI with no statement of ST elevation or non-elevation (ISD Extension)
I21.1	6167	Acute transmural myocardial infarction of inferior wall
I21.10	810	Acute transmural myocardial infarction of inferior wall -- Non-ST Elevated Myocardial Infarction (NSTEMI) (ISD Extension)
I21.11	3454	Acute transmural myocardial infarction of inferior wall -- ST Elevated Myocardial Infarction (STEMI) (ISD Extension)
I21.19	272	Acute transmural myocardial infarction of inferior wall -- MI with no statement of ST elevation or non-elevation (ISD Extension)
I21.2	560	Acute transmural myocardial infarction of other sites
I21.20	165	Acute transmural myocardial infarction of other sites -- Non-ST Elevated Myocardial Infarction (NSTEMI) (ISD Extension)
I21.21	304	Acute transmural myocardial infarction of other sites -- ST Elevated Myocardial Infarction (STEMI) (ISD Extension)
I21.29	62	Acute transmural myocardial infarction of other sites -- MI with no statement of ST elevation or non-elevation (ISD Extension)
I21.3	223	Acute transmural myocardial infarction of unspecified site
I21.30	473	Acute transmural myocardial infarction of unspecified site -- Non-ST Elevated Myocardial Infarction (NSTEMI) (ISD Extension)
I21.31	36	Acute transmural myocardial infarction of unspecified site -- ST Elevated Myocardial Infarction (STEMI) (ISD Extension)
I21.39	69	Acute transmural myocardial infarction of unspecified site -- MI with no statement of ST elevation or non-elevation (ISD Extension)
I21.4	3384	Acute subendocardial myocardial infarction
I21.40	306	Acute subendocardial myocardial infarction -- Non-ST Elevated Myocardial Infarction (NSTEMI) (ISD Extension)
I21.41	16	Acute subendocardial myocardial infarction -- ST Elevated Myocardial Infarction (STEMI) (ISD Extension)
I21.49	24	Acute subendocardial myocardial infarction -- MI with no statement of ST elevation or non-elevation (ISD Extension)
I21.9	7163	Acute myocardial infarction, unspecified
I21.90	16627	Acute myocardial infarction, unspecified -- Non-ST Elevated Myocardial Infarction (NSTEMI) (ISD Extension)
I21.91	1100	Acute myocardial infarction, unspecified -- ST Elevated Myocardial Infarction (STEMI) (ISD Extension)
I21.99	1120	Acute myocardial infarction, unspecified -- MI with no statement of ST elevation or non-elevation (ISD Extension)

I22.0	218	Subsequent myocardial infarction of anterior wall
I22.00	30	Subsequent myocardial infarction of anterior wall -- Non-ST Elevated Myocardial Infarction (NSTEMI) (ISD Extension)
I22.01	36	Subsequent myocardial infarction of anterior wall -- ST Elevated Myocardial Infarction (STEMI) (ISD Extension)
I22.09	10	Subsequent myocardial infarction of anterior wall -- MI with no statement of ST elevation or non-elevation (ISD Extension)
I22.1	428	Subsequent myocardial infarction of inferior wall
I22.10	28	Subsequent myocardial infarction of inferior wall -- Non-ST Elevated Myocardial Infarction (NSTEMI) (ISD Extension)
I22.11	92	Subsequent myocardial infarction of inferior wall -- ST Elevated Myocardial Infarction (STEMI) (ISD Extension)
I22.19	2	Subsequent myocardial infarction of inferior wall -- MI with no statement of ST elevation or non-elevation (ISD Extension)
I22.8	483	Subsequent myocardial infarction of other sites
I22.80	77	Subsequent myocardial infarction of other sites -- Non-ST Elevated Myocardial Infarction (NSTEMI) (ISD Extension)
I22.81	9	Subsequent myocardial infarction of other sites -- ST Elevated Myocardial Infarction (STEMI) (ISD Extension)
I22.89	5	Subsequent myocardial infarction of other sites -- MI with no statement of ST elevation or non-elevation (ISD Extension)
I22.9	548	Subsequent myocardial infarction of unspecified site
I22.90	643	Subsequent myocardial infarction of unspecified site -- Non-ST Elevated Myocardial Infarction (NSTEMI) (ISD Extension)
I22.91	22	Subsequent myocardial infarction of unspecified site -- ST Elevated Myocardial Infarction (STEMI) (ISD Extension)
I22.99	31	Subsequent myocardial infarction of unspecified site -- MI with no statement of ST elevation or non-elevation (ISD Extension)
I23.1	14	Atrial septal defect as current complication following acute myocardial infarction
I23.2	42	Ventricular septal defect as current complication following acute myocardial infarction
I23.4	1	Rupture of chordae tendineae as current complication following acute myocardial infarction
I23.5	7	Rupture of papillary muscle as current complication following acute myocardial infarction
I23.6	9	Thrombosis of atrium, auricular appendage, and ventricle as current complications following acute myocardial infarction
I23.8	29	Other current complications following acute myocardial infarction
I24.0	1020	Coronary thrombosis not resulting in myocardial infarction
I24.1	58	Dressler syndrome
I24.8	2912	Other forms of acute ischaemic heart disease
I24.9	1218	Acute ischaemic heart disease, unspecified
I25.0	250	Atherosclerotic cardiovascular disease, so described
I25.1	94143	Atherosclerotic heart disease
I25.2	64485	Old myocardial infarction
I25.3	257	Aneurysm of heart

I25.4	271	Coronary artery aneurysm and dissection
I25.5	480	Ischaemic cardiomyopathy
I25.50	86	Ischaemic cardiomyopathy -- Reduced Left Ventricular Ejection Fraction (ISD Extension)
I25.59	82	Ischaemic cardiomyopathy -- No information on Left Ventricular Ejection Fraction (ISD Extension)
I25.6	34	Silent myocardial ischaemia
I25.8	3251	Other forms of chronic ischaemic heart disease
I25.9	75338	Chronic ischaemic heart disease, unspecified
I50.0	4326	Congestive heart failure
I50.00	1688	Congestive heart failure -- Reduced Left Ventricular Ejection Fraction (ISD Extension)
I50.01	494	Congestive heart failure -- Preserved Left Ventricular Ejection Fraction (ISD Extension)
I50.09	5793	Congestive heart failure -- No information on Left Ventricular Ejection Fraction (ISD Extension)
I50.1	15838	Left ventricular failure
I50.10	3501	Left ventricular failure -- Reduced Left Ventricular Ejection Fraction (ISD Extension)
I50.11	496	Left ventricular failure -- Preserved Left Ventricular Ejection Fraction (ISD Extension)
I50.19	3967	Left ventricular failure -- No information on Left Ventricular Ejection Fraction (ISD Extension)
I50.9	3178	Heart failure, unspecified
I50.90	1525	Heart failure, unspecified -- Reduced Left Ventricular Ejection Fraction (ISD Extension)
I50.91	507	Heart failure, unspecified -- Preserved Left Ventricular Ejection Fraction (ISD Extension)
I50.99	4104	Heart failure, unspecified -- No information on Left Ventricular Ejection Fraction (ISD Extension)
I63.0	53	Cerebral infarction due to thrombosis of precerebral arteries
I63.1	15	Cerebral infarction due to embolism of precerebral arteries
I63.2	370	Cerebral infarction due to unspecified occlusion or stenosis of precerebral arteries
I63.3	133	Cerebral infarction due to thrombosis of cerebral arteries
I63.4	116	Cerebral infarction due to embolism of cerebral arteries
I63.5	865	Cerebral infarction due to unspecified occlusion or stenosis of cerebral arteries
I63.6	7	Cerebral infarction due to cerebral venous thrombosis, non-pyogenic
I63.8	3319	Other cerebral infarction
I63.9	11136	Cerebral infarction, unspecified
I64.0	8261	Stroke, not specified as haemorrhage or infarction
I65.0	150	Occlusion and stenosis of vertebral artery
I65.1	28	Occlusion and stenosis of basilar artery
I65.2	4409	Occlusion and stenosis of carotid artery

I65.3	21	Occlusion and stenosis of multiple and bilateral precerebral arteries
I65.8	16	Occlusion and stenosis of other precerebral artery
I65.9	8	Occlusion and stenosis of unspecified precerebral artery
I66.0	60	Occlusion and stenosis of middle cerebral artery
I66.1	80	Occlusion and stenosis of anterior cerebral artery
I66.2	77	Occlusion and stenosis of posterior cerebral artery
I66.3	41	Occlusion and stenosis of cerebellar arteries
I66.4	440	Occlusion and stenosis of multiple and bilateral cerebral arteries
I66.8	10	Occlusion and stenosis of other cerebral artery
I66.9	244	Occlusion and stenosis of unspecified cerebral artery
I69.3	550	Sequelae of cerebral infarction
I69.4	2754	Sequelae of stroke, not specified as haemorrhage or infarction
I70.2	1501	Atherosclerosis of arteries of extremities
I70.20	272	Atherosclerosis of arteries of extremities
I70.21	167	Atherosclerosis of arteries of extremities
I70.8	293	Atherosclerosis of other arteries
I70.80	101	Atherosclerosis of other arteries
I70.81	7	Atherosclerosis of other arteries
I70.9	102	Generalized and unspecified atherosclerosis
I70.90	55	Generalized and unspecified atherosclerosis
I70.91	1	Generalized and unspecified atherosclerosis
I73.9	26659	Peripheral vascular disease, unspecified
I79.2	894	Peripheral angiopathy in diseases classified elsewhere

Table S2 – Changes in risk classification and drug eligibility according to sensitivity analysis

Sensitivity analysis	Risk category	N	Absolute change (N)	Percentage age change from baseline
Baseline analysis as described in manuscript (*used as denominator throughout*)	Very high risk	188,367		
	High risk	25,957		
	Total eligible[a]	**80,830**		
	Moderate risk	51,450		
Maximal ICD-Codes • I10-120 (hypertensive disease and ischaemic heart disease) • I60-I66 (all cerebrovascular disease) • I70-I79 (atherosclerosis, aortic and other aneurysms, PVD, arterial embolism and thrombosis and capillary diseases)	Very high risk	197,233	8,866	4.71
	High risk	21,017	-4,940	-19.03
	Total eligible[a]	**82,994**	**2,164**	**2.68**
	Moderate risk	47,524	-3,926	-7.63
Microalbuminuria only	Very high risk	175,092	-13,275	-7.05
	High risk	32,428	6,471	24.93
	Total eligible[a]	**77,521**	**-3,309**	**-4.09**
	Moderate risk	58,254	6,084	13.22
Retinopathy, including background retinopathy (>R1)	Very high risk	189,090	723	0.38
	High risk	25,478	-479	-1.85
	Total eligible[a]	**80,914**	**84**	**0.10**
	Moderate risk	51,206	-244	-0.47
Age risk factor ≥60y	Very high risk	198,141	9,774	5.19
	High risk	22,901	-3,056	-11.77
	Total eligible[a]	**84,729**	**3,899**	**4.82**
	Moderate risk	44,732	-6,718	-13.06
Age risk factor ≥70y	Very high risk	178,070	-10,297	-5.47
	High risk	29,643	3,686	14.20
	Total eligible[a]	**76,722**	**-4,108**	**-5.08**
	Moderate risk	58,061	6,611	12.85
SBP ≥130mmHg	Very high risk	192,315	3,948	2.10

	High risk	25,257	-700	-2.70
	Total eligible[a]	**82,626**	**1,796**	**2.22**
	Moderate risk	48,202	-3,248	-6.31
SBP ≥140mmHg	Very high risk	185,618	-2,749	-1.46
	High risk	26,506	549	2.12
	Total eligible[a]	**79,558**	**-1,272**	**-1.57**
	Moderate risk	53,650	2,200	4.28
LDL-C ≥2.0mmol/L	Very high risk	194,027	5,660	3.00
	High risk	23,961	-1,996	-7.69
	Total eligible[a]	**83,009**	**2,179**	**2.70**
	Moderate risk	47,786	-3,664	-7.12
LDL-C ≥3.0mmol/L	Very high risk	187,164	-1,203	-0.64
	High risk	26,277	320	1.23
	Total eligible[a]	**80,294**	**-536**	**-0.66**
	Moderate risk	52,333	883	1.72
TC ≥5.0mmol/L	Very high risk	180,526	-7,841	-4.16
	High risk	28,353	2,396	9.23
	Total eligible[a]	**77,419**	**-3,411**	**-4.22**
	Moderate risk	56,895	5,455	10.58
TC ≥4.0mmol/L	Very high risk	200,716	12,349	6.56
	High risk	21,603	-4,354	-16.77
	Total eligible[a]	**85,624**	**4,794**	**5.93**
	Moderate risk	43,455	-7,996	-15.54
Eligibility Thresholds[b] - excluding those with:				
HbA1c ≤48mmol/mol (≤6.5%)	**Total eligible[a]**	**44,392**	**-38,602**	**-45.08**
HbA1c ≤53mmol/mol (≤7%)	**Total eligible[a]**	**27,159**	**-55,835**	**-66.40**
HbA1c ≤58mmol/mol (≤7.5%)	**Total eligible[a]**	**16,181**	**-66,813**	**-79.98**
≥80y[b]	**Total eligible[a]**	**63,739**	**-19,255**	**-21.14**
≥85y	**Total eligible[a]**	**73,021**	**-9,973**	**-9.66**
≥90y	**Total eligible[a]**	**78,350**	**-4,644**	**-3.06**

[a] = Total eligible only includes those people who are drug-naïve or on metformin monotherapy.

[b] = characteristics not included in risk stratification criteria (hence risk categories not reported). People above/below specified cut off excluded (having previously been either drug-naïve or on metformin monotherapy and eligible).