



Diabetes management and treatment approaches outside of North America and West Europe in 2006 and 2015

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Abstract

Aims The impact of introducing new classes of glucose-lowering medication (GLM) on diabetes management remains unclear, especially outside North America and Western Europe. Therefore, we aimed to analyse trends in glycaemic control and the usage of new and old GLMs in people with type 2 diabetes from 2006 to 2015.

Methods Summary data from clinical services from nine countries outside North America and Western Europe were collected and pooled for statistical analysis. Each site summarized individual-level data from out-patient medical records for 2006 and 2015. Data included: demographics; HbA1c and fasting plasma glucose levels; and the proportions of patients taking GLM as monotherapy, combination therapy and/or insulin.

Results Between 2006 and 2015, glycaemic control remained stable, although body mass index and duration of diabetes increased in most sites. The proportion of people on GLM increased, and the therapeutic regimens became more complex. There were increases in the use of insulin and triple therapy in most sites, while monotherapy, particularly in relation to sulphonylureas, decreased. Despite the introduction of new GLMs, such as DPP-4 inhibitors, insulin use increased over time.

Conclusions There was no clear evidence that the use of new classes of GLMs was associated with improvements in glycaemic control or reduced the reliance on insulin. These findings were consistent across a range of economic and geographic settings.

Keywords Diabetes mellitus · Glycated haemoglobin · Disease management · Therapeutics · Hypoglycaemic agents

Introduction

Based on the most recent International Diabetes Federation (IDF) report, the number of people with diabetes will increase from 425 million people in 2017 to 629 million

by 2045 [1]. The prevalence of diabetes is increasing at a greater rate in some regions, such as Asia and the Middle East compared to the Western world [1, 2]. Furthermore, approximately 80% of people with diabetes reside in low- and middle-income countries (LMIC), representing a huge economic burden to these nations [3].

The importance of glycaemic control in preventing and delaying the progression of diabetes complications is well-established [4–6]. Despite considerable efforts undertaken in introducing new classes of glucose-lowering medications (GLM) and formulating guidelines for the use of these therapies to optimise glycaemic control [7], little is known about how this is actually put into practice in the different health-care settings around the world and whether their introduction has led to significant improvement in glycaemic control.

A modest amount of information on the use of medications and the achievement of treatment targets is now

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available from large databases in North America and in Western Europe [8–12]. In the United Kingdom General Practice Research Database, increasingly aggressive management of diabetes was reflected by a substantial increase in the prescription of GLM between 2000 and 2006 [13]. Similarly, there was a substantial increase in GLM use in Portugal and Holland from 2004 to 2013 [14].

Much less is known about how treatment is actually delivered in other parts of the world. This information is important to obtain as it describes the size and nature of the gap between actual practice, and the targets and therapies set out in guidelines. It can also provide a basis for the development of interventions to improve delivery of care to people with diabetes. Obtaining large-scale information on diabetes management requires systematic access to clinical records, which is facilitated by the use of electronic medical records. The availability of such electronic databases has facilitated reporting on diabetes management in North America and Western Europe. In recent years, the use of such record systems has spread to other parts of the world, allowing the exploration of how patients with diabetes are actually managed.

This real-world evidence (RWE) study has identified a series of data sources around the world, outside North America and Western Europe, that captured individual patient-level information from all people within a given service or jurisdiction. Data sources included clinical services using either paper or electronic medical records, and regional or national registries. While individual services are not necessarily representative of the population within which they are located, their medical records provide data on all patients within that service and remove volunteer bias [15]. Given the high burden of diabetes and limited information on delivery of care, the aim of this study was to use data from RWE to describe and compare trends in glucose-lowering medication use between 2006 and 2015 across different parts of the world.

Methods

Through a series of meetings and personal links, we sought to identify clinical services outside North America and Western Europe that were able to produce clinic-wide or population-wide reports on the provision of care to people with diabetes. We identified ten data sources from nine countries (Argentina, Australia, Hong Kong, India, Japan, Russia, Saudi Arabia, South Africa and Uganda) that captured individual-level information from all patients within a given service or jurisdiction. There were eight specialist care services, one national register and one primary care/specialist care data source. Each site extracted data from medical records of all out-patients attending in the years 2006

and 2015, and then summarized their data for each of those years. All sites used the same questionnaire developed for this project to collect and report data. Data included demographics; disease history; percentages of those with type 2 diabetes on various classes of GLM, on complexity of regimens (i.e., monotherapy, combination non-insulin therapy or insulin) and mean clinic-level laboratory values related to glycaemic control. When there was more than one result for each year, the result closest to the middle of the year was chosen (30th June). If there was more than one result with the same date, the average of the two was taken. If there were two or more results with different dates equidistant to the middle of the year, the value was chosen depending on the quarter it was in, in the order of: 2nd quarter, 3rd quarter, 4th quarter, 1st quarter.

Each site reported mean HbA1c levels with standard deviations and the method of HbA1c measurement. The percentage of people who achieved the HbA1c targets of < 7.0% (53 mmol/mol), 7.0–7.9% (53–63 mmol/mol), 8.0–8.9% (64–74 mmol/mol) and \geq 9.0% (75 mmol/mol) was reported for each site. Diabetes treatment was classified into five categories: diet only, non-insulin monotherapy, non-insulin dual therapy, non-insulin triple therapy and insulin therapy (with or without other therapies). Information was also collected separately for percentages of patients treated with each class of GLM including metformin, sulphonylureas, meglitinides, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 receptor agonists (GLP-1R agonist), alpha glucosidase inhibitors, sodium-glucose co-transporter-2 (SGLT2) inhibitors, and insulin. Analyses were conducted using Stata (version 14; Stata Corp, College Station, TX, USA). We reported continuous variables as mean \pm standard deviation (SD) and categorical variables as proportions. This study was approved by the Alfred Hospital Research Ethics Committee as well as local committees of the participating countries.

Results

Study population

We used data from 10 clinical services in 9 countries, which included 4,591,840 patients with diabetes. Among these, more than 90% were categorised as type 2 diabetes (Table 1). The sample size varied from 291 in Japan, to 3,677,976 in Russia. Most of the sites were providers of secondary care, either in a hospital or in specialist out-patient practice. There was heterogeneity in the characteristics of study participants between sites. In most sites, approximately half of the study populations were men, but in Russia and South Africa the majority of participants were women. The mean age ranged from 46 to 73 years. The mean age of

Table 1 Characteristics of people with type 2 diabetes in 2006 and 2015 stratified by clinical service

Country (Centre)	Year	Centre description ^a	Sample size	Age (years)	Sex, % men (n)	BMI (kg/m ²)	Duration of diabetes (years)	Type 2 diabetes, %	HbA1c (%)			
									<7	7–8	8–9	≥9
Argentina (Centro de Endocrinología Experimental y Aplicada)	2006	Sp	2403	58.1 (11.1)	48.4 (1163)	30.1 (5.4)	9.3 (9.0)	92.1	36.5	24.1	18.8	20.7
	2015	Pr (26%) / Sp (74%)	2534	54.7 (9.9)	49.6 (1258)	32.1 (6.4)	8.9 (7.2)	94.1	40.0	18.3	14.1	26.6
Australia (Baker Heart and Diabetes Institute)	2006	Sp	4080	61.7 (15.6)	57.2 (2331)	29.8 (6.0)	9.8 (9.8)	80.5	37.0	31.7	17.6	13.8
	2015	Sp	4059	61.8 (15.7)	60.6 (2459)	29.7 (5.8)	13.8 (10.4)	77.5	30.3	35.2	19.6	14.8
Australia (Royal Prince Alfred Hospital (complications clinic cohort))	2006	Sp	1406	60.3 (13.6)	58.2 (818)	30.7 (6.3)	11.2 (8.4)	90.6	41.9	30.6	15.2	12.3
	2015	Sp	1351	59.6 (15.3)	59.5 (804)	30.2 (6.4)	14.2 (10.2)	79.6	27.9	29.8	20.2	22.1
Hong Kong (Prince of Wales Hospital)	2006	Sp	788	58.5 (12.9)	49.2 (388)	25.7 (4.2)	6.6 (7.1)	98.6	48.6	24.2	10.5	16.7
	2015	Sp	2043	59.9 (12.0)	54.2 (1108)	26.2 (4.8)	11.3 (8.8)	96.6	36.9	30.4	18.3	14.4
India (Dr. A Ramachandran's Diabetes Hospitals)	2006	Sp	6022	58.0 (12.0)	58.4 (3214)	26.9 (4.5)	13.7 (9.3)	97.0	22.7	26.0	18.9	32.4
	2015	Sp	13,348	54.0 (13.0)	59.5 (7945)	27.5 (4.8)	11.5 (9.3)	84.4	30.2	24.4	17.5	27.8
Japan [Shiga University of Medical Science (out-patient data)]	2006	Sp	384	63.0 (11.0)	53.9 (207)	24.0 (3.8)	18.0 (10.0)	92.2	27.9	34.9	24.2	9.4
	2015	Sp	291	73.0 (5.0)	59.8 (174)	23.5 (3.5)	17.0 (11.0)	89.2	47.1	37.5	8.3	6.5
Russia (Endocrinology Research Centre Moscow)	2006	NR	871,777	62.4 (13.4)	26.6 (231,893)	30.4 (6)	7.2 (7.6)	90.9	38.2	27.3	17.4	17.1
	2015	NR	3,677,976	67.5 (11.3)	29.5 (1,086,341)	31.2 (10.0)	8.2 (6.6)	93.9	45.0	31.0	12.0	11.0
Saudi Arabia (Diabetes Center at AlNoor Specialist Hospital)	2006	Sp	383	53.5 (16.8)	41.5 (159)	31.3 (5.6)	8.9 (7.7)	100.0	41.0	21.2	13.3	24.6
	2015	Sp	276	56.4 (12.1)	51.4 (142)	31.7 (6.7)	9.6 (8.8)	100.0	23.2	23.2	18.8	34.8
South Africa (Inkosi Albert Luthuli Central Hospital, Durban)	2006	Sp	601	49.3 (17.5)	34.6 (208)	30.2 (7.3)	13.2 (11.0)	77.7	10.3	13.8	18.7	57.2
	2015	Sp	681	46.5 (20.4)	36.4 (248)	29.9 (7.5)	14.0 (10.3)	59.3	17.2	21.3	17.2	44.3
Uganda (San Raphael of St. Francis Nsambya Hospital)	2006	Sp	1128	50.7 (14.5)	38.7 (437)	26.4 (6.0)	5.3 (5.8)	94.9	–	–	–	–
	2015	Sp	309	55.1 (10.1)	42.1 (130)	26.9 (5.7)	6.9 (6.6)	97.1	–	–	–	–

Data presented as mean (SD) or percentage (n)

Pr-primary care, Sp specialist care, NR national register, – data not available

^aSpecialist care includes hospital settings for diabetes care (secondary care, tertiary care and teaching hospitals)

the participants was nearly 5 years higher in 2015 compared to 2006 in Russia, Saudi Arabia and Uganda, while in Japan mean age increased from 63 to 73 years in this time period. For all other centres, the mean age was similar in 2006 and 2015. The mean duration of diabetes increased by ≥ 3 years in Australia (Melbourne and Sydney) and Hong Kong and decreased by 2.2 years in India. For other sites, the change in duration of diabetes was < 2 years.

Medication

Generally, the proportion of patients on either monotherapy or dual therapy decreased, while utilization of insulin and triple therapy increased over time (Fig. 1a). Insulin utilization increased in eight out of ten sites. We observed a shift from diet therapy to monotherapy in Russia and Hong Kong. In other countries, there was a shift from monotherapy and dual therapy towards triple and insulin therapy. In Japan, there was a decrease in mono-, dual and insulin therapy and an increase in triple therapy in parallel with an improvement in glycaemic control. Therefore, in general, treatment

patterns became more aggressive and complex from 2006 to 2015.

Metformin and sulphonylureas

The proportion of patients using each class of GLM in non-insulin regimens is presented in Table 2, with further breakdown according to whether usage was as monotherapy or as more complex regimens in the appendix. Metformin was the most popular GLM in all sites. The proportion of people on metformin as monotherapy or any non-insulin combination therapy with metformin increased substantially in South Africa (from 33.6 to 72.0%), Uganda (from 37.9 to 81.0%), Russia (from 14.5 to 56.4%) and India (from 59.3 to 90.6%). In other sites, this proportion increased, but to a lesser degree, except for Australia and Saudi Arabia where there was a decline in metformin use as monotherapy or non-insulin combination therapy. The proportion of patients on alpha glycoside inhibitors decreased in all sites except for India and Japan.

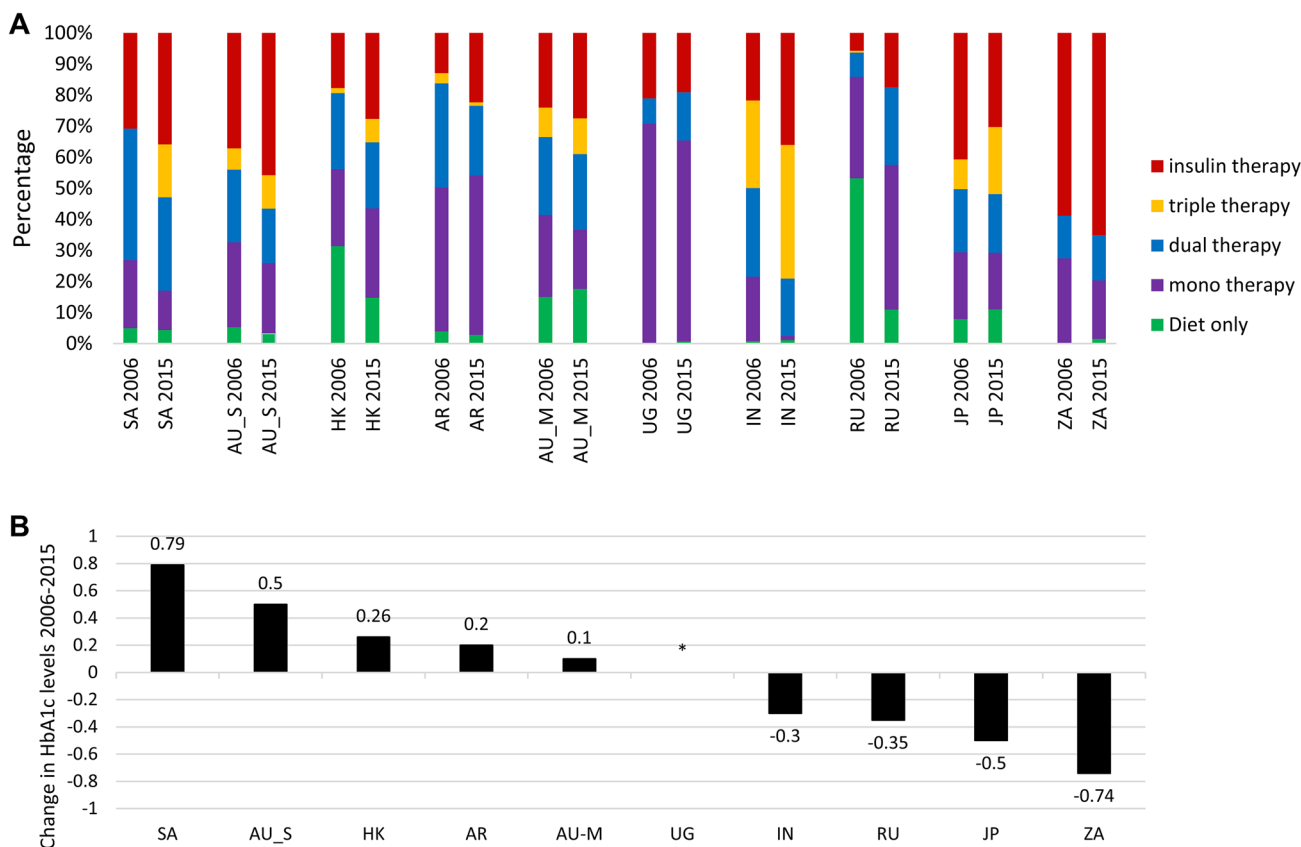


Fig. 1 a Complexity of glucose-lowering medication regimens in people with type 2 diabetes stratified by clinical service. **b** Percentage point change in HbA1c levels from 2006 to 2015 in people with type 2 diabetes stratified by clinical service. AR Argentina, AU_M Aus-

tralia, Melbourne, AU_S Australia, Sydney, HK Hong Kong, IN India, JP Japan, RU Russia, SA Saudi Arabia, UG Uganda, ZA South Africa. *Insufficient data

Table 2 Glucose-lowering medication (in non-insulin regimens) utilization in people with type 2 diabetes in 2006 and 2015 stratified by clinical service

	T2DM (n)	Metformin	Sulphonylurea	DPP-4 i	GLP-1R agonist	α -Glucosidase i	Meglitinide	SGLT2i
Argentina								
2006	2214	65.2	55.7	0	0	0.9	2.9	0
2015	2384	87.8	25.4	2.7	0.3	0	0	N/A
Australia, Melbourne								
2006	3284	49.7	40.4	0	0.03	0.6	0.6	0
2015	3144	43.7	26.5	20.2	10.0	0.4	0.03	2.0
Australia, Sydney								
2006	1274	52.7	30.0	0	0	1.7	0.3	0
2015	1075	39.5	24.7	14.7	4.1	0.93	0	4.7
Hong Kong								
2006	760	46.2	45.7	0	0	3.03	0.26	0
2015	1965	69.2	37.1	19.4	0.87	0.36	0	0.81
India								
2006	5337	59.3	71.4	0.4	0	20.9	0.17	0
2015	11,259	90.6	77.2	40.9	2.82	22.2	21.2	16.80
Japan								
2006	354	20.3	40.7	0	0	13.6	5.6	0
2015	291	40.2	32.3	50.2	2.7	19.2	6.9	0
Russia								
2006	792,185	14.5	37.5	0.01	0	0.08	1.07	0
2015	3,453,292	56.4	51.6	2.29	0.07	0.03	0.49	0
Saudi Arabia								
2006	383	58.0	48.8	0	0	0	0	0
2015	276	51.4	43.8	28.3	0	0	0	0
South Africa								
2006	467	33.6	20.3	0	0	0	0	0
2015	404	72.0	31.2	0.7	0	0	0	0
Uganda								
2006	1070	37.9	51.0	0	0	0	0	0
2015	300	81.0	15.0	0	0	0	0	0

Data presented as numbers or percentages

T2DM type 2 diabetes, N/A data not available, DPP-4 i DPP-4 inhibitors, GLP-1R agonist glucagon-like peptide-1 agonist, Alpha-glucosidase i alpha glucosidase inhibitor, SGLT2i sodium-glucose co-transporter-2 inhibitors

The proportion of people on sulphonylurea monotherapy decreased in all sites from 2006 to 2015. However, sulphonylurea use in combination with other non-insulin drugs increased in India, Russia, South Africa and Uganda, and decreased at the remaining sites. Thus, sulphonylureas remained the second most commonly used diabetes treatment in all sites in 2015.

Newer classes of GLM

The number of treatment options used in different countries varied; Australia, Hong Kong, and India used all of the new classes of glucose-lowering medications by 2015. In Saudi Arabia, South Africa and Uganda, GLP-1R agonists

and meglitinides were not prescribed. In Uganda, GLM was limited to metformin, sulphonylureas, alpha glucosidase inhibitors and insulin. In 2006, DPP-4 inhibitors were not available in any of the clinical services but many sites were using these medications by 2015. After approval of the first SGLT2 inhibitor in 2013, three countries, namely Australia, Hong Kong and India, started using this class. Use of SGLT2 inhibitors, increased by less than 5% points in Australia and Hong Kong and by 16.8% points in India.

There was virtually no use of DPP-4 inhibitors in 2006. By 2015, DPP-4 inhibitors were used by less than 5% of the patients in Argentina, Russia and South Africa, and remained unused in Uganda. In contrast, over 40% of the populations in Japan and India were using DPP-4

inhibitors in 2015. The proportion of using DPP-4 inhibitors was 15% and 20% in the two Australian sites in 2015. In Japan and India, the proportion of people on meglitinide increased from 2006 to 2015. Three sites, namely Uganda, South Africa and Saudi Arabia, did not use GLP-1R agonists for treatment of diabetes. In all other sites, the use of GLP-1R agonists increased, with the increase ranging from 0.07% points in Russia to nearly 10% points in Australia (Melbourne).

Glycaemic control

In 2015 compared to 2006, mean HbA1c was higher in five sites, including Argentina, Australia (both sites), Saudi Arabia and Hong Kong, while in four sites there was a decline in HbA1c, ranging from 0.3% points in India to 0.7% points in South Africa (Fig. 1b). Table 1 shows that BMI increased in three of the five sites where HbA1c increased, as well as in two of the four sites where HbA1c fell; age increased in two of the five sites where HbA1c increased, as well as in two of the four sites where HbA1c fell; and diabetes duration increased in four out of the five sites where HbA1c increased, as well as in two of the four sites where HbA1c fell. Figure 1 shows no consistent relationship between change in complexity of therapy and change in HbA1c.

In 2006, Hong Kong, Saudi Arabia, Australia and Russia had the highest proportion of patients with HbA1c < 7.0% (53 mmol/mol) compared to other countries (Table 1). However, the proportion reaching this target (as well as the proportion < 9.0%) fell in all of these sites, except Russia, by 2015, indicating a decline in reaching the glycaemic target in those countries with the best glycaemic control in 2006. The proportion of patients who reached the target of HbA1c < 7.0% (53 mmol/mol) increased in Argentina, India, Japan, Russia and South Africa. Among all the clinical services, South Africa had the poorest glycaemic control with only 10% and 17% in 2006 and 2015, respectively, reaching the target of HbA1c < 7.0% (53 mmol/mol). South Africa also had the highest proportion of people with HbA1c ≥ 9% (75 mmol/mol), 57% in 2006 and 44% in 2015. In 2015, Russia and Japan compared to other countries, had better glycaemic control with 45% and 47% of patients reaching the target of HbA1c < 7.0% (53 mmol/mol). Japan had the lowest proportion of patients with HbA1c ≥ 9.0% (75 mmol/mol), 9.4% and 6.5% in 2006 and 2015, respectively. There were insufficient data on HbA1c in Uganda. The method of measuring HbA1c was reported by seven sites. The method of measuring HbA1c varied between different sites but in each clinical service the method did not change between 2006 and 2015. Some clinical sites received results for HbA1c from a number of different laboratories, and so it was not possible to identify changes in methods.

Discussion

This study provides real-world information on glycaemic control and the status of diabetes treatment on more than four million people with diabetes from nine countries. In this study, while there was heterogeneity between countries in terms of diabetes management, a number of similar patterns were observed in most countries in medication use. In general, glycaemic control changed very little between 2006 and 2015, while there was an increase in BMI and duration of diabetes in most sites. In most clinical services, monotherapy decreased and diabetes management shifted towards more complex treatment such as triple therapy, and there was increased use of insulin. Nevertheless, such changes in medication utilization were not associated with improvement in glycaemic control.

There are several possible reasons why we saw little improvement in glycaemic control: (a) patients attending the clinics in 2015 tended to have a greater BMI and diabetes duration than did those in 2006. However, this did not occur in all centres, and there was no consistent relationship between these factors and change in glycaemic control. Indeed, in 50% of the centres where HbA1c fell, there was an increase in diabetes duration; (b) the lack of improvement in glycaemic control despite more complex medication regimens could be related to inadequate prescription and/or poor adherence to prescribed medications. A recent real-world study demonstrated that poor adherence to diabetes medication is one of the key factors explaining the high proportion of patients who fail to achieve glycaemic targets suggested by guidelines [16]. Unfortunately, we did not have data on actual medication usage, only on the medications listed in medical records, so we could not assess adherence properly; (c) the HbA1c measuring methodology varied among sites and some of them received data from several laboratories. Nevertheless, similar methods of measuring HbA1c in each clinical site over time, and the constant targets of HbA1c < 7% (53 mmol/mol) during the study period limited the effect of variation on HbA1c measuring methods on glycaemic change. Thus, even when the HbA1c assay methodology was not uniform, the fact that the target remained constant should minimise the impact of assay changes on achieved HbA1c levels; and (d) more recent diabetes guidelines emphasise the importance of an individualised approach for diabetes management in which higher HbA1c targets are used for some groups of patients (older or with multiple comorbidities), and so this approach might have contributed to a failure to see an improvement in glycaemic control in this study. However, if that was a major cause for the lack of significant improvement in glycaemic control, it might be expected that treatment complexity would

not increase over time. Since we observed increasing treatment complexity, it seems unlikely that higher HbA1c targets were being used for significant numbers of patients.

In this study, metformin was the most commonly prescribed GLM in most clinical services and this is in line with most guidelines for diabetes management [17]. Sulphonylureas as the second line of diabetes treatment were also prescribed widely in all sites. However, prescriptions of sulphonylureas, particularly as monotherapy, decreased and were replaced by other drugs such as DPP-4 inhibitors.

One of the advantages of the newer classes of GLM is that they might potentially avoid or delay the use of insulin. However, we saw no evidence to suggest that this has actually been a consequence of the introduction of such drugs. For example, of the four sites in which DPP-4 inhibitor use rose to 20% or more of the population, only one (Japan) had a reduction in the use of insulin. Notably, Japan had the largest increase in DPP-4 inhibitor use (50% points), suggesting that a very large increase in use of such agents may be required to influence insulin therapy. However, in India, where DPP4 inhibitor use rose by 41% points, insulin use also increased.

Our data suggest that simply prescribing more complex GLM regimens and employing newer GLMs may not be enough to produce meaningful improvements in glycaemic control. Costs and other barriers to good adherence may be relevant, as may lack of education on self-management. Thus, approaches which focus on identifying and addressing these barriers are likely to be just as important in improving metabolic control as is the use of newer pharmacological agents. Our suggestion is to follow American Diabetes Association / European Association for the Study of Diabetes guidelines with intensive and work with key performance indicators that are benchmarked for physicians treating people with diabetes.

A number of strengths and limitations of the study should be considered in interpreting the findings. We obtained real-world information about glycaemic control and treatment patterns in the management of diabetes in nine different countries. Our data include some countries that have a large number of people with diabetes, and for which there is currently very little information. Data were obtained from either national registries or medical records which eliminates volunteer and recall bias. However, generalising the results of this study to the health system of each country should be done very cautiously, because the majority of data were obtained from specialist care services. There was heterogeneity between sites in terms of sample size and ethnicity of the participants which also might affect the findings of this study. Furthermore, the variability in the nature of the services at the different sites might also influence the findings. Moreover, local treatment guidelines, the availability of financial resources, the coverage provided by the different

local health care systems, as well as the social context could each have impacted final results. This study is also limited by its cross-sectional design which does not allow to determine cause and effect, i.e., we do not know whether the increasing complexity of medication, with no improvement in HbA1c, should be interpreted as an appropriate response to increasing complexity of patients or as a failure of increasing complexity to improve glycaemic control. Furthermore, we had no data on medication adherence and our results focused only on drugs as listed in the medical record. There were no data on HbA1c levels in Uganda, thus we were not able to assess the glycaemic control in that country.

Conclusion

This real-world study showed that from 2006 to 2015, the proportion of patients with diabetes using GLMs increased. Therapeutic regimens become more complex and aggressive with increase in triple and insulin therapy and decrease in monotherapy. Despite this, there was no clear and significant improvement in glycaemic control. Lack of improvement in glycaemic control despite prescription of more complex medication regimens could be related to inadequate prescription, poor adherence to such prescriptions and higher costs of new drugs. Our findings highlight the need for more research to be performed using a population-based design with a focus on the effectiveness of new GLMs. Appropriate prescription and adherence to treatment, as the major causes of treatment failure, also need to be addressed in future studies.

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Compliance with ethical standards

Conflict of interest This study was supported by AstraZeneca.

Human and animal rights disclosure The study was approved by the Monash University Human Research Ethics Committee (number 1441), and the Alfred Ethics Committee (number 64/15) in Australia and in some of the sites, as required by local guidelines.

Informed consent For this type of study, informed consent is not required.


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