Glucose-lowering drug use, glycemic outcomes, and severe hypoglycemia: 18-Year trends in 0·9 million adults with Diabetes in Hong Kong (2002−2019)

*Aimin Yang,[a,b] Hongjiang Wu,[a] Eric S.H. Lau,[a] Xinge Zhang,[a] Mai Shi,[a] Baoqi Fan,[a] Ronald C.W. Ma,[a,b,c] Alice P.S. Kong,[a,b,c] Andrea O.Y. Luk,[a,b,d] Juliana C.N. Chan,[a,b,c] and Elaine Chow[a,b,d]**

[a]Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Prince of Wales Hospital, Hong Kong Special Administrative Region (SAR), China
[b]Hong Kong Institute of Diabetes and Obesity, The Chinese University of Hong Kong, Prince of Wales Hospital, Hong Kong SAR, China
[c]Li Ka Shing Institute of Health Sciences, The Chinese University of Hong Kong, Prince of Wales Hospital, Hong Kong SAR, China
[d]Phase 1 Clinical Trial Centre, The Chinese University of Hong Kong, Prince of Wales Hospital, Hong Kong Special Administrative Region, China

The Lancet Regional Health - Western Pacific 2022;26: 100509
Published online xxx
https://doi.org/10.1016/j.lanwpc.2022.100509

Summary

Background Improvements in glycemic outcomes have stalled since 2010 in several international surveys. We previously reported improvements in glycemic control in 2007-2014 in Hong Kong coinciding with primary care reforms, use of dipeptidyl-peptidase 4 inhibitors (DPP-4is) and metformin. The aim of this study was to estimate more recent trends in drug use and glycemic outcomes following introduction of newer classes of glucose-lowering drugs (GLDs).

Methods Using population-based data from the Hong Kong Diabetes Surveillance Database, we explored age-specific trends in proportion of patients reaching glycemic targets and incidence rates of severe hypoglycemia (SH) in 963,612 adults with diabetes in 2002-2019. We further assessed patterns of GLDs utilisation by presence of atherosclerotic-cardiovascular disease (ASCVD), heart failure, and estimated-glomerular filtration rate (eGFR).

Findings Following rapid decline in HbA1c from 7·7% to 7·2% in 2005-2014 (annual percentage change [APC]= -0·8, 95% CI:-1·0,-0·6), standardized mean HbA1c plateaued since 2014 (HbA1c 7·2% in 2019, APC=0·0, 95% CI:-0·2, 0·2). The incidence rates of SH declined from 3·4 to 0·7 events per 100-person years, but improvements levelled off since 2014. Use of metformin steadily increased (41·1 to 58·7%), sulfonylureas decreased (52·2 to 31·1%) while insulin remained static in 2002-2019. Adoption of DPP-4is slowed following initial rapid uptake in 2007-2011. DPP-4is remained the most widely prescribed newer GLD in all ages (14·3% in 2019). Use of glucagon-like-peptide 1 receptor agonists (GLP1-RAs) and sodium glucose co-transporter-2 inhibitors (SGLT2is) increased rapidly in 2015-2019 with 0·5% and 6% of users respectively in 2019.

Interpretation Following rapid improvement in 2007-2014, glycemic control and SH rates had plateaued despite changing patterns of newer GLDs use in Hong Kong.

Funding Dr. Aimin Yang was supported by a CUHK Impact Research Fellowship Scheme.

Keywords: Glucose lowering drug; Diabetes; Glycemic control; Hypoglycemia; Trends; Diabetes care

Introduction

There have been major updates in international guidelines on use of glucose-lowering drugs (GLDs) in type 2 diabetes (T2D) recommending a patient-centered and personalised approach to diabetes management.[1,2] Following publications of cardiovascular outcome trials of

*Corresponding author at: Department of Medicine and Therapeutics, Prince of Wales Hospital, The Chinese University of Hong Kong (CUHK), Shatin, Hong Kong SAR, China.
E-mail addresses: e.chow@cuhk.edu.hk, chowelaine@doctors.org.uk (E. Chow).

Research in context

Evidence before this study

We searched PubMed with the terms "diabetes", "agent", "drug", "glycated hemoglobin (HBA1c)", "hypoglycemia", "glucose", "trend", and "pattern" for original articles and reviews published up to Nov 30, 2021. Most studies on the trends in drug utilisation patterns in diabetes were conducted in Western populations. These studies have reported marked changes in prescribing patterns of glucose-lowering drugs (GLDs) with a shift towards newer agents. However, improvements in glycemic outcomes have stalled since 2010. Since 2000, Hong Kong has introduced a territory-wide, data-driven, team-based diabetes care model. We previously reported improvements in glycemic control in 2007-2014 in Hong Kong coinciding with primary care reforms and increasing use of DPP-4i and metformin, but the latest trends in drug use and glycemic outcomes following recent introduction of newer-GLDs has not been investigated.

Added value of this study

This study reports the latest real-world practice of prescribing GLDs and glycemic control in a Chinese-predominant population with mainly type 2 diabetes. Over a span of 18 years between 2002 and 2019, we observed plateauing of HbA1c after a period of reduction in HbA1c and severe hypoglycemia in 2007-2014, mainly attributed to increasing use of DPP-4is and metformin and declining use of sulphonylureas. Despite their high frequency of ASCVD, patients aged ≥75 years were less likely to be prescribed SGLT2is, GLP-1RAs, and TZDs than the 20-44 age-group who had persistently poor glycemic control. In patients with CKD, there was increasing use of DPP-4is with a lower proportions of patients treated with SGLT2is.

Implications of all the available evidence

Younger adults consistently had the highest HbA1c with the least improvement over time despite introduction of new drug classes. This real-world evidence reinforced the need to implement concerted and targeted actions to close these treatment gaps with ongoing evaluation of the impacts of these new drugs on clinical outcomes for informing practice and policies.

newer-classes of GLDs including glucagon-like peptide-1-receptor agonists (GLP-1RAs) and sodium-glucose co-transporter-2 inhibitors (SGLT2is),[3,4] the 2018 American Diabetes Association (ADA) guideline recommended use of these drugs in patients with established atherosclerotic-cardiovascular-disease (ASCVD) or heart failure.[5] The latest 2022 guideline further prioritised SGLT2is and GLP-1RAs as add-on to metformin therapy in high-risk patients with ASCVD or chronic kidney disease (CKD).[1]

In several nationwide surveys, the prescribing patterns of GLDs have shifted towards increasing use of new drugs albeit not accompanied by improvement in glycemic control.[6-10] The latest reports in adults from United States (US) showed a decline in percentage of patients achieving glycated hemoglobin-A1c (HbA1c) target of <7% since 2007.[11] Using the Hong Kong Diabetes Surveillance Database (HKDSD) with data curated from a territory-wide electronic-health-record (EHR) system in 2002-2016, we reported improving trends in HbA1c with reduced rates of hospitalization due to severe hypoglycaemia (SH).[12] This coincided with increasing use of metformin, declining use of sulfonylureas and accelerating use of dipeptidyl-peptidase-4-inhibitors (DPP-4is) against the rolling out of a data-driven risk assessment and management program in both secondary and primary care settings.[5] There is conclusive evidence regarding the cardiovascular-renal protective effects of SGLT2i and GLP-1RAs.[13] However, there is a paucity of real-world-data (RWD) on prescribing trends of these two GLDs and glycemic control in subpopulations which will provide insights on the impact of the updated diabetes care guidelines.

In the current study, we used the territory-wide HKDSD to examine updated trends in outcomes and GLDs use over an 18-year period in 2002-2019 by estimating the age-specific trends in HbA1c, SH rates and GLDs use. We performed used the data to test the hypothesis that patterns of GLDs utilisation and trends in glycemic outcomes might vary by age and presence of ASCVD, heart failure and eGFR categories.

Methods

Study participants

We conducted a retrospective cross-sectional analysis of the trends of GLDs use and glycaemic outcomes using data from the HKDSD, a real-world patient-level dataset of people with diabetes identified from the Hong Kong EHR system in 2000-2019. Hong Kong has 7·5 million population mainly of Southern Chinese descent with universal health coverage through care provision by the government-funded Hospital Authority (HA). The latter operates all hospitals and clinics with on-site drug dispensing which share a territory-wide EHR system since 2000. There were 43 hospitals/institutions, 49 specialist out-patient clinics (SOPCs), and 73 general out-patient clinics (GOPCs) in the public sector, organised into seven hospital clusters based on locations in 2020. Over 90% of patients with diabetes were captured in the HA EHR system. The HKDSD includes all people who ever have had a measurement of either fasting-plasma-glucose (FPG), random PG, 75-gram oral glucose-tolerance-test (OGTT) with fasting and 2-h PG, or HbA1c in 2000-2019. The HKDSD consists of a cohort of people with normal blood glucose levels, people with

prediabetes, women with gestational diabetes, people with diabetes and a sub-group of people with diabetes who underwent structured assessment (eye, feet, blood and urine) with data captured in the Risk Assessment and Management Programme for Diabetes Mellitus (RAMP-DM) module. The HKDSD provided comprehensive anonymised and de-identified data of clinical parameters, including demographics, inpatient admissions, diagnosis, medications, and laboratory tests. Data on type of diabetes is available in the RAMP-DM module but not in the overall HKDSD. Details of the HKDSD profile was described elsewhere.[14]

We defined people with diabetes as those who met one or more of the following criteria: 1) HbA1c ≥6·5% (48 mmol/mol); 2) FPG ≥7·0 mmol/L; 3) 2-h OGTT ≥11·1 mmol/L; 4) prescription of insulin for at least 28 days continuously; 5) prescription of non-insulin GLDs; 6) recording of diagnosis code for diabetes based on the International Classification of Diseases, Ninth Revision (ICD-9): 250 at the SOPCs and during hospitalisation; or/and 7) recording of diagnosis code for diabetes based on the International Classification of Primary Care, Second Edition (ICPC-2): T89 or T90 at the GOPCs. We excluded women with gestational diabetes, which was defined using ICD-9 code of 648·8 or/and 2-h OGTT ≥8·5 mmol/L during 24-28 gestational weeks. To avoid misclassifying acute stress hyperglycaemia as diabetes, FPG records during hospitalisation were not used for defining diabetes.

The current version of HKDSD included 964,950 people who ever had diabetes in 2000-2019. There were 963,612 unique patients identified with 93·3% of them having at least one HbA1c measurement. We limited our analyses to 2002-2019 and excluded patients who died in 2000-2001. We also excluded data from these 2 years to avoid bias due to incomplete prescription data in the early stage of establishment of the EHR.[12] Finally, we included 956,748 patients in drug utilisation and SH analyses, and 895,511 patients in glycemic control analyses (Figure S1). The study was approved by the local clinical research ethics committee. This study is reported as per the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline (Table S1).

GLDs utilisation assessment

We extracted dispensing data of GLDs from the EHR including drug name, dose, frequency, dispensing duration, start and end dates in 2000-2019. We grouped GLDs into 8 categories[12]: insulins, metformin, sulfonylureas, alpha-glucosidase-inhibitors (AGIs), thiazolidinediones (TZDs), DPP-4is, GLP-1RAs, and SGLT2is. Combination formulations were counted as two different GLDs filled in the same year based on its active ingredients. For patients who were dispensed at least one GLD, we categorised them into non-insulin GLDs (including GLP-1RAs), and insulin-only sub-groups.

Glycemic control and SH assessment

HbA1c was measured in publicly-funded accredited laboratories which were harmonised against International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) standards. For each individual, we calculated mean HbA1c within each calendar year to categorise glycemic control. Annual mean HbA1c level was divided into HbA1c ≥9·0% (75 mmol/mol), 8·0-8·9% (64-74 mmol/mol), 7·0-7·9% (53-63 mmol/mol), 6·0-6·9% (42-52 mmol/mol), and <6·0% (42 mmol/mol). Poor glycemic control was defined as HbA1c ≥9·0%. The hospital discharge diagnosis (ICD-9 codes: 250·80, 250·81, 250·82, 250·83 and 251·2; ICD-10: E10·649, E11·65 and E16·2) were used to define hospitalisation due to SH.

eGFR categories and ASCVD

For each individual, we calculated the mean eGFR within each calendar year for defining the eGFR category. The latter was defined according to the CKD epidemiological-collaboration (CKD-EPI) equation[15]: ≥60, 45-59, and <45 mL/min/1·73 m^2. The presence of ASCVD was defined by discharge diagnoses from the earliest hospitalisation records in the EHR in each calendar year. We defined ASCVD as coronary arterial disease, cerebrovascular disease, or peripheral arterial disease presumed to be of atherosclerotic origin according to the ADA 2021 Standards of Medical Care definitions (Table S2).[16]

Statistical analyses

All descriptive statistics were reported as counts (percentages) or mean (standard deviation, SD).

We calculated the annual age- and sex-standardised proportions of GLDs, incident rate of SH, and mean value of HbA1c and proportions of HbA1c categories for each calendar year using the 2008 population as the standard further divided by 5-year age groups.[12] In each calendar year, we included people with diabetes alive at the beginning of each year and people with diabetes first captured in the HKDSD considered as newly diagnosed diabetes during that year. We assumed that the distribution was binomial for proportions, normal for mean values of HbA1c, and Poisson for incidence rate of SH. In each calendar year, we determined events of SH per 100 person-years at risk. The numerator was total number of SH events, and the denominator was total observation time at risk (patent-years) within each calendar year. The time at risk for each patient started from the beginning of observation until the earliest date of occurrence of SH, death, or end of each calendar year. The

date of death was determined from the Hong Kong Death Registry.

We performed subgroup analyses by sex and age-groups. In sex subgroup analyses, we calculated age-standardised proportions, mean values, and incidence rates of SH for men and women. We categorised patients into: 20-44, 45-59, 60-74, and ≥75 years age-groups, and calculated sex- and age-standardised proportions, mean HbA1c values, and incidence rates of SH using the standard population by 5-year age groups. We performed subgroup analyses by presence of comorbidities (ASCVD, heart failure, and eGFR categories) for the proportions of use of each GLD class as well as that of treatment regimen (insulin-only, non-insulin GLDs, and GLDs) for incidence SH rate. To calculate the incidence rate of SH for each category, the total number of SH events within each category was used as the numerator and their summed total observation time, as the denominator expressed as events per 100 person-years at risk.

We used Joinpoint regression program (Version 4·9·0·0) to examine the trends over time expressed as average-annual-percentage change (AAPC) for the entire observation period and annual-percentage-change (APC) for each linear trend segment detected. We adopted the Joinpoint software with the recommended minimum and maximum number of joinpoints. It started with zero number of joinpoint with a straight line and tested whether more joinpoints were statistically significant using a Monte Carlo Permutation method. The default value for the maximum number of joinpoints depends on the number of data points (default=0 for 0-6 data points, default=1 for 7-11 data points, and default=2 for 12-16 data points). We fitted the model with the uncorrelated errors option. We repeated the analysis with different values of the autocorrelation parameter (0·1, 0·2 and 0·3), and incorporated the standard errors of the proportions, mean values, and incidence rates to correct heteroscedasticity.[17]

Sensitivity analyses

Since the proportion of patients with newly diagnosed diabetes varied over time, this raised the concern that changes of this proportion might influence the trends in the incidence rates of SH. We performed sensitivity analyses by excluding patients with incident diabetes in each calendar year, defined as the first occurrence of any episode fulfilling the criteria of diabetes. Since the incidence rate of SH might vary amongst different types of diabetes, we performed sensitivity analysis in a subgroup of patients who had physician-diagnosed type 1 or type 2 diabetes captured in the RAMP-DM module. Amongst 956,748 patients in the main SH analysis, 567,194 (59.3%) patients were included in the RAMP-DM module. Between 2002 and 2019, 3,058 (0.6%) were diagnosed to have type 1 diabetes, 545,335 (99.16%), type 2 diabetes, and 1,576 (0.3%), other/missing type of diabetes. Data were analysed using R statistical software (Version 4·0·0). A two-sided *P* value of <0·05 was considered statistically significant.

Role of the funding source

A.Y. was funded by the CUHK Impact Research Fellowship Scheme which did not have any role in study design, data collection, data analysis, data interpretation, or writing of this report. A.L. had full access to HKDSD data. E.C. is the guarantor of this work with final responsibility for the decision to submit for publication.

Results

The number of patients with diabetes in the HKDSD in each calendar year increased by 3·9 times from 188,974 in 2002 to 753,374 in 2019 (Table 1). Over 18 years, the mean (SD) age increased from 64·4 (13·3) to 67·8 (13·0) years. The percentage of newly enrolled patients per-year varied between 6·9% and 21·9% while the proportions of patients with ASCVD increased from 16·3% to 20·0%. The mean (SD) number of HbA1c test per-year per-patient increased from 1·8 (1·1) times in 2002 to 3·4 (1·9) times in 2019. The proportion of patients with eGFR ≤60 ml/min/1·73m^2 decreased during this period.

Trends in HbA1c

The overall unstandardized mean (SD) HbA1c decreased from 7·7 (1·6)% (60·3 [17·5] mmol/mol) to 7·2 (1·2)% (54·7 [13·3] mmol/mol) and the proportion of patients with HbA1c of 6-7% (42-53 mmol/mol) increased from 27·5% to 44·3% in the whole period (2002-2019). However, following an initial period of rapid decline in 2005-2014 (HbA1c 7·7 to 7·2%, APC=-0·8, 95% CI: -1·0, -0·6), standardized mean HbA1c plateaued since 2014 (HbA1c 7·2% in 2019, APC=0·0, 95% CI:-0·2, 0·2) (Figure 1A). The proportion of patients achieving HbA1c <7% increased from 27·5% to 43·6% in 2002-2014 but did not further improve in 2014-2019 (44·3% in 2019) (Table S3). The proportion with poor glycemic control HbA1c >9% decreased from 17% to 7·9% with the most rapid decline in 2005-2012 (APC=-8·9, 95% CI: -10·7, -7·1) (Table S4). Similar HbA1c trends were observed in men and women (Figure 1B). Individuals aged 20-44 years had the highest mean HbA1c with slowest decline as compared with greater improvements in those aged ≥75 years (Figure 1C). The youngest age group also had the highest proportion with HbA1c ≥9·0% (16·8% in 2019) compared with the 60-74 and the ≥75 year age groups (6·4 % and 5·5% respectively in 2019) (Table S4).

Characteristics	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
N	188,974	226,993	288,538	322,302	360,229	389,530	420,084	451,066	481,640	514,624	546,573	578,067	606,000	632,881	660,839	686,747	718,165	753,374
Men, %	45·4	45·8	46·0	46·4	46·6	47·0	47·3	47·7	48·0	48·4	48·7	48·9	49·2	49·4	49·7	49·9	50·1	50·3
Women, %	54·6	54·2	54·0	53·6	53·4	53·0	52·7	52·3	52·0	51·6	51·3	51·1	50·8	50·6	50·3	50·1	49·9	49·7
Age, mean (SD)	64·4 (13·3)	64·6 (13·3)	64·8 (13·1)	65·1 (13·1)	65·2 (13·1)	65·4 (13·1)	65·6 (13·1)	65·7 (13·2)	66·0 (13·2)	66·2 (13·1)	66·4 (13·1)	66·6 (13·1)	66·8 (13·1)	67·0 (13·1)	67·2 (13·1)	67·4 (13·1)	67·6 (13·1)	67·8 (13·0)
Age groups, %																		
20-44	8·4	7·8	7·0	6·5	6·1	5·8	5·5	5·3	5·0	4·9	4·7	4·6	4·5	4·5	4·4	4·3	4·2	4·1
45-59	26·0	26·6	27·4	27·8	28·1	28·0	27·8	27·5	27·2	26·8	26·3	26·0	25·3	24·6	23·8	23·0	22·0	21·2
60-74	41·7	40·8	40·7	39·6	38·9	38·5	38·1	38·2	38·3	38·4	38·6	38·8	39·4	40·2	41·4	42·4	43·6	44·5
≥ 75	23·9	24·8	24·9	26·1	26·8	27·7	28·5	29·0	29·5	29·9	30·3	30·6	30·7	30·7	30·4	30·3	30·2	30·3
Newly enrolled patients, %	21·9	19·4	24·1	13·2	13·4	10·2	10·0	9·7	9·1	9·1	8·4	8·1	7·2	6·9	6·9	6·5	7·0	7·4
ASCVD, %	16·3	17·0	16·2	16·7	17·0	17·6	18·1	18·7	19·4	19·8	20·0	20·1	20·1	20·1	20·1	20·1	20·0	20·0
Heart failure, %	5·1	5·3	4·8	4·9	4·7	4·8	5·1	5·2	5·5	5·5	5·5	5·5	5·4	5·3	5·2	5·2	5·1	5·1
Glycemic control (HbA1c)																		
Patients with HbA1c, %	93·2	93·5	93·9	93·9	94·0	94·2	94·5	94·8	95·1	95·4	95·7	95·9	96·0	96·2	96·3	96·4	96·4	96·2
Mean (SD), %	7·7 (1·6)	7·7 (1·6)	7·7 (1·6)	7·7 (1·6)	7·6 (1·6)	7·7 (1·5)	7·5 (1·5)	7·5 (1·4)	7·4 (1·3)	7·4 (1·3)	7·3 (1·3)	7·3 (1·3)	7·2 (1·3)	7·2 (1·3)	7·2 (1·3)	7·1 (1·2)	7·1 (1·2)	7·2 (1·2)
Mean (SD), mmol/mol	60·3 (17·5)	60·4 (17·5)	60·9 (17·2)	60·9 (17·4)	60·1 (17·0)	60·3 (16·4)	58·6 (16·1)	58·2 (15·8)	56·9 (14·7)	57·0 (14·3)	56·2 (14·2)	55·8 (14·2)	54·7 (13·9)	54·8 (13·7)	55·0 (13·9)	54·5 (13·6)	54·6 (13·6)	54·7 (13·3)
Tested times	1·8 (1·1)	1·8 (1·0)	1·9 (1·2)	1·9 (1·1)	1·8 (1·0)	1·8 (1·0)	1·9 (1·0)	2·0 (1·0)	2·1 (1·1)	2·4 (1·4)	3·0 (1·8)	3·2 (1·9)	3·2 (1·9)	3·2 (1·9)	3·2 (1·9)	3·3 (1·9)	3·3 (1·9)	3·4 (1·9)
HbA1c category, % (mmol/mol)																		
<6·0 (<42)	9·8	10·0	8·5	9·0	9·5	7·6	9·5	9·6	9·1	7·1	8·4	9·3	11·3	11·0	10·6	11·0	11·1	9·8
6·0-6·9 (42-52)	27·5	27·6	27·2	26·7	27·9	28·5	31·8	32·6	36·8	38·5	41·1	42·0	43·6	43·5	43·4	44·5	43·7	44·3
7·0-7·9 (53-63)	28·2	27·8	28·6	28·4	28·5	30·0	29·3	29·4	29·9	30·9	29·3	28·0	26·4	26·9	27·1	26·7	27·6	28·8
8·0-8·9 (64-74)	17·0	17·1	17·7	17·7	17·2	17·7	15·5	15·1	13·4	13·1	11·7	11·3	10·4	10·5	10·6	9·9	10·0	9·9
≥9·0 (75)	17·5	17·6	18·0	18·3	16·9	16·3	13·9	13·3	10·8	10·4	9·6	9·4	8·3	8·1	8·4	7·8	7·6	7·3
eGFR (mL/min/1·73 m^2)																		
Mean (SD)	65·9 (23·7)	66·5 (24·2)	67·5 (24·6)	67·6 (24·6)	69·0 (25·0)	70·4 (25·2)	70·8 (25·0)	70·7 (24·8)	72·6 (24·4)	74·0 (23·9)	74·2 (23·8)	74·4 (23·7)	74·2 (23·6)	74·3 (23·6)	74·1 (23·5)	73·6 (23·3)	74·0 (23·3)	73·8 (23·2)
Categories, %																		
≥ 60	62·3	62·8	64·0	64·3	65·8	67·8	68·6	68·7	71·6	73·8	74·1	74·5	74·4	74·6	74·4	74·0	74·5	74·5
45-60	19·1	18·7	18·0	17·5	16·5	15·5	15·3	15·4	14·4	13·5	13·3	13·2	13·2	13·0	13·1	13·4	13·0	13·1
<45	18·5	18·5	18·1	18·2	17·6	16·6	16·1	16·0	14·0	12·7	12·6	12·4	12·4	12·4	12·4	12·6	12·4	12·4

***Table 1*: Characteristics of adults with diabetes in the Hong Kong Diabetes Surveillance Database (HKDSD) 2002-2019.**

Abbreviations: GLDs, glucose lowering drugs; ASCVD, atherosclerotic cardiovascular disease; eGFR, estimated glomerular filtration rate; SD, standard deviation.

HbA1c categories (mmol/mol)			Period-1		Period-2		Period-3		Period-4	
	2002-2019	AAPC (95% CI)	Year	APC (95% CI)	Year	APC (95% CI)	Year	APC (95% CI)	Year	APC (95% CI)
Overall										
<6·0% (<42)	10·1-9·5	1·2 (-0·1, 2·5)	2002-2019	1·2 (-0·1, 2·5)						
6·0-6·9% (42-52)	27·7-43·6	2·7 (1·9, 3·6)*	2002-2006	-0·7 (-4, 2·8)	2006-2012	7·4 (5·9, 8·9)*	2012-2019	0·8 (0·3, 1·4)*		
7·0-7·9% (53-63)	28·1-28·9	0·1 (-0·4, 0·7)	2002-2011	1 (0·4, 1·6)*	2011-2015	-3·6 (-5·6, -1·5)*	2015-2019	2·1 (0·9, 3·3)*		
8·0-8·9% (64-74)	16·8-10·2	-3 (-3·8, -2·3)*	2002-2007	-0·2 (-2·2, 1·9)	2007-2014	-6·6 (-7·6, -5·6)*	2014-2019	-0·8 (-2·1, 0·6)		
≥9·0% (75)	17·2-7·9	-4·4 (-5·8, -3)*	2002-2005	3·1 (-4·6, 11·4)	2005-2012	-8·9 (-10·7, -7·1)*	2012-2019	-2·9 (-4·3, -1·4)*		
20-44 years										
<6·0% (<42)	10·8-14·3	2·5 (1·1, 3·9)*	2002-2011	0·4 (-1·8, 2·6)	2011-2019	4·9 (2·9, 6·9)*				
6·0-6·9% (42-52)	24·3-32·3	1·6 (0·4, 2·8)*	2002-2007	-1·4 (-3·9, 1·1)	2007-2011	6·8 (2·1, 11·7)*	2011-2019	1 (0·2, 1·8)*		
7·0-7·9% (53-63)	24·8-24·1	-0·4 (-0·6, -0·1)*	2002-2019	-0·4 (-0·6, -0·1)*						
8·0-8·9% (64-74)	18·0-12·6	-2 (-3·6, -0·4)*	2002-2007	0·6 (-2, 3·3)	2007-2013	-4·6 (-6·7, -2·4)*	2013-2017	0 (-4·8, 5·1)	2017-2019	-4·5 (-13·5, 5·4)
≥9·0% (75)	22·1-16·8	-1·6 (-2·4, -0·9)*	2002-2006	3·3 (0, 6·8)	2006-2019	-3·1 (-3·5, -2·7)*				
45-59 years										
<6·0% (<42)	8·4-8·5	1·8 (0·5, 3·1)*	2002-2019	1·8 (0·5, 3·1)*						
6·0-6·9% (42-52)	25·8-40·4	2·8 (1·9, 3·7)*	2002-2007	-0·1 (-2·6, 2·5)	2007-2012	8·7 (6·5, 10·9)*	2012-2019	0·9 (0·2, 1·5)*		
7·0-7·9% (53-63)	28·3-29·1	0·3 (-0·2, 0·7)	2002-2011	1 (0·5, 1·5)*	2011-2015	-2·5 (-4·2, -0·7)*	2015-2019	1·4 (0·3, 2·5)*		
8·0-8·9% (64-74)	18·2-11·7	-2·6 (-3·4, -1·9)*	2002-2007	0·7 (-1·4, 2·8)	2007-2013	-6·4 (-7·7, -5)*	2013-2019	-1·5 (-2·5, -0·4)*		
≥9·0% (75)	19·4-10·4	-3·7 (-5, -2·3)*	2002-2006	2·2 (-2·8, 7·4)	2006-2012	-8·3 (-10·7, -5·9)*	2012-2019	-2·8 (-4·3, -1·3)*		
60-74 years										
<6·0% (<42)	9·1-7·8	0·7 (-0·6, 2)	2002-2019	0·7 (-0·6, 2)						
6·0-6·9% (42-52)	28·0-45·9	2·9 (2, 3·8)*	2002-2005	-2·1 (-7·1, 3·1)	2005-2013	6·7 (5·8, 7·6)*	2013-2019	0·5 (-0·1, 1·2)		
7·0-7·9% (53-63)	29·3-30·4	0·2 (-0·4, 0·8)	2002-2011	1·1 (0·4, 1·8)*	2011-2015	-3·8 (-6·1, -1·5)*	2015-2019	2·3 (1·1, 3·6)*		
8·0-8·9% (64-74)	17·1-9·5	-3·5 (-4·3, -2·7)*	2002-2007	-0·1 (-2·4, 2·2)	2007-2014	-7·4 (-8·5, -6·3)*	2014-2019	-1·3 (-2·7, 0·1)		
≥9·0% (75)	16·5-6·4	-5·4 (-6·9, -3·8)*	2002-2005	2·6 (-5·6, 11·6)	2005-2012	-10·8 (-12·9, -8·7)*	2012-2019	-3·1 (-4·6, -1·5)*		
≥75 years										
<6·0% (<42)	13·4-12·3	0·8 (-0·4, 2·1)	2002-2019	0·8 (-0·4, 2·1)						
6·0-6·9% (42-52)	30·3-46·2	2·5 (1·7, 3·3)*	2002-2006	0·7 (-2·4, 3·8)	2006-2012	6·5 (5·2, 7·7)*	2012-2019	0·3 (-0·2, 0·8)		
7·0-7·9% (53-63)	26·8-27·1	0 (-0·7, 0·7)	2002-2011	0·9 (0·1, 1·7)*	2011-2015	-4·6 (-7·1, -2·1)*	2015-2019	2·7 (1·1, 4·2)*		
8·0-8·9% (64-74)	14·6-9·0	-3 (-4·4, -1·5)*	2002-2006	0·8 (-4·9, 6·9)	2006-2014	-6·8 (-8·3, -5·2)*	2014-2019	0·3 (-2, 2·6)		
≥9·0% (75)	14·9-5·5	-5·5 (-7·6, -3·4)*	2002-2005	0·1 (-8·6, 9·6)	2005-2010	-11·8 (-15·7, -7·7)*	2010-2014	-7 (-12·8, -0·9)*	2014-2019	-1 (-3·8, 1·8)

***Table 2*: Trends in standardised proportions of HbA1c categories by age groups.**
Asterisk means average annual percent change (APPC) or annual percent change (APC) is significantly different from zero at the alpha = 0·05 level.

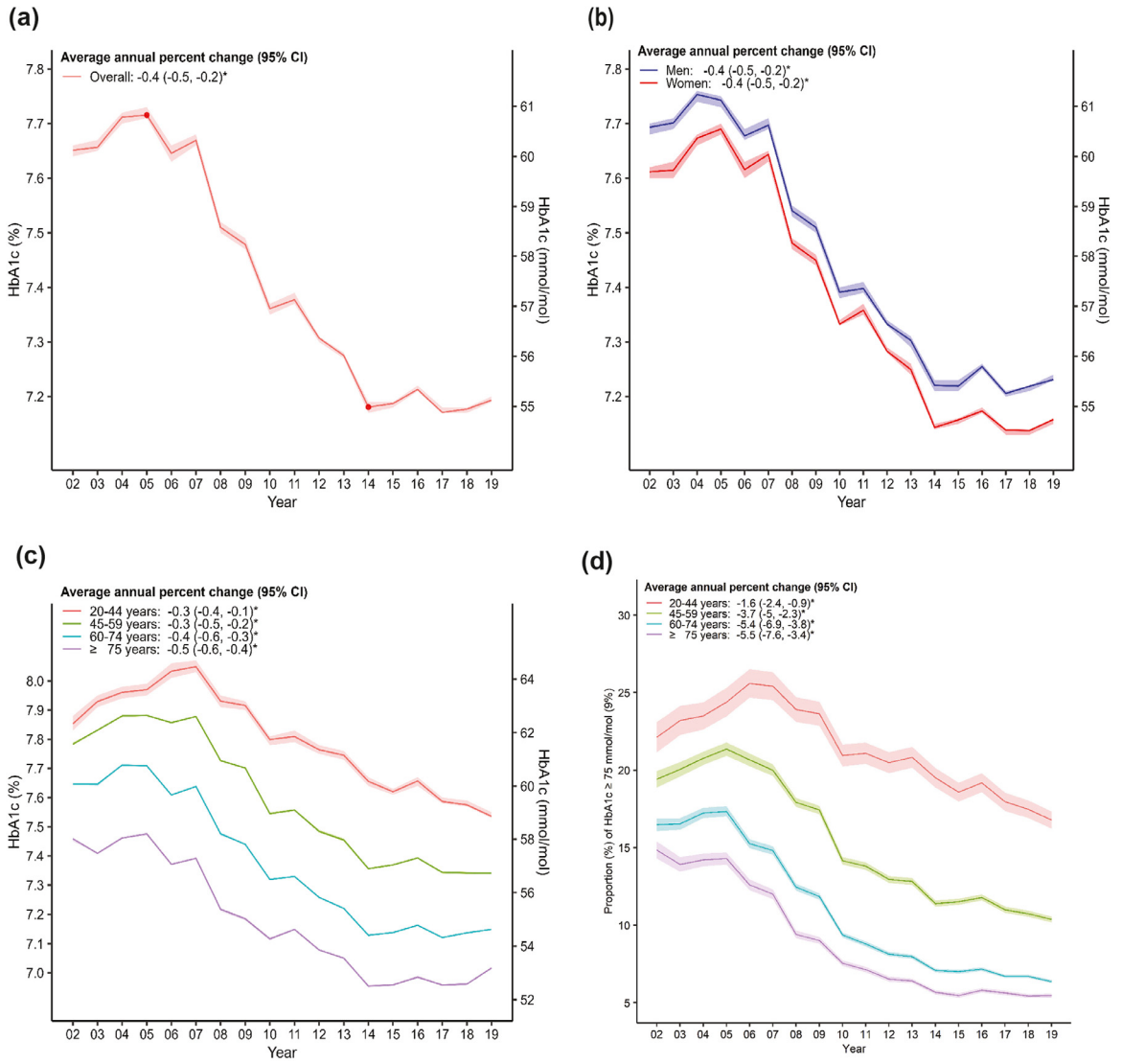

Figure 1. Trends in standardised annual mean HbA1c in overall (a) and by sex (b) and age groups (c), and proportion of poor glycemic control (HbA1c>9%, 75 mmol/mol) by age-groups (d).

Asterisk means average annual percent change (APPC) is significantly different from zero at the alpha = 0·05 level.

Trends in SH

In 2002-2019, incidence rates of SH declined from 3·4 to 0·7 events per-100-person-years. There was an initial rapid fall in 2002-2006 (APC=-22·6, 95% CI: 28·2, -16·5) followed by a further decline in 2010-2014 (APC=-11·4, 95%CI: -20·6, -1·1) (Figure 2A and Table S4). Similar trends were observed in men and women (Figure 2B). There were decreasing trends in incidence rates of SH in all age-groups with the highest rate of decline in the 60-74 (AAPC=-9·2, 95% CI: -12·3, -6·1) and ≥75 age-groups (AAPC=-8·5, 95% CI: -11·8, -5·2) (Figure 2C). Both the 20-44 and ≥75 age-groups had the highest SH rate in 2019 (0·8 and 1·0 events per-100-person-years, respectively). Incidence rates of SH were highest in those prescribed with GLDs (insulin plus non-insulin GLDs) followed by those receiving insulin-only (Figure 2D).

Trends in GLDs use

Metformin use increased from 41·1% to 58·7% in 2002-2019, while use of sulfonylureas declined since 2004 (Figure 3 and Table S5). Insulin use remained static (11·2% to 13·6% in 2002-2019). In 2009-2013, the use of TZDs declined but increased again since 2013 with 6·4% of patients on TZDs in 2019. DPP-4is remained the most widely prescribed newer GLDs (14·3%) versus SGLT2is (4·2%) and GLP1-RAs (0·6%) in 2019

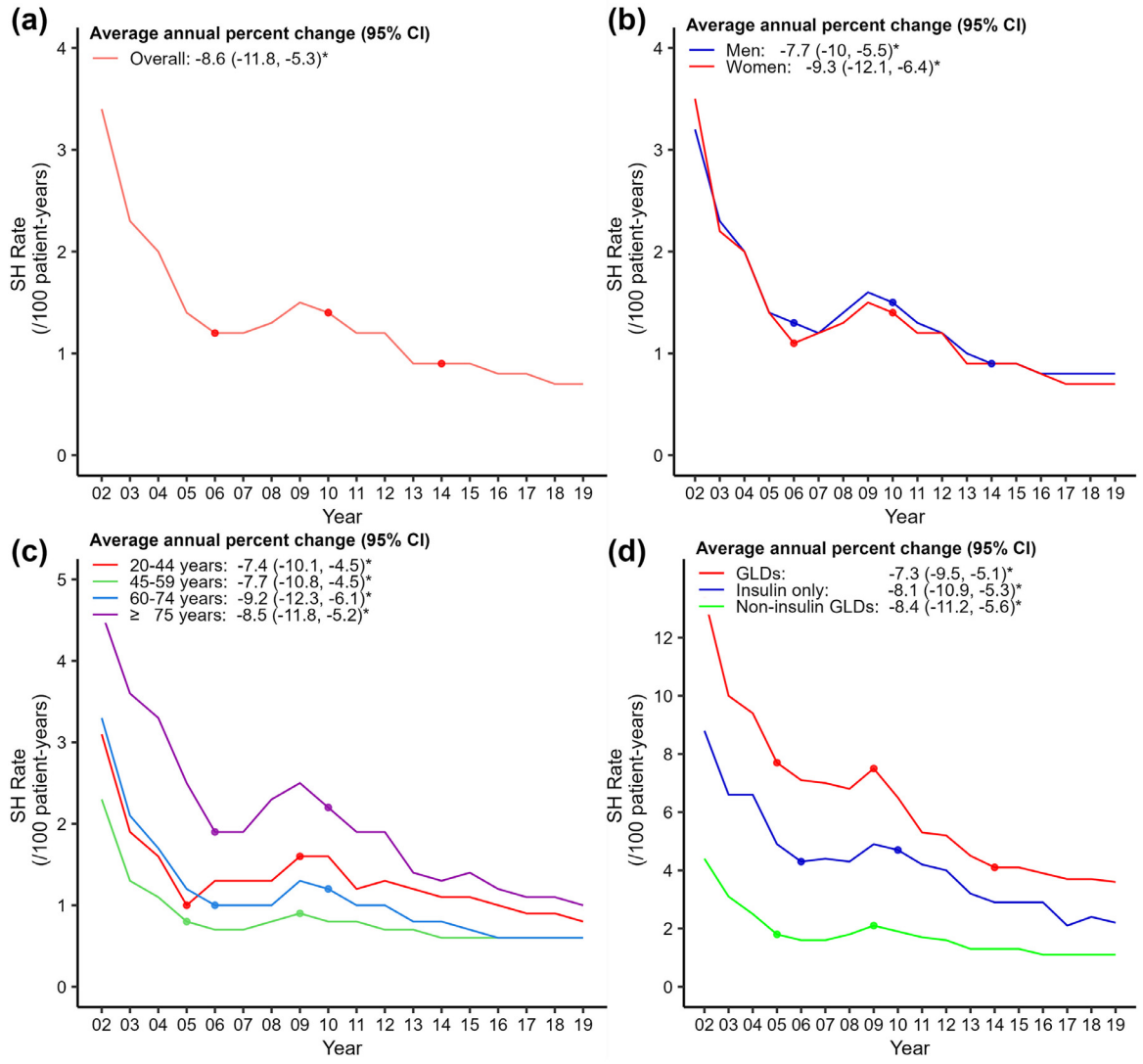

Figure 2. Trends in standardized incidence rates of severe hypoglycaemia (SH) hospitalisation (per 100 person-years) in overall (a) and by sex (b), age groups (c) and treatment regiments (d).

Asterisk means average annual percent change (APPC) is significantly different from zero at the alpha = 0·05 level. Points indicate the change points in trends detected by the Joinpoint regression model.

(Figure 3). Use of DPP-4is experienced rapid growth in 2007-2011 (APC=188·6, 95% CI: 162·9, 216·7), which slowed in 2011-2015 and 2015-2019 (Table S5). There were sharp increases in use of GLP-1RAs since 2008 and SGLT2is since 2015 when these newer oral-GLDs were introduced into the HA formulary (AAPC=28·7, 95% CI: 18·2, 40·1 and AAPC=63·7, 95% CI: 36·8, 95·9 respectively). The proportion of patients not treated with any medications gradually increased in this period (24·9% in 2019). The number of patients on ≥4 GLDs also increased in the overall cohort (AAPC=7·1, 95% CI: 4·7, 9·5) (Figure S2).

Trends in GLDs use by age-groups

There were significant variations in trends of GLDs use by age-group (Figure S3). Metformin use increased in all age-groups but was less likely to be used in the ≥75 age-group. The 20-44 age-group was least likely to be using sulfonylureas, with a notable decline from 43·1% in 2005 to 23·0% in 2019 (APC=-4·2, 95% CI: -4·5, -4·0) (Figure S3, Table S6). Compared with the ≥75 age-group, more patients in the 20-44 age-group were treated with SGLT2is (6·4% versus 1·7% in 2019), GLP-1RAs (1·5% versus 0·1% in 2019; AAPC=27·0, 95% CI: 20·5, 33·9 versus AAPC=41·5, 95% CI: 34·2-49·2), and

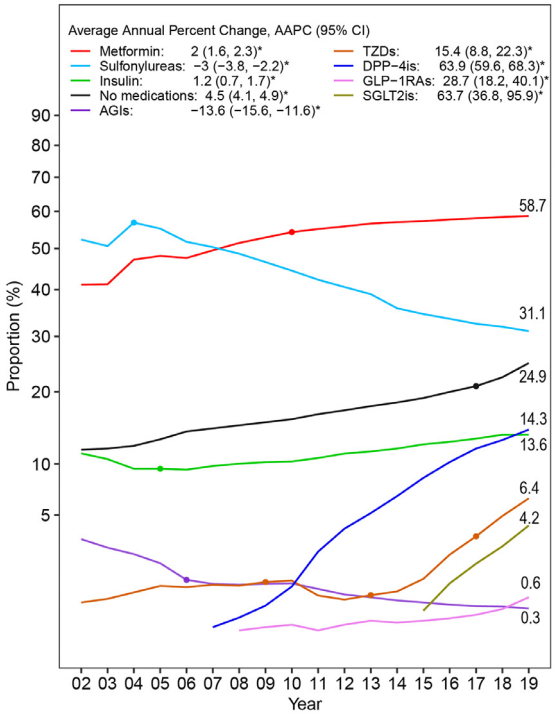

Figure 3. Overall trends in standardised proportion of glucose-lowering drugs (GLDs) among adults with diabetes in Hong Kong 2002-2019.

Points indicate the change-points in trends detected by Joinpoint regression model. AGIs, alpha glucosidase inhibitors; TZDs, thiazolidinediones; DPP-4is, dipeptidyl peptidase-4 inhibitors; GLP-1RAs, glucagon-like peptide-1 receptor agonists; SGLT2is, sodium-glucose co-transporter-2 inhibitors; Asterisk means average annual percent change (APPC) is significantly different from zero at the alpha = 0·05 level.

TZDs (8·1% versus 3·4% in 2019). The 20-44 age-group was more likely to be treated with insulin analogues than the oldest (Table S7). By contrast, trends and proportions treated with DPP-4is were similar across all age-groups. The 45-59 age-group was most intensively treated with 19·9% receiving ≥4 GLDs versus 13·7% in the ≥75 age-group in 2019.

Trends in GLDs by ASCVD, heart failure, and eGFR categories

In 2019, the proportion of patients with ASCVD treated with SGLT2is, DPP-4is, and GLP-1RAs was 6·4%, 19·9%, and 0·6%, respectively (Table S8). In 2015-2019, the growth in SGLT2is use in ASCVD patients exceeded that for DPP-4is (AAPC=89·2 [95% CI: 41·3, 153·3] versus AAPC=12·8 [95% CI: 9·9, 15·8]), but not for GLP-1RAs. There was greater increase in SGLT2i use among patients with ASCVD versus those without (6·4%-versus-3·6% in 2019). The proportion of patients with heart failure treated with SGLT2is was relatively low (5.7%) compared with DPP-4 is (22·6%) in 2019.

In 2002-2019, the use of metformin increased in patients with eGFR of 45-59 and ≥60 mL/min/1·73m^2 and to a lesser extent in those with eGFR <45 mL/min/1·73m^2 with proportions ranging from 28·2% to 37·4% (AAPC=1·6, 95% CI: 1·3-1·9) (Figure S4, Table S9). Use of sulfonylureas decreased across all eGFR categories. The largest increase in DPP-4is use occurred in those with eGFR<45 ml/min/1·73m^2, with up to 33·5% of these patients treated with DPP-4is in 2019. In patients with eGFR ≥60 mL/min/1·73m^2, SGTL2is use increased from 0·4% in 2015 to 5·3% in 2019 (AAPC=64·1, 95% CI: 26·5-112·8) with only 2·3% of patients with eGFR<45 mL/min/1·73m^2 treated with SGLT2is in 2019. There were no significant differences in trends of GLP-1RAs use by eGFR categories.

Sensitivity analyses

After excluding patients not treated with any GLDs and those with incident diabetes, we observed the same declining patterns of incident rate of SH in both sexes, all age subgroups and treatment regimens. The incident rates were highest in those prescribed with GLDs (insulin plus non-insulin GLDs) followed by those receiving insulin-only (Figure S5). In the sub-group of patients who underwent structured assessment in the RAMP-DM module, we observed the same declining patterns of incident rate of SH in patients with type 1 (AAPC=-8·3, 95% CI: -10·7, -5·8) and type 2 (AAPC=-6·6, 95% CI: -9·5, -3·6) diabetes (Table S10 and Figure S6). Compared with type 2 diabetes, patients with type 1 diabetes had a higher incidence rate of SH in 2019 (1·5 versus 0·8 events per-100-person-years). We also observed a declining trend of SH in both sexes and all age subgroups among patients with type 1 (Table S10) and 2 diabetes (Figure S7).

Discussion

In this 18-year population-based database, the significant improvements in HbA1c in 2007-2014 had stagnated in 2014-2019. Similarly, the decline in SH rates notably in 2002-2005 and 2005-2014 had also levelled off. Sulfonylurea use steadily declined by 50% during the whole period while insulin use remained static. Adoption of DPP-4is slowed following initial rapid uptake in 2007-2011. Despite the sharp increases in GLP-1RAs since 2008 and SGLT2is since 2015, only a minority (0·5% and 6% respectively) of patients were treated with these organ-protective drugs in 2019. We observed age-dependent use of GLDs with the 20-44 age-group having the highest proportion and steepest rise in use of SGLT2is, GLP-1RAs and TZDs. Despite recommendation, the use of SGLT2i and GLP-1RA in patients with ASCVD (6·4% and 0·6%) and CKD (4·2%

and 1·3%) remained low in 2019. By contrast, use of DPP-4is continued to increase irrespective of age and ASCVD with 33·5% of patients with eGFR<45 ml/min/1·73m² treated with DPP-4is.

Hong Kong has a universal healthcare system with drug prescriptions being dispensed on site at a nominal fee (USD 1·5 per item for 3 months). In 2007, DPP-4is were included in the HA formulary followed by GLP-1RAs in 2011 and SGLT2is in 2015.[18] For new medications with high unit cost or high volume of usage, a HA working group issued criteria for prescribing based on international practice guidelines.[19,20] Thus, DPP-4is could be added after failure with metformin and sulfonylureas or used as a second-line drug in patients with contraindication or intolerance with metformin or sulfonylurea or as adjunct to insulin. GLP-1RAs could be prescribed under public funding in patients with body mass index (BMI) ≥30 kg/m² as add-on to three oral-GLDs. Since 2015, SGLT2is could be used in patients with CVD as add-on to two oral-GLDs or in combination with insulin. This was lately extended to patients with macroalbuminuria and eGFR 45-60 ml/min/1·73m². These prescribing criteria are similar to other public-funded healthcare institutions such as National Institute for Health and Care Excellence (NICE).[21]

Improvements in HbA1c have levelled off since 2014 following a decade of progress. We previously suggested that glycemic improvements including reduced SH rates coincided with primary care reforms, decreased use in sulfonylureas and increased use in metformin and DPP-4is in 2007–2014. The stagnation of HbA1c since 2014 is a cause for concern calling for further quality improvement actions. In 2014–2019, there had been not major structural reforms in diabetes care in Hong Kong. During this period, we observed marked decline in use of sulfonylureas known to have greater glucose lowering efficacy than DPP-4is and SGLT2is. The substitution of sulfonylureas with these newer agents since 2014 could potentially play a role. Population-level glycemic control in the US deteriorated since 2010 following improvements in early 2000s.[11] Some researchers attributed this to publication of landmark trials implicating stringent glycemic control did not improve outcomes in patients with ASCVD[22] with a move towards personalisation of targets.[23] However, in the HKDSD, we observed continuing decline in HbA1c without increase in SH events in the ≥75 age-group, which was against the trends in deintensification due to age and comorbidities. On the other hand, we observed high usage of new-GLDs including SGLT2i and GLP-1RA in young patients who had the worst glycemic control and high BMI compared to their lower usage in patients with ASCVD and CKD.

In 2002-2019, we observed overall decline in SH in two periods, 2002-2006 and 2010-2014. This initial period of decline in SH preceded the introduction of DPP-4is which might be due to reform of the primary care diabetes service. The decline in SH was mainly observed in patients treated with non-insulin GLDs which might reflect the declining use of sulfonylureas. In the UK Clinical Practice Research Datalink, the decrease in hypoglycaemia rate was accompanied by increasing use of second-line therapy (2017 rate=5·7 events per-1000-person-years, 2010 rate=8·2 events per-1000-person-years)[24] which closely mirrored our findings.

Use of SGLT2is, GLP-1RAs and TZDs was higher in the 20-44 age-group with lower use of traditional-agents such as sulfonylureas. It remained plausible that increased awareness regarding their high lifetime risk for complications might have motivated the preferred use of these new drugs, irrespective of ASCVD status. That said, their HbA1c remained suboptimal similar to our previous findings.[25] In the US, only 11% and 13% of patients aged ≥75 years with CKD were treated with SGLT2is or GLP-1RAs respectively versus 16% and 23% in their counterparts aged <65 years in 2019. In RCT setting, these newer-GLDs had similar efficacy and safety in older adults than their younger peers.[26,27] However, the lower usage of SGLT2is in real-world practice might reflect physicians' tendency to de-intensify treatment in old adults and concerns over side effects without the close supervision under RCT settings. Resistance to injection and criteria of high BMI for subsidised use might account for the low use of GLP-1RAs in elderly patients. By contrast, the use of DPP-4is which had neutral effects on cardiovascular-renal outcomes continued to increase similarly across all age-groups including the ≥75 age-group. Despite this disconnect between guidelines and real-world practice, overall glycemic control had improved in the 60-74 and ≥75 age-groups in the past decades with lower proportions of patients in the extreme HbA1c categories (<6% and >9%) and reduction in SH.

Renal function was another important factor that might influence prescription of GLDs. Metformin use in eGFR<45 ml/min/m² increased modestly in 2000-2019 but we did not analyse whether dosage had been adjusted according to US Food and Drug Administration (FDA) recommendations.[20,28] The popularity of DPP-4is in patients with eGFR<45 ml/min/1·73m² might reflect the greater priority on safety during prescription given the low risk of hypoglycemia. Since its introduction into the HA formulary, there was a rapid increase of SGLT2is use among patients with eGFR 45-59 ml/min/1·73m² although only 2·3% of patients with eGFR <45 ml/min/1·73m² received SGLT2is. We anticipate greater use of SGLT2is in lower eGFR categories in the coming years following publication of more recent trials since 2019,[29] highlighting the importance of data in changing practice, though often with a lag phase. In our study, the proportion of heart failure patients treated with SGLT2is were relatively low despite clear evidence that SGLT2is can reduce heart failure

hospitalisations and mortality. Further action is needed to ensure such high-risk groups are appropriately treated with these organ-protective agents.

Our findings have important implications for policy and practice. Younger adults consistently had the highest and poorest glycemic control (HbA1c≥9%) with the least improvement over time despite introduction of new-GLDs. This might be further contributed by the declining use in sulfonylureas with high efficacy in glucose lowering, replaced by DPP-4is and SGLT2is. The stagnation in improvements in both HbA1c and SH despite availability of SGLT2is and GLP-1RAs call for further quality improvement strategies to ensure that their added values are realised in real-world practice. In the last 3 years, there had been a 30% increase in year-on-year expenditure with newer-GLDs in Hong Kong, notably for SGLT2is and GLP-1RAs. In US, the costs for newer oral-GLDs had increased by 88% in 2015-2017 versus 2005-2007.[30] In many settings, the increasing use of new drugs not accompanied by improved glycemic control, a surrogate for clinical outcomes, raised concerns amongst payers and policy makers.[31] As evidence evolves, SGLT2i should be used for organ protection irrespective of HbA1c with addition of other GLDs when HbA1c is not to target.[23] Our data and others highlight the pressing needs of designing a total package including regular risk assessment, evidence-based medications, patient education, blood glucose monitoring tools and psychosocial support to maximise the impact of drugs for better outcomes.

Strengths and limitations

The strengths of our study included territory-wide dispensing, laboratory, and hospitalisation data for defining glycemic control and SH over 18 years complemented by the structured data collection on risk factors and comorbidities in the RAMP-DM module. These have allowed us to evaluate the long-term trends and the relationships between changing patterns of GLDs use and glycemic control including subgroup analysis stratified by age and comorbidities. We used the 2005 ADA criteria to define SH event requiring external assistance, including hospital admission, to assess the trends throughout the entire period.[32] Our study had limitations. Type 1 diabetes could contribute to higher rates of insulin use and SH in the 20-44 age-group. However, we observed the same declining patterns in patients with type 1 and type 2 diabetes in our sub-group analysis of data from the RAMP-DM module. In 2002-2015, the age-standardised incidence rate of type 1 diabetes in the 20-39 age-group remained stable with an incidence of 2·0 for men and 2·7 for women per 100 000 person-year.[33] Although the HA provides 90% of healthcare, a small proportion of prescriptions from private sectors might not have been captured. This influence was expected to be small given the marked differences in out-of-pocket payment between private and public sectors. Our study design limits causality assessment between trends in use of GLDs and HbA1c and SH rates.

Conclusion

In this 18-year analysis of GLDs-prescribing trends in a territory-wide EHR system, following a period of reduction in HbA1c and SH in 2007-2014, mainly attributed to increasing use of DPP-4is and metformin and declining use of sulfonylureas against a backdrop of reform in primary diabetes care, improvements had stagnated in 2014-2019. The latter occurred against a background of continuing and declining use of sulfonylureas, stable use of insulin use and increasing use of SGLT2is and GLP-1RAs. Despite their high ASCVD, patients aged ≥75 years were less likely to be prescribed SGLT2is, GLP-1RAs, and TZDs than the 20-44 age-group who had persistently the worst glycemic control. Whilst the use of DPP-4is continued to increase including those with CKD, relatively lower proportions of patients were treated with SGLT2is in patients with reduced eGFR. These RWE reinforced the need to implement concerted and targeted actions to close these treatment gaps with ongoing evaluation of the impacts of these new drugs on clinical outcomes for informing practice and policies.

Contributors

AY, EC and JC contributed to conception of the article, statistical analysis, interpretation of results, drafting, revision and approval of the manuscript. HW, ESHL and MS contributed to interpretation of results, revised the manuscript critically and approved the final version. APSK, RCWM, WYS and AOYL contributed to conception of the article, revised the manuscript critically and approved the final version. EC is the guarantor of this work and takes responsibility for the integrity of the data and accuracy of the data analysis.

Data sharing statement

HKDSD welcomes collaborative research. Aggregate data may be available upon reasonable request. Proposals for future collaborations can be submitted to the HKDSD investigators (andrealuk@cuhk.edu.hk) for consideration.

Declaration of interests

JC reported received research grants, honorarium and speakers' fees from Applied Therapeutics, Astra Zeneca, Bayer, Boehringer Ingelheim, Celltrion, Hua Medicine, Lee Powder, Lilly, Merck Sharpe Dohme,

Merck Serono, Pfizer, Sanofi, Servier and Viatris Pharmaceutical. AOYL has served as a member of advisory panel for Amgen, AstraZeneca, Boehringer Ingelheim and Sanofi and received research support from Amgen, Asia Diabetes Foundation, Bayer, Boehringer Ingelheim, Lee's Pharmaceutical, MSD, Novo Nordisk, Roche, Sanofi, Sugardown Ltd, Takeda. APSK has received research grants and/or speaker honoraria from Abbott, Astra Zeneca, Bayer, Boehringer Ingelheim, Eli-Lilly, Merck Serono, Nestle, Novo Nordisk, Pfizer and Sanofi. RCWM has received research funding from AstraZeneca, Bayer, Merck Sharp & Dohme, Novo Nordisk, Pfizer and Tricida Inc. for carrying out clinical trials, and has received speaker honorarium or consultancy in advisory boards from AstraZeneca, Bayer and Boehringer Ingelheim. All proceeds have been donated to the Chinese University of Hong Kong to support diabetes research. None of these relationships had any influence on the content of the present manuscript

Acknowledgement

We acknowledge the Hong Kong Hospital Authority for providing the clinical data.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.lanwpc.2022.100509.

References

1 Draznin B, Aroda VR, Bakris G, et al. 9. Pharmacologic approaches to glycemic treatment: standards of medical care in diabetes-2022. *Diabetes Care*. 2022;45(suppl 1):S125–S143.
2 Navaneethan SD, Zoungas S, Caramori ML, et al. Diabetes management in chronic kidney disease: synopsis of the 2020 KDIGO clinical practice guideline. *Ann Intern Med*. 2020;174(3):385–394.
3 Zinman B, Lachin JM, Inzucchi SE. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med*. 2016;374(11):1094.
4 Packer M, Anker SD, Butler J, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. *N Engl J Med*. 2020;383(15):1413–1424.
5 American Diabetes Association. 9. Cardiovascular disease and risk management: standards of medical care in diabetes—2018. *Diabetes Care*. 2018;41(suppl 1):S86–S104.
6 Montvida O, Shaw J, Atherton JJ, Stringer F, Paul SK. Long-term trends in antidiabetes drug usage in the U.S.: real-world evidence in patients newly diagnosed with type 2 diabetes. *Diabetes Care*. 2018;41(1):69–78.
7 Tan YZ, Cheen MHH, Goh SY, et al. Trends in medication utilization, glycemic control and outcomes among type 2 diabetes patients in a tertiary referral center in Singapore from 2007 to 2017. *J Diabetes*. 2019;11(7):573–581.
8 Lipska KJ, Yao X, Herrin J, et al. Trends in drug utilization, glycemic control, and rates of severe hypoglycemia, 2006-2013. *Diabetes Care*. 2017;40(4):468–475.
9 Bang C, Mortensen MB, Lauridsen KG, Bruun JM. Trends in antidiabetic drug utilization and expenditure in Denmark: a 22-year nationwide study. *Diabetes Obes Metab*. 2020;22(2):167–172.
10 Chu WM, Ho HE, Huang KH, et al. The prescribing trend of oral antidiabetic agents for type 2 diabetes in Taiwan: an 8-year population-based study. *Medicine*. 2017;96(43):e8257.
11 Fang M, Wang D, Coresh J, Selvin E. Trends in diabetes treatment and control in U.S. adults, 1999-2018. *N Engl J Med*. 2021;384(23):2219–2228.
12 Yang A, Wu H, Lau ES, et al. Trends in glucose-lowering drug use, glycemic control, and severe hypoglycemia in adults with diabetes in Hong Kong, 2002–2016. *Diabetes Care*. 2020;43(12):2967–2974.
13 Draznin B, Aroda VR, Bakris G, et al. 10. Cardiovascular disease and risk management: standards of medical care in diabetes-2022. *Diabetes Care*. 2022;45(suppl 1):S144–S174.
14 Wu H, Lau ESH, Yang A, et al. Data resource profile: the Hong Kong diabetes surveillance database (HKDSD). *Int J Epidemiol*. 2021;51(2):e7–e19. https://doi.org/10.1093/ije/dyab252.
15 Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150(9):604–612.
16 American Diabetes Association. 10. Cardiovascular disease and risk management: standards of medical care in diabetes-2021. *Diabetes Care*. 2021;44(suppl 1):S125–S150.
17 Kim HJ, Fay MP, Feuer EJ, Midthune DN. Permutation tests for joinpoint regression with applications to cancer rates. *Stat Med*. 2000;19(3):335–351.
18 Hong Kong Depoartment of Health. Drug Office. Registered Pharmaceutical Products. Search Drug Database. https://www.drugoffice.gov.hk/eps/do/en/consumer/reg_pharm_products/index.html. Accessed 3 August 2021.
19 American Diabetes Association. 6. Glycemic Targets. *Diabetes Care*. 2015;38(suppl 1):S33–S40.
20 Marx N, Davies MJ, Grant PJ, et al. Guideline recommendations and the positioning of newer drugs in type 2 diabetes care. *Lancet Diabetes Endocrinol*. 2021;9(1):46–52.
21 National Institute for Health and Care Excellence (NICE). *Canagliflozin, Dapagliflozin and Empagliflozin as Monotherapies for Treating Type 2 Diabetes*. London: Technology appraisal Guidance [TA390]; 2016 https://www.nice.org.uk/guidance/ta390. Accessed 28 April 2022.
22 Cushman WC, Evans GW, Byington RP, et al. Effects of intensive blood-pressure control in type 2 diabetes mellitus. *N Engl J Med*. 2010;362(17):1575–1585.
23 American Diabetes Association. 9. Pharmacologic approaches to glycemic treatment: standards of medical care in diabetes—2022. *Diabetes Care*. 2021;45(suppl 1):S125–S143.
24 Dennis JM, Henley WE, McGovern AP, et al. Time trends in prescribing of type 2 diabetes drugs, glycaemic response and risk factors: a retrospective analysis of primary care data, 2010-2017. *Diabetes Obes Metab*. 2019;21(7):1576–1584.
25 Ke C, Lau E, Shah BR, et al. Excess burden of mental illness and hospitalization in young-onset type 2 diabetes: a population-based cohort study. *Ann Intern Med*. 2019;170(3):145–154.
26 Cahn A, Mosenzon O, Wiviott SD, et al. Efficacy and safety of dapagliflozin in the elderly: analysis from the DECLARE–TIMI 58 study. *Diabetes Care*. 2020;43(2):468–475.
27 Giugliano D, Longo M, Maiorino MI, et al. Efficacy of SGLT-2 inhibitors in older adults with diabetes: systematic review with meta-analysis of cardiovascular outcome trials. *Diabetes Res Clin Pract*. 2020;162:108114.
28 U.S. Food and Drug Administration. Drug Safety and Availability. FDA Drug Safety Communication: FDA Revises Warnings Regarding Use of the Diabetes Medicine Metformin in Certain Patients With Reduced Kidney Function. https://www.fda.gov/drugs/drug-safety-and-availability. Accessed 3 August 2021.
29 Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *New Engl J Med*. 2019;380(24):2295–2306.
30 Zhou X, Shrestha SS, Shao H, Zhang P. Factors contributing to the rising national cost of glucose-lowering medicines for diabetes during 2005-2007 and 2015-2017. *Diabetes Care*. 2020;43(10):2396–2402.
31 Caparrotta TM, Blackbourn LAK, McGurnaghan SJ, et al. 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. *Diabetes Care*. 2020;43(9):2034–2041.
32 International Hypoglycaemia Study Group. Glucose concentrations of less than 3.0 mmol/L (54 mg/dL) should be reported in clinical trials: a joint position statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care*. 2017;40(1):155–157.
33 Luk AOY, Ke C, Lau ESH, et al. Secular trends in incidence of type 1 and type 2 diabetes in Hong Kong: a retrospective cohort study. *PLoS Med*. 2020;17(2):e1003052.