Trends in Glucose-Lowering Drug Use, Glycemic Control, and Severe Hypoglycemia in Adults With Diabetes in Hong Kong, 2002–2016

Aimin Yang,[1,2] Hongjiang Wu,[1] Eric S.H. Lau,[1] Ronald C.W. Ma,[1,2,3] Alice P.S. Kong,[1,2,3] Wing Yee So,[4] Andrea O.Y. Luk,[1,2,3] Juliana C.N. Chan,[1,2,3] and Elaine Chow[1,2]

Diabetes Care 2020;43:2967–2974 | https://doi.org/10.2337/dc20-0260

OBJECTIVE

There has been a shift toward new classes of glucose-lowering drugs (GLDs) in the past decade but no improvements in glycemic control or hospitalization rates due to severe hypoglycemia (SH) in previous surveys. We examined trends in GLDs use, glycemic control, and SH rate among patients with diabetes in Hong Kong, which introduced a territory-wide, team-based diabetes care model since 2000.

RESEARCH DESIGN AND METHODS

Using population-based data from the Hong Kong Diabetes Surveillance Database, we estimated age- and sex-standardized proportion of GLD classes, mean hemoglobin A_{1c} (HbA_{1c}) levels, and SH rates in 763,809 patients with diabetes aged ≥20 years between 2002 and 2016.

RESULTS

Between 2002 and 2016, use declined for sulfonylureas (62.9% to 35.3%) but increased for metformin (48.4% to 61.4%) and dipeptidyl peptidase 4 inhibitors (DPP-4is) (0.01% in 2007 to 8.3%). The proportion of patients with HbA_{1c} of 6.0–7.0% (42–53 mmol/mol) increased from 28.6% to 43.4%, while the SH rate declined from 4.2/100 person-years to 1.3/100 person-years. The main improvement in HbA_{1c} occurred between 2007 and 2014, decreasing from mean (SD) 7.6% (1.6) (59.5 [19.0] mmol/mol) to 7.2% (1.7) (54.8 [18.9] mmol/mol) ($P < 0.001$). The 20–44 years age-group had the highest proportion of HbA_{1c} ≥9% (75 mmol/mol) and rising proportions not on GLDs (from 2.0% to 7.7%).

CONCLUSIONS

In this 15-year survey, the modest but important improvement in HbA_{1c} since 2007 coincided with diabetes service reforms, increase in metformin, decrease in sulfonylureas, and modest rise in DPP-4i use. Persistently poor glycemic control and underuse of GLDs in the youngest group calls for targeted action.

Diabetes is a complex, chronic illness requiring continuous medical care with multifactorial risk-reduction strategies (1). Over the past decade, glycemic management has changed considerably. Newer agents, including dipeptidyl peptidase 4 inhibitors (DPP-4is), glucagon-like peptide 1 receptor agonists (GLP-1RAs), and sodium–glucose cotransporter 2 inhibitors (SGLT2is) have become available. Prescribing patterns of glucose-lowering drugs (GLDs) have changed markedly, with a shift toward newer agents (2–4). Use of other drugs, such as thiazolidinediones

[1]Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Prince of Wales Hospital, Hong Kong Special Administrative Region, China
[2]Hong Kong Institute of Diabetes and Obesity, The Chinese University of Hong Kong, Prince of Wales Hospital, Hong Kong Special Administrative Region, China
[3]Li Ka Shing Institute of Health Sciences, The Chinese University of Hong Kong, Prince of Wales Hospital, Hong Kong Special Administrative Region, China
[4]Hong Kong Hospital Authority Head Office, Hong Kong Special Administrative Region, China
Corresponding author: Elaine Chow, e.chow@cuhk.edu.hk

Received 5 February 2020 and accepted 14 September 2020
This article contains supplementary material online at https://doi.org/10.2337/figshare.12970958.

(TZDs), has declined due to concern over cardiovascular safety. International treatment guidelines have been updated to reflect individualization of glycemic targets, taking into consideration specific patient factors and risks of atherosclerotic cardiovascular disease and renal complications (5–8). These changes in management approaches will influence prescribing patterns, which may affect glycemic control, hypoglycemia, and diabetes-related complications (9–12).

Most of the drug use surveys (2–4,9–12) were conducted in Western populations (3,4,9–11), which consistently report increasing use of newer agents, such as DPP-4is and SGLT2is, replacing traditional agents, such as sulfonylureas, in the past decade. However, none of these studies have demonstrated improvements in overall HbA_{1c} trends. In an international survey involving >80,000 patients from developing countries over a 12-year period, only 20–40% of patients attained HbA_{1c} <7.0% with no improvement (13). In the same vein, hypoglycemia rates have remained static, albeit some studies have reported decreasing trends in the elderly (10,14). Given the East-West differences in the phenotypic makeup of patients and health systems, the trends of drug use and glycemic control in Asia may also differ from the West (15).

Hong Kong is a cosmopolitan city in Southern China with 7 million inhabitants, mainly of Chinese ethnicity. During the past two decades, Hong Kong has introduced a series of quality improvement programs and built a comprehensive health system to optimize care by combining universal health coverage, public-private partnerships, and data-driven integrated care that covers >90% of people with diabetes (16). The single, territory-wide electronic health record (EHR) has provided a data-rich health informatics that has provided new insights relevant to many Asian populations. We used this territory-wide EHR to examine the long-term trends of different classes of GLDs, glycemic control, and rates of severe hypoglycemia (SH) among adults between 2002 and 2016.

RESEARCH DESIGN AND METHODS

Data Source

The Hong Kong Diabetes Surveillance Database (HKDSD) is a real-world patient-level data set of people with diabetes identified from the Hospital Authority (HA) EHR between 2000 and 2016 (17). The HA is a statutory body established in 1990 and operates all 43 publicly funded hospitals, 49 specialist outpatient clinics (SOPC), and 73 general outpatient clinics to serve the health care needs of the population. Since 1999, the HA has developed the territory-wide EHR system to provide a repository of all clinical data collected within the HA facilities. The current version of HKDSD includes 778,001 unique patients between 2000 and 2016.

Study Population

People with diabetes were identified based on one or more of the following qualifying criteria: *1*) recording of diagnostic code of diabetes based on *International Classification of Diseases,* 9th Revision, code of 250.xx; *2*) recording of diagnostic code of diabetes according to the Revised Edition of the International Classification of Primary Care, World Organization of National Colleges, Academics, and Academic Associations of General Practitioners/Family Physicians code T89 or code T90; *3*) HbA_{1c} ≥6.5% in any one available HbA_{1c} measurement; *4*) fasting plasma glucose (FPG) ≥7.0 mmol/L in any one available FPG measurement; *5*) prescription of any GLDs; or *6*) long-term prescription of insulin (at least 28 days continuously). We excluded people with a diagnosis of gestational diabetes. We also excluded people aged <20 years at the point that they were first captured in the HKDSD. Between 2000 and 2016, 775,359 patients were identified, with 93.3% of them having at least one HbA_{1c} laboratory measurement. We limited our analyses to 2002–2016 and excluded patients who died in 2000–2001 to avoid bias from incomplete prescription data in the establishment of the EHR system. Finally, we included 763,809 patients in drug use analyses and 719,438 patients in glycemic control and SH analyses in 2002–2016 (Supplementary Fig. 1). The study was approved by the local clinical research ethics committee (Hong Kong, China).

GLD Use Assessment

We grouped GLDs according to the Anatomical Therapeutic Chemical classification system into eight categories: insulins (A10A), metformin (A10BA), sulfonylureas (A10BB), α-glucosidase inhibitors (AGIs, A10BF), TZDs (A10BG), DPP-4is (A10BH), GLP-1RAs (A10BJ), and SGLT2is (A10BK). In each year, we determined the proportion of patients with one or more pharmacy fills for the different classes of GLDs. Combination agents were counted as two different agents filled in the same year based on the active ingredients. For patients who were prescribed at least one GLD, we categorized them into oral antidiabetic drug (OAD) only, OAD and insulin, and insulin only group.

Glycemic Control and SH Assessment

The HA adopts practice standards in accordance with international guidelines, with all HA laboratories using locally and/or externally accredited laboratory assays. We calculated the annual mean HbA_{1c} for each calendar year and determined the glycemic control category based on the annual mean HbA_{1c} during that calendar year. Poor glycemic control was defined as HbA_{1c} ≥9.0% (75 mmol/mol). The principal discharge diagnosis *International Classification of Diseases*, 9th Revision, codes (250.8, 250.81, 250.82, 250.83, and 251.2) were used to define hospitalization due to SH.

Statistical Analyses

We calculated age- and sex-standardized proportions of GLD classes, glycemic control, and SH rates as well as annual mean HbA_{1c} for each calendar year using the 2008 midyear population as the standard. The data comprise that from prevalent cases alive at the beginning of each year and any newly incident cases arising in that year. We performed subgroup analyses divided by sex, age-group, and treatment regimen. The four age-groups (20–44, 45–59, 60–74, and ≥75 years) were based on the last visit in each calendar year.

In each calendar year, we determined events of SH per 100 person-years at risk. The latter was calculated based on days the patient was alive, all-cause mortality date, date of enrollment in the EHR system, and the date of occurrence of SH. The date of all-cause mortality was determined from the Hong Kong Death Registry. To calculate the 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 to examine trends over time (18). This software

uses permutation tests to identify points where linear trends change significantly in either direction or magnitude. It calculated the average annual percentage change (AAPC) for the full study period and the annual percentage change for each linear trend segment detected.

Sensitivity Analyses

Because the number of patients with diabetes gradually increased from 2002 to 2016 and the proportion of patients with newly diagnosed diabetes varied over time, this raises concern that changes of this proportion might influence the trends in drug use and glycemic control. We performed sensitivity analyses by excluding patients not using any GLDs and patients with incident diabetes, defined as the first occurrence of any episode fulfilling the criteria of diabetes and at least 2 years of diabetes-free observation prior. We also examined HbA_{1c} trend among these new patients in the HKDSD within their 1st year of diagnosis. Analyses were performed using R version 3.5.3 software. A P value of <0.05 was considered significant.

RESULTS

During the surveillance period, the number of people with available data at the midpoint of the calendar year increased nearly four times from 151,134 in 2002 to 570,929 in 2016 (Table 1). The proportion of men increased and women decreased during this 15-year period. The proportion of adults in their 1st year of diagnosis varied between 24.3 and 7.9%. Overall, there was a declining trend in the proportion with chronic kidney disease (CKD) (Supplementary Table 1).

Trends in GLD Use

In the overall cohort, the proportions of patients prescribed with metformin and DPP-4is increased, while that with sulfonylureas, insulin, and AGIs declined (Fig. 1). Metformin use increased from 48.4 to 61.4% in the 15-year period and became the most commonly used drug since 2008. Sulfonylureas were the most commonly used drugs initially, but their proportion declined from 69.3% in 2004 to 35.3% in 2016 (annual percentage change $= -5.4$, 95% CI -5.7, -5.2). Use of insulin and AGIs also declined to a lesser extent. The use of DPP-4is rose from 0.01% in 2007 to 8.3% in 2016. The proportion on TZDs was low but increased after 2014 to 1.9% in 2016. Only few patients were on GLP-1RAs and SGLT2is. Despite overall low levels of use, our data did show a steep rise in SGLT2i use from 0.04 to 0.40% between 2015 and 2016. There was also a steady increase in insulin analog use from 2002 to 2016 (Supplementary Table 2).

Prescription patterns varied by age (Supplementary Fig. 2) but not sex (Supplementary Fig. 3). Compared with other age-groups, the 20–44 age-group had lower use of a sulfonylurea and higher use of insulin. These young patients had the highest proportion of nonuse of any GLDs, which increased from 2.0% in 2002 to 7.7% in 2016. Among patients aged ≥75 years, metformin surpassed sulfonylureas as the most commonly used drug after 2010. The use of DPP-4is increased among all age-groups. The trends for GLD use were similar between men and women.

Trends in Annual Mean HbA_{1c} and Glycemic Control

The overall unadjusted mean (SD) HbA_{1c} decreased from 7.6% (1.6) (59.3 [17.9] mmol/mol) to 7.2% (1.3) (55.3 [13.7] mmol/mol) in the whole study period ($P < 0.001$). The mean (SD) number of HbA_{1c} tests per year per patient increased from 1.8 (1.0) times in 2002 to 3.1 (1.9) times in 2016 (Table 1). There was significant decreasing trend in the overall standardized annual mean HbA_{1c} (Fig. 2*A*). After 2007, the overall standardized annual mean (SD) HbA_{1c} decreased from 7.6% (1.6) (59.5 [19.0] mmol/mol) in 2007 to 7.2% (1.7) (54.8 [18.9] mmol/mol) in 2014 ($P < 0.001$). The proportion with HbA_{1c} of 6.0–7.0% (42 to <53 mmol/mol) increased from 28.6% in 2002 to 43.4% in 2016, while that with HbA_{1c} ≥9.0% (75 mmol/mol) declined from 16.5% in 2002 to 8.5% in 2016 (AAPC $= -4.8$, 95% CI -6.7, -2.9) (Fig. 2*B*).

On subgroup analysis, the annual mean HbA_{1c} varied by age but not sex (Supplementary Fig. 4). The 20–44 age-group had the highest HbA_{1c} and no decline (AAPC $= -0.1$; 95% CI -0.5, 0.3). Poor glycemic control was most common among women and the youngest patients, with no decline compared with other age-groups (20.2–18.05% in the youngest vs. 14.5–6.0% in the oldest) (Fig. 3). When analyzed by HbA_{1c} categories, the youngest age-group and patients treated with OAD plus insulin had the poorest glycemic control (Supplementary Figs. 5 and 6).

Trends in SH Rate

The age- and sex-standardized rate of SH decreased from 4.2 (95% CI 4.1, 4.3) in 2002 to 1.3 (95% CI 1.3, 1.3) in 2016 per 100 person-years. The decreasing trends in SH rates were observed in all age groups, with the slowest rate in the 20–44 (AAPC $= -6.5$; 95% CI -8.6, -4.3) and ≥75 years age-groups (AAPC $= -6.9$; 95% CI -9.5, -4.2). The highest rate of SH was observed among the oldest and youngest patients. SH rates were highest in those prescribed with insulin only, followed by those on OAD plus insulin (Supplementary Table 3).

Sensitivity Analyses

In the whole period, HbA_{1c} among these newly included patients within the 1st year of their diagnosis also declined (AAPC $= -0.9$; 95% CI -1.1, -0.8). After excluding patients not on medication and those with incident diabetes, we observed the same prescription patterns and declining trends in overall mean HbA_{1c} since 2007. Similar trends were observed in all age-groups and both sexes (Supplementary Figs. 7 and 8).

CONCLUSIONS

In this population-based database involving 0.76 million adults with diabetes, we observed significant changes in the prescription patterns of GLDs in the last 15 years in Hong Kong in line with new drug development and practice guidelines. From 2002 to 2016, metformin use increased, while sulfonylureas use declined. There was a sharp increase in use of DPP-4is since 2007. There was an overall decline in HbA_{1c} levels, but marked improvement was most evident after 2007 with annual mean HbA_{1c} falling from 7.6% in 2007 to 7.2% in 2014. The overall rate of SH also declined from 2002 to 2016. However, compared with older patients, young patients showed no significant improvement of glycemic control, with the highest HbA_{1c} levels, and were more likely not to be treated with any GLDs. Our results are at variance with most reports that did not show improvement despite increasing use of new agents. Apart from changes in prescribing patterns, our findings coincide against the backdrop of diabetes care reform, with gradual extension of the territory-wide

Table 1—Characteristics of adults with diabetes in the HKDSD between 2002 and 2016

	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
GLDs use analysis															
N	151,134	173,677	220,768	255,412	288,747	313,103	338,057	365,809	394,356	424,597	456,436	486,582	515,316	542,515	570,929
Sex															
Men	45.6	46.2	46.4	46.8	47.1	47.4	47.9	48.2	48.5	48.9	49.2	49.4	49.7	49.9	50.1
Women	54.4	53.8	53.6	53.2	52.9	52.6	52.1	51.8	51.5	51.1	50.8	50.6	50.3	50.1	49.9
Age, years															
20–44	7.7	7.2	6.6	6.1	5.8	5.5	5.3	5.1	4.8	4.6	4.5	4.4	4.2	4.2	4.1
45–59	24.6	25.4	26.3	26.9	27.4	27.4	27.3	27.2	27	26.7	26.3	26	25.5	24.8	24.1
60–74	26.3	25.2	25.3	24.6	24.4	24.4	24.6	25.1	25.7	26.6	27.3	27.9	28.5	29.2	29.8
≥75	41.4	42.2	41.8	42.3	42.4	42.7	42.8	42.6	42.6	42.1	41.9	41.7	41.8	41.7	42
Adults in 1st year of diagnosis (%)	24.3	22	26.5	13.4	14.4	11.1	11.1	11.1	10.5	10.6	9.8	9.3	8.3	7.9	7.9
Glycemic control (HbA_{1c}) analysis															
N	142,226	165,115	211,494	245,456	277,936	301,581	325,908	352,729	380,258	409,374	439,993	468,826	496,170	521,805	548,294
Adults in 1st year of diagnosis (%)	19.7	17.7	22	11.6	12.6	9.8	9.8	9.8	9.4	9.5	8.8	8.4	7.5	7.1	6.8
Mean (SD), mmol/mol	59.3 (17.9)	59.5 (17.8)	59.6 (17.2)	59.6 (17.2)	59.5 (17.2)	59.7 (16.5)	57.7 (16.0)	57.2 (15.7)	55.9 (14.6)	56.2 (14.0)	55.9 (14.1)	55.7 (14.1)	54.7 (13.7)	54.8 (13.5)	55.3 (13.7)
Mean (SD), %	7.6 (1.6)	7.6 (1.6)	7.6 (1.6)	7.6 (1.6)	7.6 (1.6)	7.6 (1.5)	7.4 (1.5)	7.4 (1.4)	7.3 (1.3)	7.3 (1.3)	7.3 (1.3)	7.2 (1.3)	7.2 (1.3)	7.2 (1.2)	7.2 (1.3)
Testing frequency per patient, mean (SD)	1.8 (1.0)	1.8 (1.0)	1.9 (1.1)	1.8 (1.0)	1.8 (1.0)	1.8 (1.0)	1.9 (1.1)	2.0 (1.1)	2.2 (1.2)	2.4 (1.3)	2.8 (1.7)	3.0 (1.9)	3.0 (1.8)	3.0 (1.8)	3.1 (1.9)
Percentage of HbA_{1c} category (%)															
<42 mmol/mol (6%)	12.6	12.1	10.4	10.5	10.7	8.5	10.8	10.9	10.3	7.6	7.9	8.5	10.1	9.5	8.9
<53 mmol/mol (7%)	28.2	28.5	28.4	27.7	28.7	29.7	33.2	34.4	39.1	40.9	42.3	43.1	44.9	44.5	43.8
<64 mmol/mol (8%)	26.6	26.4	27.5	27.6	27.8	29.5	28.5	28.4	28.7	30.1	29.5	28.7	27.1	28	28.8
<75 mmol/mol (9%)	15.9	16.2	16.7	16.9	16.6	16.8	14.6	14	12.2	12.2	11.2	10.9	10	10.2	10.5
≥75 mmol/mol (9%)	16.8	16.8	17.1	17.3	16.1	15.5	12.9	12.2	9.8	9.3	9.1	8.9	7.9	7.8	8.1
Percentage of GLDs (%)															
No medications	19.6	19.5	16.8	16.7	17.2	16.8	17.5	18.5	19.9	21	22	22.5	23.1	22.9	22.2
Insulin only	5.3	5.1	5	5	4.9	4.5	4	3.7	3.5	3.3	3.2	3	2.8	2.6	2.3
OAD only	75.1	75.4	78.3	78.3	78.0	78.7	78.5	77.8	76.6	75.7	74.8	74.6	74.1	74.5	75.5
OAD + insulin	9.7	10.3	10.5	10.8	11.0	10.5	9.6	9.3	9	9.4	9.8	9.9	10.3	10.9	11.5

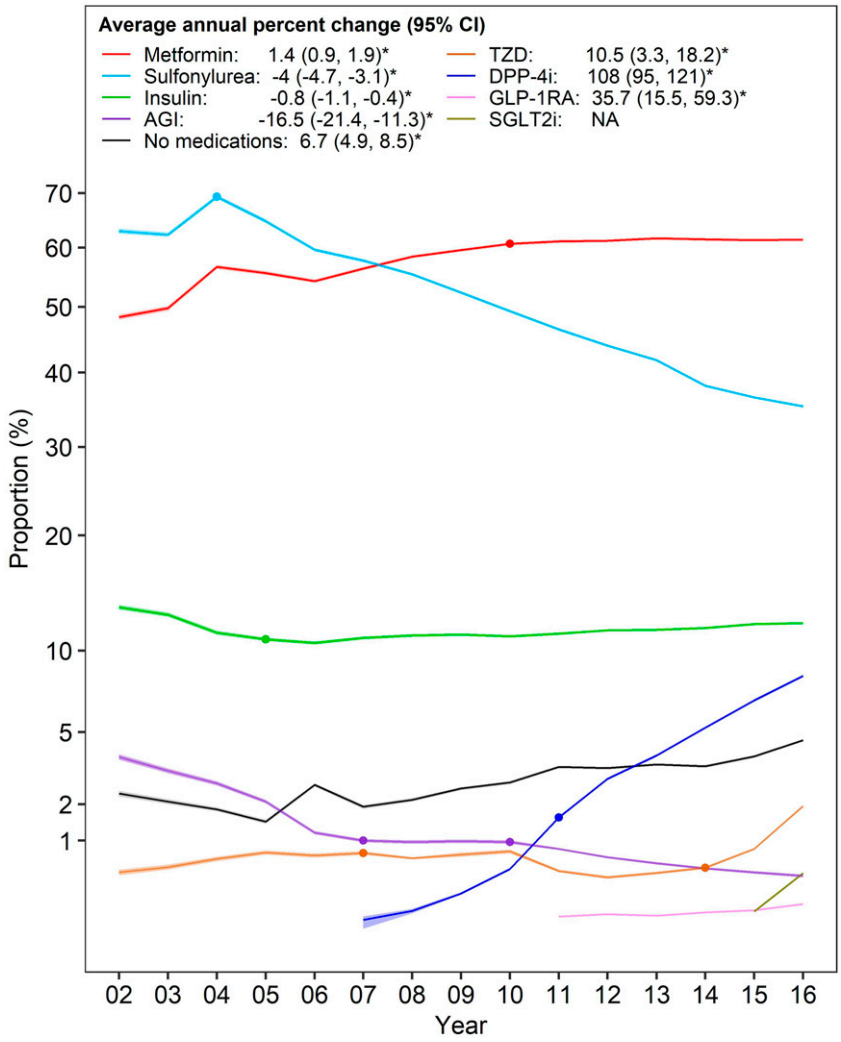

Figure 1—Trends in standardized proportion of GLDs among adults with diabetes in Hong Kong 2002–2016. The solid line and shaded area indicate the age- and sex-standardized proportion and the 95% CI. Points indicate the change points (joinpoints) in trends detected by the Joinpoint regression model. NA, not available. *The APPC is significantly different from zero at the $\alpha = 0.05$ level. Data are from the HKDSD.

diabetes assessment and management program to the primary care clinics. Our results suggest that strengthening the care system in addition to drug use might improve glycemic control. In support of this notion, we have reported the progressive decline in all-cause and cause-specific death rates during the same period (19).

Our findings on patterns of GLD use trends were largely similar to those observed in other countries (2–4,10,12). In our study, use of metformin increased from 48.4% in 2002 to 61.4% in 2016, and metformin became the most commonly used drug since 2008. This was compared with 59.6% in Singapore in 2017 (12), 74.4% in Taiwan in 2012 (2), 71.7% in Denmark in 2014 (3), 83.6% in the U.K. in 2013 (4), and 53.5% in the U.S. in 2013 (10). Although metformin has become the preferred first-line OAD, it is less frequently prescribed in patients with CKD, which is prevalent in Hong Kong and Asia (20). The decline in CKD during this period may also allow the increasing use of this drug in this population.

In other international surveys, there was declining use of sulfonylureas, accounting for 44.9% of treatment initiations in Singapore in 2017 (12), 30% in the U.K. (4) in 2017, and 30.8% in the U.S. in 2013 (10). In our survey, the proportion of patients treated with sulfonylureas more than halved, decreasing from 62.9% to 35.3% between 2002 and 2016. The decrease was greater compared with the U.S., for example, where use of sulfonylureas decreased from 38.8% to 30.8% between 2006 and 2013 (10). Sulfonylureas are associated with increased risk of hypoglycemia (21), and their use has been relegated in treatment guidelines compared with other GLDs (12).

In Hong Kong, DPP-4is were introduced in 2007, GLP-1RAs in 2011, and SGLT2is in 2015 (22). As a result of the time lag between registration and introduction to the HA formulary, our current database only registered a few patients on SGLT2is and GLP-1RAs. Despite the increasing use of DPP-4is, only 8.3% were on this drug by 2016, which was considerably lower compared with other regions in Asia (31.3% in Singapore in 2017 [12] and 19.6% in Taiwan [2] in 2012) and the U.S. (10) (14.9% in 2013). The HA has strict criteria for prescribing newly introduced high-cost medications in publicly funded institutions. Here, a DPP-4i was usually added after failure with metformin and a sulfonylurea, in patients contraindicated or intolerant to these drugs, or as adjunct to insulin. A GLP-1RA may be prescribed under public funding in patients with type 2 diabetes and BMI $\geq$30 kg/m^2 as add-on to three oral drugs. SGLT2is are indicated in patients with type 2 diabetes and established CVD as add-on to two oral drugs or in combination with insulin since 2015 in Hong Kong. These criteria might explain the lower prescription rates in Hong Kong (23).

Despite the low usage of new GLDs in our survey, there was an overall improvement in glycemic control. Because disease duration is a major determinant of HbA_{1c} (24), we excluded patients in their 1st year of inclusion in the HKDSD and found similar declining trends between 2007 and 2014. Similarly, we also found the declining HbA_{1c} trends after excluding patients not treated with any medication and those newly included patients in HKDSD within their 1st year of diagnosis. These findings contrast with the persistently poor control during the same period in low- and middle-income countries (13) and high-income countries. In Singapore (12) and the U.S. (10), there was no change in HbA_{1c} despite increased use of new GLDs. The improving patterns of glycemic control in Hong Kong are likely due to but not limited to reform of diabetes service since 2000, initially in hospital-based

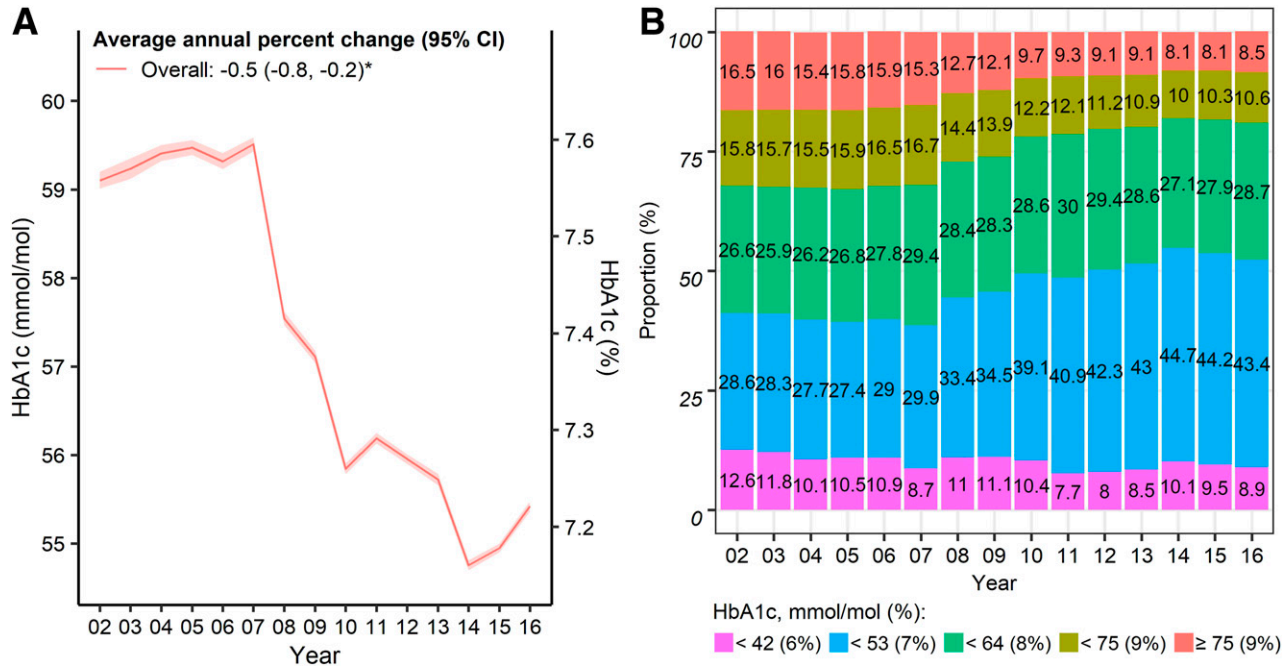

Figure 2—Trends in age- and sex-standardized annual mean HbA_{1c} (*A*) and proportion of HbA_{1c} categories (*B*) among adults with diabetes in Hong Kong, 2002–2016. The solid line and shaded area indicate age- and sex-standardized annual mean levels of HbA_{1c} and the 95% CI. *The APPC is significantly different from zero at the $\alpha = 0.05$ level. Data are from the HKDSD.

diabetes centers and later to primary care clinics since 2007. These programs focused on structured risk assessment and patient empowerment along with other policies, such as public awareness campaigns, and availability of newer GLDs such as DPP-4is (16).

In 2007, adapting from the multicomponent web-based Joint Asia Diabetes Evaluation (JADE) Program focusing on risk stratification and provider-patient communication (25), the HA progressively introduced the Diabetes Risk Assessment and Management Program (RAMP) to all public primary care clinics

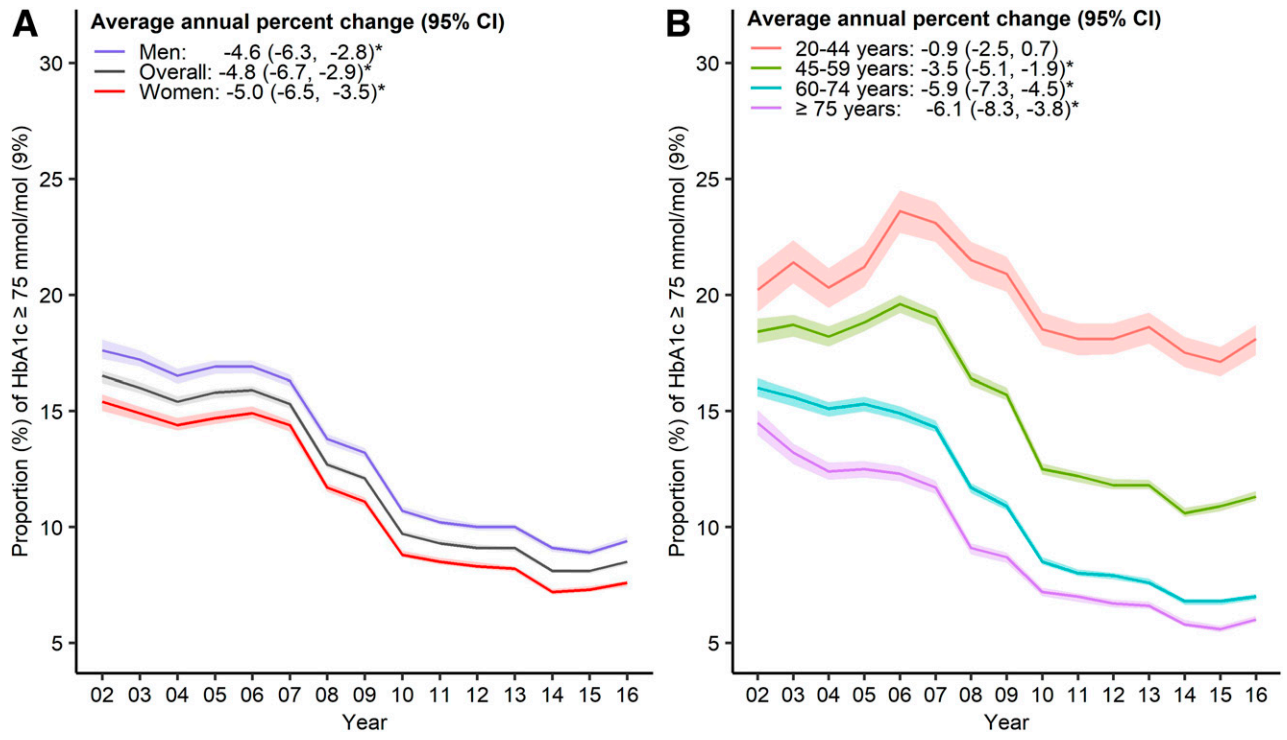

Figure 3—Trends in standardized proportion of poor glycemic control (HbA_{1c} >75 mmol/mol [9%]) among adults with diabetes and stratified by sex (*A*) and age-groups (*B*) in Hong Kong, 2002–2016. The solid line and shaded area indicate the age- and/or sex-standardized proportion and the 95% CI. *The APPC is significantly different from zero at the $\alpha = 0.05$ level. Data are from the HKDSD.

along with a patient empowerment program (16). There were differences in prescribing among patients enrolled in the RAMP program. In a propensity score–matched analysis, 90% of patients in the RAMP program were prescribed GLDs compared with 86% in the non-RAMP patients ($P < 0.001$). The program also included dedicated patient education sessions led by nurses on medication adherence (26). Although it will be challenging to demonstrate causal effects, the more accelerated improvement in HbA_{1c} since 2007 might also, in part, be attributed to the extension of this program to the primary care with enrollment of newly diagnosed patients compared with the preponderance of hospital-based patients in earlier years.

In our previous analysis of mortality trends in this cohort, we also observed a declining trend of HbA_{1c} (19). In the present in-depth analysis, there are a few observations that should call for actions. Despite the overall declining trend in HbA_{1c} between 2007 and 2014, young patients (20–44 years age-group) had the highest HbA_{1c}, with no improvement. Poor glycemic control in young adults has been reported in many counties, including the U.S. (10,27), Singapore (12), and Japan (28). In the multinational JADE register, young patients diagnosed before the age of 40 had low rates of achievement of HbA_{1c} with a high lifetime risk of hospitalization, complications, and premature death (29,30). Despite changes in guideline advocating less stringent glycemic targets in those at risk for hypoglycemia, we did not observe worsening of glycemic control in the oldest age-group together with a decrease in SH rates (31). We also noticed an increased annual standardized mean (SD) HbA_{1c} from 2014 to 2016 (54.8 [18.9] vs. 55.4 [21.9] mmol/mol; 7.2% [3.9] vs. 7.2% [4.2]), raising concerns that the trend of HbA_{1c} might rise in recent years. However, the small number of patients did not allow further trend analysis. This early warning sign emphasizes the need for ongoing surveillance.

Worryingly, the proportion of patients not on GLDs was highest in the youngest age-group. The reasons are unclear, although resistance to treatment or delayed intervention due to perceived low risk with young age is possible. Other socioeconomic, psychological, or mental health factors may be involved (12,29,30). A recent trial showed early intensive glycemic control in patients with type 2 diabetes treated with more than one GLD might improve glycemic durability and delay insulin initiation (32). These findings are particularly relevant to young patients, who face long disease duration, albeit studies are needed to confirm this hypothesis (33).

We also observed declining SH rates that contrast with other countries that show no change (10,12). These improvements might be attributed to a greater decline of sulfonylureas and/or greater use of newer GLDs with low hypoglycemic potential, particularly DPP-4is, over the 2002–2016 period. Use of sulfonylureas almost halved during this period, compared with the U.S., where the decline has been more modest. SH rates decreased more markedly in those on OAD only and those on OAD in combination with insulin. There was an overall decline in insulin use, with greater proportionate use of insulin analogs over this period. Although difficult to draw causal inferences against a backdrop of improvement in diabetes care delivery, changes in drug use patterns could have contributed to the overall decline in SH. Consistent with prior studies, SH rates were high among oldest adults (>75 years), showing a smaller decline compared with the 60–74 years age-group (10,12).

Our studies have both strengths and limitations. As a result of the huge cost differences between private and public care, this population-based database has accrued >90% of adult patients with diabetes during the last 15 years. This has allowed us to estimate long-term trends in drug use and glycemic control. However, the coding of diabetes types in the EHR is not mandatory, and type 1 diabetes may contribute proportionately to the high use of insulin and higher rates of SH in those aged 20–44. The registry data indicate >95% of Chinese patients with diabetes have type 2 diabetes (34), and even in young patients, <10% had classical type 1 diabetes, and among those diagnosed with type 2 diabetes, 8% had autoimmune markers (35). The repeated positive tests for FPG and HbA_{1c} were not included as the qualifying criteria for diabetes; however, because only a small percentage of patients were identified based on single HbA_{1c} or FPG criteria in this study, the overall potential effects should be small. Because SGLT2is were only introduced in 2015, we had limited data on trends of use. We did not have sufficient individual-level data on socioeconomic status, disease duration, and other risk factors that may influence the trends in drug use and glycemic control. Only patients receiving health care in the public sectors were captured, and patterns of drug use could be different in the minority of patients under private care. We were not able to directly measure changes in drug adherence or lifestyle changes that could influence glycemic trends, although in Hong Kong, all medications are dispensed on site in the publicly funded hospitals and community-based clinics on the same day of the clinic visit. Finally, the study design precludes causal inference, and the associations between the trends in drug use, glycemic control, and SH rates are only hypothesis generating.

Over a span of 15 years, from 2002 to 2016, the prescription of GLDs has changed dramatically among adults with diabetes in Hong Kong, coinciding with diabetes health care delivery reform in Hong Kong with expansion of the diabetes care model to primary care, increase in metformin use, decrease in sulfonylureas use, and integration of newer GLDs (particularly DPP-4is). There was a continual decline in use of sulfonylureas and an increase in DPP-4i use associated with a decline in SH rates within this period. Despite the relatively low use of new GLDs, there were overall improvements in glycemic control, coinciding with the introduction of a territory-wide risk assessment and patient empowerment program with focus on medication adherence. Our findings emphasize the need to concurrently improve health care delivery and patient education to fully exploit the glycemic benefits of newer and more expensive drugs at a population level. The persistently poor glycemic control and low use of GLDs in young adult patients emphasizes the need of targeted actions in this challenging group.

Acknowledgments. The authors acknowledge the Hong Kong Hospital Authority for providing clinical data.

Funding. A.Y. was supported by a Chinese University of Hong Kong (CUHK) Impact Research Fellowship Scheme.

The funding source had no role in study design, data collection, data analysis, data interpretation, or the writing of this report.

Duality of Interest. A.P.S.K. has received research grants and/or speaker honoraria from Abbott, AstraZeneca, Eli Lilly, Merck Serono, Nestlé, Bayer, Pfizer, Sanofi, and Novo Nordisk. The proceeds have been donated to The Chinese University of Hong Kong, American Diabetes Association, and other charitable organizations to support diabetes research and education. J.C.N.C. has received research grants and/or honoraria for consultancy or giving lectures, from AstraZeneca, Bayer, Bristol-Myers Squibb, Boehringer Ingelheim, Daiichi-Sankyo, Eli Lilly, GlaxoSmithKline, Merck Serono, Merck Sharp & Dohme, Novo Nordisk, Pfizer, and Sanofi. E.C. has received speaker fees and research support from Sanofi and Novartis. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. A.Y. and E.C. contributed to conception of the manuscript, statistical analysis, and results interpretation and drafted the manuscript, revised the manuscript critically, and approved the final version. H.W. and E.S.H.L. contributed to results interpretation, revised the manuscript critically, and approved the final version. R.C.W.M., A.P.S.K., W.Y.S., and E.C. contributed to conception of the manuscript, revised the manuscript critically, and approved the final version. A.O.Y.L., J.C.N.C., and E.C., contributed to conception of the manuscript and results interpretation, revised the manuscript critically, and approved the final version. E.C. had full access to all the data and final responsibility for the decision to submit for publication. E.C. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Prior Presentation. These data were presented in abstract form at the 80th Scientific Sessions of the American Diabetes Association, 12–16 June 2020.

References

1. American Diabetes Association. Introduction: *Standards of Medical Care in Diabetes—2020*. Diabetes Care 2020;43(Suppl. 1):S1–S2
2. 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 (Baltimore) 2017;96:e8257
3. 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;22:167–172
4. Wilkinson S, Douglas I, Stirnadel-Farrant H, et al. Changing use of antidiabetic drugs in the UK: trends in prescribing 2000-2017. BMJ Open 2018;8:e022768
5. American Diabetes Association. Standards of medical care in diabetes—2009. Diabetes Care 2009;32(Suppl. 1):S13–S61
6. Kirkman MS, Briscoe VJ, Clark N, et al. Diabetes in older adults. Diabetes Care 2012;35:2650–2664
7. Moreno G, Mangione CM, Kimbro L, Vaisberg E; American Geriatrics Society Expert Panel on Care of Older Adults with Diabetes Mellitus. Guidelines abstracted from the American Geriatrics Society guidelines for improving the care of older adults with diabetes mellitus: 2013 update. J Am Geriatr Soc 2013;61:2020–2026
8. Qaseem A, Wilt TJ, Kansagara D, Horwitch C, Barry MJ, Forciea MA; Clinical Guidelines Committee of the American College of Physicians. Hemoglobin A1c targets for glycemic control with pharmacologic therapy for nonpregnant adults with type 2 diabetes mellitus: a guidance statement update from the American College of Physicians. Ann Intern Med 2018;168:569–576
9. American Diabetes Association. 9. Pharmacologic approaches to glycemic treatment: *Standards of Medical Care in Diabetes—2020*. Diabetes Care 2020;43(Suppl. 1):S98–S110
10. Lipska KJ, Yao X, Herrin J, et al. Trends in drug utilization, glycemic control, and rates of severe hypoglycemia, 2006–2013. Diabetes Care 2017;40:468–475
11. 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;41:69–78
12. 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;11:573–581
13. Aschner P, Gagliardino JJ, Ilkova H, et al. Persistent poor glycaemic control in individuals with type 2 diabetes in developing countries: 12 years of real-world evidence of the International Diabetes Management Practices Study (IDMPS). Diabetologia 2020;63:711–721
14. Zhong VW, Juhaeri J, Cole SR, et al. Incidence and trends in hypoglycemia hospitalization in adults with type 1 and type 2 diabetes in England, 1998–2013: a retrospective cohort study. Diabetes Care 2017;40:1651–1660
15. Ma RC, Chan JC. Type 2 diabetes in East Asians: similarities and differences with populations in Europe and the United States. Ann N Y Acad Sci 2013;1281:64–91
16. Chan JCN, Lim LL, Luk AOY, et al. From Hong Kong Diabetes Register to JADE program to RAMP-DM for Data-Driven Actions. Diabetes Care 2019;42:2022–2031
17. Wu H, Lau ESH, Ma RCW, et al. Secular trends in all-cause and cause-specific mortality rates in people with diabetes in Hong Kong, 2001-2016: a retrospective cohort study. Diabetologia 2020;63:757–766
18. National Cancer Institute (NCI). Joinpoint Trend Analysis Software. Accessed 6 April 2019. Available from https://surveillance.cancer.gov/joinpoint/
19. Luk AOY, Hui EMT, Sin MC, et al. Declining trends of cardiovascular-renal complications and mortality in type 2 diabetes: the Hong Kong Diabetes Database. Diabetes Care 2017;40:928–935
20. Luk AO, Li X, Zhang Y, et al.; JADE Study Group. Quality of care in patients with diabetic kidney disease in Asia: the Joint Asia Diabetes Evaluation (JADE) registry. Diabet Med 2016;33:1230–1239
21. Sola D, Rossi L, Schianca GPC, et al. Sulfonylureas and their use in clinical practice. Arch Med Sci 2015;11:840–848
22. Drug Office. Department of Health. HKGSAR. Drug Database. Registered pharmaceutical products. 2019. Accessed 7 October 2019. Available from https://www.drugoffice.gov.hk/eps/do/index.html
23. Verghese NR, Barrenetxea J, Bhargava Y, Agrawal S, Finkelstein EA. Government pharmaceutical pricing strategies in the Asia-Pacific region: an overview. J Mark Access Health Policy 2019;7:1601060
24. Tong PC, Ko GT, So WY, et al. Use of antidiabetic drugs and glycaemic control in type 2 diabetes–The Hong Kong Diabetes Registry. Diabetes Res Clin Pract 2008;82:346–352
25. Ko GT, So WY, Tong PC, et al. From design to implementation–the Joint Asia Diabetes Evaluation (JADE) program: a descriptive report of an electronic web-based diabetes management program. BMC Med Inform Decis Mak 2010;10:26
26. Wan EYF, Fung CSC, Jiao FF, et al. Five-year effectiveness of the multidisciplinary Risk Assessment and Management Programme–Diabetes Mellitus (RAMP-DM) on diabetes-related complications and health service uses—a population-based and propensity-matched cohort study. Diabetes Care 2018;41:49–59
27. Berkowitz SA, Meigs JB, Wexler DJ. Age at type 2 diabetes onset and glycaemic control: results from the National Health and Nutrition Examination Survey (NHANES) 2005-2010. Diabetologia 2013;56:2593–2600
28. Oishi M, Yamazaki K, Okuguchi F, Sugimoto H, Kanatsuka A, Kashiwagi A; Japan Diabetes Clinical Data Management Study Group. Changes in oral antidiabetic prescriptions and improved glycemic control during the years 2002-2011 in Japan (JDDM32). J Diabetes Investig 2014;5:581–587
29. Yeung RO, Zhang Y, Luk A, et al. Metabolic profiles and treatment gaps in young-onset type 2 diabetes in Asia (the JADE programme): a cross-sectional study of a prospective cohort. Lancet Diabetes Endocrinol 2014;2:935–943
30. 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;170:145–154
31. Riddle MC, Gerstein HC, Holman RR, et al. A1C targets should be personalized to maximize benefits while limiting risks. Diabetes Care 2018;41:1121–1124
32. Matthews DR, Paldánius PM, Proot P, Chiang Y, Stumvoll M, Del Prato S; VERIFY study group. Glycaemic durability of an early combination therapy with vildagliptin and metformin versus sequential metformin monotherapy in newly diagnosed type 2 diabetes (VERIFY): a 5-year, multicentre, randomised, double-blind trial. Lancet 2019;394:1519–1529
33. Ke C, Shah BR, Luk AO, Di Ruggiero E, Chan JCN. Cardiovascular outcomes trials in type 2 diabetes: time to include young adults. Diabetes Obes Metab 2020;22:3–5
34. Chan JC, So W, Ma RC, Tong PC, Wong R, Yang X. The complexity of vascular and non-vascular complications of diabetes: the Hong Kong Diabetes Registry. Curr Cardiovasc Risk Rep 2011;5:230–239
35. Luk AOY, Lau ESH, Lim C, et al. Diabetes-related complications and mortality in patients with young-onset latent autoimmune diabetes: a 14-year analysis of the prospective Hong Kong Diabetes Register. Diabetes Care 2019;42:1042–1050