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CLINICAL RESEARCH
Coronary heart disease

The impact of the coronary collateral circulation on mortality: a meta-analysis

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Aims The coronary collateral circulation as an alternative source of blood supply has shown benefits regarding several clinical endpoints in patients with myocardial infarction (MI) such as infarct size and left ventricular remodelling. However, its impact on hard endpoints such as mortality and its impact in patients with stable coronary artery disease (CAD) is more controversial. The purpose of this systematic review and meta-analysis was to explore the impact of collateral circulation on all-cause mortality.

Methods and results We searched MEDLINE, EMBASE, ISI Web of Science (2001 to 25 April 2011), and conference proceedings for studies evaluating the effect of coronary collaterals on mortality. Random-effect models were used to calculate summary risk ratios (RR). A total of 12 studies enrolling 6529 participants were included in this analysis. Patients with high collateralization showed a reduced mortality compared with those with low collateralization [RR 0.64 (95% confidence interval 0.45–0.91); $P = 0.012$]. The RR for 'high collateralization' in patients with stable CAD was 0.59 [0.39–0.89], $P = 0.012$, in patients with subacute MI it was 0.53 [0.15–1.92]; $P = 0.335$, and for patients with acute MI it was 0.63 [0.29–1.39]; $P = 0.257$.

Conclusions In patients with CAD, the coronary collateralization has a relevant protective effect. Patients with a high collateralization have a 36% reduced mortality risk compared with patients with low collateralization.

Keywords Coronary collateral circulation • Meta-analysis • Mortality

Background

The concept that coronary arteries are pure end arteries has been disproved years ago.[1] The coronary collateral circulation (CCC) connects epicardial coronary arteries and is present in patients with and without coronary artery disease (CAD).[2,3] These collateral arteries have the potential to remodel and expand in case of an epicardial coronary artery stenosis, providing an alternative source of blood supply to jeopardized myocardium. In patients with ST elevation infarctions, a relevant protective role of collaterals has been observed regarding smaller infarct size, preservation of cardiac function after acute infarctions, reduction in post-infarct ventricular dilatation, and regarding post-infarct aneurysm formation.[3] However, the general impact of the CCC on mortality is less clear.[3]

The purpose of this systematic review and meta-analysis was to integrate all available data in order to assess the impact of the CCC on mortality in patients with stable or acute CAD.

Methods

The study was performed according to the MOOSE (meta-analysis of observational studies in epidemiology) guidelines. Planning and study design was done by three authors (C.S., P.M., and B.P.), including creation of an electronic database with variables of interest (Microsoft EXCEL). Endpoints, variables of interest, and search strategy (databases, sources for unpublished data) were defined in a strategy outline (see Supplementary material online, File 1). No language restriction was applied.

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Search strategy

We searched EMBASE, PubMed, BIOS, and ISI Web of Science from 1980 through 25 April 2011. In addition, abstract lists and conference proceedings from the 2006 to 2010 scientific meetings of the American College of Cardiology, the European Society of Cardiology, the symposium on Transcatheter Cardiovascular Therapeutics of the American Heart Association, and the World Congress of Cardiology were searched. We also considered published review articles, editorials, and internet-based sources of information (www.tctmd.com, www.theheart.org, www.europcronline.com, www.cardiosource.com, and www.crtonline.com) to assess potential information on studies of interest. Reference lists of selected articles were reviewed for other potentially relevant citations. Authors of selected studies were contacted to obtain further information if needed. All prospective studies reporting on an association between mortality and CCC were included in this analysis. Retrospective case–control studies were not eligible. The detailed search syntax for the database Medline is shown in Supplementary material online, *Table S1*. The syntax for other databases was similar but was adapted where necessary. In brief, search terms included 'collateral circulation', 'survival', 'prognosis', and 'mortality'.

Study selection

In a two-step selection process, the titles and abstracts of all citations were reviewed to identify potentially relevant studies. Selection of abstracts was by agreement of two investigators (C.S. and P.M.). In a second step, the corresponding publications were reviewed in full text to assess whether studies met the following inclusion criteria: association of mortality and the degree of coronary collateralization (*Figure 1*). Selection of manuscripts was again by agreement of two investigators (C.S. and P.M.).

Data extraction and quality assessment

Relevant information from the articles, including baseline clinical characteristics of the study population and outcome measures, were extracted using the prepared standardized extraction database. The quality of each study was assessed with the Newcastle-Ottawa Scale (NOS)[4] (see Supplementary material online, *Table S2*). Absolute numbers were recalculated when percentages were reported. These steps were performed independently by two investigators (P.M., C.S.).

Endpoint

The primary endpoint of this analysis was all-cause mortality. However, the study of Regieli *et al.* only presented cardiovascular mortality and these data were used instead.[5]

Definitions

Good collateralization was defined differently in the individual studies. Most studies performed a visual assessment (Rentrop score)[6] and used a score of ≤ 1 for low collateralization (no or only faintly visible collaterals). Four studies dichotomized their patients into 'no collaterals visible' (Rentrop 0) vs. 'any collaterals visible' (Rentrop 1–3).[5,7–9] One study based the collateral quantification on intra-coronary pressure measurements (collateral flow index, CFI)[10] (*Table 1*) and defined low collateralization as a CFI of <0.25.[11] The CFI was measured with a pressure-sensor tipped coronary guidewire which is placed distal to the coronary artery stenosis. In the presence of myocardial infarction (MI), 'acute' was defined as angiography within <12 h, 'subacute' as MI within 2–28 days.

Data synthesis and analysis

Data of included studies were combined to estimate the pooled impact (risk ratio, RR) of good collateralization vs. low collateralization. Calculations were based on a DerSimonian and Laird random-effects model.[12] Continuity correction was used when no event occurred in one group to allow calculation of an RR.[13] Heterogeneity among trials was quantified with Higgins' and Thompson's I^2. I^2 can be interpreted as the percentage of variability due to heterogeneity between studies rather than sampling error. An $I^2 > 50\%$ is considered as an at least moderate heterogeneity. All results are presented as point estimates and corresponding 95% CIs in brackets.

To assess the effect of individual studies on the summary estimate of effect, we performed an influence analysis using a jackknife procedure; pooled estimates were recalculated by omitting one study at a time.

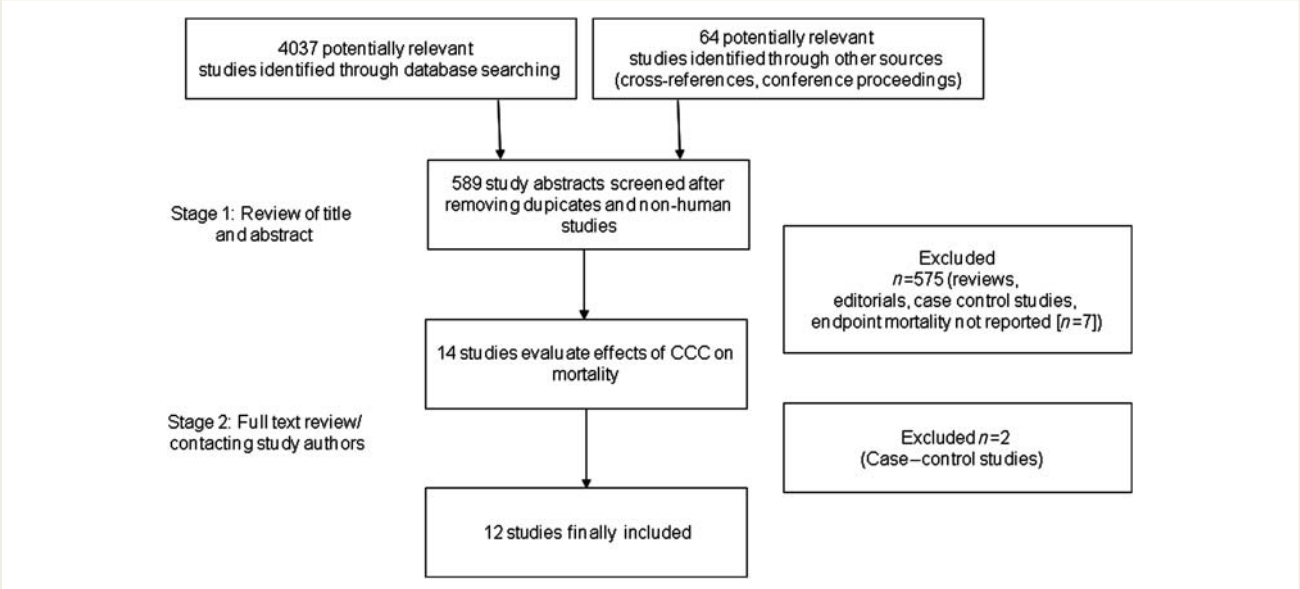

Figure 1 Study selection process.

Table 1 Summary of the characteristics of the included studies

Study	Year	Collateral assessment	Setting	Follow up (months)	PCI	Group	Mean age (y)	Female (%)	Diameter stenosis (%)
Helfant	1971	Visual	Elective	22.9	No	High CCC	na	na	na
						Low CCC	na	na	na
Williams	1976	Visual	Subcute MI	In-hospital	No	High CCC	51.0	20	na
						Low CCC	58.4	17	na
Nestico	1985	Visual	Elective	34	No	High CCC	56.0	35	98
						Low CCC	58.0	50	74
Hansen	1989	Visual	Elective	120	No	High CCC	49.2	10	na
						Low CCC	47.9	7	na
Perez-Castellano	1999	Visual	Acute MI	In-hospital	No	High CCC	64.0	18	na
						Low CCC	64.0	18	na
Nicolau	1999	Visual	Acute MI	36.4	Thrombolysis	High CCC	na	na	na
						Low CCC	na	na	na
Antioniucci	2002	Visual	Acute MI	6	Yes	High CCC	63	18	na
						Low CCC	64	23	na
Monteiro	2003	Visual	Acute MI	15.7	Yes	High CCC	63.3	11	na
						Low CCC	65.3	10	na
Meier	2007	CFI	Elective	120	Yes	High CCC	61.0	21	69
						Low CCC	62.0	24	59
Regieli	2009	Visual	Elective	24	Yes	High CCC	57.0	na	na
						Low CCC	56.0	na	na
Desch	2009	Visual	Acute MI	6	Yes	High CCC	64.0	26	na
						Low CCC	66.0	24	na
Steg	2010	Visual	Subacute MI	60	50% PCI	High CCC	58.4	23	na
						Low CCC	60.4	20	na

CFI, collateral flow index (intra-coronary wedge-pressure derived collateral assessment); high CCC, high coronary collateralization; low CCC, low collateralization; na, not available; PCI, percutaneous coronary intervention.

We assessed publication bias visually (funnel plot) and by formal tests (rank order correlation test and Egger's test of intercept).[14,15] To assess the impact of continuous (duration of follow-up, year of publication) and categorical moderator variables (study setting; type of intervention, method of collateral assessment) on the described effect of collaterals on survival, a mixed-effects model was used.

If only in-hospital outcomes were available, a median follow-up duration of 5 days was assumed. The follow-up intervals (unit: months) were log-transformed for this analysis. All analyses were performed independently by two investigators (P.M. and G.K.) using R, version 2.10.1 (package 'meta' and 'metafor').[16]

Results

Description of included studies

A total of 123 articles were reviewed and 12 studies were included that satisfied the predetermined inclusion criteria (*Figure 1*).[5,7–9,17–24] *Table 1* summarizes the characteristics of the included studies.

Mortality

Patients with a high collateralization showed a significantly reduced mortality risk compared with patients with low collateralization, RR 0.64 (95% confidence interval 0.45–0.91), $P = 0.012$ (*Figure 2*).

Subset analyses

The study setting did not have a significant impact on the relative risk estimates. For stable CAD, the RR for 'high collateralization' was 0.59 [0.39 – 0.089]; $P = 0.012$. For those with subacute MI, the RR was 0.53 [0.15–1.92], $P = 0.335$. For participants presenting with an acute MI, the RR for high vs. low collateralization was 0.63 [0.29–1.39], $P = 0.257$ (*Figure 3*). These differences in RR were not statistically significant (interaction *P*-value = 0.149).

However, the beneficial effect of collaterals was more pronounced in studies where most patients underwent PCI (RR 0.42 [0.32–0.56]; $P < 0.001$) compared with studies without PCI (RR 0.70 [0.51–0.97]; $P = 0.035$). In the one study where patients underwent thrombolysis,[19] those with high collateralization had increased mortality (RR 1.82 [1.12–2.96]; $P = 0.015$). (*Figure 4*) These differences in RR were statistically significant (*P* for interaction <0.001).

The predictive role of collaterals was significant for the 11 studies which used visual assessment for collaterals (RR 0.71 [0.50–0.99]; $P = 0.045$) and even more pronounced in one study which measured collaterals via CFI (RR 0.38 [0.26–0.56]; $P < 0.001$).[17] This RR difference was significant (*P* for interaction = 0.015).

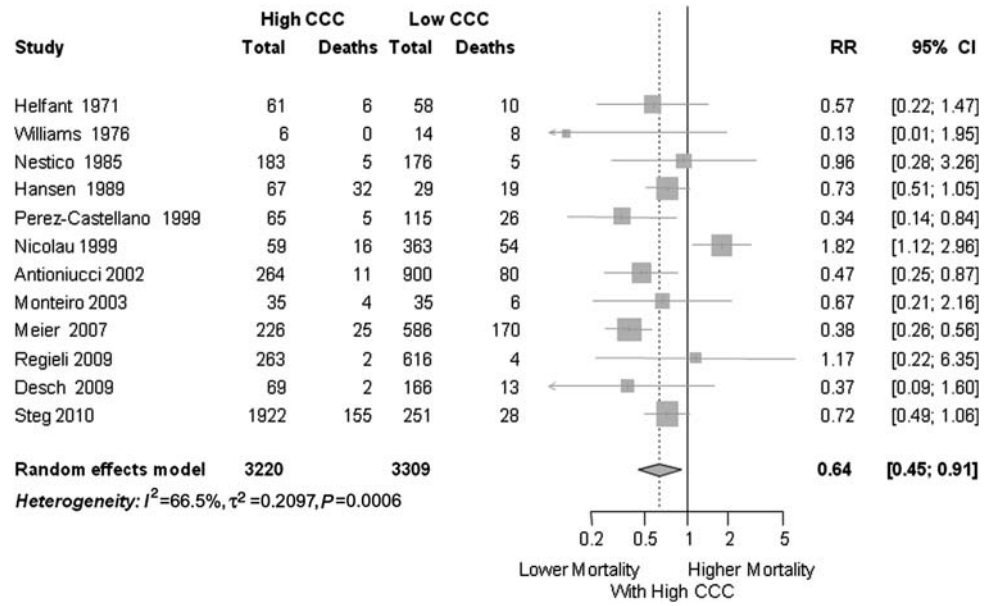

Figure 2 Forest plot of risk ratios for mortality. CCC, coronary collateral circulation; CI, confidence interval. Markers represent point estimates of risk ratios; marker size represents study weight in random-effect meta-analysis. Horizontal bars indicate 95% confidence intervals.

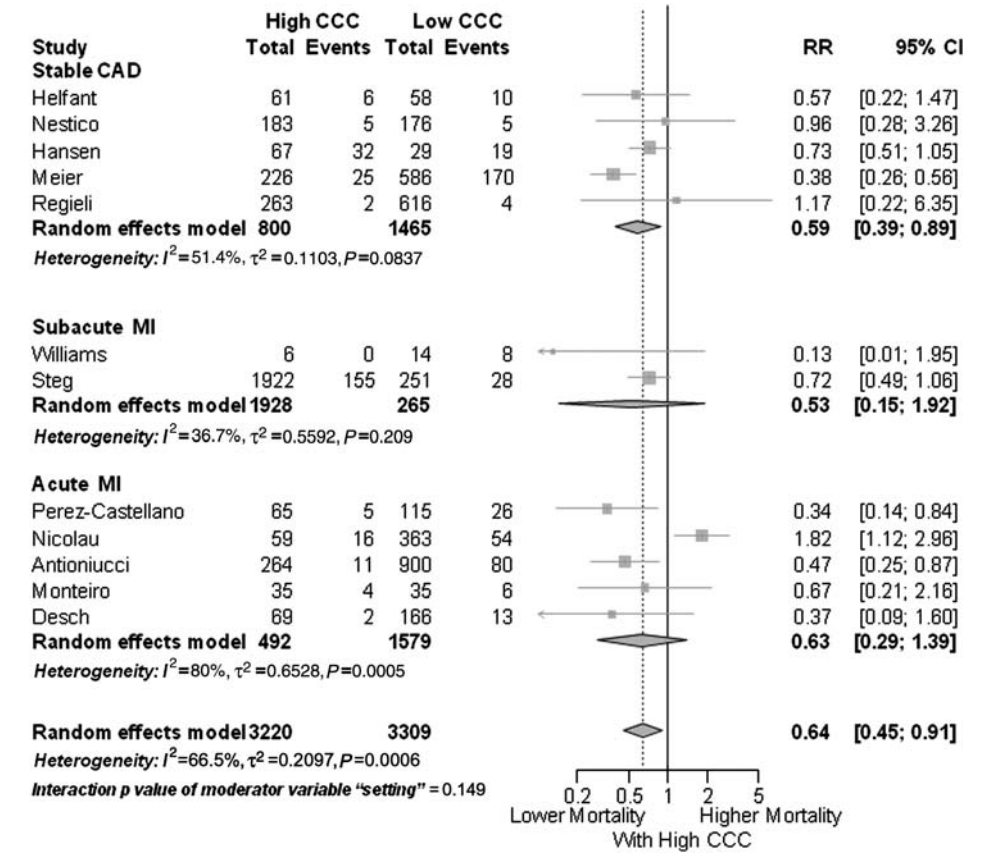

Figure 3 Forest plot of risk ratios for mortality risk, stratified by clinical setting (stable CAD, vs. subacute MI, vs. acute MI). CAD, coronary artery disease; CCC, coronary collateral circulation; CI, confidence interval; MI, myocardial infarction; Horizontal bars indicate 95% confidence intervals.

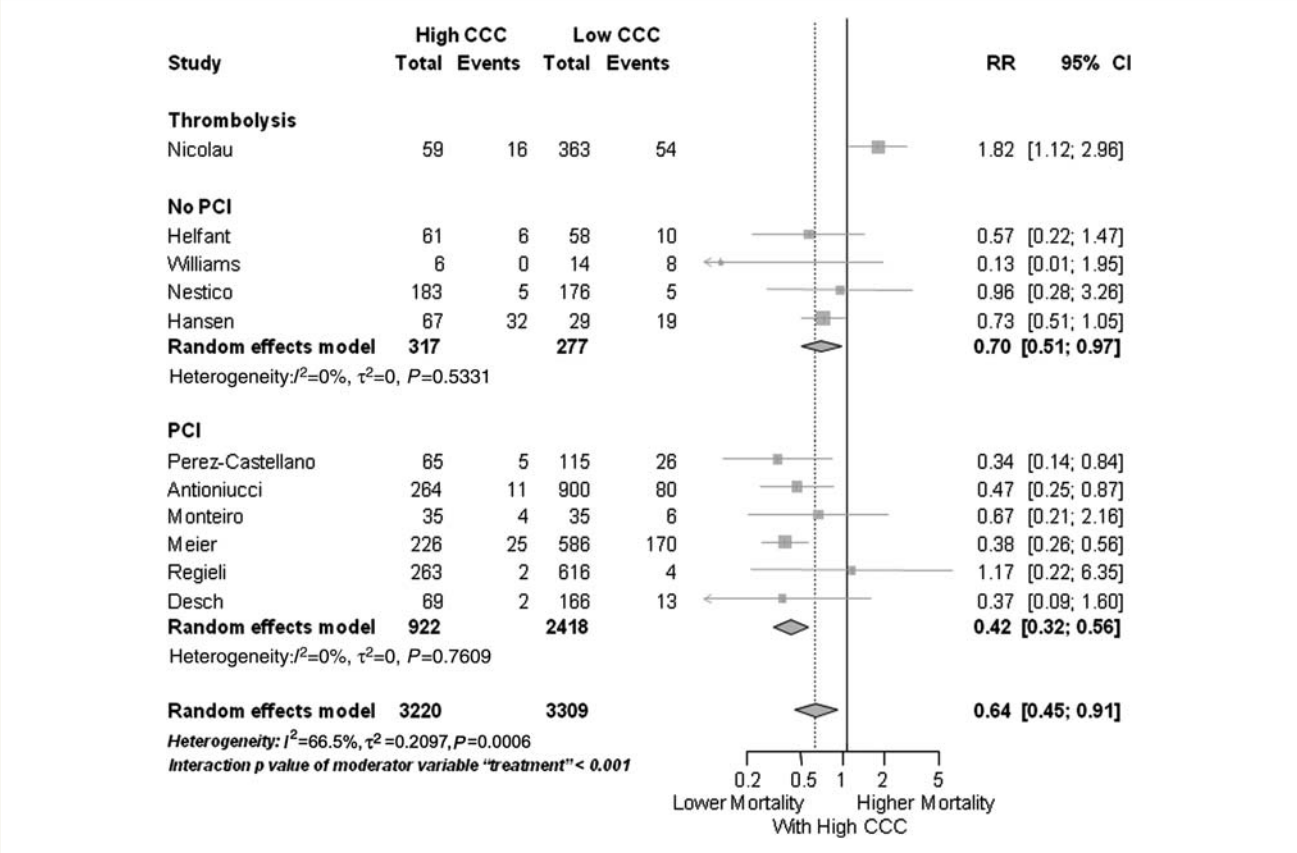

Figure 4 Forest plot of risk ratios for mortality risk, stratified by type of intervention (PCI, no PCI, and thrombolysis). CAD, coronary artery disease; CCC, coronary collateral circulation; CI, confidence interval; MI, myocardial infarction. Horizontal bars indicate 95% confidence intervals.

Effect of moderator variables

There was no effect of the year of publication on the reported effect of collaterals on survival (regression coefficient −0.003 [−0.038 to 0.033]; $P = 0.891$) nor had the duration of follow-up any significant effect (regression coefficient 0.073 [−0.076 to 0.222]; $P = 0.339$).

Sensitivity analyses

The jackknife procedure-based sensitivity analysis omitting one study at a time showed consistent estimates for the relative risk reduction in patients with high collateralization. None of the studies influenced the overall result towards statistical non-significance (*Figure 5*).

The funnel plot was rather symmetrical (*Figure 6*), formal testing did not indicate a relevant 'small study effect' or publication bias (Egger's test $P = 0.677$, rank correlation test $P = 0.641$). However, even under imputation of potentially unpublished studies with the Trim and Fill method, the overall result was not relevantly changed with an overall RR of 0.65 [0.47–0.91]; $P = 0.013$ (imputed study RR 3.26 [0.219–48.37]).

Discussion

This meta-analysis of 12 studies and 6529 patients shows that the CCC is associated with relevantly improved survival. The result was consistent whether patients underwent PCI or a diagnostic angiogram only, and whether collaterals were assessed visually or with CFI. Subgroup analyses indicate a clearly prolonged survival of well-collateralized patients with stable CAD while the analyses for subacute and acute CAD show comparable risk reductions which did not reach statistical significance; this is mainly due to a smaller sample size (limited statistical power) with wider confidence intervals.

Potential mechanisms of survival benefit of coronary collaterals

The exact underlying mechanism for the protective role of collaterals is unclear. We know that acute myocardial ischaemia leads to QT interval prolongation, which puts the patient at risk for fatal arrhythmias.[25] The collateral circulation can reduce such QT prolongation during vessel occlusion and this may contribute to the reduced mortality in patients with a well-developed CCC.[25] The collateral circulation has also demonstrated clinical benefit

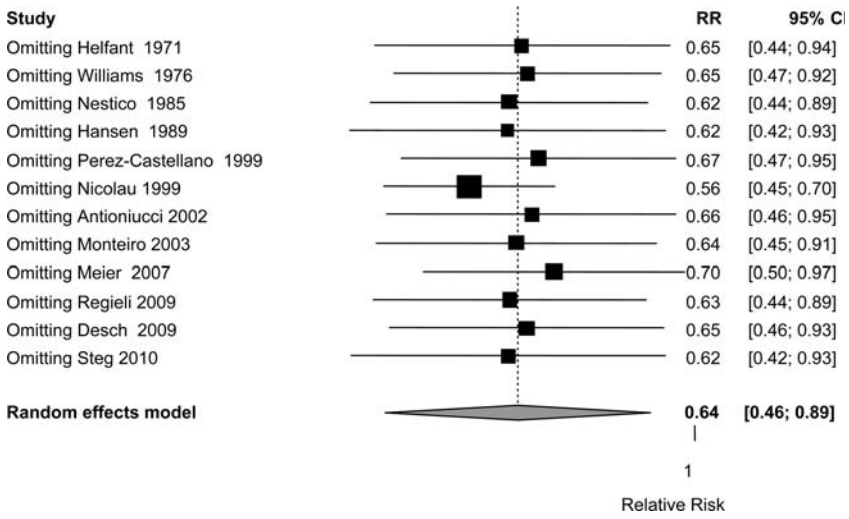

Figure 5 Influence analysis with forest plot of risk ratios for mortality. Each line represents a re-analysis of the data with exclusion of one study (inclusion of 11 studies only) at a time to assess the influence of this particular study on the overall result.

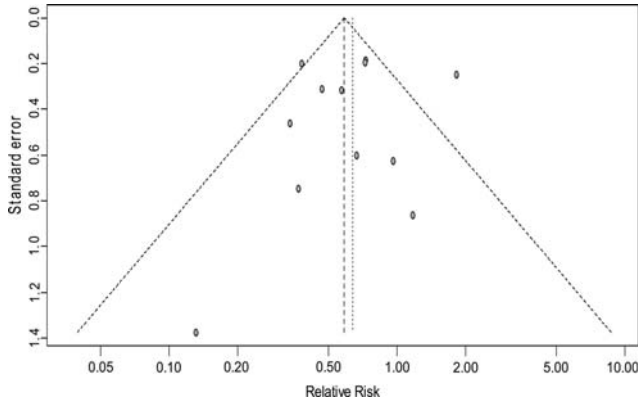

Figure 6 Funnel plot of the estimates of relative risk vs. standard error. SE, standard error. Lower standard errors indicate better precision and larger study size.

regarding smaller infarct size, preservation of cardiac function after acute infarctions, and reduction in post-infarct ventricular dilatation.[26] Over the long term, these effects are likely to contribute to a reduced mortality.

Potential clinical implications

The coronary collaterals may represent a useful prognostic marker. Patients with a low collateralization have an increased mortality risk and may be monitored more closely. Diagnostic angiography in patients with suspected CAD remains important to define the coronary anatomy and the degree of collateralization. This is optimally being done by measuring the CFI while the Rentrop score is easier and cheaper to assess but has significant limitations.[27] Alternatively, an intracoronary ECG could be used as an objective and simple method. ST-segment elevation of 0.1 mV during a 1-min balloon occlusion detects ischaemia and low collateralization[28] and it has demonstrated to predict mortality.[17]

Further, the results of this study highlight the importance of finding means to induce collateral growth. Several experimental studies and first clinical studies have demonstrated that it is possible to promote arteriogenesis with the growth factors GM-CSF, G-CSF, or with external counterpulsation.[3,29,30,31] However, these studies have demonstrated that promoting collateral growth is feasible but the studies were too small to evaluate whether this improvement in collateral function translates into improved survival.

Heterogeneity among included studies

Several aspects contribute to this heterogeneity. The most important one is the difference in study populations. Studies included

patients with stable CAD while other studies focused on patients with acute MI (*Table 1*). Further, some studies treated patients with PCI,[5,11,18,21,22] others with thrombolysis or only with medical therapy[8,9,19,20,23,24] or had a diagnostic and a PCI arm.[7] Only one study used CFI-based collateral assessment while all the others studies used visual assessment of collaterals. Visual assessment is not a very accurate method to quantify coronary collateralization and the studies used variable threshold to dichotomize the groups.[27]

Limitations of this meta-analysis

First, all included studies have specific and general limitations. All studies were observational. A causal relationship between well-developed coronary collaterals and improved survival is hypothetical and cannot be proven without an interventional study design. A high coronary collateralization may simply represent a marker which is associated with better survival. However, the main determinant of collateralization is the degree of coronary stenosis. Therefore, a high collateralization is more likely to be present in patients with an extensive CAD. Two of the included studies reported on diameter stenosis degree which was clearly higher in the group with high collateralization (*Table 1*).[32] Nevertheless, this group showed improved survival in our analysis.

Another draw-back is that most studies were rather small, the smallest study enrolled only 20 patients. Few studies were protocol-driven, most were retrospective analyses of registries or trials and, therefore, the primary objective was often quite different in the underlying primary studies. All but one studies used exclusively binary data for their analysis. The extent of variable of interest, collateralization, was dichotomized into 'high' and 'low collateralization' while in fact, the degree of collateralization is a continuous variable.

This analysis does not capture the dynamic of the coronary collaterals. The coronary collateral function has been demonstrated to decrease over a 6-month period after PCI.[33] This dynamic may explain the non-significant results in the setting of acute MI. During an acute vessel occlusion, the collaterals undergo rapid changes, a fact that limits the value of a single time-point measurement. Further, the increased left ventricular end-diastolic pressure during an acute MI impairs the accuracy of the collateral assessment.[34]

For two studies, absolute numbers of events were back-calculated from percentages which were based on Kaplan–Meier event estimates.[19,23] This can be erroneous, especially if a significant number of patients are lost to follow-up. It was not possible to verify these data with the authors of the original publication. However, these two studies had a maximum of two patients lost to follow-up. All included studies had very low drop-out rates in general, the highest rates were 5%.[8,25]

Outlook

Future research should prospectively assess the effect of coronary collaterals on clinical outcomes. Such studies should be strictly protocol driven with a clearly pre-defined primary endpoint such as mortality and where the collateralization is assessed with CFI or other quantitative measurements rather than with a visual assessment. Future studies should carefully control for possible confounding factors which has to include factors that influence the collateralization (stenosis degree) and factors that influence the outcome (mortality) such as age, gender, type of intervention, and co-morbidities. Such studies also have to be adequately powered to detect a difference in mortality. We further need larger scale interventional studies which test whether the therapeutic promotion of collaterals translates into improved clinical outcomes.

Conclusions

The results of this meta-analysis demonstrate that an high coronary collateralization indicates a reduced mortality risk. The assessment of the coronary collateralization provides useful information for the risk assessment of patients with CAD undergoing coronary angiography. The therapeutic induction of collateral growth may have significant implications on outcomes.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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Conflict of interest: None declared.

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