

The prognostic impact of the coronary collateral circulation in patients with coronary artery disease: A meta-analysis.

Huizheng Zhu^{*}, Yudan Liang, Tian Zuo, Minzhou Zhang

Division of Chest Pain Center, Guangdong Provincial Hospital, the 2nd Clinical College of Guangzhou University of Chinese Medicine, Guangzhou, PR China

Abstract

Background: Coronary Collateral Circulation (CCC) is an alternative source of blood supply to an ischemic myocardial region. The study of animal models showed that coronary collateral circulation on the myocardial had obvious protective effect of survival but it for humans the influence of the prognosis was still controversial.

Aims: The aim of this meta-analysis is to explore the impact of collateral circulation on prognosis.

Methods and results: We performed an electronic literature search of PubMed, Embase, Chinese Biomedical Database (CBM), China National Knowledge Infrastructure (CNKI) Cochrane Library, assessed the association between coronary collateral circulation and prognosis, searched from the 1989 up to July 2016, there was no language restriction. A total of 16 studies enrolling 16447 participants were included in this analysis. Patients with high collateralization showed a reduced mortality compared with those with low collateralization Risk Ratios (RR) 0.66 [95% Confidence Intervals (CI) 0.54-0.82]; P=0.0001). The RR for 'high collateralization' showed a reduced incidence of re-infarction compared with those with low collateralization was 0.69 (95% CI: 0.52~0.92 p=0.01), in patients with Major Adverse Cardiovascular Events (MACE), it was (RR 0.62 [95% CI 0.46–0.84], p=0.002).

Conclusions: Abundant collateral circulation could reduce coronary heart disease mortality, recurrence of myocardial infarction and adverse cardiovascular events. However, in the revascularization, arrhythmia, cardiac death and so on, showed not reach statistical significance.

Keywords: Coronary collateral circulation, Prognosis.

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Introduction

Coronary Heart Disease (CHD), or called Coronary Artery Disease (CAD), refers to a problem with the coronary arteries near the heart that supplies oxygen as well as nutrients to heart muscles, wherein the regional blood supply is not sufficient for delivering the oxygen required by the heart muscle. CHD is the top most cause of death in several developed nations, and makes up for around seventeen percent of all deaths as well as forty-nine percent of deaths due to cardio-vascular diseases in Australia. CHD is typically because of atheroma, which refers to fatty deposits in blood vessels; with an estimate that more than twenty percent of CHDs in the world are because of no physical activities or exercises [1]. For clinically stable patients with CHDs who are responsive to treatments, the advantages of physical activities are greater than the risks involved. Regular exercises are shown to be as efficient in secondary prevention as several drug interventions with none of the side effects that they induce. Exercises of moderate intensity has several advantages for individuals with CHDs: 1) prevention of narrowing of blood vessels (anti-atherosclerotic), 2) prevention of blood clotting (anti-thrombotic), 3) assists in the delivery of blood to heart (anti-ischaemic), as well as 4) assists in the maintenance of normal heart rhythm (anti-arrhythmic). This

decreases the load on the heart when in rest as well as in the process of doing exercises. This in turn leads to decrease in the symptoms and reduction in the risk of death due to CHDs. Further advantages due to exercises for individuals with CHDs are: 1) enhanced physical functions, 2) psychological well-being, 3) favourable change in blood pressure, 4) high density lipo-protein (HDL) cholesterol, as well as 5) insulin sensitivity [2].

CHD, characterized by myocardial ischemia or necrosis caused by vascular stenosis or occlusion, is one of the leading causes of deaths and hospital admissions worldwide and constitutes the leading cause of disease burden in the world according to the 2010 Global Burden of Disease Study (GBD) [3]. The study of animal models showed that coronary collateral circulation on the Myocardial has obvious protective effect of survival but it for humans the influence of mortality and the prognosis is still controversial [4]. The statement that coronary arteries are pure end ones has been proven false for several years now. CCC links the epi-cardial coronary arteries in individuals with as well as without CAD. The collateral arteries are capable of remodelling as well as expanding in the event of an epi-cardial coronary artery stenosis, giving an alternate source of blood supply to at risk myocardium. In

individuals with ST elevation infarction, a relevant protective role of collateral has been seen with regard to small infarct size, preserving cardiac functions post acute infarction, decrease in after infarct ventricular dilation, as well as post-infarct aneurysm formations. But, the typical effect of CCC on mortality is ambiguous. The goal of the systemic overview as well as meta-analysis is the integration of all present data for assessing the effect of CCC on mortality in individuals with stable or acute CADs [5]. There are some advantages to the present study. First of all, the related clinical researches in recent years are updated. Secondly the study is relatively complete contains the outcome indicators related with prognosis of CHD such as MACE, Arrhythmia and so on.

Literature Review

Significant advantages of collaterals were established by Meier et al. [5] and Pascal Meier et al. [6]. Another meta-analysis by illustrates the relationship between Coronary collaterals and risk for restenosis after percutaneous coronary. Thus the meta-analysis by Akin et al. [7] discusses the effects of collaterals on deaths and re-infarctions. However, the above article lack of analysis to illustrate the influence of coronary collateral circulation on the prognosis of outcome indicators such as MACE, Revascularization, Arrhythmia and so on. Hoebbers et al. [8] performed a metaanalysis and evaluated Left Ventricular Ejection Fraction (LVEF) prior as well as post Chronic Total Occlusions (CTO) Percutaneous Coronary Intervention (PCI) as well as long-term mortality. The current metaanalysis proves that successful re-canalization of a CTO led to considerable enhancement of 4.44 percent absolute LVEF points, decreased negative remodelling as well as enhancement of survival (OR: 0.52).

Akin et al. [9] studied predictors of poor coronary collaterals of 248 patient who had high-grade coronary stenosis or occlusion on their angiogram. For classification of CCC, the authors utilized the Rentrop classification. Individuals with poor CCC had considerably greater Neutrophil-to-Lymphocyte ratio (N/L) in comparison to the individuals with more developed CCC, (4.2 ± 2.8 vs. 3 ± 3.1 , $p=0.001$), while mean platelet volume, red cell distribution width as well as uric acid were not considerably distinct. Logistic regression analysis proved that N/L ratio (odds ratio 1.199, 95% confidence interval 1.045-1.375) as well as serum triglyceride levels [Odds Ratio (OR)=1.006, 95% CI=1.001-1.010] were independent predictors of poorly developed CCC. Zimarino et al. [10] conducted a metaanalysis of research that reported on clinical results of individuals with Multi-Vessel Coronary Artery Diseases (MVCAD) who got treatment with CR as well as IR, with exhaustive (>80%) usage of stents for PCI or arterial conduits in Coronary Artery Bypass Graft (CABG). Relative Risk (RR) as well as 95 percent confidence interval (CI) for all-cause mortality were evaluated as the primary endpoint, while Myocardial Infarction (MI) as well as repeat revascularization were the secondary endpoint.

Materials and Methods

Document retrieval method

We performed an electronic literature search of PubMed, Embase, CBMCNKI Cochrane Library, assessed the association between coronary collateral circulation and prognosis. Searched from the 1989 till July 2016, there was no language restriction, search terms included 'collateral circulation', 'prognosis', in addition, we also hand-searched the bibliographies of all relevant reviews and the selected articles for other potential studies. Our systematic review and meta-analysis was conducted according to the checklist of Meta-analysis of Observational Studies in Epidemiology (MOOSE) [11], and the Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines (PRISMA) [12].

Rules of the documents incorporation

The rules that the literature could be incorporated into this study included: Content of coronary collateral follow study on the prognosis of patients with coronary heart disease clinical research in both Chinese and English articles. Observation method of the literature on coronary collateral circulation is clear, on the basis of basis rentrop grade or collateral circulation collateral blood flow number of CFI. Can offer data directly or via get full text in full Computed data available to prognosis, and the following documents were excluded: Case reports, review the literature, the original data is not complete and the same or similar, in vain to contact the author, Choose one of the most complete data references included.

Filtering and extraction of the data

Two investigators independently extracted data from all of the included studies using a standardized excel file. Disagreements were resolved by consensus. The following information on study characteristics was extracted from each article: first author, Publication year, Group, age, Female, Outcome and multivariable-adjusted or unadjusted risk estimates and their 95% CI.

Quality evaluation of the references

Based on the Newcastle-Ottawa Scale (NOS) [13] evaluation criteria, the quality assessments were carried out for the documents, so as to examine whether there is a bias in the documents and the extent of its impact (Table 1). Selection of research objects: the determination of the cases; the representation of the cases; the selection of control objects; the determination of control objects; each item was 1 points, respectively. Comparability between groups: the comparability of cases and controls needed to be considered in the design and statistical analysis; this entry was 2 points. Exposure factor measurement: the determination of exposure factors; the same method was to determine the exposure factors of patients and control group; No response rate. The determination of exposure factors was 2 points and other exposure factor

measurements were 1 points. The total score was greater than or equal to 5 points then the quality was reliable.

Table 1. Evaluation of the quality of the sixteen included studies by using the Newcastle-Ottawa Scale.

Lead author	Representativeness	Control Group	Ascertainment	Endpoint not present at start	Assessment Of outcome	Follow-up duration	Adequacy follow-up
Hansen	*	*		*	*	*	*
Perez	*	*		*	*	*	
Antioniucci	*	*		*	*	*	*
Monteiro		*		*	*	*	*
Xueling	*	*		*	*	*	
Meier	*	*	*	*	*	*	*
Regieli	*	*		*	*	*	*
Desch	*	*		*	*	*	*
Steg		*		*	*	*	*
Llia	*	*		*	*		*
Tomasz	*	*		*	*	*	*
Laiwenwen	*	*		*	*	*	
Seiler	*	*		*	*	*	*
Angela	*	*		*	*	*	*
Monteiro	*	*		*	*	*	*
Hara	*	*		*	*	*	*

Definitions

Collateral circulation was studied as per the Rentrop grading system from “0” to “3”. Grade 0: undeveloped no filling of collateral vessel; Grade 1: lesser developed filling of sides of arteries, however no main trunk visualised via collateral; Grade 2: more developed partial filling of epi-cardial part of stenosed arteries via collateral; and Grade 3: entire filling of epi-cardial part [14]. On the basis of Rentrop Grading, the examined patients were split into two sets: those with poor collateral (grades 0 & 1), as well as those with good collateral (grades 2 & #). Correlation of duration of hypertension was performed through grading collateral.

Evaluation of coronary collateral circulation in most study is a method of using coronary angiography under visual Rentrop Grading, grading level is considered to be less than 1 of coronary collateral circulation is not rich. Rich, more than 2 grade level for the coronary collateral circulation is abundant. In the study, the grading of coronary collateral circulation is not rich (Rentrop 0). Abundant collateral circulation (Rentrop 1-3). The number of CFI was evaluated, and the CFI <0.25 was considered as the coronary collateral circulation is not rich, CFI=0.25 for coronary collateral circulation is abundant.

Statistical methods

The statistical analysis of the data was carried out by the use of Review Manager 5.3, the differences of statistical significance were compared by the use of p=0.05, and the fixed effect model and random effect model of the two kinds of modeling methods were used to merge the data. The random effects model was used when the statistical heterogeneity (p<0.05), and the random effect model was used in the good homogeneity. Besides, analysis of "funnel plot" in the production of bias of literature results was carried out, and the research literature was analyzed according to the influencing factors.

Results

Search results

Among 7585 potentially relevant citations, 872 articles were considered of interest and fully reviewed. Of these 857 studies were excluded because of use of 1) reviews; 2) editorials; 3) case control studies; 4) mortality and prognosis not reported (Figure 1). Therefore a total of 16 trials [15-28] were finally included.

Table2. Characteristics of the sixteen studies included in the meta-analysis.

Study	Year	Follow (months)	PCI	Group	Mean age (y)	Female (%)	endpoints
Hansen	1989	120	No	High CCC	49.2	10	mortality
				Low CCC	47.9	7	
Perez	1999	In-hospital	No	High CCC	64.0	18	mortality
				Low CCC	64.0	18	
Antioniucci	2002	6	Yes	High CCC	63	18	mortality re-infarction revascularization MACE
				Low CCC	64	18	
Monteiro	2003	15.7	Yes	High CCC	63.3	11	mortality re-infarction MACE heartfailure recurrent angina pectoris
				Low CCC	65.3	10	
Xueling	2003	In-hospital	Yes	High CCC	62	na	mortality
				Low CCC	58	na	
Meier	2007	120	Yes	High CCC	61.0	21	mortality re-infarction
				Low CCC	62.0	24	
Regieli	2009	24	Yes	High CCC	57.0	na	mortality re-infarction MACE cardiac death
				Low CCC	56.0	na	
Desch	2009	6	Yes	High CCC	64.0	26	mortality MACE
				Low CCC	66.0	24	
Steg	2010	60	50% PCI	High CCC	58.4	23	mortality re-infarction heart failure
				Low CCC	60.4	20	
Llia	2011	84	Yes	High CCC	54	na	mortality
				Low CCC	59	na	
Tomasz	2012	24	Yes	High CCC	59	24	mortality revascularization
				Low CCC	57	29	
Laiwenwen	2013	In-hospital	Yes	High CCC	64.76	19.8	mortality MACE arrhythmia heart failure recurrent angina pectoris
				Low CCC	62.13	14.6	
Seiler	2014	84	Yes	High CCC	61	na	mortality re-infarction revascularization MACE cardiac death stroke
				Low CCC	62	na	
Angela	2014	12	Yes	High CCC	62	24	mortality re-infarction revascularization arrhythmia heart failure recurrent angina pectoris
				Low CCC	60	33	

					stroke		
Meier	2014	12	Yes	High CCC	61	24	mortality
				Low CCC	60	38	
Hara	2016	60	Yes	High CCC	64.5	22.1	mortality
				Low CCC	65	22.1	

CFI: Collateral Flow Index; CCCL: Coronary Collateralization; na: not available; PCI: Percutaneous Coronary Intervention.

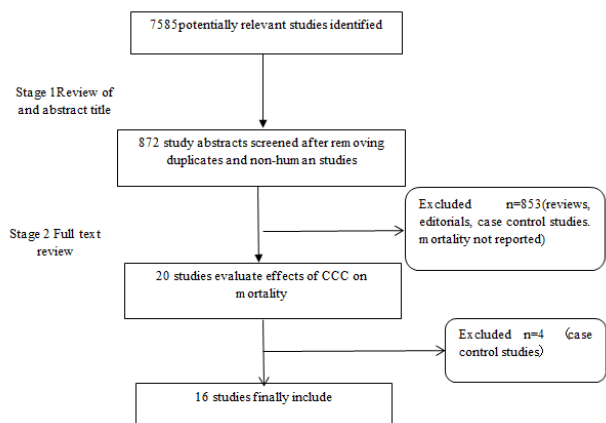


Figure 1. Flow chart of literature.

Document statistics of the rule

16 documents were chosen as the research objects, there were 16447 participants. (Table 2). The included studies were published from 1989 to 2016.

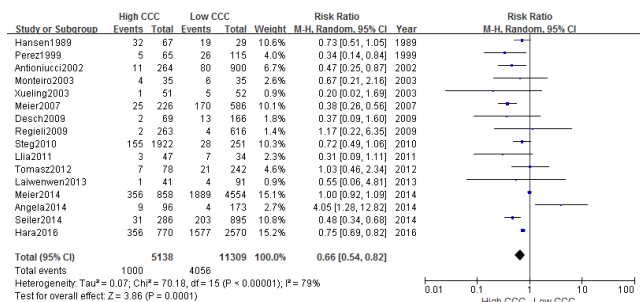


Figure 2. Forest plot for the impact of CCC on mortality. CCC: Coronary Collateral Circulation; CI: Confidence Interval. Horizontal bars indicate 95% confidence intervals.

Mortality

All causes mortality was observed in 1000 out of 5138 patients (19.4%) patients in High CCC versus 4056 out of 11309 patients (45.4%) in Low CCC (RR [95% CI]=0.66 [0.54-0.82], p=0.0001; z=3.86), to heterogeneous data into 16 documents, according to the inspection. There is heterogeneity among studies (chi-square=70.18, P<0.00001, I²=79%), the random

utility model meta analysis is adopted to produce. Forest plot show difference is statistically significant (Z=3.86 p=0.0001). A value of RR is 0.66 (95% CI: 0.54~0.82), illustrates that coronary collateral group of patients, mortality is lower than no coronary collateral circulation (Figure 2).

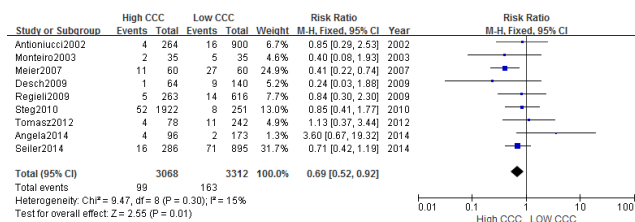


Figure 3. Forest plot for the impact of CCC on Re-infarction.

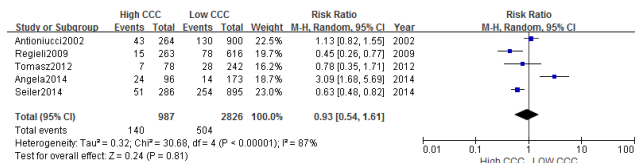


Figure 4. Forest plot for the impact of CCC on Revascularization.

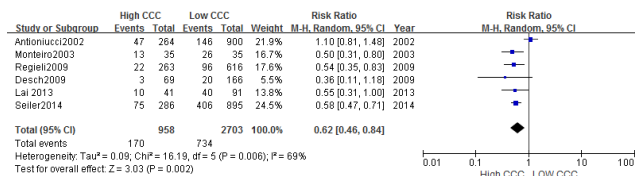


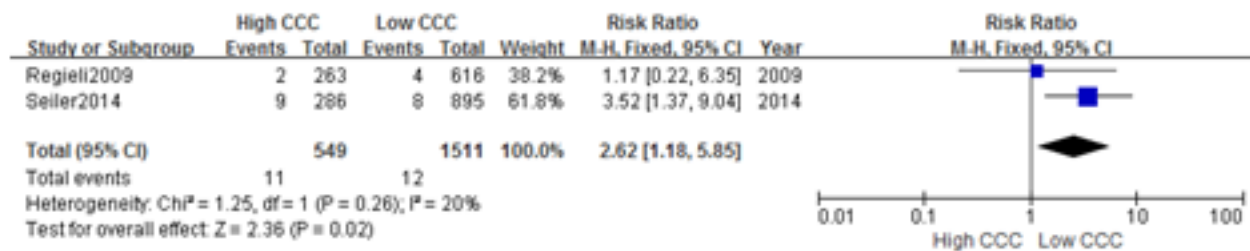
Figure 5. Forest plot for the impact of CCC on MACE CCC.

Re-infarction

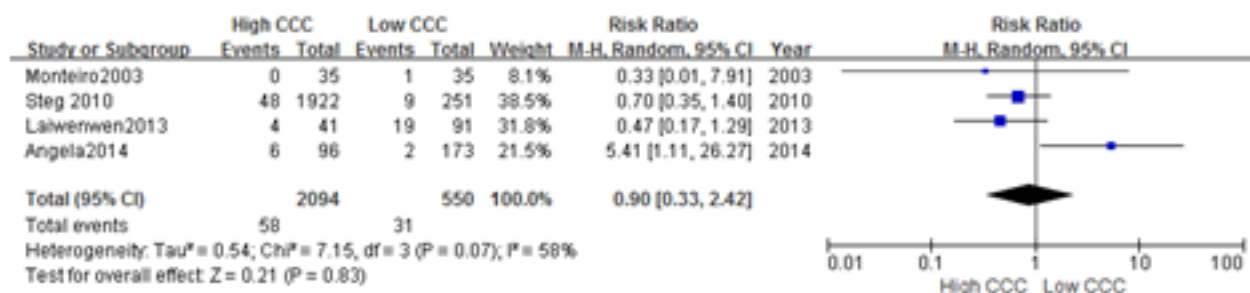
Data regarding myocardial infarction were available in 262 patients. Re-infarction was observed in 99 out of 3068 patients in High CCC versus 163 out of 3312 patients in Low CCC (RR [95% CI]=0.69 [0.52-0.92], p=0.01; z=2.55), to heterogeneous data into 9 documents, according to the inspection. There is heterogeneity among studies (chi-square=9.47, P=0.30, I²=15%), the fixed utility model meta analysis is adopted to produce. Forest plot showed difference was statistically significant (Z=2.55, p=0.01). A value of RR 0.69 (95% CI: 0.52~0.92), showed that the incidence of re-infarction of High CCC less than Low CCC (Figure 3).



A



B



C



D



E

Figure 6. Forest plot for the impact of CCC on Arrhythmia(A), Cardiac death(B), Heart failure(C), Recurrent angina pectoris (D), Stroke(E).

Revascularization

Data regarding revascularization were available in 644 patients. Revascularization was observed in 140 out of 987 patients in High CCC versus 504 out of 2826 patients in Low CCC (RR [95% CI]=0.93 [0.54-1.61], p=0.81; z=0.24), to

heterogeneous data into 5 documents, according to the inspection. There is heterogeneity among studies (chi-square=30.68, P<0.00001, I²=87%), the random utility model meta analysis is adopted to produce. Forest plot showed difference was no statistically significant (Z=0.24, p=0.81)

RR .A value of 0.93 (95% CI: 0.54~1.61), showed that the incidence of revascularization of High CCC and Low CCC had no statistical significance (Figure 4).

Mace

Data regarding MACE were available in 904 patients. MACE was observed in 170 out of 958 patients in High CCC versus 734 out of 2703 patients in Low CCC (RR [95% CI]=0.62 [0.46-0.84], p=0.002; z=3.03), to heterogeneous data into 6 documents, according to the inspection. There is heterogeneity among studies (chi-square=16.19, P=0.006, I2=69%), the random utility model meta analysis is adopted to produce. Forest plot showed difference was statistically significant (Z=3.03 p=0.002) RR. A value of 0.62 (95% CI: 0.46~0.84), showed that the incidence of MACE of High CCC less than Low CCC (Figure 5).

Arrhythmia, Cardiac death, Heart failure, Recurrent angina pectoris, Stroke

In Arrhythmia(A), Cardiac death(B), Heart failure(C), Recurrent angina pectoris (D), Stroke(E) the incidence in High CCC group and Low CCC group have no statistical and clinical significance (Figure 6).

Publication bias

For the above analyses comparing High CCC and Low CCC with Prognosis, In this paper, to analyze the bias of the publication of the 16 articles, and the funnel diagram was drawn (Figure 7), there was no statistical significance in the likelihood of occurrence of bias, therefore, there was no publication bias in the published articles.

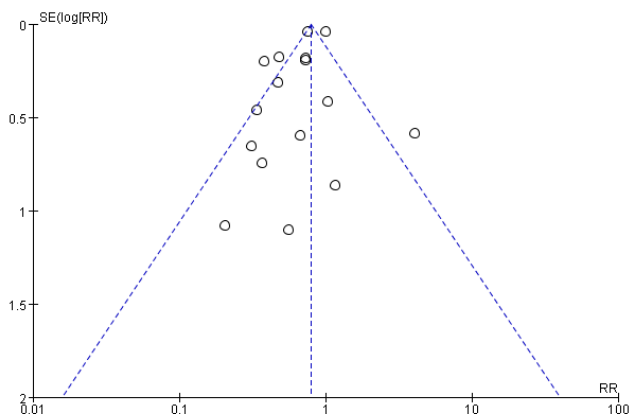


Figure 7. Funnel plot of the Mortality.

Sensitive analysis

Sensitivity analyses by excluding any single study at each turn indicated that there were no changes in the direction of pooling risk estimate of all-cause mortality (pooled RR ranges from 0.61 to 0.71) (Table 3).

Table 3. Sensitive analyses for the impact of CCC on Mortality.

Study	Model	RR (95%CI)	P
Overall	Random	0.66	0.0001
Omitting Hansen 1989	Random	0.65	0.0002
OmittingPerez 1999	Random	0.68	0.0004
Omitting Antonucci 2002	Random	0.68	0.0004
Omitting Monteiro 2003	Random	0.66	0.0002
Omittingxueling2003	Random	0.67	0.0002
Omitting Meier 2007	Random	0.71	0.0009
Omitting Regieli 2009	Random	0.66	0.0001
Omitting Desch 2009	Random	0.67	0.0002
Omitting Steg 2010	Random	0.65	0.0002
Omitting Liia 2011	Random	0.67	0.0002
Omitting Tomasz2012	Random	0.65	0.0001
Omittinglai2013	Random	0.66	0.0001
Omitting Seiler2014	Random	0.69	0.0007
Omitting Angela2014	Random	0.63	0.0001
Omittingmier2014	Random	0.61	0.0001
Omitting Hara2016	Random	0.64	0.005

Discussion

The result showed that compared with the poor collateral, well-collateralized group could obviously reduce mortality and incidence of re-infarction and MACE, however in the revascularization, arrhythmia, cardiac death and so on, showed not reach statistical significance. According to the present research, The CCC can improve the survival rate of patients with coronary heart disease and the accuracy of the mechanism is still not clear, may be mainly due to the following aspects. First, the collateral circulation is an important compensatory mechanism of myocardial ischemia. The narrow degree of coronary artery narrow is an important factor in the formation of collateral circulation. The incidence of collateral circulation was 97%~68%. 5%~41% was significantly increased, while the stenosis was less than 90% of the collateral circulation rarely open. Therefore, when a certain part of the myocardial ischemia, normal the potential of microvascular open change between myocardium and ischemic myocardium Coarse, forming a functional collateral circulation, to a certain extent improving myocardial ischemia in this area. Second, the collateral circulation can be reduced Infarct size and cardiac function. Dewood reported in acute Q wave in myocardial infarction, collateral circulation can change the infarct type, reduced infarct size and even the occurrence of myocardial infarction. The establishment of collateral circulation after myocardial infarction can prevent left ventricular remodelling, to reduce the incidence of left ventricular aneurysm. Third, the collateral circulation can be prevent and reduce the occurrence of adverse cardiovascular events, and abundant collateral circulation can reduce the incidence of ventricular arrhythmia,

thereby reducing the incidence of ventricular arrhythmia. Occurrence of adverse cardiovascular events such as fibrillation and sudden death, coronary collaterals are an important factor that can potentially alter morbidity and mortality in ischemic heart disease.

The present meta-analysis lack of the prognosis of outcome indicators such as MACE, Arrhythmia, Cardiac death, Stroke and so on. There are some advantages to the present study. First of all, the related clinical researches in recent years are updated. Secondly the study is relatively complete contains the outcome indicators related with prognosis of CHD such as MACE, Arrhythmia and so on. Nevertheless, there are some several limitations in the present meta-analysis. The data included in this analysis are both observational studies. The studies were associated with extensive coronary collateral circulation and prognosis. The causal relationship is hypothesized to exist, and only the intervention of the study is set up. The number of patients was small.

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***Correspondence to**

Huizheng Zhu

Division of Chest Pain Center

Guangdong Provincial Hospital

The 2nd Clinical College of Guangzhou University of Chinese Medicine

PR China