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ORIGINAL REPORT

Incidence rates of heart failure, stroke, and acute myocardial infarction among Type 2 diabetic patients using insulin glargine and other insulin†

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SUMMARY

Purpose The aim of this study was to compare incidence rates of heart failure, stroke, and acute myocardial infarction (AMI) in Type 2 diabetic patients using different types of insulin.

Methods Included were patients with a diagnosis of Type 2 diabetes and at least one insulin prescription from May 2001 to July 2007. Incidence rate ratios (RRs) of heart failure, stroke, and AMI were estimated using Poisson regression with adjustment for age, gender, history of hypertension, dyslipidemia history, days supply, and duration of diabetes.

Results Incidence rates of heart failure, stroke, and AMI in the insulin glargine group were 306.9 (95%CI: [278.9, 334.8]), 174.8 (95%CI: [153.7, 195.8]), and 105.2 (95%CI: [88.9, 121.5]) cases per 10 000 person–years, respectively. After adjustment for covariates, the incidence rates of CVD events in the insulin glargine were comparable to those in the other long/intermediate acting insulin group (reference), except for AMI, which tended to be lower in the insulin glargine group (RR = 0.81, 95%CI: [0.65, 1.02]). Using the same reference, the incidence rate of stroke was higher in patients taking rapid/short acting insulin, premixed insulin, or mixed use of insulin except insulin glargine (RR = 1.20, 95%CI: [1.04, 1.40]).

Conclusion This study suggested that insulin glargine use might be associated with a lower risk of AMI, compared to the other long/intermediate acting insulin use, and that insulin regimen of rapid/short acting insulin, premixed insulin, or mixed use of insulin except insulin glargine was associated with a higher risk of stroke using the same reference. Copyright © 2009 John Wiley & Sons, Ltd.

KEY WORDS — insulin glargine; stroke; acute myocardial infarction; heart failure; epidemiology

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INTRODUCTION

In the US, a number of epidemiological studies have shown that the incidence of cardiovascular diseases (CVDs) was higher in diabetic than non-diabetic individuals.[1–4] The increased risk of CVD in diabetic patients may partly be explained by abnormal endogenous insulin (e.g., insulin resistance and hyperinsulinemia).[5–9] As summarized in a systematic review,[10] an increased risk of myocardial infarction (MI) and/or coronary heart disease (CHD) have been found to be associated with higher 2-hour plasma insulin after an oral glucose tolerance test in three studies.[5–7] Higher fasting insulin has also been found to be associated with increased risk of MI and CHD in two studies.[8,9] However, the findings of the association between CVD and endogenous insulin have been inconsistent in previous studies.[5,6,9,11,12] Three more recent studies[9,11,12] have found MI or CVD was not associated with 2-hour plasma insulin after an oral glucose tolerance test. Likewise, a null association between fasting insulin and MI or CHD has been observed in two earlier studies.[5,6] It is unclear if the inconsistent findings were due to methodological differences or a result of chance.

A recent study showed that insulin treatment was associated with an increased incidence of ischemic cardiac outcomes among diabetic patients in the UK.[13]

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It has also been shown to be associated with fatal CVD among Pima Indians with Type 2 diabetes[14] and with non-fatal CVD among German patients with Type 2 diabetes.[15] Other studies have shown no association between insulin treatment and CVD.[12,16] To the best of our knowledge, there has been no published study comparing the incidence of CVD across the treatments of different types of insulin. The objective of the study was to examine the incidence rates of heart failure, stroke, and acute myocardial infarction (AMI) in Type 2 diabetic patients using insulin glargine and other types of insulin.

METHODS

Database and study population

This was a retrospective cohort study. The data source selected for this study was a subset of the PharMetrics integrated claims database, a longitudinal health benefit claims database that combines data from Medicaid, Medicare, and over 60 private health maintenance organizations (HMOs) and preferred provider organizations (PPOs) across the US. This proprietary database, that encompasses over 50 million lives, has been in existence since 1995. Data on age, gender, and the type of health plan are available for all members. Information available in each claim includes dates and location of service (outpatient, inpatient, or other health care facilities), diagnosis codes, procedure codes, and physician specialty. A claim for a single outpatient visit or a hospital admission may contain more than diagnoses or procedures. Information in each pharmacy dispensing includes the drug dispensed, the date of dispensing, and the quantity and number of therapy-days dispensed. This database has been used for various pharmacoepidemiologic studies before.[17–19]

Included in this study were patients with a diagnosis of Type 2 diabetes (International Classification of Diseases, Ninth Revision, Clinical Modification, ICD-9CM codes of 250.x0 and 250.x2) and at least one insulin prescription during the period from May 2001 (the launch date of insulin glargine in the US) to July 2007 (the latest data available). Only adult patients with drug benefit coverage and who have been continuously enrolled for at least 6 months prior to baseline were eligible for selection. Patients were excluded from this study if they had the following conditions at baseline: (1) less than 18 years old; (2) any history of diagnosis of heart failure, stroke, or MI (prevalent cases) in the past; (3) no information on the enrollment status in the database; (4) an insulin medication history in the past (to focus only on patients with no prior history of insulin use). The index date (baseline) was defined as the date of the first insulin prescription during the study period.

Because PharMetrics is an anonymous electronic database, neither an ethics committee nor an informed consent was available or needed for the present study.

Exposure measurement

Exposure was defined based on insulin prescription during the study period. The lists of insulin used in this study are shown in Table 1. Insulin was ascertained using the National Drug Code (NDC) directory. Patients were categorized into the following mutually exclusive groups (drug cohorts): (1) insulin glargine; (2) other long/intermediate acting insulin excluding insulin glargine; (3) insulin glargine and other insulin: insulin glargine preceded or followed by one or more of other insulin (including long acting, intermediate acting, short acting, rapid acting, and premixed insulin); (4) other insulin regimen: any other insulin regimen, including rapid/short acting insulin or premixed insulin alone, or a mixed sequence of any two or more types of insulin except insulin glargine.

Outcomes of interest

ICD-9CM codes were used to identify CVD events, including heart failure (ICD-9CM code of 428), stroke (ICD-9CM codes of 430–438), and AMI (ICD-9CM code of 410) (see Appendix I for the specific codes for each event). Only hospitalized cases were included for the analyses. The use of hospitalized cases to define the outcome has been done in previous studies using the PharMetrics database.[17–19] A similar method to define CVD events in Type 2 diabetes patients has also been used in one study using the same database.[17]

We analyzed the incidence rate for each CVD event separately. A patient was followed from the index date to the earliest date of: (1) the first occurrence of the CVD event; (2) the recorded last enrollment; or (3) the

Table 1. Types of insulin

	Type of insulin
Very long acting insulin	Insulin glargine
Long acting insulin	Ultralente insulin
Rapid acting insulin	Insulin lispro (Humalog)
	Insulin aspart (Novolog)
Short acting insulin	Regular (R) insulin
Intermediate acting insulin	NPH (N) insulin
	Lente insulin
	Lente (L) insulin
Premixed	Mixture of different insulin

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Table 2. Characteristics of the Type 2 diabetic patients at baseline, the PharMetrics database May 2001–July 2007

		Insulin glargine		Long/intermediate acting insulin		Insulin glargine and other insulin combined		Other insulin regimen	
		N	%	*N*	%	*N*	%	*N*	%
Overall		11 534	100.0	6566	100.0	16 540	100.0	30 979	100.0
Age (years)	18–30	255	2.2	309	4.7	1390	8.4	2356	7.6
	30–40	884	7.7	862	13.1	2116	12.8	4971	16.0
	40–50	2498	21.7	1097	16.7	3882	23.5	5808	18.7
	50–60	3968	34.4	1684	25.6	4742	28.7	7717	24.9
	60+	3929	34.1	2614	39.8	4410	26.7	10 127	32.7
Women		5147	44.6	3598	54.8	7916	47.9	17 034	55.0
History of hypertension		6846	59.4	2891	44.0	6865	41.5	13 163	42.5
History of dyslipidemia		4834	41.9	1774	27.0	4770	28.8	7524	24.3
Duration of diabetes (months)	<6	4736	41.1	3371	51.3	9779	59.1	17 364	56.1
	6–12	1229	10.7	655	10.0	1346	8.1	2835	9.2
	12–24	1982	17.2	1142	17.4	2106	12.7	4761	15.4
	24+	3587	31.1	1398	21.3	3309	20.0	6019	19.4
		Mean (SD)		Mean (SD)		Mean (SD)		Mean (SD)	
Days supply (days)		202.7	(241.4)	189.4	(254.6)	504.4	(447.5)	254.3	(317.2)

end of the study period (31 July 2007). The follow-up time was calculated as the period from the index date to the end of follow-up.

Covariates

Age on index date, gender, history of hypertension, history of dyslipidemia, days supply, and duration of diabetes were the covariates adjusted in the multivariate analyses. History of hypertension was defined as all patients who had an indication of hypertension based on ICD-9CM codes (ICD-9CM codes: 401–405) on or before the index date. History of dyslipidemia was defined as all patients who had a medication of anti-dyslipidemia drugs on or before the index date by looking up 'antihyperlipidemics' in the NDC directory. Days supply was calculated as the total days of prescriptions since the index date until the end of follow-up. Duration of diabetes was defined as the interval since the first record of diagnosis of Type 2 diabetes or the first record of oral medications in the database until the index date. The same method has been used to define the duration of diabetes in another study utilizing the same database.[20]

Statistical analysis

Incidence rate of each CVD event and its 95% confidence interval (CI) was calculated for each exposure group. The incidence rate was defined as the number of new cases divided by the total person-years of follow-up, and expressed as the number of cases per 10 000 person-years. Poisson regression was used to calculate the incidence rate ratio (RR) of each CVD event in insulin glargine and other groups using other long/intermediate acting insulin group as a reference, adjusted for age, gender, history of hypertension, history of dyslipidemia, days supply, and duration of diabetes.[21]

RESULTS

A total of 65 619 Type 2 diabetic patients were included in the study. As shown in Table 2, the distributions of age, gender, history of hypertension, history of dyslipidemia, days supply, and duration of diabetes were different across exposure groups ($p < 0.05$). The proportion of patients aged 40–60 years and those with a history of hypertension or dyslipidemia was higher in insulin glargine than in the long/intermediate acting insulin group. The insulin glargine group also had a larger proportion of men and a longer duration of Type 2 diabetes.

Table 3 displays the incidence rates of heart failure, stroke, and AMI by age, gender, and exposure group. The incidence rates of heart failure, stroke, and AMI were 243.2 (95%CI: [234.2, 252.2]), 150.8 (95%CI: [143.7, 157.9]), and 97.4 (95%CI: [91.8, 103.1]) cases per 10 000 person–years, respectively. The incidence rate of each CVD event increased with age and tended to be higher in men than in women. In the insulin glargine group, the incidence rates of heart failure, stroke, and AMI were 306.9 (95%CI: [278.9, 334.8]), 174.8 (95%CI: [153.7, 195.8]), and 105.2 (95%CI:

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Table 3. Incidence rates (per 10 000 person–years) of heart failure, stroke, and acute myocardial infarction, the PharMetrics database May 2001–July 2007

	Heart failure		Stroke		Acute myocardial infarction	
	# Cases	Rate (95%CI)	# Cases	Rate (95%CI)	# Cases	Rate (95%CI)
Overall	2786	243.2 (234.2, 252.2)	1746	150.8 (143.7, 157.9)	1134	97.4 (91.8, 103.1)
Age (years)						
18–30	21	26.6 (15.2, 38.0)	19	24.0 (13.2, 34.9)	5	6.3 (0.8, 11.8)
30–40	74	45.3 (35.0, 55.6)	58	35.4 (26.3, 44.5)	36	21.9 (14.8, 29.1)
40–50	264	109.0 (95.8, 122.1)	176	72.3 (61.6, 82.9)	157	64.5 (54.4, 74.6)
50–60	730	225.3 (209.0, 241.7)	481	147.1 (134.0, 160.3)	371	113.2 (101.7, 124.8)
60+	1697	503.7 (479.8, 527.7)	1012	293.9 (275.8, 312.0)	565	161.7 (148.3, 175.0)
Gender						
Women	1386	234.2 (221.9, 246.6)	863	144.3 (134.7, 153.9)	484	80.4 (73.3, 87.6)
Men	1400	252.7 (239.5, 266.0)	883	157.8 (147.4, 168.2)	650	115.6 (106.7, 124.5)
Drug cohort						
Insulin glargine	463	306.9 (278.9, 334.8)	265	174.8 (153.7, 195.8)	160	105.2 (88.9, 121.5)
Long/intermediate acting insulin	363	318.7 (285.9, 351.5)	208	181.2 (156.6, 205.9)	147	127.9 (107.2, 148.5)
Insulin glargine and other insulin combined	535	150.8 (138.1, 163.6)	373	103.3 (92.8, 113.8)	266	73.1 (64.3, 81.9)
Other insulin regimen	1425	270.8 (256.8, 284.9)	900	169.7 (158.6, 180.8)	561	105.3 (96.6, 114.0)

[88.9, 121.5]) cases per 10 000 person–years, respectively. The corresponding rates for the long/intermediate acting insulin group (reference) were 318.7 (95%CI: [285.9, 351.5]), 181.2 (95%CI: [156.6, 205.9]), and 127.9 (95%CI: [107.2, 148.5]) cases per 10 000 person–years.

Table 4 shows the RRs of CVD events in the insulin glargine and other groups compared to the long/intermediate acting insulin group (reference) before and after adjustment for the covariates. After adjustment for the covariates, the incidence rates of CVD events in the insulin glargine group were comparable to those in the reference group, except for AMI, which tended to be lower in the insulin glargine group. The adjusted RRs in the insulin glargine group were 1.03 (95%CI: [0.90, 1.18]) for heart failure, 1.00 (95%CI: [0.83, 1.20]) for stroke, and 0.81 (95%CI: [0.65, 1.02]) for AMI. The association between insulin glargine and AMI was not statistically significant (p-value = 0.075). In the insulin glargine combined with other insulin group, although lower incidence rates of CVD events were found, no significant association was observed after adjustment for the covariates. The adjusted RRs were 1.01 (95%CI: [0.88, 1.16]) for heart failure, 1.16 (95%CI: [0.98, 1.38]) for stroke, and 1.04 (95%CI: [0.84, 1.28]) for AMI. In the other insulin regimen, the incidence rate of stroke was significantly higher than that in the reference. The adjusted RR was 1.20 (95%CI: [1.04, 1.40]).

DISCUSSION

The present study suggested that the incidence rate of AMI in Type 2 diabetic patients using insulin glargine might be lower than in those using other long/intermediate acting insulin after adjustment for age, gender, history of hypertension, history of dyslipidemia, days supply, and duration of diabetes; no differences were found with regard to the incidence rates of heart failure and stroke. To date, we know of no published studies comparing the incidence rates of CVD across treatments of different types of insulin. A few studies have shown an association between increased blood glucose level with an increased risk

Table 4. Incidence rate ratios (RRs) of heart failure, stroke, and acute myocardial infarction, the PharMetrics database May 2001–July 2007

	Heart failure		Stroke		Acute myocardial infarction	
	Unadjusted	Adjusted*	Unadjusted	Adjusted*	Unadjusted	Adjusted*
	RR (95%CI)	RR (95%CI)	RR (95%CI)	RR (95%CI)	RR (95%CI)	RR (95%CI)
Insulin glargine	0.96 (0.84, 1.10)	1.03 (0.90, 1.18)	0.96 (0.80, 1.16)	1.00 (0.83, 1.20)	0.82 (0.66, 1.03)	0.81 (0.65, 1.02)
Long/intermediate acting insulin (reference)	1.00	1.00	1.00	1.00	1.00	1.00
Insulin glargine and other insulin combined	0.47 (0.41, 0.54)	1.01 (0.88, 1.16)	0.57 (0.48, 0.68)	1.16 (0.98, 1.38)	0.57 (0.47, 0.70)	1.04 (0.84, 1.28)
Other insulin regimen	0.85 (0.76, 0.95)	1.11 (0.99, 1.25)	0.94 (0.81, 1.09)	1.20 (1.04, 1.40)	0.82 (0.69, 0.99)	1.04 (0.86, 1.24)

*Adjusted for age, gender, history of hypertension, history of dyslipidemia, days supply, and duration of diabetes.

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of CVD[22–25] and insulin glargine may have a better glucose control than the traditional intermediate acting neutral protamine hagedorn (NPH) insulin, based on the measurements of HbA1c, fasting glucose and intra-subject variability in blood glucose, as indicated in one systematic review of clinical trials.[26] Therefore, insulin glargine may potentially be associated with a lower risk of CVD events than other long/intermediate acting insulin because of at least its better effect on glucose control. However, other more recent systematic review of eight clinical trials suggested that insulin glargine was not different from NPH in lowering levels of HbA1c, indicating they may have similar effects on long-term blood glucose control and thus potentially similar effects on the CVD risk.[27] Unfortunately, in this study, neither blood glucose nor HbA1c data were available for further evaluation of the glucose control across different types of insulin.

In this study, we found lower incidence rates of heart failure, stroke, and AMI in Type 2 diabetic patients using insulin glargine combined with other insulin than in those using other long/intermediate acting insulin alone. However, the association disappeared after adjustment for the covariates. The shorter duration of diabetes in this group might be one of the primary factors for lower incidence rates of CVD events, as shown in a sensitivity analysis by excluding duration of diabetes from the multivariate adjustment (data not shown). Two previous studies have shown that the duration of diabetes was positively associated with the incidence rate of fatal CVD[28] in Type 1 diabetic patients and with the incidence rate of CVD[1] in Type 2 diabetic patients. Another reason for lower incidence rates of CVD events in patients using insulin glargine combined with other insulin than in those using other long/intermediate acting insulin alone is a lower diabetes severity in the combination group, as indicated by lower prevalence of co-morbidities (hypertension and diabetes). Since the precise duration and severity of diabetes were unknown in this claim data, these adjustments might not completely eliminate the confounding effect of the two factors.

In this study, we also found an increased incidence rate of stroke associated with insulin regimen other than insulin glargine or other long/intermediate acting insulin. The reason for this was not clear. It was possible that this group was associated with a poor glucose control, which has been shown to be associated with an increased risk of CVD.[13,22–25]

The question of whether insulin treatment decreased the risk of CVD events, through its effect on an improved glucose level, or increased the risk of CVD events could not be answered in the present study. On the one hand, insulin treatment has been shown to be associated with an increased risk of CVD,[13–15] which may be considered the adverse event of insulin treatment. On the other hand, effective insulin treatment is associated with a decreased glucose level, which may result in a decreased risk of CVD.[22–25] Because the number of diabetic patients without any medications in the database was too small to allow for an analysis in this group in this study, we could not compare the incidence rates of CVD events in patients without diabetic medication and in those with insulin treatment and thus we were not able to answer the above question.

One of the limitations in this study is that cases of the outcome of interest were not adjudicated because medical records that could be used to confirm these events were not available in this claims database. However, we used only hospitalized cases as an outcome which have been shown to be more valid in database studies than using other outcomes.[29,30] Another limitation of this study is the potential confounding by the use of aspirin, glycemic control (e.g., HbA1c level), hypertension control, and body weight. Unfortunately these variables were not available in claims databases and could not be adjusted in the present study. Obese patients might have a higher risk of MI, stroke, or CHF to begin with[31,32] but there has been no study showing a difference of obesity prevalence in different insulin users. If the proportion of obese patients with Type 2 diabetes was higher in newer or long-acting insulin, such as insulin glargine, the RRs observed among insulin glargine users might have been biased toward null since CVD risk was higher in the obese patients than the non-obese. On the contrary, if the proportion of aspirin users was higher in insulin glargine, the RR observed in insulin glargine might have been biased away from the null because aspirin has been shown to be associated with a lower risk of CVD events.[33] As for HbA1c level, it might be a mediator in the causal pathways of insulin–CVD relationships as mentioned before. However, HbA1c level might also have confounded the relation between insulin glargine and CVD events. For example, a lower incidence of MI in insulin glargine users might have been confounded by a better HbA1c level in this group and the RR might have been biased away from the null. Blood pressure information is not available in the database and, therefore, hypertension control could not be adjusted in the analyses. However, we did include history of hypertension in the model as a confounder. This meant that the results were, at least partially, adjusted for hypertension medications because, in this database, the majority of hypertensive patients were

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KEY POINTS

- Comparable incidence rates of heart failure and stroke in insulin glargine and in other long/intermediate acting insulin users.
- Possible lower incidence rate of MI in insulin glargine than in other long/intermediate acting insulin users.
- Higher incidence rate of stroke in patients taking insulin regimen other than insulin glargine or other long/intermediate acting insulin.

treated. More studies are needed to elucidate the roles of these factors in the insulin–CVD relationship. Finally, as study subjects were patients with insurance coverage, the results might not be applicable to those without the coverage. Despite these limitations, our study had also advantages. The sample size was large enough to allow for comparisons between different types of insulin, which have not been done in previous studies.[12–16] In addition, the study groups were representative of various population groups captured by Medicaid, Medicare, and various HMOs, leading to relatively generalizable study findings.

To the best of our knowledge, there has been no study that examined the associations between different types of insulin and incidence rates of CVD events. A recent meta-analysis reported no difference in glycemic control between insulin glargine and NPH insulin, but less patient-reported hypoglycaemia with insulin glargine in adults with Type 2 diabetes.[34] Given the potentially lower risks of cardiovascular events suggested in this study and a lower incidence rate of hypoglycaemia with glargine found in the previous studies, the choice of a long-acting analog, particularly insulin glargine in Type 2 diabetic patients is an important therapeutic consideration for clinical decision making.

CONCLUSION

Our study indicated that incidence rates of CVD events in the insulin glargine and in other long/intermediate acting insulin groups were comparable, except for AMI where our study suggested a lower incidence rate associated with insulin glargine use. A higher incidence rate of stroke was observed in patients taking insulin regimen other than insulin glargine or other long/intermediate acting insulin.

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APPENDIX 1 ICD-9CM CODES FOR HEART FAILURE, STROKE, AND MI

Heart failure
- 428 heart failure
  - 428.0 congestive heart failure, unspecified
  - 428.1 left heart failure
  - 428.2 systolic heart failure
  - 428.3 diastolic heart failure
  - 428.4 combined systolic and diastolic heart failure
  - 428.9 heart failure, unspecified

Continues

APPENDIX 1. Continued

Stroke
- 430 subarachnoid hemorrhage
- 431 intracerebral hemorrhage
- 432 other and unspecified intracranial hemorrhage
  - 432.0 non-traumatic extradural hemorrhage
  - 432.1 subdural hemorrhage
  - 432.9 unspecified intracranial hemorrhage
- 433 occlusion and stenosis of precerebral arteries
  - 433.0 basilar artery
  - 433.1 carotid artery
  - 433.2 vertebral artery
  - 433.3 multiple and bilateral
  - 433.8 other specified precerebral artery
  - 433.9 unspecified precerebral artery
- 434 occlusion of cerebral arteries
  - 434.0 cerebral thrombosis
  - 434.1 cerebral embolism
  - 434.9 cerebral artery occlusion, unspecified
- 435 transient cerebral ischemia
  - 435.0 basilar artery syndrome
  - 435.1 vertebral artery syndrome
  - 435.2 subclavian steal syndrome
  - 435.3 vertebrobasilar artery syndrome
  - 435.8 other specified transient cerebral ischemias
  - 435.9 unspecified transient cerebral ischemia
- 436 acute, but ill-defined, cerebrovascular disease
- 437 other and ill-defined cerebrovascular disease
  - 437.0 cerebral atherosclerosis
  - 437.1 other generalized ischemic cerebrovascular disease
  - 437.2 hypertensive encephalopathy
  - 437.3 cerebral aneurysm, non-ruptured
  - 437.4 cerebral arteritis
  - 437.5 moyamoya disease
  - 437.6 non-pyogenic thrombosis of intracranial venous sinus
  - 437.7 transient global amnesia
  - 437.8 other
  - 437.9 unspecified
- 438 late effects of cerebrovascular disease
  - 438.0 cognitive deficits
  - 438.1 speech and language deficits
  - 438.2 hemiplegia/hemiparesis
  - 438.3 monoplegia of upper limb
  - 438.4 monoplegia of lower limb
  - 438.5 other paralytic syndrome
  - 438.6 alterations of sensations
  - 438.7 disturbances of vision
  - 438.8 other late effects of cerebrovascular disease
  - 438.9 unspecified late effects of cerebrovascular disease

AMI
- 410 acute myocardial infarction
  - 410.0 of anterolateral wall
  - 410.1 of other anterior wall
  - 410.2 of inferolateral wall
  - 410.3 of inferoposterior wall
  - 410.4 of other inferior wall
  - 410.5 of other lateral wall
  - 410.6 true posterior wall infarction
  - 410.7 subendocardial infarction
  - 410.8 of other specified sites
  - 410.9 unspecified site

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