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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 risk of stroke and its adverse sequelae. Approximately 20%–33% of patients with stroke have diabetes. In China, however, it is unclear how stroke affects healthcare utilisation, medications and complications among people with diabetes. This study aimed to analyse the clinical characteristics, treatment options, medical expenses and complications of hospital outpatient healthcare associated with stroke 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 The study included patients with diabetes whose data included 2016–2018 outpatient medication records and who had Beijing medical insurance. Patients who did not have continuous prescription records for more than 2 months were excluded from the analysis. In total, 2 853 036 people with diabetes were included, and patients who had and did not have a stroke were compared.

Results In our study, 19.75%–22.30% of patients with diabetes suffered from stroke between 2016 and 2018. The average annual medical cost for a patient diagnosed with diabetes is ¥9606.65, and the cost increases to ¥13 428.39 when diabetes was combined with stroke; thus, stroke increases the medical cost for patients with diabetes by 39.78% (p<0.0001). Among patients with diabetes who had a stroke, 4.76 medications were used (1.8 hypoglycaemic drugs and 2.97 non-hypoglycaemic drugs); these numbers were significantly greater than for patients with diabetes who did not have a stroke receiving both hypoglycaemic drugs and non-hypoglycaemic drugs (p<0.0001). Among patients with diabetes who did not have a stroke, 3.58 medications were used (1.66 hypoglycaemic drugs and 1.92 non-hypoglycaemic drugs). Patients with diabetes who had a stroke also had significantly greater incidences of diabetic peripheral neuropathy, diabetic kidney disease, diabetic retinopathy and diabetic angiopathy than those who did not have a stroke (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 the medical costs and medication regimens stratified by sex, age group and complications.

Conclusions Stroke is associated with a significant increase in complications and medications for patients with diabetes and greatly adds to the economic burden of these patients. Early identification of stroke risk factors in patients with diabetes, as well as targeted poststroke diabetes management, is crucial from a socioeconomic perspective for a 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 the economic burden of stroke among patients with diabetes.
⇒ This analysis covered the medications and medical costs for patients with diabetes for 3 consecutive years from 2016 to 2018, increasing the objectivity and credibility of the data.
⇒ Stratified analyses according to demographic characteristics were performed, along with analysis of the specific proportion of each additional complication that increased patients' medications 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.

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 represented 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.[1] The per capita medical cost for patients with diabetes is 2.3 times that of patients without diabetes.[2] In 2015, the global economic burden of diabetes was $1.3 trillion (95% CI 1.3 to 1.4) and is forecasted to increase to $2.2 trillion (95% CI 2.2 to 2.3) at baseline by 2030.[3 4]

The financial burden on patients with diabetes increases significantly when complications develop.[5] Stroke is the second most common complication of type 2 diabetes mellitus (T2DM) after coronary artery disease[6 7] and the second most common cause of death in patients with diabetes. Stroke is also the leading cause of disability and mortality in ageing populations.[8] T2DM is associated with a 2.5-fold to 3.5-fold increased risk of ischaemic 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 increased relative risk of stroke, while women have a 2.3-fold increased risk.[10] Approximately 20%–33% of patients who had a stroke have diabetes.[11–13] Diabetes is closely related not only to stroke but also to the risk of adverse stroke sequelae. Pre-existing diabetes is also associated with increased hazards of death, admission to long-term care, readmission for stroke and incident dementia.[14] Persistent hyperglycaemia, characterised by significantly elevated plasma glucose or glycated haemoglobin levels, is considered a key indicator and a major cause of vascular complications in patients with diabetes. 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 patients with diabetes compared with those without diabetes.[17] Yan Sun *et al*[18] reported patients with diabetes mellitus who had ischaemic stroke incurred 10% higher hospital costs compared with their counterparts in the non-diabetes mellitus group in Singapore. However, it is unclear how stroke affects healthcare utilisation, medications and complications among outpatients with diabetes in China.

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

METHODS

Study design

We conducted a multicentre, observational study to analyse the treatment options and medical expenses of patients with diabetes who had and did not have a stroke.

Study population and data collection

The data for this study were obtained from the Beijing Municipal Medical Insurance Database, which includes outpatient medication records of 2 853 036 patients with diabetes 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 patients with diabetes 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 WHO's diagnostic criteria in 1999. Patients who did not have continuous prescription records 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 2 months. A more detailed description is provided in online supplemental figure 1. We collected information from the Beijing Municipal Medical Insurance Database, including date of birth, race, International Classification of Disease (ICD) diagnosis, age, sex, 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 ICD codes. Diabetes-related complications included diabetic peripheral neuropathy, diabetic retinopathy, diabetic nephropathy and diabetic angiopathy. 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, 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. 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 mean with SD. Continuous variables that were not normally distributed were statistically analysed by Wilcoxon rank-sum test; these variables included the number of drugs, medical costs, comorbidities and complications. When the distribution of variables was overspread, we used a negative binomial model and a logarithmic link function. A negative binomial model and a log-linked function were used to assess the amount of drugs because the distribution of outcome variables was not normal. This method is suitable for counting data that are characterised by overdispersion. 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. Categorical variable data are presented as frequencies and percentages and were analysed by χ^2 test or Fisher's exact probability method. All statistical analyses were performed with SAS V.9.4 software. 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 patients with diabetes (897 385 patients in 2016, 959 509 patients in 2017 and 996 142 patients in 2018). Online supplemental figure 1 shows the flow chart of patient enrolment. Among patients with diabetes, 19.75%–22.30% had a stroke (200 143 out of 897 385 (22.30%) in 2016; 207 408 out of 959 509 (21.62%) in 2017; and 196 711 out of 996 142 (19.75%) in 2018). Among patients with diabetes who had a stroke, those aged 15–44 years accounted for 2.53%–2.94%, those aged 45–64 years accounted for 45.72%–48.89%, those aged 65–84 years accounted for 44.94%–47.60% and those aged >84 years accounted for 3.21%–4.14%. The proportion of patients with diabetes who had a 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 found in the online supplemental table 1.

Impressively, patients with diabetes who had a stroke also had significantly greater incidences of diabetic peripheral neuropathy, diabetic nephropathy, diabetic retinopathy and diabetic angiopathy than those who did not have a stroke (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 patients with diabetes who had and did not have a stroke

	Non-stroke			Stroke		
Variables	**2016**	**2017**	**2018**	**2016**	**2017**	**2018**
Total, n (%)	697 242 (77.7)	752 101 (78.38)	799 431 (80.25)	200 143 (22.30)	207 408 (21.62)	196 711 (19.75)
Age group (years), n (%)						
16–44	68 241 (9.78)	73 496 (9.77)	75 643 (9.46)	5902 (2.94)	5949 (2.86)	4964 (2.52)
45–64	380 788 (54.61)	403 660 (53.67)	419 820 (52.51)	97 860 (48.89)	98 589 (47.53)	89 943 (45.72)
65–84	234 211 (33.59)	257 841 (34.28)	283 128 (35.41)	89 952 (44.94)	95 332 (45.96)	93 653 (47.60)
≥85	14 002 (2.0)	17 104 (2.27)	20 840 (2.60)	6429 (3.21)	7538 (3.63)	8151 (4.14)
Gender, n (%)						
Male	352 908 (50.61)	387 104 (51.46)	421 917 (52.77)	98 518 (49.22)	103 787 (50.04)	100 144 (50.90)
Female	344 334 (49.38)	364 997 (48.53)	377 514 (47.22)	101 625 (50.77)	103 621 (49.95)	96 567 (49.09)
DPN, n (%)	76 331 (10.94)	83 014 (11.03)	95 277 (11.91)	39 168(19.57)	40 547 (19.54)	40 879 (20.78)
DKD, n (%)	30 935 (4.43)	29 566 (3.93)	28 078 (3.51)	12 144 (6.06)	11 213 (5.40)	8813 (4.48)
DR, n (%)	29 319 (4.20)	30 184 (4.01)	30 186 (3.77)	12 578 (6.28)	13 205 (6.36)	11 555 (5.87)
DA, n (%)	19 533 (2.80)	19 575 (2.60)	20 618 (2.57)	9712 (4.85)	10 285 (4.95)	9636 (4.89)

Values in the table represent the number of people in the year. Values inside parentheses represent the percentage of the total number of people in that year. DPN, DR, DKD and DA were also detected.
DA, diabetic angiopathy; DKD, diabetic kidney disease; DN, diabetic nephropathy; DPN, diabetic peripheral neuropathy; DR, diabetic retinopathy.

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

The annual medical expenses of patients with diabetes from 2016 to 2018 ranged from ¥9248.17 to ¥10 118.04; the average annual medical expense for these 3 years was ¥9606.65. The annual medical expenses of diabetes combined with stroke from 2016 to 2018 ranged from ¥13 049.88 to ¥14 239.78; the average annual medical expense in these 3 years was ¥13 428.39, indicating that diabetes combined with stroke increased medical expenses by 39.78% (p<0.0001; table 2).

On average, patients with diabetes who did not have a stroke used 3.58 medications (1.66 hypoglycaemic drugs and 1.92 non-hypoglycaemic drugs), while those who had a stroke used 4.76 medications (1.8 hypoglycaemic drugs and 2.97 non-hypoglycaemic drugs); these numbers were significantly greater than those of patients with diabetes who did not have stroke receiving both hypoglycaemic drugs and non-hypoglycaemic drugs (p<0.0001; table 2).

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

Stroke contributed to high healthcare costs in patients with diabetes stratified by demographics and complications

To obtain more detailed information, we analysed the medical costs for patients with diabetes 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 years age groups, the cost of treatment for the 65–85 age group was ¥10 259.32 in the diabetes without stroke group, which was the highest among all age groups (table 3). The cost of treatment for the 45–64 age group was ¥13 658.58 for the diabetes with stroke group, which was the highest among all age groups (table 3). For patients with diabetes who had a stroke, the medical costs were greater than those who did not have a stroke in all age groups or in both sexes (table 3). The costs increased dramatically if patients with diabetes

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

Variables	Non-stroke				Stroke			
	Total	2016	2017	2018	Total	2016	2017	2018
Annual cost of medication (¥)	9606.65±9622.86	10 118.04±10 543.8	9248.17±9259.31	9497.9±9082.87	13 428.39±11 134.39	14 239.78±11 825.74	13 049.88±10 951.9	13 001.92±10 539.1
Type 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 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
Cost of hypoglycaemic drugs (¥)	5206.23±7304.56	5408.25±8011.86	5016.95±7003.71	5208.12±6920.18	5818.75±7538.65	5994.19±7816.92	5671.02±7420.89	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

Table 3 Stroke increased healthcare costs for patients with diabetes 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 renminbi (¥). Complications of diabetes included DPN, DR, DKD and DA. The number of complications represents the occurrence of one to four of the diabetic complications.
DA, diabetic angiopathy; DKD, diabetic kidney disease; DPN, diabetic peripheral neuropathy; DR, diabetic retinopathy.

developed 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, patients with diabetes who had a stroke incurred greater medical costs than those who did not have a stroke when the same complications described above were present (table 3).

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

We analysed medication use in people with diabetes stratified by demographic factors and complications. Among the 15–44, 45–64, 65–84 and ≥85 years age groups, the 65–84 age group used the most drugs (table 4). Patients with diabetes who had a stroke took more medications than those who did not have a stroke in all age groups and in both sexes (table 4). The use of medications significantly increased if patients with diabetes 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, patients with diabetes who had a stroke used more medications than those who did not have a stroke when the same complications arose, as described earlier (table 4).

Use of OADs and insulin in patients with diabetes who had and did not have a 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 patients with diabetes who had and did not have a stroke, while the use of intermediate-acting insulin, premixed insulin and short-acting insulin gradually

Table 4 Stroke 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. Complications of diabetes included DPN, DR, DKD and DA. The number of complications represents the occurrence of one to four of the diabetic complications.
DA, diabetic angiopathy; DKD, diabetic kidney disease; DPN, diabetic peripheral neuropathy; DR, diabetic retinopathy.

decreased (online supplemental table 1). Patients with diabetes who had a stroke used more fast-acting, longer-acting and more premixed insulin than patients in the non-stroke group from 2016 to 2018 (online supplemental table 1). There was no difference in the use of short-acting insulin or intermediate-acting insulin between the two groups (online supplemental table 1).

Patients with diabetes who had a stroke used more antidiabetic drugs than those who did not have a stroke (90.66% vs 88.59%, 2018, p<0.0001; table 5). In particular, oral combination therapy was used (54.69% vs 50.91%, 2018, p<0.0001; table 5), as well as combinations of oral drugs and insulin (25.29% vs 20.49%, 2018, p<0.0001; table 5). 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, AGIs 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 to 2018. Compared with patients who did not have a stroke, patients with diabetes 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).

Changes in the prescription of antiglycaemic drugs

Among the antiglycaemic drugs, AGIs and metformin were the most frequently prescribed for patients with diabetes who had and did not have a stroke (online supplemental figure 2). The use of AGIs, metformin and

Table 5 Hypoglycaemic drug treatment among patients with diabetes who had and did not have a stroke from 2016 to 2018

	Non-stroke			Stroke		
Medication for diabetes	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	6186	5699	4793
Premixed insulin	35 507	31 869	28 366	10 096	7629	5772
DPP-4i	–	2218	5967	–	281	895
Glinides	8121	7185	6339	1861	1544	1287
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+sulfonylurea	37 573	41 128	42 197	8878	9272	8837
AGI+metformin+sulfonylurea	33 983	39 247	41 543	11 530	12 779	12 664
Metformin+DPP-4i	–	4094	11 267	–	471	1490
Metformin+glinides	10 049	9816	9161	2203	2112	1916
AGI+glinides	8028	7484	6815	2413	2271	1798
Oral+insulin	119 730	135 533	145 174	44 682	48 662	45 120
AGI+premixed insulin	23 464	23 407	21 830	10 583	10 070	8070
AGI+metformin+insulin	12 450	15 638	16 741	5574	7273	6655
Metformin+premixed insulin	13 740	15 018	14 942	4667	4537	3911

Values in the table represent the number of people who used the drug that year.
AGI, α-glucosidase inhibitor; DPP-4i, dipeptidyl peptidase-4 inhibitor.

DPP-4i tended to increase annually, whereas the use of insulin, sulfonylureas and glinides tended to decrease annually (online supplemental figure 2).

DISCUSSION

In this study, we reported the population characteristics, treatment costs, drug regimens and complications of patients with diabetes who had and did not have a stroke. We found that patients with diabetes who had a stroke used more drugs and had total annual drug costs to treat more complications than those who did not have a stroke. To our knowledge, this is the largest current study 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 for patients with diabetes is 2.3 times greater than those 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 patients with diabetes.

Studies have reported that 20%–33% of inpatients who had acute stroke have diabetes.[11–13] Diabetes mellitus is an established and independent risk factor for stroke and is associated with a 1.8-fold to 6-fold greater risk than in patients without diabetes.[21 22] Our study revealed that 19.75%–22.30% of patients with diabetes suffered from stroke, similar to previously reported rates.[11–13]

The proportion of patients with diabetes who had a stroke varied significantly by age group, with most patients affected from 2016 to 2018 ranging in age from 45 to 84 years (89.83%–93.49%). The estimated life expectancy of people aged 40 years who had a stroke was 21.1–26.2 years, while for people aged 60 years it was nearly 13 years and for people aged 80 years nearly 4 years.[23] Therefore, stroke seriously affects quality of life, leads to premature death in patients with diabetes and greatly exacerbates productivity loss and indirect financial burden.[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 patients with diabetes with one, two or three conditions among patients who had stroke, heart disease or diabetic kidney disease were 1.91, 2.90 or 3.88 times greater, respectively,

than for patients without complications.[27] Our data showed that in China the average medical cost for patients with diabetes who had a stroke was approximately 39.78% greater than those who did not have a stroke, and that for patients with diabetes the average medical cost 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 patients with diabetes who had a stroke had more complications, which may indicate that patients with diabetes with more complications are more susceptible to stroke. In addition to these complications and comorbidities, patients with diabetes 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 expense (€12 199) for patients with diabetes who had a stroke is three times greater than for patients with diabetes who did not have a stroke.[33] In Sweden, the average annual total cost (€11 397) for patients with diabetes who had a stroke is 2.2 times higher than for those who did not have a stroke.[34] Differences between countries may reflect varying economic levels and blood glucose management levels. However, globally, the average medical expenses for patients with diabetes who had a stroke far exceed those for patients with diabetes who did not have a stroke, emphasising the necessity for strong and strict primary and secondary prevention of complications such as stroke in the diabetic population.

Compared with patients with diabetes who did not have a stroke, those who had a stroke use more oral combination therapy and less monotherapy. Our results revealed that, in China, from 2016 to 2018, AGIs and metformin were the most commonly used antidiabetic agents in patients with diabetes who had or did not have a stroke, followed by premixed insulin, sulfonylureas, glinides, thiazolidinediones and DPP-4is. A 2013 nationwide survey of OADs in China reported that metformin was used by 53.7% of patients with T2DM, followed by sulfonylureas (42.7%) and AGIs (35.9%).[35] Our study showed that sulfonylureas were used 24.44% of the time, which is lower than that used in previous research. Our data also showed a gradual decrease in use of sulfonylureas. This may be due to changes in doctors' medication habits, secondary failures and the emergence of additional new varieties of drugs. DPP-4i usage has grown rapidly since it was included in the healthcare system of China, from 0% to 7.35% increase in 2016–2018. There may be several reasons for the changes in medication usage and costs: the first being 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 secondary failure of sulfonylureas and thiazolidinediones which may increase cardiovascular risk.

According to the 2023 American Diabetes Association guidelines, the use of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and sodium-glucose cotransporter-2 (SGLT-2) inhibitors is recommended for individuals diagnosed with or at high risk for cardiovascular disease.[36] In previous studies, the use of GLP-1 RA in patients with diabetes 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 in 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 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 due to severe health and economic burden.

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

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 patients with T2DM, 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 patients with diabetes, 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 to patients with diabetes at risk of stroke, which eventually will inform policy interventions aimed at reducing healthcare costs and improving patient outcomes.

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Contributors YZ, SL and HW acquired the data, performed the analysis and interpretation of the data, and wrote and revised the manuscript. JZ, YL, WW, JQ and JF 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. LG and ZZ 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. LG and ZZ acted as guarantors.

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Patient consent for publication Not required.

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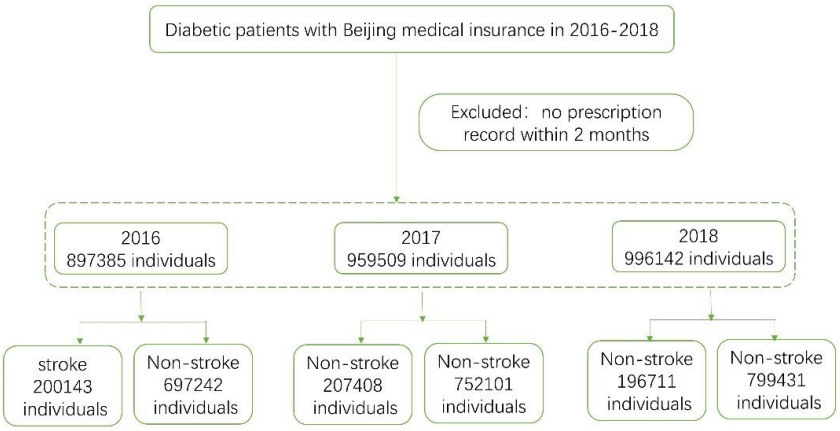
Supplemental Fig 1. Patient enrollment flow chart.

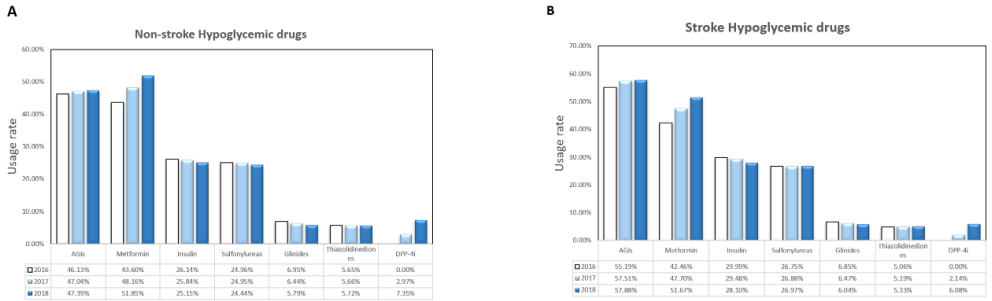


Supplemental table 1

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)