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Stroke Increases Medical Costs, Medication, and Complications for People with Diabetes: A Retrospective Study of 2,853,036 People

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Abstract

Background

Stroke is the second most common cause of death in diabetic patients. However, there are few in-depth studies on medication regimens and medical expenditures for patients with diabetes and stroke. This study aimed to analyze the treatment options, medical

expenses and complications of hospital outpatient healthcare associated with stroke complications in patients with diabetes in China from 2016 to 2018.

Methods

A total of 2,853,036 people with diabetes were recruited from the Beijing Medicare database between 2016 and 2018. The present study investigated the clinical characteristics, treatment options, and medical expenses of diabetic patients with and without stroke.

Results

In our study, 19.75%-22.30% of diabetic patients suffered from stroke from 2016 to 2018. The average annual medical cost of a patient diagnosed with diabetes is ￥9606.65, and the cost increases to ￥13428.39 when stroke is combined with stroke; stroke increases the medical cost of diabetic patients by 39.78%. Among diabetic patients without stroke, 3.58 medications were used (1.66 hypoglycemic drugs and 1.92 nonhypoglycemic drugs), while among diabetic patients with stroke, 4.76 medications were used (1.8 hypoglycemic drugs and 2.97 nonhypoglycemic drugs); these numbers were significantly greater than those of diabetic patients without stroke receiving both hypoglycemic drugs and non- hypoglycemic drugs. Interestingly , diabetic patients with stroke also had significantly greater incidences of DPN, DKD, DR, and DA than did nonstroke patients. These drugs and costs increase with the number of complications. We also analyzed medical costs and medication regimens stratified by sex, age group, and complications.

Conclusions:

Patients with diabetes had a higher incidence of complications and used more medications due to stroke events. Stroke greatly increases the economic burden on people with diabetes, highlighting the need to consider the comprehensive management and treatment of stroke in diabetic patients from a socioeconomic perspective.

Keywords: Diabetes, Stroke, Diabetic vascular disease, Medications, Healthcare costs

Introduction

Diabetes is a highly prevalent and costly chronic disease that imposes a substantial burden on individuals, families and society through reduced quality of life and life expectancy. In 2021, diabetes represents a major health burden affecting an estimated 537 million people. This number is expected to increase to 643 million by 2030 and 783 million by 2045 worldwide, according to the International Diabetes Federation (IDF)[1]. The per capita medical cost of diabetes patients is 2.3 times that of nondiabetic patients[2]. The global economic burden of diabetes was $1.3 trillion (95% CI 1.3–1.4) in 2015, which is forecasted to increase to $2.2 trillion (2.2–2.3) at baseline by 2030[3]. In 2021, 140 million people aged >20–79 years were diagnosed with diabetes, accounting for 1/4 of all adults living with diabetes globally, and this number is still growing rapidly[1]. Diabetes cost China approximately $109.8 billion in 2017, as estimated by IDF(International Diabetes Federation)[4].

The financial burden on diabetic patients increases significantly when complications develop[5]. Stroke is the second most common complication of T2DM after coronary artery disease (CAD) [6,7] and the second most common cause of death in diabetic patients. Stroke is also the leading cause of disability and mortality in aging populations[8]. Type 2 diabetes is related to a 2.5-3.5-fold increased risk of ischemic stroke and a 1.5-fold increased risk of hemorrhagic stroke[9]. Studies have also reported that men with diabetes have a 1.8-fold increase in the relative risk of stroke, while women have a 2.3-fold increase[10]. Approximately 20-33% of all stroke patients have diabetes[11,12,13]. Diabetes is closely related not only to stroke but also to the risk of adverse stroke sequelae. Preexisting diabetes was associated with increased hazards of death, admission to long-term care, readmission for stroke, and incident dementia[14]. However, there are still few in-depth studies on medication regimens and medical expenditures in this population.

In this study, the Beijing Municipal Medical Insurance Database from China was used to estimate the economic burden, demographic characteristics and medication use used

for patients with diabetes with or without stroke from 2016 to 2018. This study provides reliable evidence for assessing the socioeconomic burden and medication trends of people with diabetes and stroke comorbidities. This study may help identify cost-effective interventions and inform clinical and policy efforts to improve diabetes care.

METHODS

Study design and ethical approval

We conducted a multicenter, observational study to analyze the treatment options and medical expenses of diabetes patients with or without stroke. This study was approved by the ethics committee of Beijing Hospital (2021BJYYEC-022-01).

Study population and data collection

The study recruited diabetic patients whose data included 2016–2018 outpatient medication records and who had Beijing medical insurance. All patients were at least 16 years of age. The diagnosis of diabetes was confirmed by the diagnostic criteria of the World Health Organization (WHO) in 1999. Patients who did not have a continuous prescription record for more than 2 months were excluded from this study because Beijing hypoglycemic drugs are prescribed for less than 30 days according to the current medical insurance system and because patients need to return to the hospital to take the drug within two months. We collected information from the Beijing Medical Insurance Database, including date of birth, race, ICD diagnosis, age, sex, prescription, prescription (hypoglycemic and nonhypoglycemic drugs), dosage, and medical expenses. Each prescription has a unique serial number in the Medicare database.

Definition of complications and comorbidities

Complications were defined using International Classification of Diseases (ICD) codes. The diabetes-related complications included diabetic peripheral neuropathy (DPN), diabetic retinopathy (DR), diabetic nephropathy (DN) and diabetic angiopathy (DA). Stroke includes cerebrovascular disease, cerebral infarction, cerebral infarction sequelae, stroke, lacunar cerebral infarction, cerebrovascular disease sequelae, cerebral thrombosis, and cerebral hemorrhage.

Definition of medical therapy

The medical drugs used were hypoglycemic drugs and nonhypoglycemic drugs. Hypoglycemic drugs include oral antidiabetic drugs (OADs) and insulin. OADs include α-glucosidase inhibitors (AGIs), metformin, sulfonylureas (SUs), glinides, thiazolidinediones, and dipeptidyl peptidase 4 inhibitor (DPP-4i). Insulin consists of fast-acting insulin, short-acting insulin, intermediate-acting insulin, long-acting insulin and premixed insulin. The diabetes treatment strategies included the following: 1) monotherapy: patients who had received only one prescription hypoglycemic drug in the last year; 2) oral combination therapy: patients who had received two or more different OAD treatments in the last year; and 3) oral and insulin combined therapy: patients who had received at least one insulin and at least one OAD drug in the last year. Changes in the use of hypoglycemic drugs were assessed by drug class for each study year.

Statistical analysis

Quantitative variables are presented as the means±SDs. Continuous variables that were not normally distributed were statistically analyzed by the Wilcoxon rank−sum test; these variables included the number of drugs, medical costs, comorbidities, and complications. When the distribution of variables is overspread, we use a negative binomial model and a logarithmic link function. Confounding factors were controlled for using a multivariate regression model. The categorical variable data are presented as frequencies and percentages and were analyzed by the chi-square test or Fisher's exact probability method. All the statistical analyses were performed with SAS software, version 9.4 (SAS Institute, Inc.). $P<0.05$ was considered to indicate statistical significance.

Results

Demographic characteristics of the study population

This study included 2,853,036 diabetes patients (897,385 diabetes patients in 2016; 959,509 diabetes patients in 2017; and 996,142 diabetes patients in 2018).

Supplemental figure 1 shows a flow chart of patient enrollment. Among them, 19.75%–22.30% of diabetes patients had stroke (200,143/897,385 (22.30%) in 2016; 207,408/959,509 (21.62%) in 2017; and 196,711/996,142 (19.75%) in 2018). Among diabetic patients with stroke, those aged 15-44 years accounted for 2.53%-2.94%, 45-64 years accounted for 45.72%-48.89%, 65-84 years accounted for 44.94%-47.60%, and those aged >84 years accounted for 3.21%-4.14%. The proportion of diabetes patients with stroke varied significantly by age group, with most patients aged 45–84 years (89.83%-93.49%) affected. In the nonstroke group, men outnumbered women in 2016-2018, while there were more women in the stroke group than in the nonstroke group in 2016-2018 ($p < 0.0001$; Table 1).

Impressively, diabetic patients with stroke also had significantly greater incidences of diabetic peripheral neuropathy, diabetic nephropathy, diabetic retinopathy, and diabetic angiopathy than did nonstroke patients (all $p < 0.0001$ from 2016 to 2018; Table 1). The most prevalent complication among these patients was diabetic nephropathy, whereas diabetic angiopathy was the least common complication (Table 1).

TABLE 1. Demographic characteristics and complications of diabetes patients with and without stroke.

Variables		Non-stroke			stroke			X^2 test p value non-stroke vs. stroke		
		2016	2017	2018	2016	2017	2018	2016	2017	2018
Total		697242 (77.7%)	752101 (78.38%)	799431 (80.25%)	200143 22.30%	207408 21.62%	196711 19.75%	<.0001	<.0001	<.0001
Age group	16-44y	68241 (9.78%)	73496 (9.77%)	75643 (9.46%)	5902 (2.94%)	5949 (2.86%)	4964 (2.52%)	<.0001	<.0001	<.0001
	45-64y	380788 (54.61%)	403660 (53.67%)	419820 (52.51%)	97860 (48.89%)	98589 (47.53%)	89943 (45.72%)	<.0001	<.0001	<.0001
	65-84y	234211 (33.59%)	257841 (34.28%)	283128 (35.41%)	89952 (44.94%)	95332 (45.96%)	93653 (47.60%)	<.0001	<.0001	<.0001
	≥85y	14002 (2.0%)	17104 (2.27%)	20840 (2.60%)	6429 (3.21%)	7538 (3.63%)	8151 (4.14%)	<.0001	<.0001	<.0001
Gender	Male	352908 (50.61%)	387104 (51.46%)	421917 (52.77%)	98518 (49.22%)	103787 (50.04%)	100144 (50.90%)	<.0001	<.0001	<.0001
	Female	344334 (49.38%)	364997 (48.53%)	377514 (47.22%)	101625 (50.77%)	103621 (49.95%)	96567 (49.09%)	<.0001	<.0001	<.0001

DPN	76331 (10.94%)	83014 (11.03%)	95277 (11.91%)	39168 (19.57%)	40547 (19.54%)	40879 (20.78%)	<.0001	<.0001	<.0001
DKD	30935 (4.43%)	29566 (3.93%)	28078 (3.51%)	12144 (6.06%)	11213 (5.40%)	8813 (4.48%)	<.0001	<.0001	<.0001
DR	29319 (4.20%)	30184 (4.01%)	30186 (3.77%)	12578 (6.28%)	13205 (6.36%)	11555 (5.87%)	<.0001	<.0001	<.0001
DA	19533 (2.80%)	19575 (2.60%)	20618 (2.57%)	9712 (4.85%)	10285 (4.95%)	9636 (4.89%)	<.0001	<.0001	<.0001

The number represents the number of people in the year. The percentage in parentheses represents the percentage of the total number of people in that year. Diabetic peripheral neuropathy (DPN), diabetic retinopathy (DR), diabetic nephropathy (DN) and diabetic angiopathy (DA) were also detected.

Stroke treatment increased the types of medications and costs for people with diabetes from 2016 to 2018

The annual medical expenses of diabetic patients from 2016 to 2018 were ¥9248.17-10118.04, the average annual medical expenses for these three years were ¥9606.65, the annual medical expenses of diabetes combined with stroke from 2016 to 2018 were 13049.88-14239.78, and the average annual medical expenses in these three years were ¥13428.39, which indicates that diabetes combined with stroke increased medical expenses by 39.78% (p <.0001, Table 2).

On average, diabetic patients who did not stroke used 3.58 medications (1.66 hypoglycemic drugs and 1.92 nonhypoglycemic drugs), while diabetic patients who had stroke used 4.76 medications (1.8 hypoglycemic drugs and 2.97 nonhypoglycemic drugs); these numbers were significantly greater than those of diabetic patients without stroke receiving both hypoglycemic drugs and nonhypoglycemic drugs (p <0.0001; Table 2).

Among the medical expenses of diabetic patients, hypoglycemic drugs cost ¥5206.23, and nondiabetic drugs cost ¥4400.42. In diabetic patients complicated with stroke, the cost of hypoglycemic drugs was ¥5818.75 (p <0.0001; Table 2), the cost of nonhypoglycemic drugs was ¥7609.64 (p <0.0001; Table 2), and stroke not only increased the cost of hypoglycemic drugs in diabetic patients by 10.83%-13.04% but also increased the cost of nondiabetic drugs by 67.98%-75.07% (p <0.0001; Table 2).

The medical cost of diabetes patients with stroke decreased annually from 2016 to 2018, which was mainly attributed to the decrease in the cost of nonantiglycemic drugs (p <.0001; Table 2). As expected, the cost/drug use of diabetes patients in the stroke group was significantly greater than that of patients in the nonstroke group (¥2763.95 ± 2081.42 vs. ¥2583.03 ± 2730.96, p <0.0001; Table 2); cost/antiglycemic drugs (¥2874.4 ± 3297.19 vs. ¥2698.91 ± 3470.24, p <0.0001; Table 2); and cost/nonantiglycemic drugs (¥2352.01 ± 2068.14 vs. ¥1672.42 ± 2013.33, p <0.0001; Table 2).

TABLE 2

Stroke increased the types of medications and cost of medication for people with diabetes in 2016-2018

Variables	Non-stroke				stroke				p value non-stroke vs. stroke		
	Total	2016	2017	2018	total	2016	2017	2018	2016	2017	2018
Annual cost of medication ¥	9606.65± 9622.86	10118.04± 10543.8	9248.17± 9259.31	9497.9± 9082.87	13428.39± 11134.39	14239.78± 11825.74	13049.88± 10951.9	13001.92± 10539.1	<.0001	<.0001	<.0001
Types of medications	3.58± 2.3	3.46± 2.28	3.6± 2.31	3.67± 2.3	4.76± 2.4	4.66± 2.38	4.81± 2.43	4.83± 2.39	<.0001	<.0001	<.0001
Hypoglycemic drugs	1.66± 1.06	1.58± 1.03	1.66± 1.06	1.73± 1.07	1.8± 1.09	1.71± 1.06	1.81± 1.09	1.87± 1.11	<.0001	<.0001	<.0001
Non-hypoglycemic drugs	1.92± 1.83	1.88± 1.82	1.94± 1.83	1.94± 1.82	2.97± 1.89	2.95± 1.89	3± 1.91	2.96± 1.87	<.0001	<.0001	<.0001
Cost of Hypoglycemic drugs ¥	5206.23± 7304.56	5408.25± 8011.86	5016.95± 7003.71	5208.12± 6920.18	5818.75±7 538.65	5994.19± 7816.92	5671.02±7 420.89	5796.01± 7367.98	<.0001	<.0001	<.0001
Cost of Non-hypoglycemic Drugs ¥	4400.42± 5516.58	4709.79± 6050.25	4231.22± 5307.27	4289.78± 5201.7	7609.64± 7153.16	8245.59± 7777.21	7378.86± 6995.23	7205.91± 6588.89	<.0001	<.0001	<.0001
Annual cost/drug, ¥	2583.03± 2730.96	2798.35± 3129.79	2465.7± 2494.49	2505.63± 2553.93	2763.95± 2081.42	2992.1± 2256.28	2654.64± 2011.6	2647.08± 1944.92	<.0001	<.0001	<.0001
Cost/hypoglycemic drug ¥	2698.91± 3470.24	2895.67± 3932.27	2591.25± 3268.53	2628.57± 3207.61	2874.4± 3297.19	3067.97± 3512.65	2783.25± 3207.88	2773.57± 3151.88	<.0001	<.0001	<.0001
Cost/non-hypoglycemic drug ¥	1672.42± 2013.33	1800.41± 2244.37	1596.97± 1920.69	1631.76± 1875.39	2352.01± 2068.14	2563.36± 2295.59	2247.76± 1955.34	2246.9± 1917.82	<.0001	<.0001	<.0001

Stroke Contributes to High Health Care Costs in diabetic patients stratified by demographics and complications

To obtain more detailed information, we analyzed the medical costs of diabetic patients

by stratification according to demographic factors and complications. The population distributions of patients according to age, sex and complication status are shown in Table 3. Among the 15-44, 45-64, 65-84, and ≥85 age groups, the cost of treatment for the 65-85 age group was ¥10259.32 in the diabetic without stroke group, which was the highest among all age groups (Table 3). The cost of treatment for the 45-64 years group was ¥13658.58 for the diabetic with stroke group, which was the highest among all age groups (Table 3). For diabetic patients with stroke, medical costs were greater than those for nonstroke patients in all age groups or for both sexes (Table 3). The costs increase dramatically if diabetic patients develop complications, including diabetic peripheral neuropathy, diabetic nephropathy, diabetic retinopathy, and diabetic vasculopathy. Additionally, as the number of complications increased, the annual cost increased (Table 3). Moreover, diabetic patients with stroke incurred greater medical costs than did nonstroke patients when the same complications were described above were present (Table 3).

TABLE 3

Stroke Contributes to High Health Care Costs in diabetic Patients Stratified by Demographics and Complications

		Cost of medications ¥ (Non-stroke)			Cost of medications ¥ (Stroke)				Wilcoxon test
Variables	**N**	**Mean**	**Adjusted Mean**	**SD**	**N**	**Mean**	**Adjusted Mean**	**SD**	**P value**
Age									
15-44	217380	7455.14	7421.23	9415.03	16815	11976.69	11988.46	10851.35	<.0001
45-64	1204268	9559.72	9550.03	9572.83	286392	13658.58	13658.26	11333.06	<.0001
65-84	775180	10259.32	10258.89	9662.41	278937	13312.06	13311.72	10923.02	<.0001
≥85	51946	9958.64	9968.65	9702.45	22118	13018.42	13018.15	11273.78	<.0001
Gender									
Male	1161929	9761.82	9426.69	9821.9	302449	13354.21	12915.71	10994.52	<.0001
Female	1086845	9440.77	9031.74	9402.58	301813	13502.72	13042.91	11272.34	<.0001
DPN									
no	1994152	9279.34	8938.29	9404.13	483668	13121.2	12687.85	10857.01	<.0001
yes	254622	12170.12	11586.55	10852.8	120594	14660.44	14202.88	12105.58	<.0001
DKD									
no	2160195	9429.5	9070.66	9449.74	572092	13199.16	12766.76	10933.15	<.0001
yes	88579	13927.04	13287.78	12397.18	32170	17504.91	16958.09	13616.3	<.0001

DR									
no	2159085	9443.93	9086.09	9496.97	566924	13239.14	12810.24	11030.33	<.0001
yes	89689	13523.93	12938.98	11600	37338	16301.76	15792.65	12255.67	<.0001
DA									
no	2189048	9506.37	9139.86	9536.51	574629	13301.68	12860.30	11072.55	<.0001
yes	59726	13282.28	12589.27	11804.94	29633	15885.48	15384.26	12010.97	<.0001
Number of Complications									
0	1850162	9019.91	8710.64	9158.06	433150	12816.4	12408.04	10652.92	<.0001
1	316966	11686.23	11172.38	10782.56	130059	14298.55	13873.00	11785.88	<.0001
2	70057	14458.19	13791.39	11923.88	34029	16757.09	16271.98	12761.19	<.0001
3	10820	16883.24	16093.97	12666.86	6478	18745.38	18220.45	13281.43	<.0001
4	769	19735.3	18796.01	16356.42	546	21106.87	20525.02	16826.81	0.078

N Indicates the number of people. MEAN represents the average cost in RMB. The complications of diabetes included diabetic peripheral neuropathy (DPN), diabetic retinopathy (DR), diabetic nephropathy (DN) and diabetic angiopathy (DA). The number of complications represents the occurrence of one to four of the above diabetic complications.

Stroke significantly increased the use of various medications among people with diabetes stratified by demographics and complications

Next, we analyzed medication use in people with diabetes stratified by demographic factors and complications. Among the 15-44, 45-64, 65-84, and ≥85 age groups, the 45-64 age group, which was 3.86 years, used the most drugs (Table 4). Diabetic patients with stroke took more medications than nonstroke patients in all age groups or both sexes (Table 4). The use of medications significantly increases if diabetic patients develop complications, including diabetic peripheral neuropathy, diabetic nephropathy, diabetic retinopathy, and diabetic vasculopathy. Moreover, as the number of complications increased, more drugs were used (Table 4). In addition, diabetic patients with stroke use more medications than nonstroke patients when the same complications arise, as described above (Table 4).

TABLE 4.

Stroke significantly increased the use of various medications among people with diabetes stratified by demographics and complications

	Types of medications (Non-stroke)				Types of medications (Stroke)				Wilcoxon test
Variables	**N**	**Mean**	**Adjusted Mean**	**SD**	**N**	**Mean**	**Adjusted Mean**	**SD**	**P value**
Age									

15-44	217380	2.61	2.60	1.99	16815	4.29	4.29	2.36	<.0001
45-64	1204268	3.57	3.57	2.27	286392	4.77	4.77	2.39	<.0001
65-84	775180	3.86	3.86	2.36	278937	4.81	4.81	2.42	<.0001
≥85	51946	3.66	3.67	2.28	22118	4.57	4.57	2.38	<.0001
Gender									
Male	1161929	3.65	3.47	2.3	302449	4.81	4.65	2.38	<.0001
Female	1086845	3.51	3.31	2.3	301813	4.72	4.56	2.42	<.0001
DPN									
no	1994152	3.48	3.30	2.26	483668	4.66	4.51	2.37	<.0001
yes	254622	4.4	4.11	2.43	120594	5.18	5.00	2.5	<.0001
DKD									
no	2160195	3.55	3.35	2.28	572092	4.72	4.56	2.39	<.0001
yes	88579	4.48	4.19	2.54	32170	5.52	5.32	2.59	<.0001
DR									
no	2159085	3.53	3.34	2.27	566924	4.7	4.55	2.38	<.0001
yes	89689	4.77	4.48	2.57	37338	5.69	5.49	2.56	<.0001
DA									
no	2189048	3.55	3.36	2.29	574629	4.72	4.56	2.39	<.0001
yes	59726	4.75	4.41	2.44	29633	5.58	5.38	2.51	<.0001
Number of Complications									
0	1850162	3.41	3.24	2.23	433150	4.59	4.44	2.33	<.0001
1	316966	4.17	3.91	2.43	130059	5.03	4.86	2.48	<.0001
2	70057	5.03	4.69	2.45	34029	5.72	5.53	2.52	<.0001
3	10820	5.65	5.27	2.42	6478	6.28	6.07	2.5	<.0001
4	769	6.18	5.77	2.46	546	6.75	6.53	2.47	<.0001

N Indicates the number of people. MEAN represents the average medication type. The complications of diabetes included diabetic peripheral neuropathy (DPN), diabetic retinopathy (DR), diabetic nephropathy (DN) and diabetic angiopathy (DA). The number of complications represents the occurrence of one to four of the above diabetic complications.

Use of OADs and insulin in diabetic patients with or without stroke

Among the various types of insulin, premixed insulin is the most commonly used. From 2016 to 2018, the use of fast-acting insulin and long-acting insulin gradually increased in diabetic patients with or without stroke, while the use of intermediate-acting insulin, premixed insulin and short-acting insulin gradually decreased in diabetic patients with or without stroke (Supplemental table 1). Diabetic patients with stroke used more fast-acting, longer-acting and more premixed insulin than did the nonstroke group from 2016–2018 (Supplemental table 1). There was no difference in the use of short-acting

insulin or intermediate-acting insulin between the two groups (Supplemental table 1). Diabetic patients with stroke used more antidiabetic drugs than did patients without stroke (90.66% vs. 88.59%, 2018, p <.0001; Table 5). In particular, oral combination therapy was used (54.69% vs. 50.91%, 2018, p <0.0001; Table 5), and combinations of oral drugs and insulin were used (25.29% vs. 20.49%, 2018, p <0.0001; Table5). The proportion of patients treated with monotherapy was lower in the stroke group than in the nonstroke group (32.85% vs. 37.42%, 2018, p <0.0001; Table 5). Among the antidiabetic drugs, α-glucosidase inhibitors were the most commonly used drugs, followed by metformin, premixed insulin, sulfonylureas, and dipeptidyl peptidase-4 (Table 5). Among the oral combination therapies, α-glucosidase+metformin was the most common, and its prevalence increased annually from 2016–2018. Compared with nonstroke patients, diabetic patients in the stroke group used more α-glucosidase+metformin, α-glucosidase+sulfonylureas, α-glucosidase+metformin+sulfony and α-glucosidase+glinides, while they used less metformin+sulfonylureas, metformin+DPP-4i, and metformin+glinides (Table 5).

TABLE 5

Hypoglycemic drug treatment among diabetes patients with and without stroke in 2016-2018

Medication for diabetes	Non-stroke						stroke						P value		
	2016		2017		2018		2016		2017		2018		2016	2017	2018
	N	%	N	%	N	%	N	%	N	%	N	%			
Antidiabetic drugs	597,971	85.76%	655,166	87.11%	708,234	88.59%	176,527	88.20%	185,691	89.52%	178,357	90.66%	<.0001	<.0001	<.0001
Monotherapy	246,553	41.23%	254,992	38.92%	265,046	37.42%	65,327	37.00%	63,812	34.36%	58,605	32.85%	<.0001	<.0001	<.0001
AGIs	83,550	13.97%	83,918	12.80%	84,625	11.94%	27,636	15.65%	27,545	14.83%	24,639	13.81%	<.0001	<.0001	<.0001
Metformin	77,889	13.02%	89,781	13.70%	101,412	14.31%	16,277	9.22%	18,112	9.75%	18,496	10.37%	<.0001	<.0001	<.0001
sulfonylureas	24,233	4.05%	23,215	3.54%	21,652	3.05%	6,186	3.50%	5,699	3.06%	4,793	2.68%	<.0001	<.0001	<.0001
premixed insulin	35,507	5.93%	31,869	4.86%	28,366	4.00%	10,096	5.71%	7,629	4.10%	5,772	3.23%	0.0006	<.0001	<.0001
DPP-4i	.	.	2,218	0.33%	5,967	0.84%	.	.	281	0.15%	895	0.50%		<.0001	<.0001
Glinides	8,121	1.35%	7,185	1.09%	6,339	0.89%	1,861	1.05%	1,544	0.83%	1,287	0.72%	<.0001	<.0001	<.0001
Oral combination therapy	272,184	45.51%	317,825	48.51%	360,571	50.91%	84,625	47.93%	96,083	51.74%	97,554	54.69%	<.0001	<.0001	<.0001
AGIs +Metformin	53,616	8.96%	64,650	9.86%	74,068	10.45%	16,279	9.22%	19,732	10.62%	20,409	11.44%	0.001	<.0001	<.0001
AGIs+sulfonylurea	39,488	6.60%	38,320	5.84%	35,851	5.06%	12,958	7.34%	12,098	6.51%	10,363	5.81%	<.0001	<.0001	<.0001
Metformin+sulfonylureas	37,573	6.28%	41,128	6.27%	42,197	5.95%	8,878	5.02%	9,272	4.99%	8,837	4.95%	<.0001	<.0001	<.0001

AGIs+Metformin+sulfony	33,983	5.68%	39,247	5.99%	41,543	5.86%	11,530	6.53%	12,779	6.88%	12,664	7.10%	<.0001	<.0001	<.0001
Metformin+DPP-4i	.	.	4,094	0.62%	11,267	1.59%	.	.	471	0.25%	1,490	0.83%		<.0001	<.0001
Metformin+Glinides	10,049	1.68%	9,816	1.49%	9,161	1.29%	2,203	1.24%	2,112	1.13%	1,916	1.07%	<.0001	<.0001	<.0001
AGIs +Glinides	8,028	1.34%	7,484	1.14%	6,815	0.96%	2,413	1.36%	2,271	1.22%	1,798	1.00%	0.4349	0.0042	0.0777
Oral+Insulin	119,730	20.02%	135,533	20.68%	145,174	20.49%	44,682	25.31%	48,662	26.20%	45,120	25.29%	<.0001	<.0001	<.0001
AGIs +Premixed insulin	23,464	3.92%	23,407	3.57%	21,830	3.08%	10,583	5.99%	10,070	5.42%	8,070	4.52%	<.0001	<.0001	<.0001
AGIs+Metformin+insulin	12,450	2.08%	15,638	2.38%	16,741	2.36%	5,574	3.15%	7,273	3.91%	6,655	3.73%	<.0001	<.0001	<.0001
Metformin+Premixed insulin	13,740	2.29%	15,018	2.29%	14,942	2.10%	4,667	2.64%	4,537	2.44%	3,911	2.19%	<.0001	0.0001	0.0298

The number represents the number of people who used the drug that year. The percentage represents the number of people using the drug as a percentage of the total population.

Changes in the Prescription of Antiglycemic Drugs

Among the antiglycemic drugs, AGIs and metformin were the most frequently prescribed drugs for diabetic patients with or without stroke (Supplemental Figure 2). The use of AGIs, metformin and DPP-4i tends to increase annually, whereas the use of insulin, sulfonylureas and glinides tends to decrease annually (Supplemental Figure 2).

Discussion

In this study, we reported the population characteristics, treatment costs, drug regimens, and complications of diabetes with and without stroke. We found that diabetic patients who had a stroke used more drugs and had total annual drug costs to treat more complications than did those who did not. To our knowledge, this study is the largest current sample of studies in Asia on the drug and medical costs of diabetes combined with stroke.

Diabetes imposes a large economic burden on families and society. The annual medical cost of patients with diabetes is 2.3 times greater than that of patients without diabetes[2], and the cost doubles when complications occur[15]. Among the complications of diabetes, cerebrovascular disease and coronary heart disease are the

most common[16]. Our study investigated diabetic patients treated with Beijing Medical Insurance from 2016 to 2018, eliminating the heterogeneity caused by COVID-19, to determine whether stroke has an effect on medical costs and drugs for diabetes.

Studies have reported that 20–33% of acute stroke inpatients have diabetes[11-13]. Diabetes mellitus is an established and independent risk factor for stroke and is associated with a 1.8-6-fold greater risk than is diabetes mellitus in nondiabetic patients[17,18]. Our study showed that 19.75%-22.30% of diabetic patients suffered from stroke, which was similar to previously reported levels [11-13]. The proportion of diabetes patients with stroke varied significantly by age group, with most patients aged 45–84 years (89.83%-93.49%) affected from 2016 to 2018. The estimated life expectancy loss for people with stroke aged 40 years was 21.1-26.2 years, that for people aged 60 years was nearly 13 years, and that for people aged 80 years was nearly 4 years[19]. Therefore, stroke seriously affects the quality of life and leads to premature death in diabetic patients and greatly exacerbates productivity loss and indirect financial burdens[20,21]. There were more men than women in the diabetes population; however, the difference in diabetes with stroke incidence between men and women was not significant, and women outnumbered men in 2016. Consistent with previous findings, the risk of stroke associated with diabetes is significantly greater in women than in men[22].

The average medical costs for diabetic patients with one, two, or three conditions among stroke, heart disease, or CKD patients were 1.91, 2.90, or 3.88 times greater, respectively, than those for patients without complications[23]. Our data showed that the average medical cost for diabetic patients with stroke was approximately 39.78% greater than that for diabetic patients without stroke in China, and that for diabetic patients was approximately 6.38% greater for hypoglycemic drugs and approximately 33.41% greater for nonhypoglycemic drugs. Acute hyperglycemia and diabetes are associated with poorer outcomes after stroke, including worse neurological and functional outcomes, greater readmission and stroke recurrence, longer hospital stays,

and greater mortality[24-28]. This study demonstrated that diabetic patients with stroke had more complications, which may indicate that diabetic patients with more complications are more susceptible to stroke. In addition to these complications and comorbidities, diabetic patients can easily develop other complications when one complication arises. The medical cost increases by approximately ¥2000-3000 for each additional complication.

Compared with diabetic patients without stroke, diabetic patients with stroke use more oral combination therapy and less monotherapy. Our results revealed that AGIs and metformin are the most commonly used antidiabetic agents in diabetes patients with or without stroke, followed by premixed insulin, sulfonylureas, glinides, thiazolidinediones and DPP-4i in China 2016-2018. A 2013 nationwide survey of OADs in China reported that metformin was used by 53.7% of T2DM patients, followed by sulfonylureas (42.7%) and AGIs (35.9%)[29]. Our study showed that sulfonylureas were used 24.44% of the time, which was lower than that used in previous research, and our data also showed a gradual decrease in sulfonylureas use. This may be because of changes in doctors' medication habits, secondary failures, and the emergence of additional new varieties of drugs. DDP4i usage has grown rapidly since it was included in the health-care system of China, from a 0% increase to 7.35% from 2016 to 2018. Studies have shown that pioglitazone and GLP-1RA could reduce the risk of stroke, while metformin, AGIs, DPP-4i, and SGLT-2 inhibitors are ineffective[30,31]. Because GLP-1RA and SGLT2i were included in the 2020 Beijing Medical Insurance Catalog, we did not discuss these two drugs in this study. Our data showed that overall insulin use decreased annually in patients treated with the most commonly used type of premixed insulin; however, the use of premixed insulin was greater in the diabetes with stroke group than in the nonstroke group. Evidence suggests that insulin use may be a marker of increased risk of stroke, but it is not necessarily a causative factor[32]. Previous antidiabetic drug selection has focused more on cardiovascular and renal benefits, while cerebrovascular complications, particularly stroke, should also be given more attention because of severe health and economic

burdens.

In summary, this study included 2,853,036 individuals with diabetes diagnosed between 2016 and 2018, and the economic burden of stroke in individuals with diabetes was found to be compelling. Stroke significantly increases the types of medications, complications, and medical costs for diabetic patients. The study also revealed changes and trends in the use of hypoglycemic drugs in people with diabetes, as well as the impact of stroke on diabetes drug choice.

Cost estimation and evaluation of medication regimens help quantify economic impact, identify more cost-effective interventions, and inform clinical management strategies and policy efforts to improve patients with diabetes or stroke comorbidity.

Ethics approval

This study was approved by the ethics committee of Beijing Hospital (2021BJYYEC-022-01).

Consent to participate

Not applicable.

Consent for publication

Not applicable

Author contributions

Yi Zeng, Siting Liang and Hanming Wang acquired the data, performed the analysis and interpretation of the data, and wrote and revised the manuscript. Jiadong Zeng, Ying Luo, Weihao Wang, Jingtao Qiao, and Jingwen Fan performed the analysis and interpretation of the data and contributed to the drafting of the manuscript. All the authors approved the final version of the manuscript. LiXin Guo and Zhen Zhang are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Competing interests

The authors declare no conflicts of interest.

Availability of data and materials

The data sets generated during the current study are available from the corresponding author upon reasonable request.

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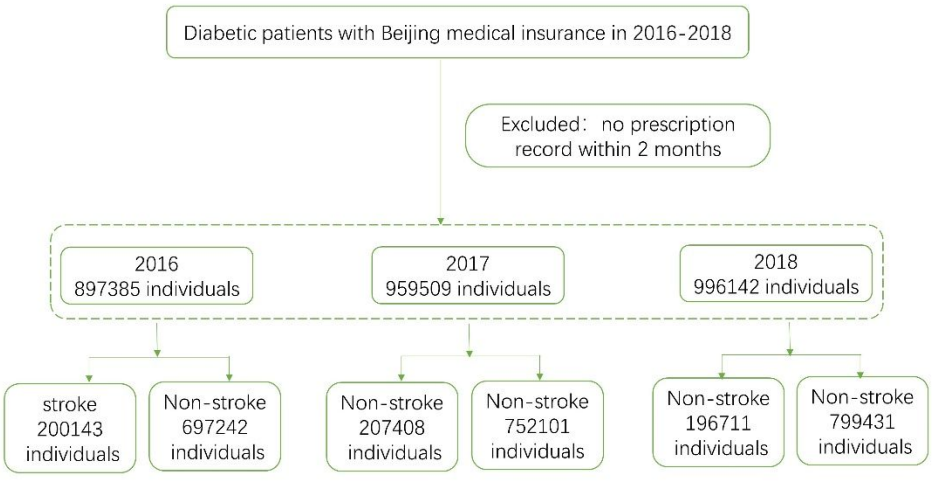
Supplemental Fig 1. Patient enrollment flow chart.

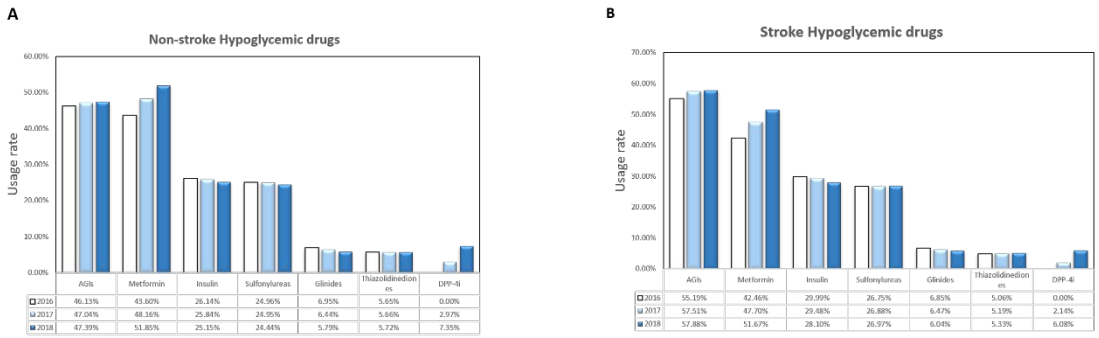


Supplemental table 1

Utilization rates of different types of insulin among diabetes patients with and without stroke in 2016-2018

Type of insulin	Non-stroke			stroke			P value		
	2016	2017	2018	2016	2017	2018	2016	2017	2018
Fast-acting	16,433 (9.01%)	21,423 (11.02%)	25,532 (12.69%)	3,473 (5.78%)	4,626 (7.56%)	4,965 (8.97%)	<.0001	<.0001	<.0001
Short-actin	23,786 (13.04%)	22,572 (11.61%)	21,221 (10.55%)	7,323 (12.20%)	7,052 (11.53%)	6,074 (10.98%)	<.0001	0.5852	0.0034
Intermediate-acting	28,159 (15.44%)	26,739 (13.75%)	24,735 (12.29%)	8,961 (14.92%)	8,272 (13.52%)	6,987 (12.63%)	0.0023	0.1494	0.0329
Long-acting	41,338 (22.67%)	51,309 (26.39%)	61,301 (30.47%)	9,175 (15.28%)	11,461 (18.73%)	12,654 (22.88%)	<.0001	<.0001	<.0001
Premixed	105,653 (57.94%)	109,164 (56.15%)	106,982 (53.19%)	40,983 (68.27%)	40,422 (66.09%)	34,359 (62.13%)	<.0001	<.0001	<.0001

The number indicates the number of people who used that insulin that year. The percentage in brackets indicates the percentage of the total population using this type of insulin.



Supplemental Fig 2. Changes in the use of nonhypoglycemic drugs and hypoglycemic drugs in DM patients with or without stroke.

(A). Changes in the use of hypoglycemic drugs (in DM patients without stroke)

(B). Changes in the use of hypoglycemic drugs (in DM patients with stroke)

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Treatments, medical expenses and complications of hospital outpatient healthcare associated with stroke in patients with diabetes in China: a retrospective analysis of the Beijing Municipal Medical Insurance Database

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Treatments, medical expenses and complications of hospital outpatient healthcare associated with stroke in patients with diabetes in China: a retrospective analysis of the Beijing Municipal Medical Insurance Database

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Abstract

Objectives

Diabetes is closely associated with the risk of stroke and its adverse sequelae. Approximately 20-33% of all stroke patients have diabetes. However, it is unclear how stroke affects healthcare utilization, medications, and complications in people with diabetes in China. This study aimed to analyse the clinical characteristics, treatment options, medical expenses and complications of hospital outpatient healthcare associated with stroke complications in patients with diabetes in China.

Design

A retrospective, multicentre, observational study.

Setting

Beijing Municipal Medical Insurance Database, with data from 2016 to 2018.

Participants

Patients with diabetes whose data included 2016–2018 outpatient medication records and who had Beijing medical insurance. Patients who did not have a continuous prescription record for more than 2 months were excluded from the analysis. In total, 2,853,036 people with diabetes were included, and patients with and without stroke were compared.

Results

In our study, 19.75%-22.30% of diabetic patients suffered from stroke between 2016 and 2018. The average annual medical cost of a patient diagnosed with diabetes is ¥9606.65, and the cost increases to ¥13428.39 when diabetes was combined with stroke; thus, stroke increases the medical cost of diabetic patients by 39.78% ($p < 0.0001$). Among diabetic patients with stroke, 4.76 medications were used (1.8 hypoglycaemic

drugs and 2.97 non-hypoglycaemic drugs); these numbers were significantly greater than those of diabetic patients without stroke receiving both hypoglycaemic drugs and non-hypoglycaemic drugs (p <0.0001). Among diabetic patients without stroke, 3.58 medications were used (1.66 hypoglycaemic drugs and 1.92 non-hypoglycaemic drugs). Diabetic patients with stroke also had significantly greater incidences of DPN, DKD, DR, and DA than did non-stroke patients (p <0.0001). These drugs and costs increased with the number of complications (p <0.0001). The increased medical costs for each specific complication are also listed. We also analysed medical costs and medication regimens stratified by sex, age group, and complications.

Conclusions

Stroke is associated with significant increases in the complications and medications for diabetic patients and greatly adds to the economic burden of diabetes patients. Early diagnosis of stroke risk factors in diabetic patients, as well as targeted post-stroke diabetes management, is crucial from a socioeconomic perspective for the comprehensive management and treatment of stroke in patients with diabetes.

Strengths and limitations of this study

- This study represents the largest sample in Asia concerning medication usage and medical expenses related to diabetes complications such as stroke, providing a comprehensive assessment of medication regimens and economic burdens for stroke among diabetes patients.
- This analysis covered the medication and medical costs of diabetic patients for three consecutive years from 2016 to 2018, increasing the objectivity and credibility of the data.
- Stratified analyses according to the demographic characteristics were performed, and the study also analysed the specific proportion of each additional

complication that increased the patient's medication and medical costs.

- Data on clinical variables (including glycated haemoglobin, lipid profile, and blood pressure measurements) were not available to explore potential explanations for the observed treatment patterns at baseline and poststroke.
- We did not analyse adverse sequelae of stroke, such as recurrence rates.

Keywords: Diabetes, Stroke, Diabetic vascular disease, Medications, Healthcare costs

INTRODUCTION

Diabetes is a highly prevalent and costly chronic disease that imposes a substantial burden on individuals, families and society through reduced quality of life and life expectancy. In 2021, diabetes represents a major health burden affecting an estimated 537 million people. This number is expected to increase to 643 million by 2030 and 783 million by 2045 worldwide, according to the International Diabetes Federation (IDF)[1]. The per capita medical cost of diabetes patients is 2.3 times that of nondiabetic patients[2]. The global economic burden of diabetes was $1.3 trillion (95% CI 1.3–1.4) in 2015, which is forecasted to increase to $2.2 trillion (2.2–2.3) at baseline by 2030[3,4].

The financial burden on diabetic patients increases significantly when complications develop[5]. Stroke is the second most common complication of T2DM after coronary artery disease (CAD) [6,7] and the second most common cause of death in diabetic patients. Stroke is also the leading cause of disability and mortality in aging populations[8]. Type 2 diabetes is related to a 2.5 to 3.5-fold increased risk of ischemic stroke and a 1.5-fold increased risk of haemorrhagic stroke[9]. Studies have also reported that men with diabetes have a 1.8-fold increase in the relative risk of stroke,

while women have a 2.3-fold increase[10]. Approximately 20-33% of all stroke patients have diabetes[11,12,13]. Diabetes is closely related not only to stroke but also to the risk of adverse stroke sequelae. Preexisting diabetes was associated with increased hazards of death, admission to long-term care, readmission for stroke, and incident dementia[14]. Persistent hyperglycaemia, characterized by significantly elevated plasma glucose or glycated haemoglobin levels, is considered a key indicator and a major cause of vascular complications in diabetic patients. The use of specific antidiabetic medications, and integrated care approaches could reduce stroke incidence and improve outcomes in patients with diabetes[15,16].

Studies from different regions, including Europe, and North America, have demonstrated substantially higher healthcare costs associated with stroke in diabetic patients compared to those without diabetes[17]. Yan Sun et.al reported DM patients with ischemic stroke incurred 10% higher hospital costs, compared with their counterparts in the non-DM group in Singapore[18]. However, it is unclear how stroke affects healthcare utilization, medications, and complications in outpatients with diabetes in China.

This study utilized the medical insurance database of Beijing, China, to analyse hospital outpatient treatment plans, medical expenses, and complications related to stroke in diabetic patients from 2016 to 2018, it may help identify cost-effective interventions and inform clinical and policy efforts to improve diabetes care.

METHODS

Study design and ethical approval

We conducted a multicentre, observational study to analyse the treatment options and medical expenses of diabetes patients with or without stroke. This study was approved by the ethics committee of Beijing Hospital (2021BJYYEC-022-01).

Study population and data collection

The data for this study were obtained from the Beijing medical insurance database, which includes outpatient medication records of 2,853,036 diabetic patients from 2016 to 2018. The resident population of Beijing was 21.729 million in 2016, 21.707 million in 2017, and 21.542 million in 2018. The study recruited diabetic patients whose data included 2016–2018 outpatient medication records and who had Beijing medical insurance. All patients were at least 16 years of age. The diagnosis of diabetes was confirmed by the diagnostic criteria of the World Health Organization (WHO) in 1999. Patients who did not have a continuous prescription record for more than 2 months were excluded from this study because in Beijing hypoglycaemic drugs are prescribed for less than 30 days according to the current medical insurance system and because patients need to return to the hospital to take the drug within two months. A more detailed description is provided in Supplemental Figure 1. We collected information from the Beijing Municipal Medical Insurance Database, including date of birth, race, ICD diagnosis, age, sex, prescription, prescription (hypoglycaemic and non-hypoglycaemic drugs), dosage, and medical expenses. Each prescription has a unique serial number in the database.

Definition of complications and comorbidities

Complications were defined using the International Classification of Diseases (ICD) codes. Diabetes-related complications included diabetic peripheral neuropathy (DPN), diabetic retinopathy (DR), diabetic nephropathy (DN) and diabetic angiopathy (DA). Stroke includes cerebrovascular disease, cerebral infarction, cerebral infarction sequelae, stroke, lacunar cerebral infarction, cerebrovascular disease sequelae, cerebral thrombosis, and cerebral haemorrhage.

Definition of medical therapy

The medical drugs used were hypoglycaemic drugs and non-hypoglycaemic drugs. Hypoglycaemic drugs include oral antidiabetic drugs (OADs) and insulin. OADs

include α-glucosidase inhibitors (AGIs), metformin, sulfonylureas (SUs), glinides, thiazolidinediones, and dipeptidyl peptidase 4 inhibitors (DPP-4is). Insulin consists of fast-acting insulin, short-acting insulin, intermediate-acting insulin, long-acting insulin and premixed insulin. The diabetes treatment strategies included the following: 1) monotherapy: patients who had received only one prescription hypoglycaemic drug in the last year; 2) oral combination therapy: patients who had received two or more different OAD treatments in the last year; and 3) oral and insulin combined therapy: patients who had received at least one insulin and at least one OAD drug in the last year. Changes in the use of hypoglycaemic drugs were assessed by drug class for each study year.

Statistical analysis

Quantitative variables are presented as the means with SDs. Continuous variables that were not normally distributed were statistically analysed by the Wilcoxon rank−sum test; these variables included the number of drugs, medical costs, comorbidities, and complications. When the distribution of variables is overspread, we use a negative binomial model and a logarithmic link function. A negative binomial model and a log-linked function were used to assess the amounts of drugs because the distribution of outcome variables was not normal. This method is suitable for counting data that is characterized by over-dispersion. For cost models, the estimated cost is log-transformed. To correct for heteroskedasticity-induced retransformation bias, tailing estimates are used, which provide an estimate of the adjusted arithmetic mean of annual cost on a linear scale to improve interpretability. Confounding factors were controlled using a multivariate regression model. The categorical variable data are presented as frequencies and percentages and were analysed by the chi-square test or Fisher's exact probability method. All the statistical analyses were performed with SAS software, version 9.4 (SAS Institute, Inc.). $P<0.05$ was considered to indicate statistical significance.

Patient and public involvement

None.

RESULTS

Demographic characteristics of the study population

This study included 2,853,036 diabetes patients (897,385 diabetes patients in 2016; 959,509 diabetes patients in 2017; and 996,142 diabetes patients in 2018). Supplemental Figure 1 shows a flow chart of patient enrolment. Among them, 19.75%–22.30% of diabetes patients had stroke (200,143/897,385 (22.30%) in 2016; 207,408/959,509 (21.62%) in 2017; and 196,711/996,142 (19.75%) in 2018). Among diabetic patients with stroke, those aged 15-44 years accounted for 2.53%-2.94%, 45-64 years accounted for 45.72%-48.89%, 65-84 years accounted for 44.94%-47.60%, and those aged >84 years accounted for 3.21%-4.14%. The proportion of diabetes patients with stroke varied significantly by age group, with most patients aged 45–84 years (89.83%-93.49%). In the non-stroke group, men outnumbered women from 2016 to 2018, while there were more women in the stroke group than in the non-stroke group from 2016 to 2018 ($p < 0.0001$; Table 1). The full table is attached for the attached material.

Impressively, diabetic patients with stroke also had significantly greater incidences of diabetic peripheral neuropathy, diabetic nephropathy, diabetic retinopathy, and diabetic angiopathy than did non-stroke patients (all $p < 0.0001$ from 2016 to 2018; Table 1). The most prevalent complication among these patients was diabetic nephropathy, whereas diabetic angiopathy was the least common complication (Table 1).

Table 1. Demographic characteristics and complications of diabetes patients with and without stroke

Variables	Non-stroke	stroke

		2016	2017	2018	2016	2017	2018
Total		697242	752101	799431	200143	207408	196711
		(77.7%)	(78.38%)	(80.25%)	22.30%	21.62%	19.75%
Age group	16-44y	68241	73496	75643	5902	5949	4964
		(9.78%)	(9.77%)	(9.46%)	(2.94%)	(2.86%)	(2.52%)
	45-64y	380788	403660	419820	97860	98589	89943
		(54.61%)	(53.67%)	(52.51%)	(48.89%)	(47.53%)	(45.72%)
	65-84y	234211	257841	283128	89952	95332	93653
		(33.59%)	(34.28%)	(35.41%)	(44.94%)	(45.96%)	(47.60%)
	≥85y	14002	17104	20840	6429	7538	8151
		(2.0%)	(2.27%)	(2.60%)	(3.21%)	(3.63%)	(4.14%)
Gender	Male	352908	387104	421917	98518	103787	100144
		(50.61%)	(51.46%)	(52.77%)	(49.22%)	(50.04%)	(50.90%)
	Female	344334	364997	377514	101625	103621	96567
		(49.38%)	(48.53%)	(47.22%)	(50.77%)	(49.95%)	(49.09%)
DPN		76331	83014	95277	39168	40547	40879
		(10.94%)	(11.03%)	(11.91%)	(19.57%)	(19.54%)	(20.78%)
DKD		30935	29566	28078	12144	11213	8813
		(4.43%)	(3.93%)	(3.51%)	(6.06%)	(5.40%)	(4.48%)
DR		29319	30184	30186	12578	13205	11555
		(4.20%)	(4.01%)	(3.77%)	(6.28%)	(6.36%)	(5.87%)
DA		19533	19575	20618	9712	10285	9636
		(2.80%)	(2.60%)	(2.57%)	(4.85%)	(4.95%)	(4.89%)

The number represents the number of people in the year. The percentage in parentheses represents the percentage of the total number of people in that year. Diabetic peripheral neuropathy (DPN), diabetic retinopathy (DR), diabetic nephropathy (DN) and diabetic angiopathy (DA) were also detected.

Stroke treatment increased the types of medications and costs for people with diabetes from 2016 to 2018

The annual medical expenses of diabetic patients from 2016 to 2018 were ¥9248.17-10118.04, the average annual medical expenses for these three years were ¥9606.65, the annual medical expenses of diabetes combined with stroke from 2016 to 2018 were 13049.88-14239.78, and the average annual medical expenses in these three years were ¥13428.39, which indicates that diabetes combined with stroke increased medical expenses by 39.78% ($p < 0.0001$, Table 2).

On average, diabetic patients who did not have stroke used 3.58 medications (1.66

hypoglycaemic drugs and 1.92 non-hypoglycaemic drugs), while diabetic patients who had stroke used 4.76 medications (1.8 hypoglycaemic drugs and 2.97 non-hypoglycaemic drugs); these numbers were significantly greater than those of diabetic patients without stroke receiving both hypoglycaemic drugs and non-hypoglycaemic drugs (p <0.0001; Table 2).

Among the medical expenses of diabetic patients, hypoglycaemic drugs cost ¥5206.23, and nondiabetic drugs cost ¥4400.42. In diabetic patients complicated with stroke, the cost of hypoglycaemic drugs was ¥5818.75 (p <0.0001; Table 2), the cost of non-hypoglycaemic drugs was ¥7609.64 (p <0.0001; Table 2), and stroke not only increased the cost of hypoglycaemic drugs in diabetic patients by 10.83%-13.04% but also increased the cost of nondiabetic drugs by 67.98%-75.07% (p <0.0001; Table 2). The medical cost of diabetes patients with stroke decreased annually from 2016 to 2018, which was mainly attributed to the decrease in the cost of non-anti-glycaemic drugs (p <.0001; Table 2). As expected, the cost/drug use of diabetes patients in the stroke group was significantly greater than that of patients in the non-stroke group (¥2763.95 ± 2081.42 vs. ¥2583.03 ± 2730.96, p <0.0001; Table 2); as was the cost/anti-glycaemic drugs (¥2874.4 ± 3297.19 vs. ¥2698.91 ± 3470.24, p <0.0001; Table 2); and the cost/non-anti-glycaemic drugs (¥2352.01 ± 2068.14 vs. ¥1672.42 ± 2013.33, p <0.0001; Table 2).

Table 2. Stroke increased the types of medications and cost of medication for people with diabetes from 2016-2018

Variables	Non-stroke				stroke			
	Total	2016	2017	2018	total	2016	2017	2018
Annual cost of medication ¥	9606.65± 9622.86	10118.04± 10543.8	9248.17± 9259.31	9497.9± 9082.87	13428.39± 11134.39	14239.78± 11825.74	13049.88± 10951.9	13001.92± 10539.1
Types of medications	3.58± 2.3	3.46± 2.28	3.6± 2.31	3.67± 2.3	4.76± 2.4	4.66± 2.38	4.81± 2.43	4.83± 2.39
Hypoglycaemic drugs	1.66± 1.06	1.58± 1.03	1.66± 1.06	1.73± 1.07	1.8± 1.09	1.71± 1.06	1.81± 1.09	1.87± 1.11
Non-hypoglycaemic	1.92±	1.88±	1.94±	1.94±	2.97±	2.95±	3±	2.96±

drugs	1.83	1.82	1.83	1.82	1.89	1.89	1.91	1.87
Cost of hypoglycaemic drugs ¥	5206.23± 7304.56	5408.25± 8011.86	5016.95± 7003.71	5208.12± 6920.18	5818.75±7 538.65	5994.19± 7816.92	5671.02±7 420.89	5796.01± 7367.98
Cost of non-hypoglycaemic Drugs ¥	4400.42± 5516.58	4709.79± 6050.25	4231.22± 5307.27	4289.78± 5201.7	7609.64± 7153.16	8245.59± 7777.21	7378.86± 6995.23	7205.91± 6588.89
Annual cost/drug, ¥	2583.03± 2730.96	2798.35± 3129.79	2465.7± 2494.49	2505.63± 2553.93	2763.95± 2081.42	2992.1± 2256.28	2654.64± 2011.6	2647.08± 1944.92
Cost/hypoglycaemic drug ¥	2698.91± 3470.24	2895.67± 3932.27	2591.25± 3268.53	2628.57± 3207.61	2874.4± 3297.19	3067.97± 3512.65	2783.25± 3207.88	2773.57± 3151.88
Cost/non-hypoglycaemic drug ¥	1672.42± 2013.33	1800.41± 2244.37	1596.97± 1920.69	1631.76± 1875.39	2352.01± 2068.14	2563.36± 2295.59	2247.76± 1955.34	2246.9± 1917.82

Stroke contributes to high health care costs in diabetic patients stratified by demographics and complications

To obtain more detailed information, we analysed the medical costs of diabetic patients by stratification according to demographic factors and complications. The population distributions of patients according to age, sex and complication status are shown in Table 3. Among the 15-44, 45-64, 65-84, and ≥85 age groups, the cost of treatment for the 65-85 age group was ¥10259.32 in the diabetic without stroke group, which was the highest among all age groups (Table 3). The cost of treatment for the 45-64 -year-old group was ¥13658.58 for the diabetic with stroke group, which was the highest among all age groups (Table 3). For diabetic patients with stroke, medical costs were greater than those for non-stroke patients in all age groups or for both sexes (Table 3). The costs increase dramatically if diabetic patients develop complications, including diabetic peripheral neuropathy, diabetic nephropathy, diabetic retinopathy, and diabetic vasculopathy. Additionally, as the number of complications increased, the annual cost increased (Table 3). Moreover, diabetic patients with stroke incurred greater medical costs than did non-stroke patients when the same complications described above were present (Table 3).

Table 3. Stroke contributes to high health care costs in diabetic patients, stratified by demographics and complications

	Cost of medications ¥ (non-stroke)	Cost of medications ¥ (stroke)

Variables	N	Mean	Adjusted Mean	SD	N	Mean	Adjusted Mean	SD
Age								
15-44	217380	7455.14	7421.23	9415.03	16815	11976.69	11988.46	10851.35
45-64	1204268	9559.72	9550.03	9572.83	286392	13658.58	13658.26	11333.06
65-84	775180	10259.32	10258.89	9662.41	278937	13312.06	13311.72	10923.02
≥85	51946	9958.64	9968.65	9702.45	22118	13018.42	13018.15	11273.78
Gender								
Male	1161929	9761.82	9426.69	9821.9	302449	13354.21	12915.71	10994.52
Female	1086845	9440.77	9031.74	9402.58	301813	13502.72	13042.91	11272.34
DPN								
no	1994152	9279.34	8938.29	9404.13	483668	13121.2	12687.85	10857.01
yes	254622	12170.12	11586.55	10852.8	120594	14660.44	14202.88	12105.58
DKD								
no	2160195	9429.5	9070.66	9449.74	572092	13199.16	12766.76	10933.15
yes	88579	13927.04	13287.78	12397.18	32170	17504.91	16958.09	13616.3
DR								
no	2159085	9443.93	9086.09	9496.97	566924	13239.14	12810.24	11030.33
yes	89689	13523.93	12938.98	11600	37338	16301.76	15792.65	12255.67
DA								
no	2189048	9506.37	9139.86	9536.51	574629	13301.68	12860.30	11072.55
yes	59726	13282.28	12589.27	11804.94	29633	15885.48	15384.26	12010.97
Number of Complications								
0	1850162	9019.91	8710.64	9158.06	433150	12816.4	12408.04	10652.92
1	316966	11686.23	11172.38	10782.56	130059	14298.55	13873.00	11785.88
2	70057	14458.19	13791.39	11923.88	34029	16757.09	16271.98	12761.19
3	10820	16883.24	16093.97	12666.86	6478	18745.38	18220.45	13281.43
4	769	19735.3	18796.01	16356.42	546	21106.87	20525.02	16826.81

N indicates the number of people. MEAN represents the average cost in RMB. The complications of diabetes included diabetic peripheral neuropathy (DPN), diabetic retinopathy (DR), diabetic nephropathy (DN) and diabetic angiopathy (DA). The number of complications represents the occurrence of one to four of the above diabetic complications.

Stroke significantly increased the use of various medications among people with diabetes stratified by demographics and complications

Next, we analysed medication use in people with diabetes stratified by demographic factors and complications. Among the 15-44, 45-64, 65-84, and ≥85 age groups, the 65-84 age group, which was used the most drugs (Table 4). Diabetic patients with stroke took more medications than non-stroke patients in all age groups and both sexes (Table 4). The use of medications significantly increased if diabetic patients developed

complications, including diabetic peripheral neuropathy, diabetic nephropathy, diabetic retinopathy, and diabetic vasculopathy. Moreover, as the number of complications increased, more drugs were used (Table 4). In addition, diabetic patients with stroke use more medications than non-stroke patients when the same complications arise, as described above (Table 4).

Table 4. Stroke significantly increased the use of various medications among people with diabetes stratified by demographics and complications

	Types of medications (non-stroke)				Types of medications (stroke)			
Variables	**N**	**Mean**	**Adjusted Mean**	**SD**	**N**	**Mean**	**Adjusted Mean**	**SD**
Age								
15-44	217380	2.61	2.60	1.99	16815	4.29	4.29	2.36
45-64	1204268	3.57	3.57	2.27	286392	4.77	4.77	2.39
65-84	775180	3.86	3.86	2.36	278937	4.81	4.81	2.42
≥85	51946	3.66	3.67	2.28	22118	4.57	4.57	2.38
Gender								
Male	1161929	3.65	3.47	2.3	302449	4.81	4.65	2.38
Female	1086845	3.51	3.31	2.3	301813	4.72	4.56	2.42
DPN								
no	1994152	3.48	3.30	2.26	483668	4.66	4.51	2.37
yes	254622	4.4	4.11	2.43	120594	5.18	5.00	2.5
DKD								
no	2160195	3.55	3.35	2.28	572092	4.72	4.56	2.39
yes	88579	4.48	4.19	2.54	32170	5.52	5.32	2.59
DR								
no	2159085	3.53	3.34	2.27	566924	4.7	4.55	2.38
yes	89689	4.77	4.48	2.57	37338	5.69	5.49	2.56
DA								
no	2189048	3.55	3.36	2.29	574629	4.72	4.56	2.39
yes	59726	4.75	4.41	2.44	29633	5.58	5.38	2.51
Number of complications								
0	1850162	3.41	3.24	2.23	433150	4.59	4.44	2.33
1	316966	4.17	3.91	2.43	130059	5.03	4.86	2.48
2	70057	5.03	4.69	2.45	34029	5.72	5.53	2.52
3	10820	5.65	5.27	2.42	6478	6.28	6.07	2.5
4	769	6.18	5.77	2.46	546	6.75	6.53	2.47

N indicates the number of people. MEAN represents the average medication type. The complications of diabetes included diabetic peripheral neuropathy (DPN), diabetic retinopathy (DR), diabetic nephropathy (DN) and diabetic angiopathy (DA). The number of complications

represents the occurrence of one to four of the above diabetic complications.

Use of OADs and insulin in diabetic patients with or without stroke

Among the various types of insulin, premixed insulin is the most commonly used. From 2016 to 2018, the use of fast-acting insulin and long-acting insulin gradually increased in diabetic patients with or without stroke, while the use of intermediate-acting insulin, premixed insulin and short-acting insulin gradually decreased in diabetic patients with or without stroke (Supplemental Table 1). Diabetic patients with stroke used more fast-acting, longer-acting and more premixed insulin than did the non-stroke group from 2016–2018 (Supplemental Table 1). There was no difference in the use of short-acting insulin or intermediate-acting insulin between the two groups (Supplemental Table 1). Diabetic patients with stroke used more antidiabetic drugs than did patients without stroke (90.66% vs. 88.59%, 2018, p <.0001; Table 5). In particular, oral combination therapy was used (54.69% vs. 50.91%, 2018, p <0.0001; Table 5), and combinations of oral drugs and insulin were used (25.29% vs. 20.49%, 2018, p <0.0001; Table5). The proportion of patients treated with monotherapy was lower in the stroke group than in the non-stroke group (32.85% vs. 37.42%, 2018, p <0.0001; Table 5). Among the antidiabetic drugs, α-glucosidase inhibitors were the most commonly used, followed by metformin, premixed insulin, sulfonylureas, and dipeptidyl peptidase-4 (Table 5). Among the oral combination therapies, α-glucosidase+metformin was the most common, and its prevalence increased annually from 2016–2018. Compared with non-stroke patients, diabetic patients in the stroke group used more α-glucosidase+metformin, α-glucosidase+sulfonylureas, α-glucosidase+metformin+sulfonylureas and α-glucosidase+glinides, while they used less metformin+sulfonylureas, metformin+DPP-4i, and metformin+glinides (Table 5).

Table 5. Hypoglycaemic drug treatment among diabetes patients with and without stroke from 2016-2018

Medication for diabetes	Non-stroke			stroke		
	2016	2017	2018	2016	2017	2018
Antidiabetic drugs	597,971	655,166	708,234	176,527	185,691	178,357

Monotherapy	246,553	254,992	265,046	65,327	63,812	58,605
AGIs	83,550	83,918	84,625	27,636	27,545	24,639
Metformin	77,889	89,781	101,412	16,277	18,112	18,496
sulfonylureas	24,233	23,215	21,652	6,186	5,699	4,793
premixed insulin	35,507	31,869	28,366	10,096	7,629	5,772
DPP-4i	.	2,218	5,967	.	281	895
Glinides	8,121	7,185	6,339	1,861	1,544	1,287
Oral combination therapy	272,184	317,825	360,571	84,625	96,083	97,554
AGIs +Metformin	53,616	64,650	74,068	16,279	19,732	20,409
AGIs+sulfonylurea	39,488	38,320	35,851	12,958	12,098	10,363
Metformin+sulfonylureas	37,573	41,128	42,197	8,878	9,272	8,837
AGIs+Metformin+sulfony	33,983	39,247	41,543	11,530	12,779	12,664
Metformin+DPP-4i	.	4,094	11,267	.	471	1,490
Metformin+Glinides	10,049	9,816	9,161	2,203	2,112	1,916
AGIs +Glinides	8,028	7,484	6,815	2,413	2,271	1,798
Oral+Insulin	119,730	135,533	145,174	44,682	48,662	45,120
AGIs +Premixed insulin	23,464	23,407	21,830	10,583	10,070	8,070
AGIs+Metformin+insulin	12,450	15,638	16,741	5,574	7,273	6,655
Metformin+Premixed insulin	13,740	15,018	14,942	4,667	4,537	3,911

The number represents the number of people who used the drug that year.

Changes in the prescription of anti-glycaemic drugs

Among the anti-glycaemic drugs, AGIs and metformin were the most frequently prescribed for diabetic patients with or without stroke (Supplemental Figure 2). The use of AGIs, metformin and DPP-4i tended to increase annually, whereas the use of insulin, sulfonylureas and glinides tended to decrease annually (Supplemental Figure 2).

DISCUSSION

In this study, we reported the population characteristics, treatment costs, drug regimens, and complications of diabetes patients with and without stroke. We found that diabetic

patients who had a stroke used more drugs and had total annual drug costs to treat more complications than those who did not. To our knowledge, this study is the largest current sample of studies in Asia on the drug and medical costs of diabetes combined with stroke.

Diabetes imposes a large economic burden on families and society. The annual medical cost of patients with diabetes is 2.3 times greater than that of patients without diabetes[2], and the cost doubles when complications occur[19]. Among the complications of diabetes, cerebrovascular disease, and coronary heart disease are the most common[20]. Moreover, stroke is the second most common cause of death in diabetic patients.

Studies have reported that 20–33% of acute stroke inpatients have diabetes[11-13]. Diabetes mellitus is an established and independent risk factor for stroke and is associated with a 1.8 to 6-fold greater risk than diabetes mellitus in nondiabetic patients[21,22]. Our study revealed that 19.75%-22.30% of diabetic patients suffered from stroke, which was similar to previously reported rates [11-13].

The proportion of diabetes patients with stroke varied significantly by age group, with most patients affected from 2016 to 2018 aged 45–84 years (89.83%-93.49%). The estimated life expectancy loss for people with stroke aged 40 years was 21.1-26.2 years, that for people aged 60 years was nearly 13 years, and that for people aged 80 years was nearly 4 years[23]. Therefore, stroke seriously affects quality of life, leads to premature death in diabetic patients, and greatly exacerbates productivity loss and indirect financial burdens[24,25]. There were more men than women in the diabetes population; however, the difference in the incidence of diabetes with stroke between men and women was not significant, and women outnumbered men in 2016. Consistent with previous findings, the risk of stroke associated with diabetes was significantly greater in women than in men[26].

The average medical costs for diabetic patients with one, two, or three conditions

among stroke, heart disease, or CKD patients were 1.91, 2.90, or 3.88 times greater, respectively than those for patients without complications[27]. Our data showed that the average medical cost for diabetic patients with stroke was approximately 39.78% greater than that for diabetic patients without stroke in China, and that for diabetic patients was approximately 6.38% greater for hypoglycaemic drugs and approximately 33.41% greater for non-hypoglycaemic drugs. Acute hyperglycaemia and diabetes are associated with poorer outcomes after stroke, including worse neurological and functional outcomes, greater readmission and stroke recurrence, longer hospital stays, and greater mortality[28-32].

This study demonstrated that diabetic patients with stroke had more complications, which may indicate that diabetic patients with more complications are more susceptible to stroke. In addition to these complications and comorbidities, diabetic patients can easily develop other complications when one complication arises. The medical cost increases by approximately ￥2000-3000 for each additional complication. In France, the annual total medical expenses for diabetic patients with stroke (€12,199) are 3 times greater than those for diabetic patients without stroke[33]. In Sweden, the average annual total cost for diabetic patients with stroke (€11,397) is 2.2 times higher than that for diabetic patients without stroke[34]. Differences between countries may reflect varying economic levels and blood glucose management levels. However, globally, the average medical expenses for diabetic patients with stroke far exceed those for diabetic patients without stroke, emphasizing the necessity for strong and strict primary and secondary prevention of complications such as stroke in the diabetic population.

Compared with diabetic patients without stroke, diabetic patients with stroke use more oral combination therapy and less monotherapy. Our results revealed that AGIs and metformin are the most commonly used antidiabetic agents in diabetes patients with or without stroke, followed by premixed insulin, sulfonylureas, glinides, thiazolidinediones and DPP-4i in China from 2016-2018. A 2013 nationwide survey of OADs in China reported that metformin was used by 53.7% of T2DM patients, followed by sulfonylureas (42.7%) and AGIs (35.9%)[35]. Our study showed that

sulfonylureas were used 24.44% of the time, which was lower than that used in previous research, and our data also showed a gradual decrease in sulfonylureas use. This may be because of changes in doctors' medication habits, secondary failures, and the emergence of additional new varieties of drugs. DDP4i usage has grown rapidly since it was included in the health-care system of China, from a 0% increase to 7.35% from 2016 to 2018. There may be several reasons for the involvement of changes in medication usage and costs, the first is the change in the reimbursement ratio of drugs by medical insurance policies, the second is the use of new hypoglycaemic drugs, and the third is that the side effects of some drugs may affect the proportion of use, such as the secondary failure of sulfonylureas and thiazolidinediones may increase cardiovascular risk.

According to the 2023 ADA guidelines, the use of GLP-1 RA and SGLT2 inhibitors is recommended for individuals diagnosed with cardiovascular disease or those at high risk of cardiovascular disease[36].In previous studies, the use of GLP-1 RA in diabetic patients diagnosed with stroke was extremely low, at only 6.6%[34]. This may reflect the years covered by the studies and the lack of expert recommendations for stroke prevention and treatment. Strengthening compliance with clinical guidelines among specialist physicians is crucial for expanding the use of cardiovascular protective medications in this high-risk population. While GLP-1 RA has evident cardiovascular benefits, the CAPTURE study revealed significant regional differences in treatment guidelines for diabetes and heart disease. Additionally, drug approval and reimbursement, including for GLAs, may affect their primary use at the national level[12].

Our data showed that overall insulin use decreased annually in patients treated with the most commonly used type of premixed insulin; however, the use of premixed insulin was greater in diabetes with stroke group than in the non-stroke group. Evidence suggests that insulin use may be a marker of increased risk of stroke, but it is not necessarily a causative factor[37]. Previous antidiabetic drug selection has focused more on cardiovascular and renal benefits, while cerebrovascular complications,

particularly stroke, should also be given more attention because of severe health and economic burdens.

As stroke imposes significant health and economic burdens, evidence suggests that blood glucose control levels may be related to the severity of stroke[38]. Improving glycaemic management may have benefit the incidence and severity of stroke, thereby alleviating individual and societal economic burdens[39]. Diabetic patients should develop self-management skills and cultivate habits of self-monitoring. Continuing to improve basic medical insurance coverage for diabetic patients, optimizing the allocation of high-quality medical resources, implementing various diabetes management channels for vulnerable populations, and strengthening governmental management functions are essential for alleviating individual and societal economic burdens.

Despite the large sample size of this study, data on key clinical variables (including glycated haemoglobin, lipid profile, and blood pressure measurements) were not available to explore potential explanations for the observed treatment patterns at baseline and poststroke. Another limitation of this study is that we did not analyse adverse sequelae of stroke in T2D patients, such as recurrence rates. Considering that the risk of some stroke recurrences occurs immediately after a stroke, a considerable number of recurrent strokes may have been excluded.

In summary, stroke significantly increases the types of medications, complications, and medical costs for diabetic patients, bringing a heavy economic burden to individuals and society. The study also revealed changes and trends in the use of hypoglycaemic drugs in people with diabetes, as well as the impact of stroke on diabetes drug choice.

In the future, we could further explore the mechanism of how diabetes exacerbates stroke risk by performing functional studies and longitudinal studies, and focus on investigating the economic implications of integrated care models and preventive strategies tailored for diabetic patients at risk of stroke, which will finally inform policy

interventions aimed at reducing healthcare costs and improving patient outcomes.

Ethics approval

This study was approved by the ethics committee of Beijing Hospital (2021BJYYEC-022-01).

Consent to participate

Not applicable.

Consent for publication

Not applicable.

Contributors

Yi Zeng, Siting Liang and Hanming Wang acquired the data, performed the analysis and interpretation of the data, and wrote and revised the manuscript. Jiadong Zeng, Ying Luo, Weihao Wang, Jingtao Qiao, and Jingwen Fan performed the analysis and interpretation of the data and contributed to the drafting of the manuscript. All the authors approved the final version of the manuscript. LiXin Guo and Zhen Zhang had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. LiXin Guo and Zhen Zhang acted as guarantors.

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Competing interests

The authors declare no conflicts of interest.

Data availability statement

The datasets generated during the current study are available from the corresponding author upon reasonable request.

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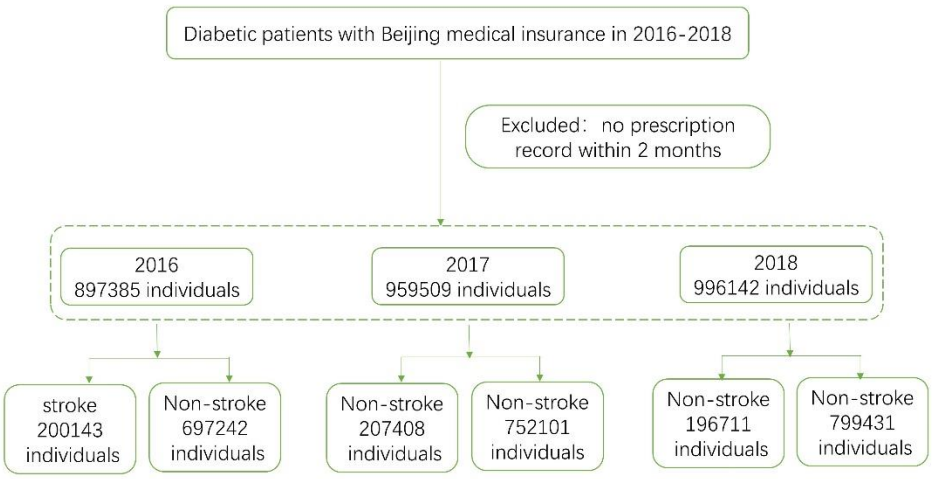
Supplemental Fig 1. Patient enrollment flow chart.

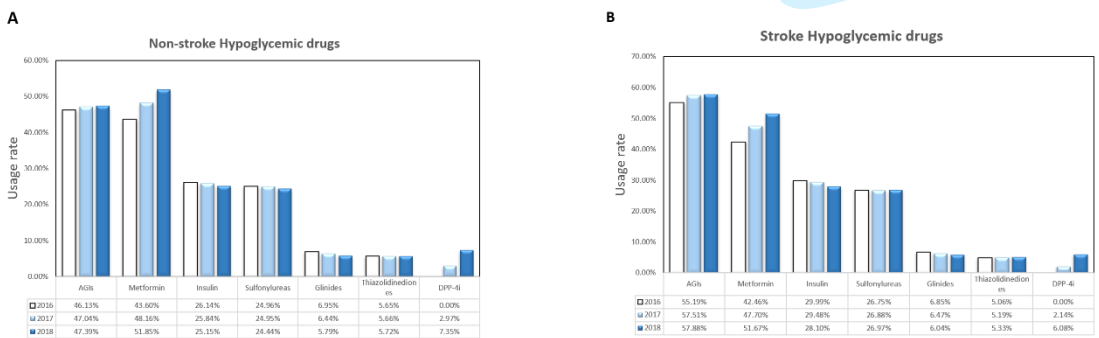


Supplemental table 1

Utilization rates of different types of insulin among diabetes patients with and without stroke in 2016-2018

Type of insulin	Non-stroke			stroke			P value		
	2016	2017	2018	2016	2017	2018	2016	2017	2018
Fast-acting	16,433 (9.01%)	21,423 (11.02%)	25,532 (12.69%)	3,473 (5.78%)	4,626 (7.56%)	4,965 （8.97%）	<.0001	<.0001	<.0001
Short-actin	23,786 (13.04%)	22,572 (11.61%)	21,221 (10.55%)	7,323 (12.20%)	7,052 （11.53%）	6,074 （10.98%）	<.0001	0.5852	0.0034
Intermediate-acting	28,159 (15.44%)	26,739 (13.75%)	24,735 (12.29%)	8,961 (14.92%)	8,272 （13.52%）	6,987 （12.63%）	0.0023	0.1494	0.0329
Long-acting	41,338 (22.67%)	51,309 (26.39%)	61,301 (30.47%)	9,175 (15.28%)	11,461 （18.73%）	12,654 (22.88%)	<.0001	<.0001	<.0001
Premixed	105,653 (57.94%)	109,164 (56.15%)	106,982 (53.19%)	40,983 (68.27%)	40,422 （66.09%）	34,359 (62.13%)	<.0001	<.0001	<.0001

The number indicates the number of people who used that insulin that year. The percentage in brackets indicates the percentage of the total population using this type of insulin.



Supplemental Fig 2. Changes in the use of nonhypoglycemic drugs and hypoglycemic drugs in DM patients with or without stroke.

(A). Changes in the use of hypoglycemic drugs (in DM patients without stroke)

(B). Changes in the use of hypoglycemic drugs (in DM patients with stroke)