Achievement of the ESC recommendations for secondary prevention of cardiovascular risk factors in high-risk patients with type 2 diabetes: A real-world national cohort analysis

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Abstract

Aim: To assess compliance with European Society of Cardiology (ESC) secondary prevention recommendations in a nationwide contemporary population with diabetes mellitus (DM) and coronary artery disease.

Method: We conducted a retrospective observational study using linked health data in patients across Wales with DM undergoing percutaneous coronary intervention (2012 – 2017). The follow-up was for one year. We analysed the clinical characteristics, medications, target levels for HbA1c, low-density lipoprotein cholesterol (LDL-C), non-high-density lipoprotein cholesterol (non-HDL-C) and blood pressure against the ESC prevention guidelines.

Results: Overall, 3,478 patients with diabetes had available data at 1-year post-PCI. Only 43% had HbA1c levels <53mmol/L, but 81% had blood pressure <140/80 (current ESC targets).

Prescribing frequency of the newer hypoglycaemic agents (glucagon-like peptide-1 receptor agonists and sodium-glucose co-transporter 2 inhibitors) was suboptimal, with a higher rate in patients with HbA1c ≥53 mmol/mol.

51% & 27% of the patients had LDL-C levels <1.8 &1.4 mmol/L (2016 & 2019 guidelines recommendations respectively), and 55% & 34% had non-HDL-C levels <2.6 & 2.2 mmol/L (2016 & 2019 guidelines respectively). Of the uncontrolled LDL-C patients, only 42% (2016 target) and 35% (2019 target) were prescribed high-intensity statins. Females were more likely to have LDL-C targets above the recommended level.

Conclusion: Achievement of ESC treatment goals in this very-high risk cohort for DM and hyperlipidaemia was far from optimal, with a low prescription rate of the guidelines-recommended therapy. Target goals for hypertension were met more frequently. An up-to-date analysis reflecting the current practice against the most recent guidelines is warranted.

Keywords: Diabetes, lipids, cholesterol, statins, hypertension, pharmacoepidemiology, percutaneous coronary intervention, secondary prevention

Introduction

Patients with diabetes mellitus (DM) and previous atherosclerotic cardiovascular disease (ASCVD) are at very high risk of future cardiovascular disease (CVD), with a quoted 10-year risk of CVD death >10% (1). To mitigate against this risk, the European Society of Cardiology (ECS) guidelines advocate optimal glycaemic control post-percutaneous coronary intervention (PCI) along with associated risk factors. A near-normal HbA1c level of <7.0% (<53 mmol/mol) is the recommended target to reduce vascular complications (2). Furthermore, these guidelines recommend adding the relatively newer agents, glucagon-like peptide-1 receptor agonists (GLP-1RA) and sodium-glucose co-transporter 2 inhibitors

(SGLT2 inhibitors) to the standard glucose-lowering regime due to cardiovascular (CV) benefits demonstrated in several Cardiovascular Outcome Trials (CVOTs) (3,4). In addition, there is also an emphasis on controlling the lipid profile and blood pressure (BP) to prevent CVD. Currently, for very high-risk patients, the ESC (2019 guidelines) recommends a therapeutic regime that will achieve a 50% reduction in low-density lipoprotein cholesterol (LDL-C) from the baseline with an LDL-C target level of <1.4 mmol/L (reduced from <1.8 mmol/L in the 2016 guidelines) and non-high-density lipoprotein cholesterol (non-HDL- C) targets of <2.2 mmol/L (reduced from <2.6 mmol/L in the 2016 guidelines) (1,5). Furthermore, patients with DM and hypertension should be treated in an individualised manner. The recommended systolic BP (SBP) target is 130 mmHg in patients with DM and even <130 mmHg if tolerated. In older adults (aged >65 years), the SBP target is 130 - 139 mmHg. The recommended diastolic BP (DBP) target is <80 mmHg (2).

Approximately 8% of the population in Wales aged 17 years and over are living with DM – the highest prevalence in the UK (6), with 4% known to have coronary artery disease (CAD) (7). Little is known about the proportion of those patients who achieve the ESC targets of HbA1c, lipids and BP. A better understanding of these relationships will offer a valuable opportunity to optimise CVD risk factors. Therefore, this study aims to examine the achievement of the ESC guideline recommendations in a contemporary national cohort of patients from Wales with DM and known CAD.

Methods

We undertook a retrospective, observational cohort study of glycaemic control and CVD risk factor management for patients with DM who had a PCI in Wales, UK, between January 2012 and December 2017 and had a one-year follow-up period. Data linkage was performed using the Secure Anonymised Information Linkage (SAIL) data bank (8). SAIL is part of the

national e-health records research infrastructure for Wales; the following linked data sources are held within SAIL: secondary care hospital admission data within the Patient Episode Database for Wales (PEDW), primary care General Practitioner (GP) data within the Welsh Longitudinal General Practice (WLGP), demographic data and GP registration history within the Welsh Demographic Service Dataset (WDSD).

All study subjects were >18 years of age, with at least 90 days of follow-up data available in the WLGP with a documented history of DM. The index date was assigned to the date of the first PCI during the study period for each patient. The follow-up duration was set at 1 year from the discharge date of the index hospital admission. The WLGP data was used to describe the presence of hypertension, ischemic heart disease, chronic kidney disease (CKD) stage IV+, chronic liver disease, dementia, recorded lipid levels, HbA1c and blood pressure levels, prescriptions of glucose-lowering agents, lipid-lowering therapy and anti-hypertensive agents. In addition, PEDW and WLGP data were used to describe a prior history of myocardial infarction, heart failure and ischaemic stroke.

HbA1c levels and glucose-lowering agents

Medical prescriptions of all the glucose-lowering agents were documented in the first 90 days after discharge following the index PCI. These medications were grouped a priori as - (i) oral anti-diabetic agents (including Metformin, Gliclazide, and Dipeptidyl peptidase-4 [DPP-4] inhibitors), (ii) newer anti-diabetic agents (SGLT2 inhibitors or GLP-1 RAs) with or without any other oral anti-diabetic agents, (iii) insulin-based therapy (any type of insulin with or without oral agents – excluding SGLT2 inhibitors and GLP-1 RAs), (iv) other treatments (including acarbose, meglitinides and thiazolidinedione), (v) no treatment.

We identified the number (and proportions) of patients achieving the ESC HbA1c target of <53 mmol/mol (controlled group) or above target HbA1c ≥53 mmol/mol (non-controlled group) and their respective glucose-lowering regimen.

Lipid profile levels and lipid-modifying therapies

An optimised LDL-C was defined as a level <1.4 mmol/L and <1.8 mmol/L (according to the 2019 and 2016 ESC guidelines for dyslipidaemias, respectively). Similarly, an optimised non-HDL level was defined as <2.2 mmol/L and <2.6 mmol/L (according to 2019 and 2016 guidelines, respectively) (1,5). Patients with lipid targets outside these ranges were counted as having a non-controlled lipid profile. Lipid-lowering therapy (LLT) was documented within 90 days following discharge after a PCI and classified as described in our previous study (9) as (i) high-intensity statin (HI-statin; atorvastatin ≥40 mg/d and rosuvastatin ≥20 mg/d), (ii) non-high-intensity statin (NI-statin; any other statin prescription), (iii) combination therapy (e.g. combination of ezetimibe with either HI- or NI-statin), (iv) other monotherapy treatment (e.g. ezetimibe or fibrate), (v) no treatment.

Blood pressure readings and anti-hypertensive therapies

Since the mean age group of all patients was 66 ± 11 years, patients with SBP <140 mmHg and/or DBP <80 mmHg were categorised as meeting the ESC recommended BP targets and labelled as the controlled BP group (2). Patients with BP recordings above this range were classified as the non-controlled BP group. The medical prescription of all the anti-hypertensive agents was documented in the first 90 days following PCI.

Statistical analysis

Continuous variables were presented as mean ± standard deviation, and differences were assessed by independent t-test. Categorical variables were described as a number (n) with percentage (%), and differences were analysed by Pearson $\chi 2$ or Fisher exact. Comparisons between groups during follow-up were performed using a two-sample t-test as appropriate. All tests were 2-tailed, and $p < 0.05$ was considered statistically significant. Model selection for all analyses was conducted using a forward stepwise approach in SPSS (v22.0).

Results

Baseline characteristics of the study sample with diabetes

The sample size during the study consisted of 25,690 patients admitted to the hospital for PCI. 18,302 (71%) patients had linked primary care data available. Of those, 4,184 (23%) patients had documented history of DM. Altogether, 3,478 (83%) patients with diabetes had available information on SAIL at a 1-year follow-up. Out of the 706 patients with no data at 1 year, 351 (50%) had died, and the remaining 355 patients were counted as follow-up loss. Supplementary material figure 1 summarises the study population cohort selection and numbers excluded.

Patients who completed the follow-up period were more likely to be males and had a younger age ($p < 0.001$ and 0.02, respectively) compared to their counterparts. In addition, a history of heart failure with reduced ejection fraction (HFrEF), chronic kidney disease (CKD) stage IV and previous stroke were more common in the group of patients without 1-year follow-up ($p < 0.001$, 0.03 and < 0.001, respectively). The other variables were comparable.

Table 1 in the supplementary material summarises the characteristics of patients with diabetes with and without 1-year available follow-up data.

HbA1c levels and glucose-lowering agents

In total, 3,031 (87%) of the cohort had at least one documented HbA1c during the follow-up period (mean HbA1c 59 ±16 mmol/mol), of which 1,298 (43%) had controlled glucose levels with at least one HbA1c reading <53mmol/L (Figure 1). The median time between discharge post PCI and the lowest recorded HbA1c level was 113 days. These patients were more likely to be older or have a history of hypertension compared to the non-controlled group ($p < 0.001$ and < 0.001, respectively). Patients with a history of a previous MI (prior to the index admission) and CKD stage IV were more likely to have uncontrolled HbA1c ($p=0.04$ and 0.003, respectively). Table 1 summarises the personal characteristics of both groups.

In total, 180 (10%) patients in the non-controlled group did not receive any hypoglycaemic drug treatment compared to 482 (37%) patients in the control group (p <0.001). There were 619 (36%) patients receiving insulin therapy in the non-controlled group, compared to 101 (8%) patients in the controlled group (p <0.001).

There were 934 (54%) patients treated with non-insulin-based therapy compared to 715 (55%) in the controlled group. Of these, only 85 (8%) patients from the non-controlled group received either an SGLT2 inhibitor or GLP-1 RA (33 patients on SGLT2 inhibitor and 56 patients on GLP-1 RA, 4 patients were on both agents). In comparison, 28 (2%) patients in the controlled group were treated with those agents (11 patients on SGLT2 inhibitor and 16 patients on GLP-1 RA, p <0.001). Figure 2 shows the frequency distribution of prescribed hypoglycaemic medications among both groups.

Lipid profile levels and lipid-modifying therapies

Of 3,478 diabetes individuals, 2,551 (73%) patients had LDL-C recorded during the 1-year follow-up (mean LDL-C 1.9 ±0.8 mmol/L). Of these, 300 (8.5%) patients had their first lipid profile checked within 30 days of discharge (Supplementary material Figure 2).

The mean time between discharge post PCI and the lowest LDL -C was 126 days. The median time between discharge post PCI and the last recorded lipid profile was 130 days.

In total, 1313 (51%) patients had achieved LDL-C levels below the 2016 ESC target of 1.8 mmol/L, but only 694 (27%) were below the 2019 target of 1.4 mmol/l (figure 3A). Females were less likely to achieve the 2016 LDL-C recommended target <1.8 mmol/L (23.5% vs 76.5% male patients, p <0.001). This percentage was reduced with further stringent of the LDL-C target to <1.4 mmol/L in the 2019 guidelines (21% vs 79% male patients, p <0.001).

Regarding patients with documented LDL-C levels ≥1.4 and 1.8 mmol/L, only 774 (42 %) and 438 (35%) respectively, were prescribed HI-statins; 77 (4%) and 57 (5%) respectively

were prescribed a combination of ezetimibe and/or fibrate plus a statin, with 54 (3%) and 52 (4%) prescribed ezetimibe and/or fibrate without a statin (p <0.001) (Figure 4A & 4B).

Non-HDL-C levels were documented in 1171 patients (mean Non-HDL-C 2.1 ±1.1 mmol/L), of whom 401 (34%) patients had non-HDL-C levels <2.2 mmol/L (2019 guidelines) and 639 (55%) had non-HDL-C levels <2.6 mmol/L (2016 guidelines) (figure 3B).

Of patients with non-HDL-C levels ≥2.2 mmol/L and ≥2.6, only 366 (48%) and 439 (69%) respectively were prescribed HI-statins, 35 (4.5%) and 27 (5%) respectively were prescribed a combination of ezetimibe and/or fibrate plus a statin and 22 (3.0%) and 21 (4%) respectively were prescribed ezetimibe and/ or fibrate without a statin (p <0.001) (Figure 3 - supplementary materials).

Blood pressure readings and anti-hypertensive therapies

In total, 3,374 (97%) patients had at least one recorded BP reading during the 1-year follow-up period (mean ±SD: SBP 121 ±14 mmHg, DBP 67 ±12 mmHg). 3,259 (97%) patients had controlled BP (3,040 (90%) with controlled SBP; 2,958 (88%) with controlled DBP; and 2,739 (81%) with both controlled SBP and DBP) (figure 4 - supplementary materials).

Figure 5 - supplementary materials shows the frequency distribution of prescribing anti-hypertensive medications among both groups.

Discussion

This study examined the achievement of the ESC recommendations in a contemporary post-PCI Welsh population with DM. Notably, less than half achieved the target HbA1c, and just over a quarter achieved the target LDL-C. Achievement of the BP target was high at 81%. Only 7% of patients met the most up-to-date recommended targets for three parameters combined. This percentage went up to 13% if the lipid targets were adjusted to the 2016 guidelines recommendation.

Of the three main CVD risk factors, achievement of LDL-C was the lowest overall. In the 2019 ESC guidance, the recommended lipid level targets in patients with DM and CAD were an LDL-C reduction of ≥50% from baseline and a level of <1.4 mmol/L (<55 mg/dl) (1), reduced from the level of <1.8 mmol/L (<70 mg/dl) in 2016 (5). This class I level recommendation was updated based on new convincing evidence of improved CVD outcomes with further reduction in LDL (10,11). Registry-based outcome data have subsequently supported these 2019 LDL-C target recommendations (12). However, our results show that very few patients within this national sample (27%) achieved this target during one year of follow-up post-PCI. Even considering the less stringent targets suggested by the 2016 guidelines that were used at the time this data was collected, only 51% of our patients met the target of <1.8 mmol/L. These are similar observations to our previously published study examining a larger cohort of post-PCI patients with and without diabetes (9). Moreover, we found that the female sex was consistently associated with a lower probability of achieving optimal LDL-C control (whether according to 2016 or 2019 guidelines targets). This finding was also observed in an Italian retrospective study examining cholesterol control of a larger population cohort (13), highlighting the possibility of underestimation of CV risk in these patients.

Globally, similar studies investigating the proportion of patients with DM and CAD meeting the LDL-C target of <1.8 mmol/L showed mixed results, with achievement rates between 14%-45% (14,15). Additionally, cross-sectional study data of very-high risk patients with and without diabetes in the United States has demonstrated a high proportion of patients to be taking statin therapy, with the prevalence of patients taking lipid-lowering therapies to be as high as >90% (16), confirming that a high rate of statin use is feasible. However, LDL-C goal attainment is not always achievable, even when prescribed the highest tolerated statin doses.

Even prior to the 2019 ESC guidance update, there has been a gap in the attainment of LDL guideline recommendations in those at very high risk (17). Whilst uptake and persistence with statins have generally been poor historically (18,19), this has been particularly concerning in patients with DM as they may have the most to gain from statin therapy (20). Whilst poor adherence to statin treatment is mostly due to concerns over adverse effects, the prevalence of intolerance has been reported to only be between 10-20% (21,22). Therefore, it is unlikely to account for most of the discrepancies we have identified. Recently it has become more apparent that whilst self-reported symptoms from statins may be high, the objective risk of clinically confirmed adverse events is low (23). Moreover, another trial has demonstrated that the ratio of symptom intensity from a placebo versus a statin was only 0.9, suggesting a large proportion of symptoms be attributable to a placebo effect (24). However, on a promising note, contemporary data are more encouraging, showing that patients with DM may now be more likely to attain LDL guidance than in earlier studies (25).

Current consensus indicates that glycemic control should be individualised according to the duration of DM, comorbidities, age and the impact of these features on the risk of therapy side effects (e.g., hypoglycemia and weight gain) (26). Nevertheless, the ESC guidelines (2013 & 2019) recommend tight glucose control in high-risk patients, targeting HbA1c <53 mmol/mol (<7.0%) to decrease microvascular complications (2,27).

Relatively few of our participants (43%) met this target, compared to similar studies in the last 5 years of patients with CAD and DM ranging from approximately 50% to 60% (28–30). We also noted low usage rates of SGLT2 inhibitors and GLP-1RAs of only 10% in both groups. This is despite the clear cardioprotective impact highlighted in the CVOTs, especially in patients with DM and CAD (31,32). The 2019 ESC diabetes guidelines give a ‘I A’ recommendation for using either SGLT2 inhibitors or GLP-1RAs in patients with DM and at high/very high risk of coronary disease as a first-line therapy – even before metformin. Our

data (2012-2017) was collected before the release of these updated guidelines; however, experimental and early clinical observation data indicated favourable effects of these agents on myocardial performance before they were examined in randomisation trials (32), and this was reflected on in the 2013 DM guidelines (27).

Moreover, results from the EMPA-REG OUTCOME and LEADER trials (two of the CVOTs pillars) were published during our data-collection phase and provided insight into clinical decision-making for high-risk patients with T2DM (32,34).

According to national registry data from Denmark, the prescription gap of those new agents has been noted globally; however, the prescription frequency is far less across Europe than in the US (35). This 22-year Danish registry data showed congruent results with our report, with only 12% prescription shares for SGLT-2 inhibitors and GLP-1RAs among hypoglycaemic drugs across all patients with T2DM by 2017.

Pharmacy cost doesn't seem to be a barrier to the suboptimal prescription rate of those agents. SGLT-2 inhibitors and GLP-1RAs are similarly priced as DPP-4 inhibitors, whether in Denmark or US (35,36); however, DPP-4 inhibitors still have a higher prescribing rate despite their neutral CVD effects (37). In our report, DPP-4 inhibitors had a 25% prescription rate (versus 10% for SGLT-2 inhibitors and GLP-1RA combined) across all patients with DM.

Schernthaner G et al. argued that the slow uptake of SGLT2i and GLP-1 RA following CVOT disclosures is attributed to clinical inertia among clinicians with limited knowledge of the current evidence and a preference for agents with more personal clinical experience (38). More reassuringly, we observed effective BP control in 81% of patients. One explanation for this is that patients had undergone recent PCIs; therefore, the blood pressure was managed initially by cardiology specialists rather than primary care physicians (PCP), with the majority of the patients prescribed the guideline-recommended medications for ischaemic

heart disease, including beta blockers and Angiotensin-converting enzyme (ACE) inhibitors or Angiotensin Receptor Blockers, as well as other anti-hypertensive medications on discharge as a standard of care management. This was also shown in similar studies, where CVD risk factors were better managed if treatment was initiated by specialist physicians rather than PCP (39). Another explanation is that higher blood pressure targets were aimed for (systolic pressure <140 mmHg and diastolic pressure <80 mmHg), considering the mean age of our cohort group being >65 years. Interestingly, this level of control is considerably higher than in other cohorts of patients with CAD and DM, ranging from 13% to 67% (15,40–43). In a German/Austrian population with T2DM and CVD, the prevalence of achieving the target BP was as high as 90%. However, higher target values were set for patients (70–90 mmHg for diastolic; 120–140 mmHg for systolic blood pressure) (42).

In a large European registry which recruited 20,588 symptomatic patients with established CAD from 18 European countries, 59% of the patients had optimal control of 3 or more risk factors combined (44). Disappointingly, the number of patients meeting the three recommended targets for HbA1c, LDL, and BP combined in our study is much lower than this. Although this is far from optimal, our findings appear relatively better than those reported by other European healthcare systems, which follow the same guidelines (45).

It is possible that the lack of awareness by many physicians regarding the benefits of effectively controlling CVD risk factors might contribute to the observed suboptimal results across the population. Another barrier to full optimisation may be an inaccurate perception of how well-controlled the patients' risk factors are in a stable outpatient compared to a more acute setting, e.g. acute coronary syndrome. Healthcare economics and patients' compliance may also influence the level of care provided.

Future studies assessing the changes made before and after PCI are needed to better describe this pattern.

Regardless of the reasons, there is clearly a need for improvement in the delivery of evidence-based preventive care in these patients at the very highest CVD risk to limit unnecessary morbidity and mortality.

Strengths and Limitations

The major strengths of this study are the use of a large, nationwide sample owing to the data-linkage nature of the SAIL database. It is clinically relevant, representative data that is directly used by clinicians and can be used to optimise relevant upstream decision-making. The main limitation is that this is a retrospective, observational study. Nonetheless, these data represent real-world assessments and analyses. This study uses relatively older data (from 2012 to 2017), reflecting the clinical practice against the guidelines available when these data were collected (i.e., according to ESC 2013-2016 Guidelines). Nevertheless, it may offer a 'snapshot' of the current patient management in the welsh clinical settings and assesses the attainment of the ESC guidance. It is possible that prescription rates and lipid, glucose and BP control may have improved in the interim, so a more up-to-date analysis is warranted. Still, previous amendments to guidelines have not rapidly changed practice in the past (46). We couldn't make an assessment on unmeasured variables such as medication compliance or the quantity of medications taken, as well as other potential confounders such as patients' socio-economic class. Although, it is unlikely that adjustment for these factors would change our conclusions significantly.

Similarly, it was not possible to differentiate patients with type 1 and type 2 DM from the SAIL data set. Since SGLT2 inhibitors and GLP-1 RA are not currently licenced to use in type 1 DM, we only analysed the prescription rate of those new agents in patients receiving non-insulin-based therapy in both groups, assuming they all have type 2 rather than type 1 DM. Nevertheless, it's unlikely that the prescription rate would differ much if the percentage of patients with T2DM were known.

Finally, reports from the welsh healthcare system may not be generalisable to other healthcare systems as prescriptions are free, abolishing the affordability barrier that may be relevant in different settings.

Conclusion

In this study of a very high-risk welsh cohort of patients, we revealed a large gap between the real-life management of CVD risk factors and the recommendations laid out in guidelines at the time. It is likely that increased use of novel therapies will be required, where appropriate, in order to close this therapeutic gap. An updated analysis assessing compliance with the most up-to-date guidelines is needed to reflect the current clinical practice.

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