

Treatment Outcomes of Clopidogrel in Patients With ACS and Diabetes Undergoing PCI-analysis of Beijing Medicare Database

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Original investigation

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Abstract

Background

There are several clinical trials that proved the efficacy of clopidogrel treatment for patients with percutaneous coronary intervention. There are few large-scale research to explore the mortality associated with different duration use of clopidogrel in patients with diabetes and ACS undergoing PCI in the Chinese population.

Objectives

The objective of this analysis was to determine the efficacy of long-term clopidogrel therapy (≥ 12 months) versus short-term use (< 12 months) in Chinese patients with diabetes after PCI.

Methods

Using the Beijing Medicare database provided by Beijing Medical Security Bureau. The Beijing Medicare database contains medical data of about 16 million people, including about 990,000 patients with diabetes and a history of taking antidiabetic medicines. Patients were divided into two groups, one group of 9,116 patients receiving consecutive clopidogrel for one year or more, and another group of 3290 patients receiving consecutive clopidogrel less than one year. The primary of this analysis was the risk of all-cause death, myocardial infarction and revascularization.

Results

In patients with diabetes after PCI, long-term clopidogrel treatment was associated with a reduced risk of all-cause death (HR, 0.57[95%CI, 0.49–0.67], $P < 0.0001$), myocardial infarction (HR, 0.79[95%CI, 0.68–0.93], $P = 0.0035$) and an increased risk of angina (HR, 1.18[95%CI, 1.10–1.27], $P < 0.0001$) and revascularization (HR, 1.07[95%CI, 1.01–1.13], $P = 0.02$). There was no significant difference in the incidence of all-cause re-hospitalization ($P = 0.7529$), diabetes-related re-hospitalization and cerebrovascular re-hospitalization.

Conclusion

The present study concluded that long-term dual anti-platelet therapy including clopidogrel and aspirin could decrease the risks of all-cause death, myocardial infarction. But it could increase the risks of angina and revascularization. Further studies should interpret the cause of this question.

Introduction

There are several clinical trials that proved the efficacy of clopidogrel treatment for patients with the percutaneous coronary intervention(PCI)^{1,2}. For patients with PCI, current guidelines suggest clopidogrel treatment for at least 12 months³. Non-adherence with clopidogrel after coronary stent implantation could be related to some adverse like increased mortality⁴. Diabetes is one of the four significant non-communicable diseases and is a major cause of premature death and disability. Among patients with diabetes, the adherence therapy of clopidogrel after myocardial infarction leads to a lower induction in the risk of death(all-cause death and cardiovascular death)⁵ compared with it in patients without diabetes. It is well known that patients accompanied by diabetes and acute coronary syndrome(ACS) undergoing PCI are at higher risk for some adverse effects like death⁶. The prevalence of diabetes in China has increased 10-fold in the past decade and reached 114 million, making it the country with the highest diabetic population in the world^{7,8}. Among Chinese patients with ACS, 37.6% accompanied diabetes or possible diabetes. Even in patients with diabetes younger than 45 years old, 26.9% accompanied by diabetes or possible diabetes⁹. There are few large-scale research to explore the mortality associated with different duration use of clopidogrel in patients with diabetes and ACS undergoing PCI in the Chinese population.

All medicare citizens are registered with a personal number in China. Since the establishment of China's medicare system, there has been little relevant large-scale clinical data analysis. Beijing medicare system covers medical data of thousands of hospitals and community clinics.

In China, the length of clopidogrel therapy is consistent with guidelines. We conducted large-scale research of 12406 PCI treated patients with diabetes to evaluate the effect of different duration use of clopidogrel on mortality and other indicators.

Methods

Data Source

In China, all medicare citizens are registered with a personal number in the Medicare System. The Beijing Medical Security Bureau holds all the information on all outpatients and hospitalizations in Beijing. The Medicare System records all the prescriptions and diagnosis information dispensed from hospitals and clinics in Beijing. For calculating the expenses of medicare, all the treatment and use of drugs are registered in the Medicare System in China. The study was approved by the ethics committee of Beijing Hospital.

Population

The population included in this study were all enrolled in the Beijing Medical Security Bureau with available treatment records from 2012–2016. First of all, patients with diabetes diagnoses were searched in Medicare System. Then among the patients with diabetes, PCI treatment was identified to locate the

patients diagnosed with acute coronary syndrome and diabetes. Patients with survival days of less than 30 days were excluded. Diabetic patients who had at least one time PCI treatment were eligible for further selection. Then patients who have continuous treatment(≥ 1 year) of aspirin were selected for further investigation in this research. The Beijing Medicare System contains demographic and clinical data like age, sex, history and time of drug use and surgery treatment. The data extracted from the Medicare System contains all medical prescriptions and surgery history.

Medication Therapy

The Beijing Medical Security Bureau provided medications and diagnosis used from 2012–2016 in patients with diabetes after PCI. Since the drug name appearing in the medicare system may be the chemical name or trade name, we classified the drugs into categories according to the clinical guidelines, such as metformin, sulfonylurea, DPP-4 inhibitors, thiazolidinediones(TZDs), α -glucosidase inhibitors and glinides (hypoglycemic drugs), diuretics, CCBs, ARB/ACEI, β -receptor inhibitors(antihypertensive drugs), etc. We tracked the dates of prescription of aspirin and clopidogrel up to 4 years after PCI. Patients were considered as not taking aspirin or clopidogrel if the prescription lapsed over 30 days from the last day of the supply. Clopidogrel use was defined as either long-term(≥ 12 months therapy after PCI) or short term(< 12 months therapy after PCI) therapy.

Outcomes

Clinical outcomes in patients with diabetes after PCI were identified from the Beijing Medical Security Bureau through the medicare system until December 2016. These outcomes included all-cause death, myocardial infarction, all-cause re-hospitalization, diabetes-related re-hospitalization, cerebrovascular re-hospitalization, angina and revascularization.

Statistical Analysis

Quantitative variables were expressed as mean \pm SD and categorical variables as frequencies and percentages. Continuous variables with normal distribution were compared between the two groups by the t-test and continuous variables without normal distribution by the Wilcoxon rank-sum test. Categorical variables were compared between groups using the chi-square test or Fisher's exact probability method (when the expected frequency of cells greater than 25% is less than 5). Events were summarized with Kaplan–Meier curves and estimates at three years. Hazard ratios (HRs) comparing treatment groups were derived from univariate Cox regression models. Subgroups were analyzed with a Cox model, including subgroup, treatment, and the subgroup-by-treatment interaction. Multivariate Cox regression models were derived for the event by the use of a backward selection algorithm. The significance level for staying in the model was set to 0.05 two-sides. All data were prospectively analyzed using the SAS, version 9.4.

Results

Population Selection

The selection process was showed in Fig. 1. The Beijing Medicare database contains medical data of about 16 million people, including about 990,000 patients with diabetes and a history of taking antidiabetic medicines. Among them, 18,799 patients had a record of PCI surgery in 2014–2016. Among them, 13,693 patients have continuous aspirin withdrawal records in the medicare system. After excluding patients with a survival time of less than one year or no continuous clopidogrel medication withdrawal records, the patients were divided into two groups, one group of 9,116 patients receiving consecutive clopidogrel for one year or more, and another group of 3290 patients receiving consecutive clopidogrel less than one year.

Demographics Of Drugs Treatment

We summarized the medication situation of the two groups of patients as showed in Table 1. Classifications of drugs contains antidiabetic medicine(Thiazolidinediones, α -glucosidase inhibitors, metformin, sulfonylureas, DPP-4 inhibitors, glinides, insulin), antihypertensive medicine(ARB/ACEI, CCB, β -receptor inhibitors, diuretic), related cardiovascular medicine(statin, nitrate, proton pump inhibitors). In group of patients receiving clopidogrel less than 1 years, 4.5% patients treated with TZD, 53.4% with α -glucosidase inhibitors, 43.3% with metformin, 6.5% with glinides, 25.2% with sulfonylureas, 0.5% with DPP-4i, 32.8% with insulin, 63.4% with ARB/ACEI, 48.4% with CCB, 72.8% with β -receptor inhibitors, 19.1% with diuretic, 93.4% with statin, 0.5% with ticagrelor, 50% with nitrate, 16.5% with PPI more than 1 year. There are 7.0% patients treated with TZD, 22.2% with α -glucosidase inhibitors, 23.2% with metformin, 8.2% with glinides, 17.2% with sulfonylureas, 21.2% with ARB/ACEI, 23.3% with CCB, 17.4% with β -receptor inhibitors, 25.4% with diuretic, 6.2% with statin, 3.5% with ticagrelor, 38.4% with nitrate, 43.9% with PPI less than one year. There are 88.5% patients without treated with TZD, 24.3% without α -glucosidase inhibitors, 33.5% without metformin, 85.4% without glinides, 57.6% without sulfonylureas, 15.3% without ARB/ACEI, 28.4% without CCB, 9.8% without β -receptor inhibitors, 55.4% without diuretic, 0.3% without statin, 96.0% without ticagrelor, 11.6% without nitrate, 39.6% without PPI.

In the group of patients receiving clopidogrel more than one years, 4.0% patients treated with TZD, 55.6% with α -glucosidase inhibitors, 45.5% with metformin, 6.7% with glinides, 26% with sulfonylureas, 65.2% with ARB/ACEI, 52% with CCB, 77.3% with β -receptor inhibitors, 19.4% with diuretic, 97% with statin, 0.1% with ticagrelor, 60% with nitrate, 17.8% with PPI more than one year. There are 7.4% patients treated with TZD, 21.1% with α -glucosidase inhibitors, 21.3% with metformin, 8.2% with glinides, 16.4% with sulfonylureas, 18.7% with ARB/ACEI, 21% with CCB, 13.1% with β -receptor inhibitors, 24.6% with diuretic, 2.7% with statin, 0.9% with ticagrelor, 31.2% with nitrate, 41.7% with PPI less than one year.

There are 88.6% patients without treated with TZD, 23.3% without α -glucosidase inhibitors, 33.3% without metformin, 85.1% without glinides, 57.6% without sulfonylureas, 16% without ARB/ACEI, 27% without

CCB, 9.7% without β -receptor inhibitors, 56.1% without diuretic, 0.3% without statin, 99% without ticagrelor, 8.9% without nitrate, 40.6% without PPI.

Mortality And Incidence Of Recurrent Myocardial Infarction And Hospitalization

The mortality was lower in patients treated with clopidogrel more than one year compared with the group treated with clopidogrel less than one year (4.6% vs 7.7%, HR, 0.57[95%CI, 0.49–0.67], $P < 0.0001$) (Fig. 2). The incidence of myocardial infarction was lower in patients treated with clopidogrel more than one year compared with patients treated with clopidogrel less than one year (8.2% vs 10.1%, HR, 0.79[95%CI, 0.68–0.93], $P = 0.0035$) (Fig. 3). However, there were no significant differences in the incidence of all-cause re-hospitalization ($P = 0.7529$), diabetes-related re-hospitalization ($P = 0.9727$) and cerebrovascular re-hospitalization ($P = 0.2958$) (Fig. 4–6).

Incidence Of Angina And Revascularization

The rate of angina and revascularization was 35.8% and 54.5% in long-term dual anti-platelet therapy group compared with 31.1% and 51.8% in placebo group (HR, 1.18[95%CI, 1.10–1.27], $P < 0.0001$) (HR, 1.07[95%CI, 1.01–1.13], $P = 0.02$) (Fig. 7–8). Long-term combination of aspirin and clopidogrel could cause higher risks of angina and revascularization.

Discussion

From 2012 to 2016, we screened a cohort of 12,406 patients who underwent PCI surgery among 990,000 diabetic patients in Beijing. The results showed that clopidogrel could reduce all-cause mortality and the probability of recurrent myocardial infarction after more than one year's regular treatment, but had no significant effect on all-cause readmission, cerebrovascular readmission and diabetes-related readmission. But long-term dual anti-platelet treatment including aspirin and clopidogrel could increase the risks of angina and revascularization. In the past published articles in the Veterans Health Administration database, in patients with diabetes mellitus who received drug-eluting stents, prolonged clopidogrel (more than 12 months) was associated with a reduced risk of death¹⁰. This result is consistent with the long-term use of clopidogrel in patients without diabetes^{11,4}. However, similar studies on the Chinese medicare database are still lacking.

High risk of poor clinical outcomes were observed in patients with diabetes after PCI^{12,13}. The DAPT study concluded a result that the treatment of thienopyridine beyond one year could decrease the risks of stent thrombosis and major cerebrovascular and cardiovascular events¹⁴. As expected, long-term dual anti-platelet therapy could increase the risk of bleeding. That was why our results showed that over 50% of patients had used PPI. However, other research showed that different stents¹⁵ and P2Y12 inhibitors¹⁶

had been related to different rates of stent thrombosis and myocardial infarction. Our research has not focused on this difference as for inconvenient of the China medicare database to distinguish different stents. The rate of all-cause death and myocardial infarction in the DAPT study was 2.0% and 2.1% in the long-term thienopyridine treatment and 1.5%, 4.1% in the placebo group. But in our study, the rate of all-cause death and myocardial infarction in the long-term dual anti-platelet therapy group was 4.6% and 8.1% compared with 7.7% and 10.1% in the placebo group. This was a big difference between the DAPT study and our results. This result also proved that patients with diabetes after PCI had a higher risk of poor clinical outcomes compared with patients without diabetes. The same aspect between the two studies was that long-term therapy did not affect cerebrovascular outcomes.

Another finding is that long-term dual anti-platelet therapy could increase the risks of angina and revascularization in patients with diabetes undergoing PCI. Controversies still exist with the combination use of clopidogrel and PPI following coronary stenting. The previous meta-analysis¹⁷ showed that the continuous use of clopidogrel and PPI was associated with higher MACES with OR:1.27, 95%CI[1.13–1.42]. Another meta-analysis¹⁸ found that long-term dual therapy leads to increase MACES, myocardial infarction, stent thrombosis and target vessel revascularization. Our results showed that 17.8% of patients with long-term dual therapy and 16.5% of patients with short-term dual therapy had used PPI for more than one year. That may be the cause of increased rates of angina and revascularization. The possible reason for increased adverse effects was that PPI involved in the same metabolic pathway(CYP2C19 isoenzyme and so on) with that of clopidogrel¹⁹. However, several studies found different results. From the results of Guthrie Health Off-label Stent(GHOST) research, the combination of PPI and clopidogrel was not related to any increase in MACES outcomes after PCI²⁰. The specific conclusion still needs further investigation.

Ticagrelor is the first reversibly binding direct P2Y12 inhibitor. Compared with clopidogrel and prasugrel, it does not need enzymatic activation, and it can inhibit platelets faster, better and more stably compared with clopidogrel^{21,22}. Meanwhile, regardless of revascularization or not, ticagrelor could reduce the risk of all-cause death with no significant increase in risk of overall bleeding compared with clopidogrel²³. Our results showed that over 95% of diabetic patients after PCI surgery never used ticagrelor. This may be related to the drug price and the prescription habits of Chinese doctors.

At the same time, we also summarized the medication situation of patients with diabetes and PCI. We found that the most commonly used antidiabetic drug was alpha-glucosidase inhibitors, followed by metformin. According to the guidelines, most of the lipid-lowering drugs selected for patients with diabetes after PCI are statins^{3,24}, which is consistent with our results. More than 90% of patients have used statins for more than one year. But recent research found that treatment with fenofibrate and metformin produces the cardioprotective effect in acute myocardial infarction and diabetes rat model²⁵. And the possible mechanism may interact through PPAR α activation.

Limitations

There was no specific classification of drugs and diseases of the Chinese medicare database. Researchers achieved the classification, and there was no patients' laboratory indicators in the database. It was hard to distinguish the different types of stents to go through further investigation. This study also did not include more potent anti-platelet agents.

Conclusion

The present study concluded that long-term dual anti-platelet therapy including clopidogrel and aspirin could decrease the risks of all-cause death, myocardial infarction and did not affect the incidence of all-cause re-hospitalization, diabetes-related re-hospitalization and cerebrovascular re-hospitalization in patients with diabetes after PCI. But it could increase the risks of angina and revascularization.

Declarations

Acknowledgements

Not applicable.

Authors' contributions

WWH, XXW and LNZ made substantial contributions to study design, data collection, data analysis and manuscript writing. QP and LXG made substantial contributions to study design and intellectual direction. JZ and FLM made contributions to data collection and analysis. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval

The study protocol was approved by the Ethics Committee of Beijing Hospital.

Consent for publication

Not applicable.

Competing interests

The authors declared that they have no conflict of interest.

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Tables

Table 1. Demographics of drugs treatment.

Drug names	Duration of drug treatment	Number of patients with clopidogrel < 1 year (%)	Number of patients with clopidogrel ≥ 1 year (%)	P value
Metformin	none	1089 (33.5)	3032 (33.3)	0.0346
	< 1 year	755 (23.2)	1940 (21.3)	
	≥ 1 year	1407 (43.3)	4144 (45.5)	
α-glucosidase inhibitor	none	791 (24.3)	2126 (23.3)	0.1094
	< 1 year	723 (22.2)	1925 (21.1)	
	≥ 1 year	1737 (53.4)	5065 (55.6)	
thiazolidinedione (TZD)	none	2878 (88.5)	8076 (88.6)	0.3075
	< 1 year	227 (7.0)	679 (7.4)	
	≥ 1 year	146 (4.5)	361 (4.0)	
Sulfonylureas	none	1873 (57.6)	5252 (57.6)	0.4824
	< 1 year	559 (17.2)	1496 (16.4)	
	≥ 1 year	819 (25.2)	2368 (26.0)	
Glinides	none	2776 (85.4)	7759 (85.1)	0.8629
	< 1 year	265 (8.2)	743 (8.2)	
	≥ 1 year	210 (6.5)	614 (6.7)	
DPP-4 inhibitor	none	3056 (94.0)	8589 (94.2)	0.3037
	< 1 year	178 (5.5)	497 (5.5)	
	≥ 1 year	17 (0.5)	30 (0.3)	
insulin	none	1835 (56.4)	5193 (57.0)	0.5542
	< 1 year	351 (10.8)	923 (10.1)	
	≥ 1 year	1065 (32.8)	3000 (32.9)	

Drug names	Duration of drug treatment	Number of patients with clopidogrel < 1 year (%)	Number of patients with clopidogrel ≥ 1 year (%)	P value
ticagrelor	none	3122 (96.0)	9029 (99.0)	<0.0001
	< 1 year	114 (3.5)	85 (0.9)	
	≥ 1 year	15 (0.5)	2 (0.1)	
ARB/ACEI	none	499 (15.3)	1463 (16.0)	0.0077
	< 1 year	690 (21.2)	1706 (18.7)	
	≥ 1 year	2062 (63.4)	5947 (65.2)	
CCB	none	922 (28.4)	2461 (27.0)	0.0011
	< 1 year	757 (23.3)	1915 (21.0)	
	≥ 1 year	1572 (48.4)	4740 (52.0)	
β receptor blocker	none	317 (9.8)	883 (9.7)	<0.0001
	< 1 year	566 (17.4)	1190 (13.1)	
	≥ 1 year	2368 (72.8)	7043 (77.3)	
diuretic	none	1802 (55.4)	5110 (56.1)	0.6018
	< 1 year	827 (25.4)	2238 (24.6)	
	≥ 1 year	622 (19.1)	1768 (19.4)	
statin	none	11 (0.3)	29 (0.3)	<0.0001
	< 1 year	202 (6.2)	249 (2.7)	
	≥ 1 year	3038 (93.4)	8838 (97.0)	
nitrate	none	377 (11.6)	808 (8.9)	<0.0001
	< 1 year	1248 (38.4)	2841 (31.2)	
	≥ 1 year	1626 (50.0)	5467 (60.0)	
PPI	none	1288 (39.6)	3700 (40.6)	0.0597
	< 1 year	1427 (43.9)	3797 (41.7)	
	≥ 1 year	536 (16.5)	1619 (17.8)	

Figures

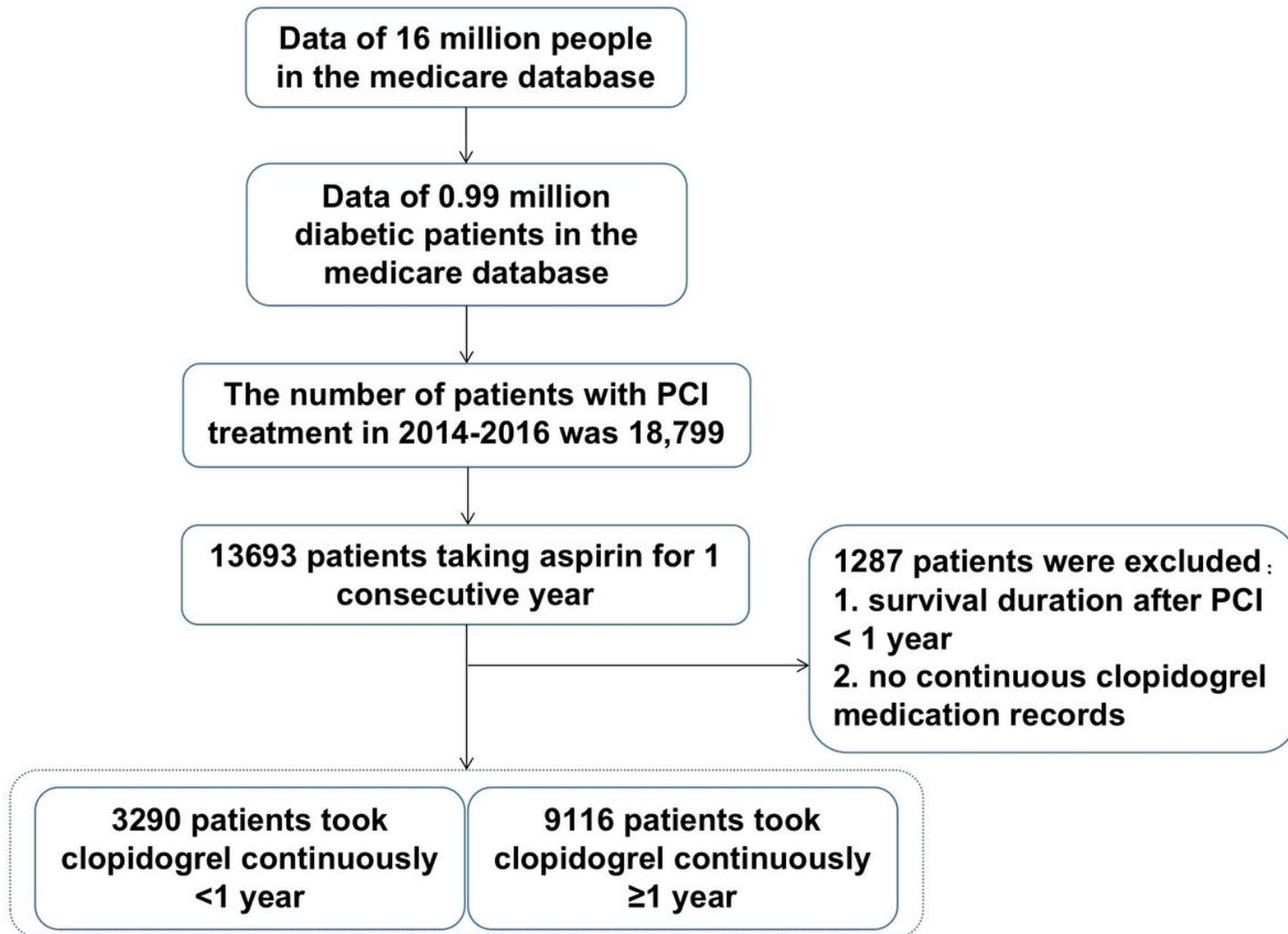


Figure 1

Selection process of included patients.

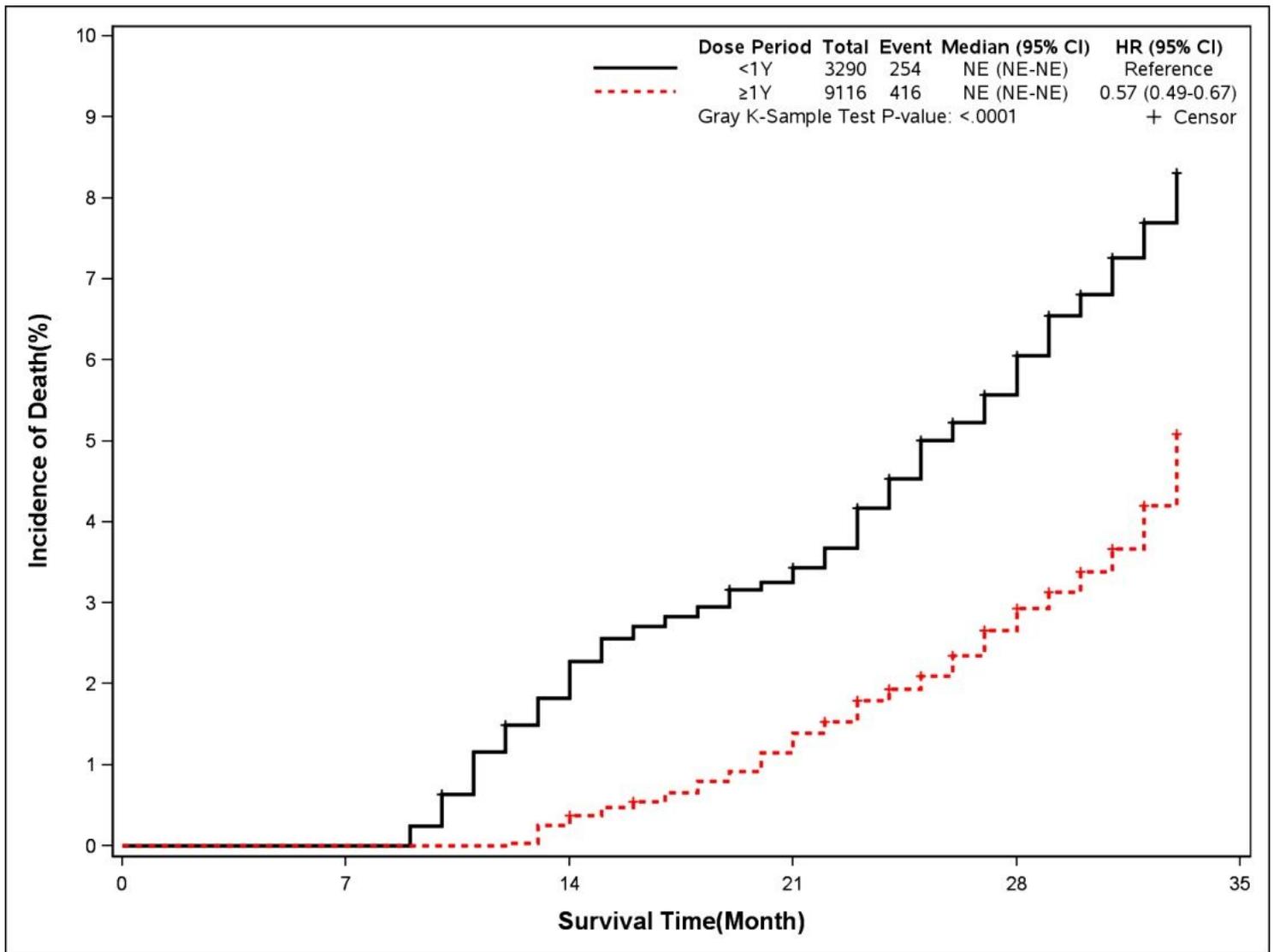


Figure 2

Incidence of all-cause death in two groups. Black line: patients took clopidogrel continuously < 1 year; Red line: patients took clopidogrel continuously ≥ 1 year.

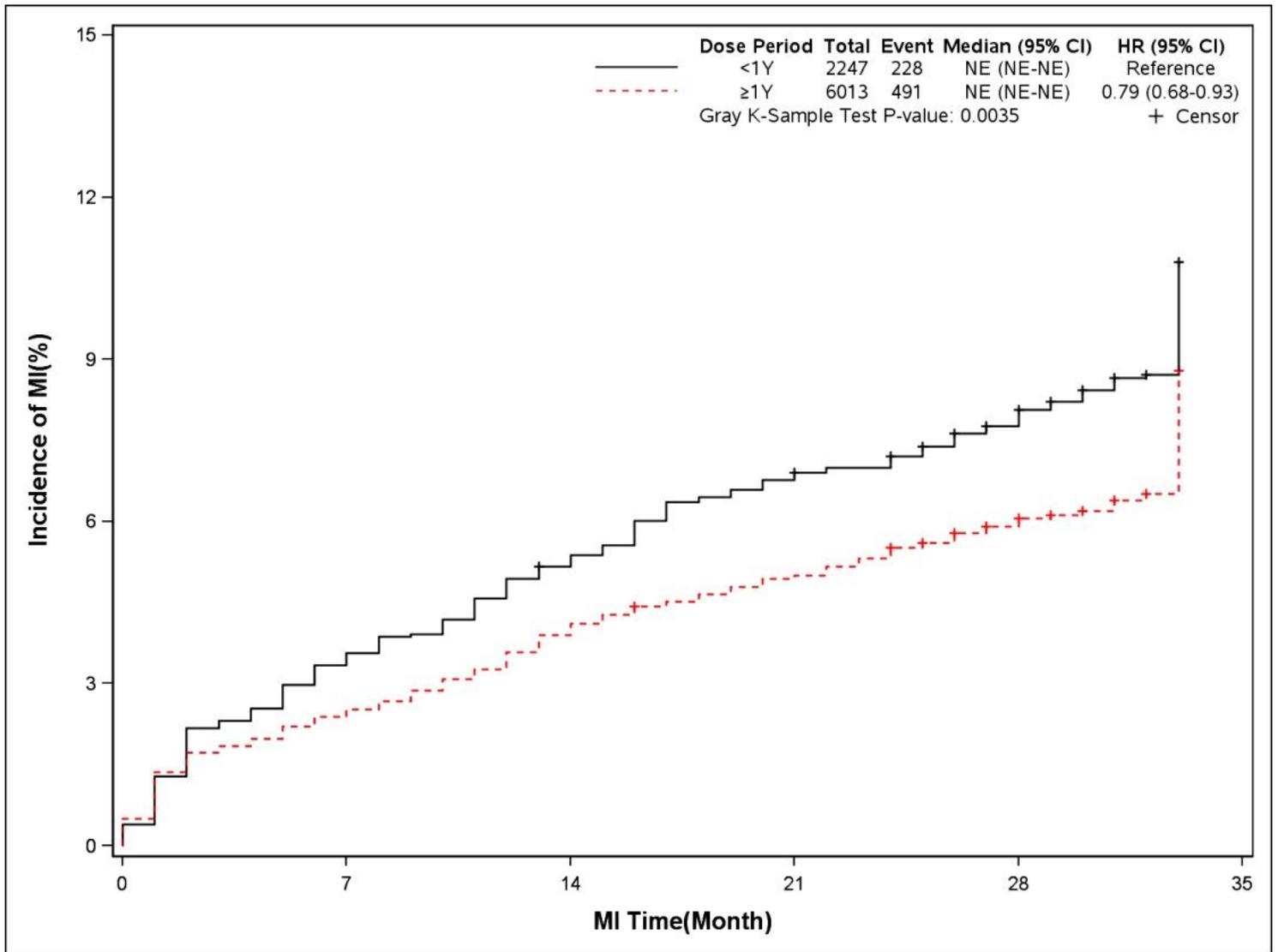


Figure 3

Incidence of recurrent myocardial infarction in two groups. Black line: patients took clopidogrel continuously < 1 year; Red line: patients took clopidogrel continuously ≥ 1 year.

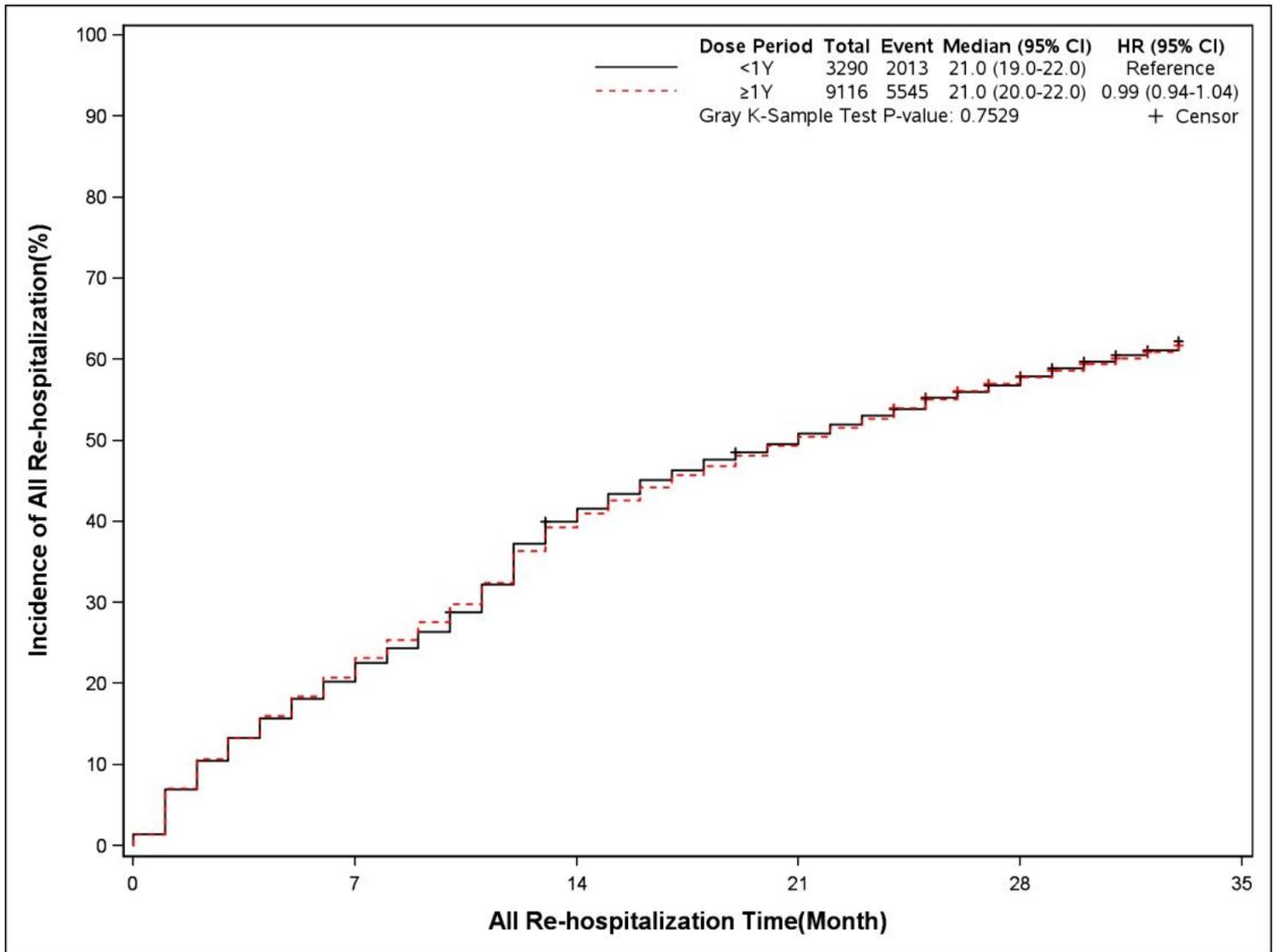


Figure 4

Incidence of all-cause rehospitalization in two groups. Black line: patients took clopidogrel continuously < 1 year; Red line: patients took clopidogrel continuously ≥ 1 year.

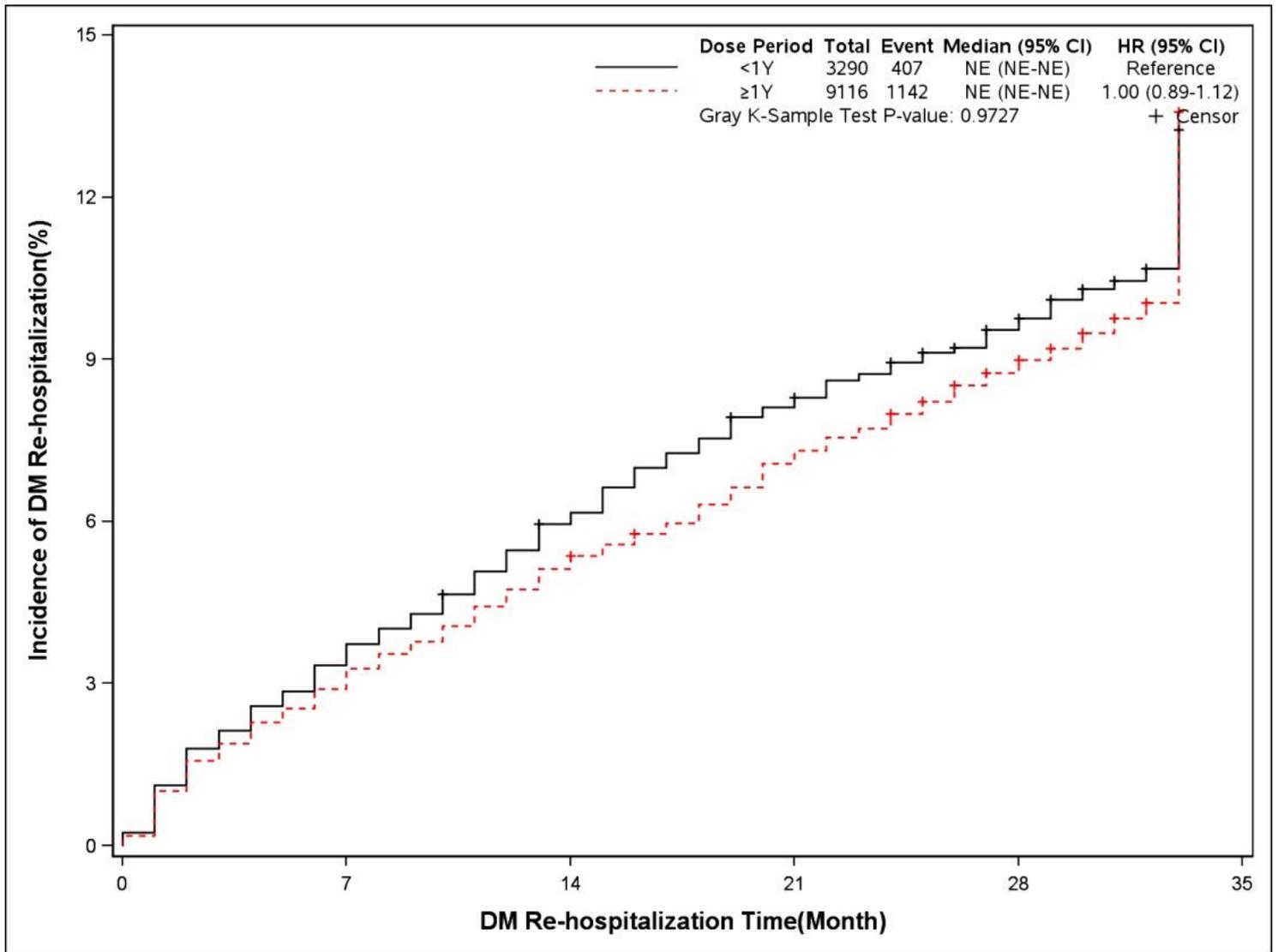


Figure 5

Incidence of diabetes-related rehospitalization in two groups. Black line: patients took clopidogrel continuously < 1 year; Red line: patients took clopidogrel continuously ≥ 1 year.

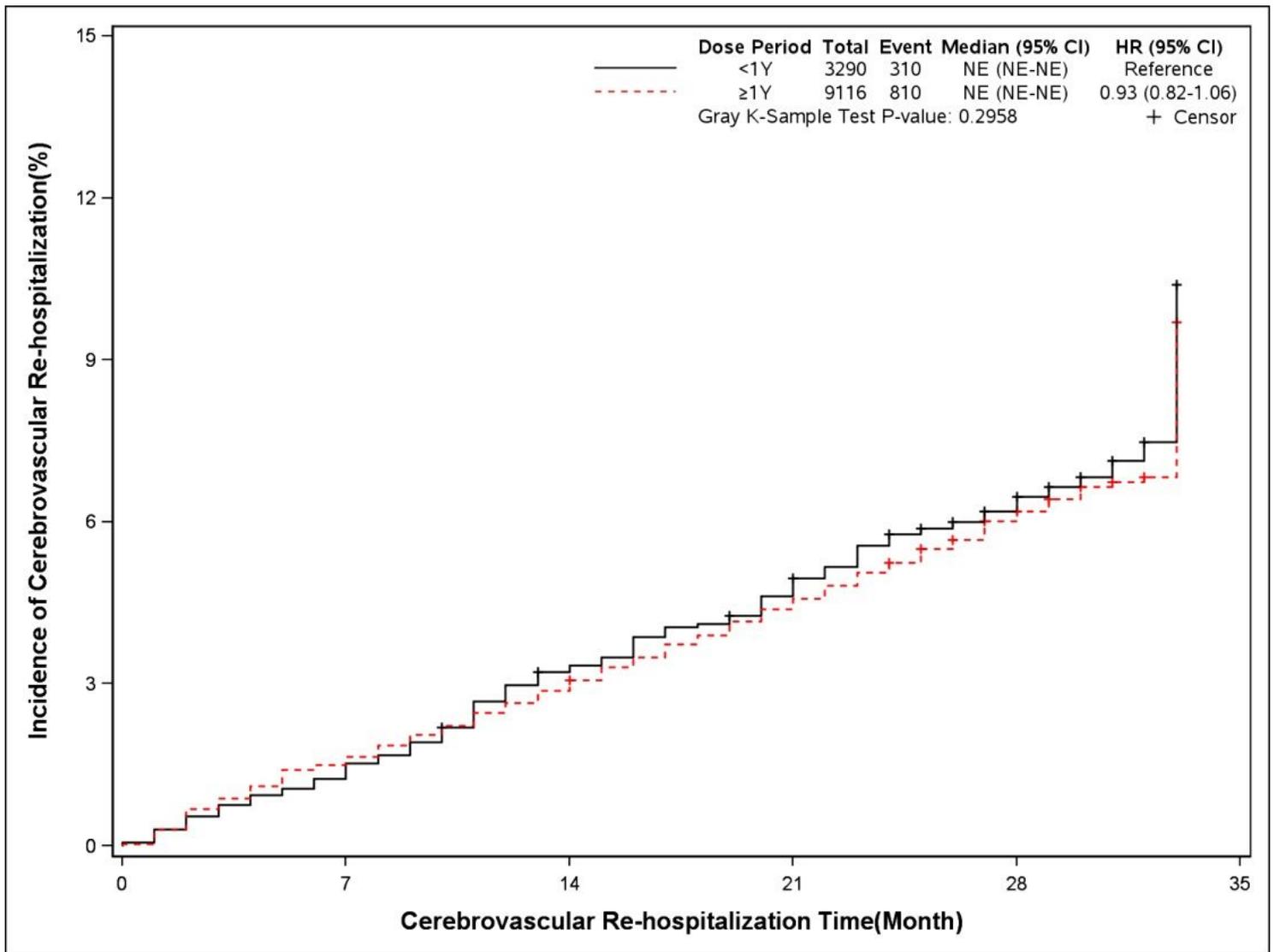


Figure 6

Incidence of cerebrovascular rehospitalization in two groups. Black line: patients took clopidogrel continuously < 1 year; Red line: patients took clopidogrel continuously ≥ 1 year.

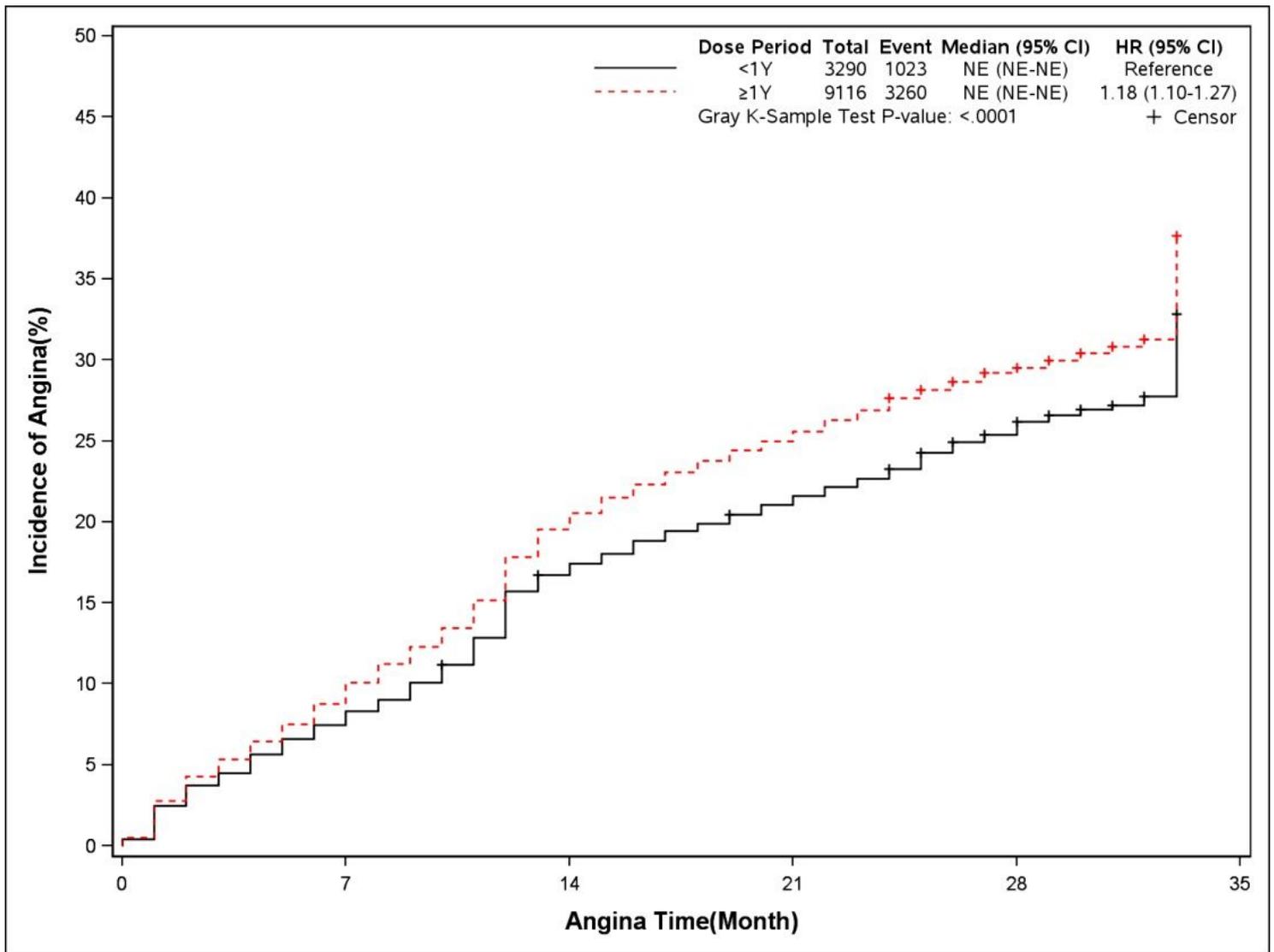


Figure 7

Incidence of angina in two groups. Black line: patients took clopidogrel continuously < 1 year; Red line: patients took clopidogrel continuously ≥ 1 year.

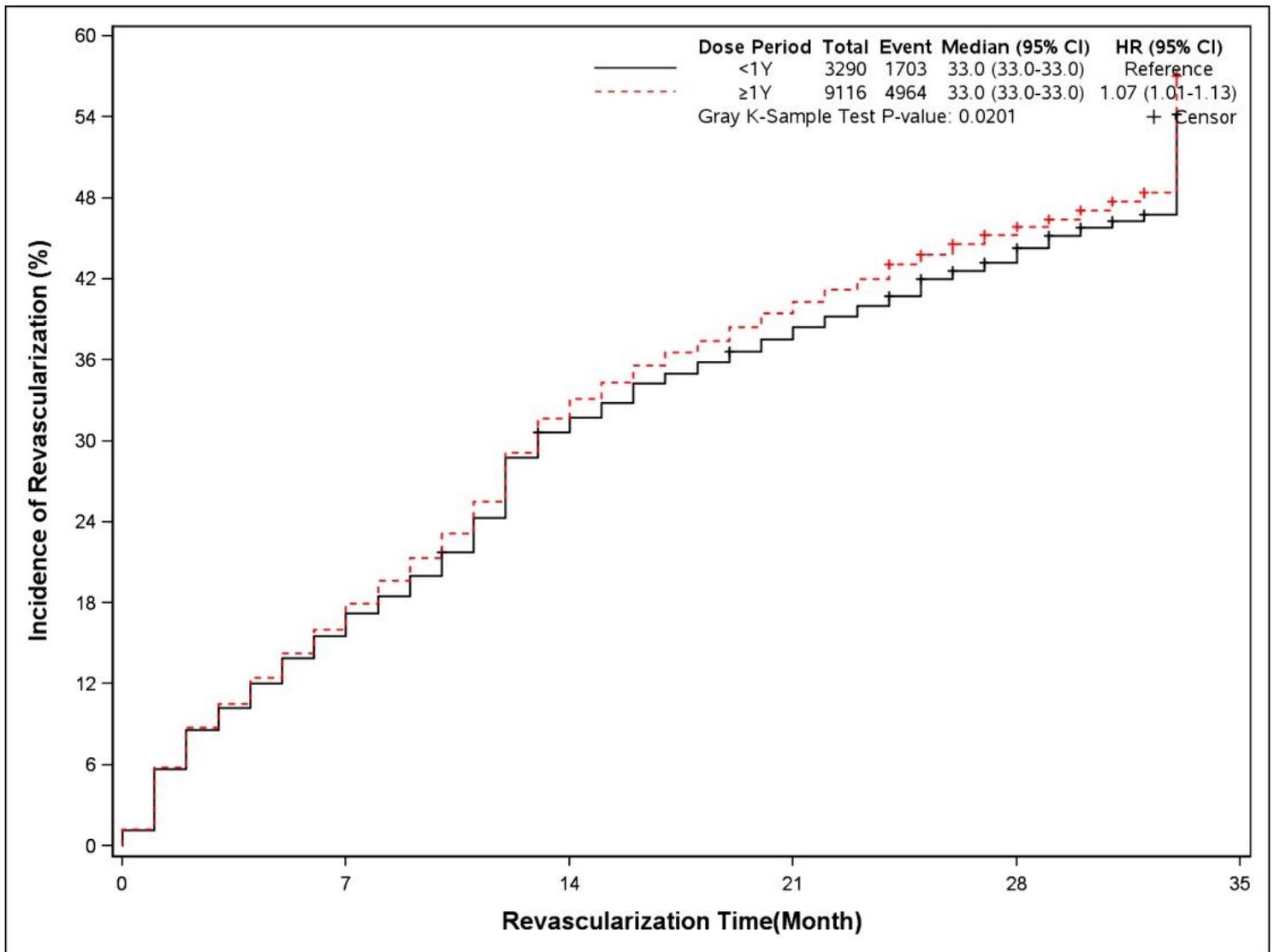


Figure 8

Incidence of revascularization in two groups. Black line: patients took clopidogrel continuously < 1 year; Red line: patients took clopidogrel continuously ≥ 1 year.