Prognostic Impact of Coronary Collaterals in Acute Coronary Syndrome (PICC-ACS): A Meta-analysis of Observational Studies

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Abstract

Introduction: The coronary collateral circulation (CCC) is an alternative source of blood supply in coronary artery disease (CAD). The prognostic value of the presence of CCC at the time of acute coronary syndrome (ACS) is undefined with regards to hard outcomes, particularly reduction in mortality. The study's aim is to determine if the presence of CCC demonstrated by coronary angiography during an ACS is associated with a reduction in mortality.

Methods: We conducted a systematic search of studies using MEDLINE, EMBASE, ScienceDirect, Scopus, and Cochrane Central Register of Controlled Trials databases in all languages and examined reference lists of studies. The inclusion criteria were 1) observational; 2) population included adults >19 years old with an acute coronary syndrome; 3) reported data on mortality in association with the presence or absence of CCC on angiography; and 4) should have controlled for confounders by using logistic regression analysis. Study quality was assessed using the Newcastle-Ottawa Quality Assessment Scale for observational studies. The outcome of interest was reduction in all-cause mortality, assessed using Mantel-Haenzel analysis of random effects to compute for risk ratios.

Results: Pooled analysis from 11 identified trials with 8,370 subjects showed that among patients with ACS who underwent coronary angiography, the presence of CCC showed a trend towards benefit in terms of mortality, but was not statistically different from those without CCC (RR 0.65, (95% CI 0.38 to 1.12), p<0.0001, I^2=74%). In those ACS patients with CCC treated with PCI, a significant reduction in mortality was found (RR 0.43, (95% CI 0.29 to 0.64), *p*< 0.0001, I^2=0%).

Conclusion: The presence of CCC during ACS showed a trend towards mortality reduction. Further, among patients treated with PCI, those with CCC had an incrementally significant reduction in mortality compared to those without CCC.

Keywords: coronary collaterals, acute coronary syndrome

Introduction

The coronary collateral circulation (CCC) is an important adaptation of the myocardium to prevent damage from ischemic injury. Collaterals are usually part of the microcirculation, existing as arterial-arterial anastomotic connections. As an adaptation to injury, they have a propensity to remodel into components of the macrocirculation with a decreased resistance to blood flow.[1] These collateral arteries provide an alternative source of blood supply to the ischemic or threatened myocardium. Using the Rentrop grading system for CCC, grades of collateral filling from the contralateral vessel were: 0=none (ie. No visible filling of any collateral channels); 1=filling of side branches of the artery to be dilated via collateral channels without visualization of the epicardial segment; 2=partial filling of the epicardial segment via collateral channels; 3=complete filling of the epicardial segment of the artery being dilated via collateral channels.[2] It has been demonstrated in past studies that in patients with myocardial infarction, CCCs have a relevant protective role regarding smaller infarct size, preservation of cardiac function, reduction in post-infarct ventricular dilation, and reduction of post-infarct aneurysm formation.[3]

A meta-analysis on the impact of CCCs on mortality among patients with coronary artery disease (CAD) was published in 2011. A total of 12 studies with 6,529 patients were included in the analysis. Overall, the presence of high collateralization showed a reduced mortality compared to those with low collateralization. These effects were driven by significant reduction in mortality for those patients with stable CAD (RR 0.59 (CI 0.39, 0.89), *p*=0.012); however, the reduction among patients with acute myocardial infarction (AMI) was not significant (RR 0.63 (0.29, 1.39), *p*=0.257).[4]

Intuitively, CCC should have a positive impact on the outcomes of patients with ACS. However, studies

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have conflicting results. As described previously, the ACS subgroup of the most recent meta-analysis did not show a significant reduction in mortality.[4] Among patients with ACS, surrogate end-points such as infarct size, systolic function, ventricular dilatation and post-infarct aneurysm formation have positive results in relation to the presence of CCC.[3] Analysis of studies specifically intended to determine the effect of CCC on hard outcomes such as mortality among patients with ACS is imperative.

In this study, we wanted to specifically look at the impact of CCC in ACS patients. In the meta-analysis described above, Meier failed to reach a statistically significant result for AMI, and attributed this to the limited statistical power of the subgroup (small sample sizes).[4] We wanted to address this limitation by pre-specifying this important subgroup of patients, obtain more relevant studies, and increase the number of ACS patients analyzed. The researchers aim to determine if the presence of CCC demonstrated on coronary angiography during an ACS is associated with a reduction in mortality.

Methods

We conducted a meta-analysis following the proposed reporting guidelines of the Meta-analysis for Observational Studies in Epidemiology (MOOSE) group.

Literature Search

We conducted a systematic search of studies using MEDLINE, EMBASE, Science Direct, Scopus, Google Scholar, and Cochrane Central Register of Controlled Trials databases with no language restrictions. The search terms used were coronary collateral circulation, acute coronary syndrome, and mortality (in both free text and MESH strategies when using MEDLINE). We also searched for local studies on the topic, both published and unpublished. We reviewed the reference lists of original and review articles, and related links of the relevant publications. The titles and abstracts of all the studies were individually screened and the full texts of relevant articles were obtained, when available. Authors of studies were contacted when there was no available full text.

Study Selection

Studies were included if they are 1) observational; 2) population included adults >19 years old with an acute coronary syndrome; 3) reported data on mortality in association with the presence or absence of CCC on angiography, and 4) should have controlled for confounders by using logistic regression analysis. Four reviewing authors independently evaluated the eligibility of each study included in this meta-analysis. The validity and quality of each study was assessed using the Newcastle-Ottawa Quality Assessment Scale for Observational Studies (Appendix 1). Disagreements were resolved by discussion and a consensus among the reviewers.

Data Collection and Analysis

Relevant information such as patient and study characteristics, data on the presence or absence of CCC, and mortality outcomes were then extracted independently by the three authors using a data collection table. We assessed the prognostic value of coronary collaterals in ACS using Mantel-Haenzel statistical analysis of random effects to compute for risk ratios, with 95% confidence intervals, and generate forest plots. Heterogeneity was assessed through the I^2 test. Subgroup analysis would be carried out by excluding those studies that involved only thrombolysis as a management. Likewise, data from the remaining studies will be extracted to include only those patients who underwent PCI. Studies were treated as statistical outliers if the k minus 1 estimate produced a 95% CI that did not overlap with the 95% CI of the aggregated estimate. $P < 0.05$ was considered statistically significant. Publication bias was examined using funnel plot analysis.

Analyses were carried out using Review Manager (RevMan) 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen).

Results

Search for Studies and Strategy

Our MEDLINE search yielded a total of 111 potential articles. Search from other databases, from reference lists, and local studies yielded additional 33 studies. We evaluated a total of 144 titles and abstracts. Out of these, 133 were rejected for relevance. The full articles of the remaining 11 articles[5-15] were obtained and reviewed. All met the specified inclusion criteria. A summary of the search strategy is shown in Figure 1.

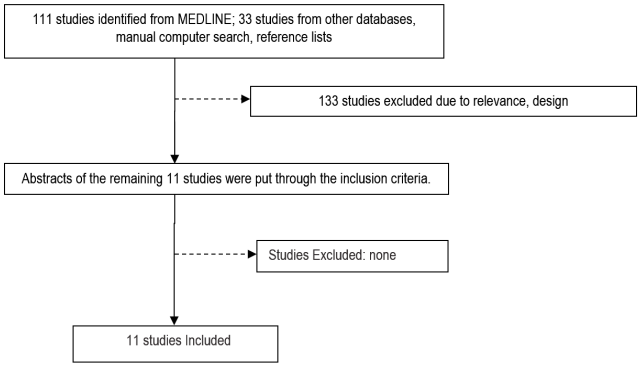

Figure 1. Summary of search strategy

Study Characteristics and Quality

Data were reviewed from the 11 studies[5-15] included. Table I summarizes the pertinent data of the studies included. Studies included were mostly on ST-elevation myocardial infarction (STEMI) patients who were managed accordingly via thrombolysis or percutaneous coronary intervention (PCI). The presence or absence of extensive CCC were classified using the Rentrop classification. Most were observational prospective studies. All of the included studies rated highest quality in the Newcastle-Ottawa Quality Assessment Scale for Observational Studies, and had high agreement among the reviewers (Appendix A).

Mortality and the Presence or Absence of Coronary Collateral Circulation

Pooled analysis from 11 identified trials showed that among patients with ACS who underwent coronary angiography, the presence of CCC showed a trend towards benefit in terms of mortality, but was not statistically different from those without CCC (RR 0.65, (95% CI 0.38 to 1.12), $p<0.0001$) (Figure 2). Funnel plot analysis showed no evidence of publication bias (Appendix B). There was high heterogeneity with this analysis ($I^2=74\%$).

Sensitivity analysis did not reveal a statistical outlier (Appendix C). Subgroup analysis was done by extracting the data for only those patients who had undergone PCI (i.e. those patients who were managed medically or thrombolysis were excluded). This analysis showed that those patients with an ACS and CCC treated with PCI had a significant reduction in mortality as compared to those with an ACS without CCC treated with PCI (RR 0.43, (95% CI 0.29 to 0.64), $p<0.0001$) (Figure 3). Data was homogenous ($I^2=0\%$). Funnel plot also showed no evidence of publication bias (Appendix D).

Discussion

This meta-analysis of 11 observational studies, consisting of 8,370 patients, demonstrates that among all patients with acute coronary syndromes, the presence of CCC on angiography does not significantly predict reduction in overall mortality; but with a trend towards benefit. These results were similar to the meta-analysis[4] cited earlier: extensive CCCs significantly reduces mortality in CAD, but this reduction was driven primarily by the effects of CCCs on stable CAD (rather than on ACS).

In the advent of recent and larger studies done during the PCI era, when patients with ACS were treated with early invasive strategy or primary PCI, the presence of extensive CCC was associated with lower overall mortality in the secondary analysis done in our review. With the presence of CCC among PCI-treated ACS patients, there was significant relative reduction of 57%. The subgroup analysis clearly indicate reduced mortality of ACS with extensive CCC.

Potential Mechanisms of Survival Benefit

Coronary collateral circulation (CCC) provides an alternative blood supply to the myocardium during ischemia or infarction.[1] They are anastomotic channels that develop in the heart as an adaptation to ischemia.[1] Survival benefits in ACS may have stemmed from surrogate outcomes, demonstrated by earlier studies. Notably, majority of these studies have shown that extensive CCC preserves LV function,[12-14, 5] reduces infarct size,[16] and prevents formation of left ventricular aneurysms.[17] Meier (2011)[4] cites his own study showing that coronary collaterals reduce QT interval prolongation, a risk factor for fatal arrhythmias, during acute vessel occlusion.

Potential Implications in Management

Our meta-analysis demonstrated that among patients with ACS and CCC on coronary angiography, there is a trend towards reduction in mortality. We have also demonstrated that among patients with ACS and CCC on angiography, managed with PCI, a significant reduction in mortality occurred.

These findings may affect current practice in management of ACS, especially with regards to timelines of revascularization among patients with ST elevation myocardial infarction (STEMI). In the presence of CCC, STEMI patients may not necessarily rapidly develop infarcted myocardium as previously predicted. The presence of CCC may prolong the viability of injured myocardium at risk when its blood supply is occluded. Given the mortality benefit in our review, the presence of extensive CCC may rationalize performance of delayed revascularization, even in patients with STEMI past the "golden period" of viability.

The idea on inducing coronary collateral growth as a possible therapeutic strategy has also been explored. The induction of collateral growth has been demonstrated in several small experimental and clinical studies, using granulocyte-macrophage colony-stimulating factor and external counterpulsation,[18-20] but this remains largely hypothetical and is unknown whether such strategy would translate to improved survival.[4]

Another important implication of our study is on determining the patient who most likely would have good collateralization sans a coronary angiogram. Pre-angiographic clinical factors have been explored in an effort to predict which patients might have better prognoses because of the presence of good coronary collateral formation, both in stable CAD and ACS. Akgullu et al. (2014) showed that ejection fraction < 55% and mean

Table I. Study characteristics

No.	Author	Patients	Rentrop classification of CCC	Outcome	Type of study	Intervention
1	Williams 1976 [5]	Acute MI	0 versus 1-3	In-hospital death	Observational Prospective	Thrombolysis
2	Habib 1990 [6]	STEMI	0 versus 1-3	Death at 6 months	Review of Database (TIMI)	Thrombolysis
3	Castellano 1999 [7]	Anterior STEMI	0 versus 1-3	In-hospital death	Observational	All PCI
4	Nicolau 1999 [8]	STEMI	0-1 versus 2-3	Death at 3 years	Observational Prospective	Thrombolysis
5	Antioniucci 2002 [9]	STEMI	0-1 versus 2-3	Death at 6 months	Observational Prospective	All PCI
6	Monteiro 2003 [10]	STEMI	0 versus 1-3	Death at 15 months	Observational Prospective	Thrombolysis and PCI
7	Sorajja 2007 [11]	STEMI	0-1 versus 2-3	Death at 6 months	Review of Database (Emerald)	All PCI
8	Desch 2010 [12]	STEMI	0-1 versus 2-3	Death at 6 months	Observational Prospective	All PCI
9	Wang 2011 [13]	Anterior STEMI	0 versus 1-3	Death at 1 year	Observational Prospective	All PCI
10	Meier 2014 [14]	Moderate to high risk ACS	0 versus 1-3	Death at 1 year	Review of Database (ACUITY Trial)	Thrombolysis and PCI
11	Yaylak 2015 [15]	Inferior STEMI	0 versus 1-3	In-hospital death	Observational Prospective	All PCI

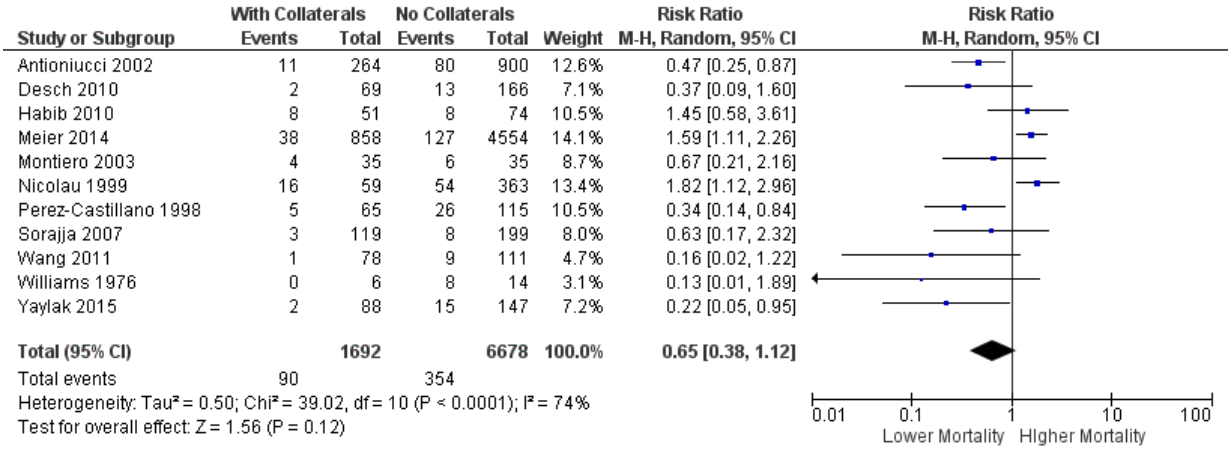

Figure 2. Forest Plot of All Trials (PCI and Thrombolysis)

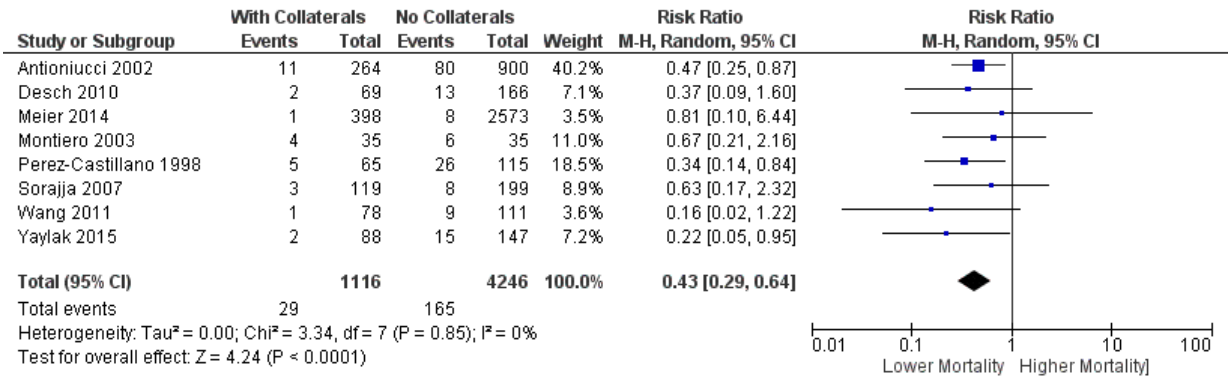

Figure 3. Forest Plot of Trials that Included Only PCI.
Data from Meier and Monteiro were re-analyzed.
Data of only those who had undergone PCI were included in this sub-analysis.

platelet volume > nine femtoliter are predictive of coronary collateral development in patients with stable CAD.[21] In a cohort of acute MI patients, a history of angina pectoris was a significant predictor of collateral development.[22] In non-ST elevation MI patients (NSTEMI), a high neutrophil-lymphocyte ratio (NLR) may predict good collateral development.[23] It would be interesting to pursue this type of study in our local setting.

Limitations

By virtue of the clinical question to be answered, most studies included are observational studies. The inherent limitations of observational studies cannot be eliminated, and this is evident in the observed heterogeneity in the primary analysis.

This is to be expected given the observational nature of the included studies. Factors likely contributing to this heterogeneity include different study design (retrospective versus prospective design), different clinical settings and/or patient characteristics (e.g. timing of STEMI, type of ACS included), varying primary outcomes (e.g., time to follow-up), different study sizes, and different methods of determining the presence or absence of extensive CCC and the method of dichotomization i.e. some studies used an all-or-none classification (Rentrop 0 vs. 1-3)[5-7, 10, 13-15,] while some used a low-or-high approach (Rentrop 0-1 vs 2-3).[8-9, 11-12.] The precision of some of the included studies, especially the larger ones, may have conferred an artificially high I^2. We were able to mitigate this heterogeneity by pre-specifying a subgroup and sensitivity analysis. Removing outliers would be the first step in correcting for heterogeneity for this reason, as this removed the possible effect of an artificially high I^2. As shown in our sensitivity analysis, however, not one of the studies included was a statistical outlier. In our study, the heterogeneity appears to be attributable primarily to the treatment strategy, as shown in the subsequent subgroup analysis. In the subgroup analysis done by excluding the studies that used thrombolysis as therapy and limiting the analysis only to those that utilized PCI, we achieved a homogenous data set.

Conclusion

The presence of CCC during ACS showed a trend towards mortality reduction. After exclusion of those treated with thrombolysis, patients with extensive CCC treated with PCI was associated with a significant reduction in mortality compared to those without extensive CCC. The presence of extensive CCC may prolong the viability of injured myocardium at risk when its blood supply is totally occluded. Findings in this meta-analysis may guide physicians in management, especially in patients with ACS who are candidates for revascularization via PCI.

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Appendix A.

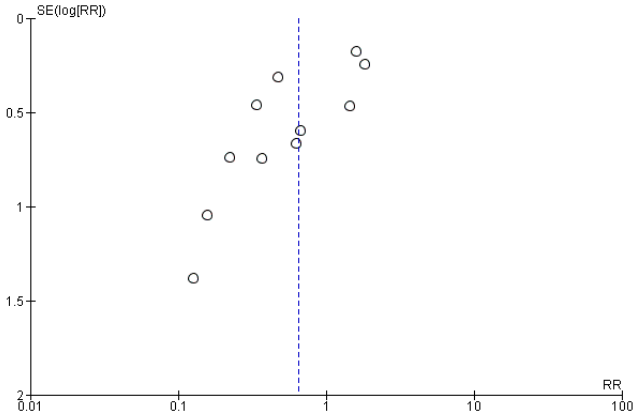
Newcastle-Ottawa Quality Assessment Scale for Cohort Studies†.

SOURCE	SELECTION				COMPARABILITY	OUTCOMES ASSESSMENT		
	Representativeness of the Exposed Cohort	Selection of the Nonexposed Cohort	Ascertainment of Exposure	Demonstration that outcome of interest was not present at start of study		Assessment of Outcome	Follow-up Period Long Enough for Outcome to Occur	Adequacy of Follow-up Period Among Cohorts
Williams 1976	*	*	*	*	**	*	*	*
Habib 1990	*	*	*	*	**	*	*	*
Castellano1999	*	*	*	*	**	*	*	*
Nicolau 1999	*	*	*	*	**	*	*	*
Antioniucci 2002	*	*	*	*	**	*	*	*
Monteiro 2003	*	*	*	*	**	*	*	*
Sorajja 2007	*	*	*	*	**	*	*	*
Desch 2010	*	*	*	*	**	*	*	*
Wang 2011	*	*	*	*	**	*	*	*
Meier 2014	*	*	*	*	**	*	*	*
Yaylak2015	*	*	*	*	**	*	*	*

†- a study is graded highest quality if it has a total of 9 stars

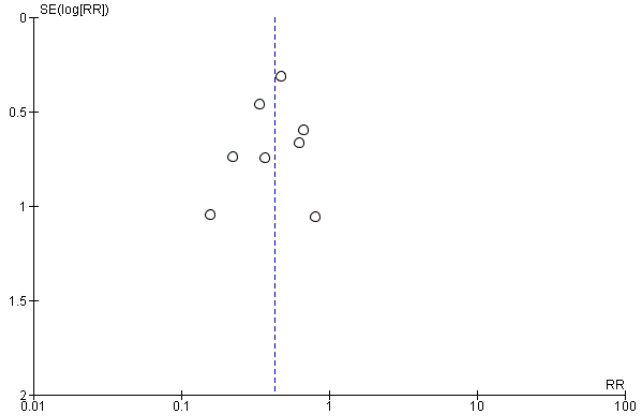
APPENDIX B

Funnel plot of the primary analysis showing no evidence of publication bias. Lower standard errors indicate better precision and larger study size.



APPENDIX D

Funnel plot of the secondary analysis showing no evidence of publication bias. Lower standard errors indicate better precision and larger study size.



APPENDIX C

Sensitivity analysis with risk ratios for mortality. Each line represents a re-analysis of the data with exclusion of one study (inclusion of 10 studies only) at a time to assess the influence of this particular study on the overall result. A study was treated as statistical outlier if the k minus 1 estimate (where k is the number of studies) produced a 95% CI that did not overlap with the 95% CI of the aggregated estimate. None of the studies met the qualifier for a statistical outlier.

Study	RR	95% CI
Removing Antoniucci 2002	0.69	(0.39, 1.21)
Removing Desch 2010	0.68	(0.39, 1.19)
Removing Habib 2010	0.58	(0.32, 1.06)
Removing Meier 2014	0.56	(0.30, 1.02)
Removing Monteiro 2003	0.64	(0.36, 1.15)
Removing Nicolau 1999	0.55	(0.31, 1.00)
Removing Perez-Castellano 1998	0.72	(0.42, 1.24)
Removing Sorajja 2007	0.65	(0.37, 1.15)
Removing Wang 2011	0.71	(0.41, 1.21)
Removing Williams 1976	0.69	(0.41, 1.18)
Removing Yaylak 2015	0.72	(0.42, 1.23)
Random Effects Model	0.65	(0.38, 1.12)