Prescribing Paradigm Shift? Applying the 2019 European Society of Cardiology–Led Guidelines on Diabetes, Prediabetes, and Cardiovascular Disease to Assess Eligibility for Sodium–Glucose Cotransporter 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

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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 cotransporter 2 inhibitors (SGLT-2is) and some glucagon-like peptide 1 receptor agonists (GLP-1RAs) in type 2 diabetes (T2D). A key recommendation is that all those with T2D who are (antihyperglycemic) drug naïve or on metformin monotherapy should be CVD risk stratified and an SGLT-2i or a GLP-1RA initiated in all those at high or very high risk, irrespective of glycated hemoglobin. 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, using 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 people who were drug naïve or on metformin monotherapy and the anticipated prescribing change calculated.

RESULTS

Of the 265,774 people with T2D in Scotland, 53,194 (20.0% of those with 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.

CONCLUSIONS

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 health care costs will need careful consideration.

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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 cotransporter 2 inhibitors (SGLT-2is) and specific glucagon-like peptide 1 receptor agonists (GLP-1RAs), large cardiovascular (CV) and renal outcomes trials have variously demonstrated a lowering of the risk of future CV events, admissions because of heart failure (HF), and chronic kidney disease (CKD) progression, as well as mortality postponement in people with T2D at elevated CV 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, prediabetes, and CVD (9). These not only aimed to incorporate the beneficial effect on CVD of SGLT-2is and some GLP-1RAs in those with T2D into evidence-based guidelines but also aligned the management recommendations for T2D to a CV risk–stratified approach to initial treatment selection, rather like the modern management of other aspects of CV risk, particularly statins for hypercholesterolemia.

The ESC-led guideline [table 7 and figure 3 (9)] first divides people with T2D into whether they are (antihyperglycemic) drug naïve or on metformin monotherapy and then to one of three risk categories for CVD, depending on the presence or absence of the following 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 GLP-1RA or an SGLT-2i with proven CV benefit (2–8) initiated, irrespective of baseline glycated hemoglobin (HbA_{1c}) or age (see Table 2 for initial treatment algorithm modified from the guidelines) (9).

Although not currently adopted or endorsed in the U.K., Scotland, or other countries, these guidelines are likely to influence clinical practice in many parts of Europe. Despite the commendable aim of the ESC-led guidelines to reduce CVD in T2D, there is a departure from convention in some aspects of the risk stratification and initial treatment selection for T2D: *1*) the disregarding of baseline HbA_{1c} for initial treatment selection, when the trials had a minimum HbA_{1c} in their inclusion criteria; *2*) the offering of the agents to people who were drug naïve when those included in the trials were on background treatment; and *3*) the 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 (9)] 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.

RESEARCH DESIGN AND METHODS

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 health care data (Scottish Morbidity Record 01), all hospital discharges. SCI-Diabetes has previously been described in detail (10,11).

We assessed eligibility for GLP-1RAs and SGLT-2is in all those alive and observable (an active patient on the basis of recent evidence of laboratory results, prescribing, screening, or hospital admission data) with T2D and who were 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 and linked to prior hospitalizations for CVD in the Scottish Morbidity Record 01. 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 CV, cerebrovascular, or peripheral vascular ICD-10 code (see Supplementary Table 1). 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 nonproliferative/moderate preproliferative or worse retinopathy or referable maculopathy (the criterion for referral to an eye clinic in our screening program).

The guideline specifies that the risk factors that should be considered are age, hypertension, dyslipidemia, smoking, and obesity but does not actually define what thresholds of these to use. Therefore, we used the following cutoffs to define presence of the risk factor: age ≥65 years, systolic blood pressure ≥135 mmHg or treated hypertension, an LDL cholesterol ≥2.5 mmol/L or total cholesterol ≥4.5 mmol/L, current smoking, or BMI ≥30 kg/m^2. Diabetes duration was based on date of diagnosis and verified

Table 1—Risk category definition modified from table 7 in the ESC-led guideline (9), references to type 1 diabetes removed

Risk category	Characteristics
Very high risk	Patients with DM and established CVD, 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, LVH, or retinopathy
Major risk factors	Age, hypertension, dyslipidemia, smoking, obesity

DM, diabetes mellitus.

Table 2—Initial therapy selection only, as modified from figure 3 of the ESC-led guideline (9)

T2D: antihyperglycemic drug naïve		T2D: on metformin monotherapy	
↓		↓	
ASCVD or high/very high CV risk (target organ damage or multiple risk factors)		ASCVD or high/very high CV risk (target organ damage or multiple risk factors)	
Present	Absent	Present	Absent
↓	↓	↓	↓
SGLT-2i or GLP-1RA monotherapy	Metformin monotherapy	Add SGLT-2i or GLP-1RA	Continue metformin monotherapy

against prescribing data, presence of diabetes codes on hospital discharge data, and HbA_{1c} data. Drug prescribing records were then used to define whether individuals were T2D drug naïve or on metformin monotherapy and to define the current level of exposure to SGLT-2is and GLP-1RAs. Like the algorithm used in the guidelines, we treated individuals who were drug naïve and on metformin monotherapy separately (but also calculated the risk strata in the whole population for reference) and then assigned people to having *1*) moderate, *2*) high, or *3*) very high risk of CVD. Table 3 describes the distribution of the various characteristics in the whole Scottish population with T2D and in people who are drug naïve and on metformin monotherapy.

In light of the definitions of *1*) some forms of target organ damage and *2*) the cutoffs 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 HbA_{1c} for prescribing to examine how this changed eligibility for these medicines because although ESC-led guidelines do not recommend consideration of these for eligibility, current prescribing guidelines in the U.K. 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 HbA_{1c} and age (which is considered a risk factor as a binary variable $\geq$65 years but not an eligibility criterion) (all sensitivity analyses in Supplementary Table 2).

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 (9)] because the other downstream components are conditional statements that are based on initial treatment response, as assessed by HbA_{1c}, which cannot be known.

RESULTS

A total of 265,774 people with T2D were alive and observable 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 three or more 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 more than one of these. A total of 115,756 (43.6%) people with T2D had diabetes duration >10 years and least one additional risk factor, which are 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 with the whole T2D population, the drug-naïve or metformin monotherapy groups had fewer people with prevalent ASCVD, fewer people with organ damage, and fewer people with a diabetes duration >10 years. The drug-naïve and metformin monotherapy groups had similar levels of hypertension and smoking prevalence, but the drug-naïve group was older (71.0 years [interquartile range (IQR) 61.8, 79.3] vs. 66.4 years [57.1, 74.7]), with fewer people with obesity (50.2% vs. 56.0%) and more with dyslipidemia (47.9% vs. 40.3%). The median HbA_{1c} was lower in the drug-naïve than in the metformin monotherapy group (47 mmol/mol [IQR 42, 52] [6.5% (6.0%, 6.9%)] vs. 53 mmol/mol [47, 61] [7.0% (6.5%, 7.7%)]), and there was a lower prevalence of those with an HbA_{1c} $\geq$53 mmol/mol ($\geq$7%) (23.3% vs. 51.5%) (13,14). In Table 3, we also show the levels of exposure to drugs that affect CVD risk (all CV drugs, antihypertensives, antiplatelets, anticoagulants, and cholesterol-lowering drugs) in the groups. Most people in the drug-naïve and metformin monotherapy groups 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. People in the drug-naïve group also had a higher prevalence of ASCVD (33.2% vs. 30.3%) and three or more major risk factors (57.1% vs. 51.2%), which accounts for the differences in high-risk and very-high-risk proportions (see Fig. 1 for risk stratification breakdown).

Thus, 74.5% (n = 39,630 of 53,194) of individuals who were drug naïve and 72.4% (n = 41,200 of 56,906) of those on metformin monotherapy (see Fig. 2) would be eligible to receive an SGLT-2i or a GLP-1RA (n = 80,830 beyond current prescribing levels of n = 31,228 people currently exposed to SGLT-2is and/or GLP-1RAs in Scotland). In other words, this would mean initiation of either an SGLT-2i or a GLP-1RA in almost one-third (30.4%, n = 80,830 of 265,774) of people with T2D were this guideline implemented as is.

Table 3—Overall distribution of population characteristics contributing to risk stratification

Characteristic	Population, *n* (%)		
	Total T2D	Drug naïve	Metformin monotherapy
Contributing to risk stratification			
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
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 ≥65 years	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)
Dyslipidemia	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)
Three or more 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)
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)
HbA_{1c}, median (IQR)			
mmol/mol	55 (47, 67)	47 (42, 52)	53 (47, 61)
%[c]	7.2 (6.4, 8.3)	6.5 (6.0, 6.9)	7.0 (6.5, 7.7)
HbA_{1c} ≥53 mmol/mol (≥7%)[c]	151,708 (57.1)	12,373 (23.26)	29,314 (51.5)
All CV 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)
Antiplatelet agents[c,d]	83,230 (31.3)	15,044 (28.3)	16,042 (28.1)
Antihypertensives[c,d]	195,291 (73.5)	39,082 (73.5)	41,451 (72.8)
Anticoagulants[c,d]	23,665 (8.90)	5,500 (10.3)	4,328 (7.61)

NA, not available. [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 because of 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 3 for Anatomical Therapeutic Chemical (ATC) codes of drugs in these classes.

While during 2019 the number of people exposed will likely have increased, most of this increase is expected to have occurred in those with T2D previously on one or more drugs, 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 more than ±6%. The greatest decrease in eligibility occurred by increasing the limit of the age risk factor to ≥70 years (cf., ≥65 years), resulting in 4,108 (−5.1%) fewer people being eligible for an SGLT-2i or a GLP-1RA. The greatest increase in eligibility came by lowering the threshold of the dyslipidemia risk factor total cholesterol component to ≥4.0 mmol/L (cf., ≥4.5 mmol/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 HbA_{1c} threshold for prescribing eligibility. In this instance, those eligible for treatment fell with an increasing HbA_{1c} threshold for prescribing (−45.1% [$n = -38{,}602$] from baseline analysis at a >48 mmol/mol [>6.5%] threshold to −80.0% [$n = -66{,}813$] at a >58 mmol/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 ≥80 years to −3.06% [$n = -4{,}644$] from baseline at ≥90 years). Neither the HbA_{1c} nor the age threshold are part of the risk stratification or initial therapy selection criteria in the guideline. All sensitivity analyses are reported in Supplementary Table 2.

CONCLUSIONS

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 a GLP-1RA on the basis of CV risk stratification in our baseline analysis. Current guidelines in the U.K. and Scotland recommend SGLT-2is as second- or subsequent-line therapy and GLP-1RAs as third- or subsequent-line therapy on the basis of failure to achieve prespecified HbA_{1c} targets (although the guidelines do make allowance for earlier introduction in contemplation of preexisting CVD) (13,14).

On the basis of the guidelines, 74.5% of people who are drug naïve and 72.4% on metformin monotherapy would be eligible to receive these new classes of drugs straight away (where 4.0% and 6.5% were considered high risk and 70.5% and 65.9% considered 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

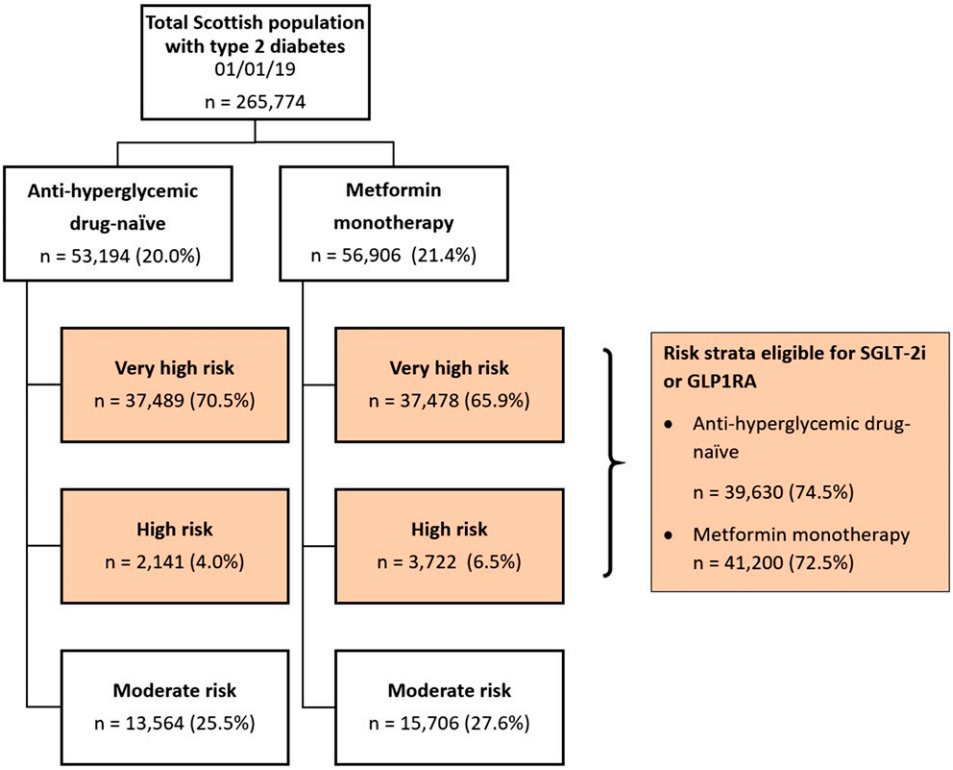

Figure 1—Risk stratification of drug-naïve and metformin monotherapy populations.

risk, with a smaller proportion considered high risk (9.8%).

Our findings remained stable in sensitivity analysis (less than a ±6% shift in eligibility for people who are drug naïve 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 HbA_{1c} threshold for prescribing introduced, this would lead to a significant decrease in eligibility for these drugs from baseline of −45.1% to −77.8% from the baseline analysis (at >48 mmol/mol [>6.5%] vs. >58 mmol/mol [>7.5%]). If an age-related prescribing threshold were set, this would also reduce eligibility from baseline more modestly than an HbA_{1c} threshold of −21.0% to −3.06% from baseline (at age >80 vs. age >90 years), with the reduction attenuating with increasing age.

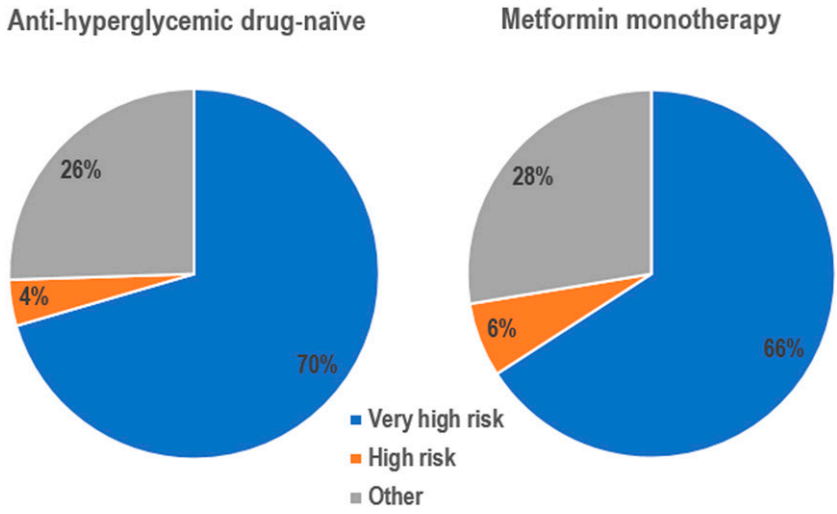

Figure 2—Risk stratification of only drug-naïve and metformin monotherapy populations with T2D.

Whether our findings of an overwhelming increase in immediate eligibility of SGLT-2i and GLP-1RA prescribing by applying the ESC-led guidelines generalize to other countries remains to be seen. In Scotland, we found that 38.0% of the population living with T2D have prevalent ASCVD, and a 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%, 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 people with T2D who were drug naïve in Sweden was found to be 37.9% in 2015 (16) and 38.5% for those on metformin monotherapy in 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 a GLP-1RA under the 2019 ESC-led guidelines is likely to be broadly similar in most other European countries. As a rough calculation, taking the National Institute for Health and Care Excellence per person per annum, costs for the cheapest SGLT-2i (canagliflozin at £477.26 per annum) given to all 80,830 people eligible would be ~£38.6 million in Scotland (18).

The strengths of this study include the 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 GLP-1RA or results in overestimation of CV risk and consequently overprescribing, particularly in light of more complex risk assessment tools currently being shown to overestimate CV risk in T2D (19,20). The guidelines's algorithm for risk stratification might, indeed, be considered crude in light of more-refined CV risk engines for T2D becoming available (20). Whether it is possible to have specific risk scores that include risk for major adverse CV events and HF should also be urgently investigated.

We did not perform a cost-effectiveness analysis because of the number of agents considered by the guidelines (at least four) and, thus, do not provide the estimated cost benefit of CVD/CKD risk reduction, mortality postponement, and reduced hospitalization, another limitation of the study. This limitation is a result of our study's main focus on 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 modeling that accounts for the prescribing of SGLT-2is/GLP-1RAs, which would occur beyond initial treatment selection in the algorithm on the basis of the conditional statements of not achieving an HbA_{1c} target, which we did not attempt to do. However, the order of magnitude of the expected reduction in major adverse CV events can be gleaned from the hazard ratios of the CV outcomes trials: liraglutide 0.87 (95% CI 0.78, 0.97) (5), semaglutide 0.74 (0.58, 0.95) (6), empagliflozin 0.86 (0.74, 0.99) (4), and canagliflozin 0.86 (0.75, 0.97) (3).

In addition, it remains to be seen whether ignoring glycemic control for initial therapy selection is advised in future national guidelines because those with acceptable glycemic control (typically $HbA_{1c} \leq 53$ mmol/mol [$\leq 7\%$]) were not eligible for outcomes trial participation. Thus, it is unclear whether the benefits observed extend to these people (2–8). However, given more recent trial evidence, the American Diabetes Association (ADA) and the EASD have issued a brief update to their 2018 management of hyperglycemia in T2D guidelines (21), which state that in appropriate high-risk individuals with established T2D, the decision to treat with a GLP-1RA or an SGLT-2i to reduce CV and CKD outcomes should be considered independently of baseline HbA_{1c} or individualized HbA_{1c} target (22). In brief, recently published outcomes trials for *1*) dulaglutide showed equivalent efficacy both above and below the median HbA_{1c} of 56 mmol/mol (7.3%) and had no lower minimum HbA_{1c} for enrollment (7) and for *2*) dapagliflozin in HF showed a reduction in HF and CV mortality outcomes in people with and without diabetes (23). On this basis, it appears that the beneficial effects of these medicines may indeed be independent of glycemia, so disregarding baseline HbA_{1c} for eligibility for these classes of drugs is likely to become more commonplace in the future. It will be interesting to see whether 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 on achieving an individualized HbA_{1c} target rather than choosing initial therapy on the basis of CVD risk (which is the major difference in the ESC-led guidelines), our sensitivity analysis of HbA_{1c} 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 antihyperglycemic therapy (usually at least metformin), so whether the same CV advantage is seen in those who are drug naïve is unclear. The guideline justifies this by stating that the results obtained from these trials, using both GLP-1RAs and SGLT-2is, 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 CV 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 guidelines'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-2is and gastrointestinal adverse effects and potential worsening of retinopathy with GLP-1RAs (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 80 years for prescribing only reduced eligibility by ~20% from baseline.

For the first time in the management of T2D, drug therapies that not only improve glycemic control but also 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 CV benefit of SGLT-2is and GLP-1RAs. Such benefits are independent of glycemia 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 (e.g., 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 with cost savings brought about by the expected reduction in CV, HF, and 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-2is and GLP-1RAs with proven CV benefit in T2D, especially in those at elevated CV, renovascular, or HF risk. We believe that policymakers will find our analysis useful when considering whether, or how, to apply the recommendations in the ESC-led 2019 guidelines on diabetes, prediabetes, and CVD. More importantly, we hope that our work can help to improve future iterations of such guidelines.

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