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REVIEW

Stable Coronary Artery Disease: When is Percutaneous Coronary Intervention Indicated?

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ABSTRACT

In patients with chronic coronary artery disease (CAD) and good left ventricular function, percutaneous coronary intervention (PCI) does not confer any clear benefit in terms of hard long-term clinical outcomes, such as mortality, myocardial infarction or the need for subsequent revascularization, as compared with medical conservative treatment. Indeed, a meta-analysis of early data from 6 randomised controlled trials has showed convincingly that PCI improves anginal symptoms compared to conservative management, but there has been limited evidence on the effect of PCI on hard clinical outcomes. At the same time, the early fear of increased need for revascularization after PCI is probably not warranted. By comparing the benefits against cost considerations, it seems that many percutaneous interventions that are currently performed in patients with non-acute CAD are probably not justified.

KEY WORDS: *coronary artery disease; coronary angioplasty; coronary stenting; percutaneous coronary intervention; coronary bypass surgery; acute coronary syndromes; ischemic heart disease; myocardial infarction*

INTRODUCTION

List of Abbreviations:
CABG = coronary artery bypass grafting
CAD = coronary artery disease
MI = myocardial infarction
PCI = percutaneous coronary intervention

Significant coronary stenoses in patients with ischemic heart disease represent an established indication for revascularization. In longitudinal studies on patients with known or suspected coronary artery disease (CAD), positive thallium 201 studies predict a significantly higher overall mortality, cardiac death or myocardial infarction,[1,2] whereas scintigraphy studies identify patients with a good prognosis at a low risk for future cardiac events.[3] However, the possible benefits and consequently indications of percutaneous coronary intervention (PCI) in the management of stable patients with CAD in non-acute settings have been debated for more than a decade. A meta-analysis of early data from 6 randomised controlled trials had showed convincingly that PCI improves anginal symptoms compared to conservative management,[4] but there has been limited evidence on the effect of PCI on hard clinical outcomes, such as the risk of death, myocardial infarction (MI) and subsequent revascularization.

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EVIDENCE FROM RANDOMIZED STUDIES

We have recently performed a meta-analysis of all randomized trials comparing

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PCI to conservative treatment in patients with stable CAD.[5] We identified 11 eligible randomized trials with pertinent data.[6-20] These were the Second Randomized Intervention Treatment of Angina (RITA2) trial, the Angioplasty Compared to Medicine (ACME) study group with two separately enrolled strata on single-vessel and two-vessel disease (designated here as ACME 1 and ACME 2, respectively), the Atorvastatin versus Revascularization Treatment (AVERT) trial, the Medicine, Angioplasty, or Surgery Study (MASS), and Medicine, Angioplasty, or Surgery Study II (MASS II) trial, a trial conducted by the Arbeitsgeneinschaft Leitende Kardiologische Krankenheusartzte (ALKK) group, and trials by Dakik et al, Sievers et al., Hambrecht et al., and Bech et al. Patient and disease characteristics are shown in Table 1. Mostly patients with single-vessel or two-vessel disease were included, but a considerable proportion of patients in MASS II had three-vessel disease. The large majority of patients had at least some anginal symptoms, but some trials included also a few patients without symptoms (Table 1). The reported average left ventricular ejection fraction was <60% in only one trial that lowered the eligibility threshold for ejection fraction to 35% (mean 46%).[17]

RESULTS OF META-ANALYSIS

A total of 2,950 patients were included in the meta-analysis (1,476 receiving PCI and 1,474 receiving conservative treatment). There were a total of 196 deaths (PCI arm n=95 vs. conservative arm n=101), 235 patients had cardiac death or suffered an MI (PCI arm n=126 vs. conservative arm n=109), and 153 patients had non-fatal MIs (PCI arm n=87 vs. conservative arm n=66), while 215 patients underwent coronary artery bypass grafting (CABG) (PCI arm n=109 vs. conservative arm n=106) and 462 had PCI during follow-up (PCI arm n=219 vs. conservative arm n=243).

There was no significant difference between the two treatment strategies regarding mortality, cardiac death or MI, non fatal MI, and CABG or PCI during follow-up. By random effects, the risk ratios (95% confidence intervals) for the PCI vs. conservative treatment arms were 0.94 (0.72-1.24), 1.17 (0.88-1.57), 1.28 (0.94-1.75), 1.03 (0.80-1.33), and 1.23 (0.80-1.90), for these 5 outcomes, respectively (Table 2). The summary estimates showed no difference between PCI and conservative treatment in the mortality risk and the 95% confidence intervals clearly excluded relative risk differences of 28% (Figure 1a). If anything, there was a trend for more cardiac deaths or MIs, in particular non-fatal MIs (Figure 1b), in patients who underwent PCI, with the point estimate suggesting approximately a 30% increase in the relative risk of non-fatal MI with PCI. A possible survival benefit was seen for PCI only in trials of patients who had a relatively recent MI (risk ratio 0.40, 95% confidence interval 0.17-0.95). Except for PCI during follow-up, there was no significant between-study heterogeneity for any outcome.

There was absolutely no difference in the need for CABG between the two compared treatment strategies (Table 2). The 95% confidence intervals also excluded differences in the relative risk exceeding 20% in favour of PCI and 33% in favour of conservative treatment. There was also no overall difference in the risk for PCI during follow-up.

Table 1. Patient and Disease Characteristics in the Eligible Studies

Study	Sample MT/PCI	Age mean (yrs)	Male (%)	DM (%)	Prior MI (%)	No symptoms (%)	LVEF (%)	F/U (years)
RITA 2	514/504	58 median	82	9	47	20	ND*	7
ACME 1	115/112	60	100	18	31	9	68	2.4-5
ACME 2	50/51	60	100	18	41	18	67	2.4-5
AVERT	164/177	59	84	16	42	16	61	1.5
Dakik	22/19	53	59	ND	100	0	46	1
MASS	72/72	56	58	18	0	0	76	5
MASS II	203/205	60	68	30	41	ND	67	1
ALKK	151/149	58	87	16	100	0	ND†	4.7
Sievers	44/44	56	ND	0	55	ND	ND	2
Hambrecht	51/50	61	100	23	46	0	63	1
Bech	91/90	61	64	12	25	0	65	2

CAD: coronary artery disease; DM: diabetes mellitus; EF: ejection fraction; F/U= follow-up; MI: myocardial infarction; MT: medical treatment; PCI: percutaneous coronary intervention; ND: no data available. See text for trial name abbreviations.
The ACME trial consists of two separately enrolled strata of patients with single-vessel (ACME 1) and two-vessel (ACME 2) disease.
*93% of the patients had very good or excellent wall motion score
Adapted from Katritsis et al (reference 5).

TABLE 2. Summary Risk Ratios for Major Outcomes with PCI vs. Conservative Medical Treatment

Outcome	RE Risk Ratio (95% CI)	p-value	FE Risk Ratio (95% CI)	p-value
Death	0.94 (0.72-1.24)	0.68	0.95 (0.72-1.23)	0.68
Cardiac death or MI	1.17 (0.88-1.57)	0.28	1.16 (0.91-1.48)	0.24
Non-fatal MI	1.28 (0.94-1.75)	0.12	1.32 (0.97-1.79)	0.077
CABG	1.03 (0.80-1.33)	0.82	1.04 (0.81-1.34)	0.76
PCI	1.23 (0.80-1.90)	0.34	0.91 (0.77-1.07)	0.25

CABG: coronary artery bypass grafting; CI= confidence intervals; FE: fixed effects; MI: myocardial infarction; PCI: percutaneous coronary intervention; RE: random effects
Adapted from Katritsis et al (reference 5).

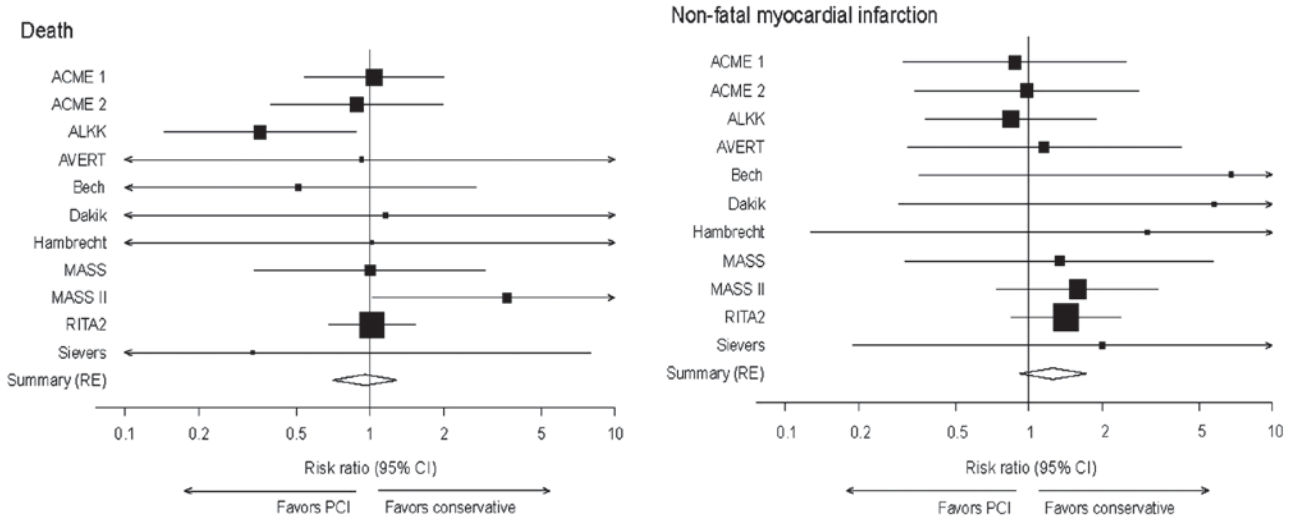

FIGURE 1. Comparison of percutaneous coronary intervention (PCI) vs. conservative medical treatment for (**a**) death, and (**b**) non-fatal myocardial infarction. Each study is shown by its name along with the point estimate of the risk ratio and the respective 95% confidence intervals. In each panel, the size of the box denoting the point estimate in each study is proportional to the weight of the study. Also shown are the summary risk ratio and 95% confidence intervals according to the DerSimonian and Laird random effects model. [Adapted from Katritsis et al (reference 5)].

SUBGROUP ANALYSES

DOCUMENTED ISCHEMIA

Subgroup analyses (Table 3) produced no evidence that trials with definitive documentation of ischemia by exercise test and/or scintigraphy had different risk ratios compared with trials where functional ischemia was not as thoroughly documented (Table 3).

EFFECT OF STENTS

The availability or not of stents also did not make any substantial difference for any of the 5 considered endpoints. Several of these trials were conducted in the time period before stents were routinely introduced in clinical practice. However, our meta-analysis found no evidence of superiority for the PCI strategy, even when analyses were limited to trials using stents. Finally, the impact of drug-eluting stents cannot be predicted, but the currently available data suggest that they may not offer any benefits besides reducing the need for revascularization, while the risk of death and MI is not affected.[21]

RECENT MYOCARDIAL INFARCTION

The two trials that enrolled exclusively patients with relatively recent MI[17,18] showed a statistically significant reduction in the risk of death (p=0.037) and in the risk for subsequent PCI (p=0.029) and possibly also CABG (p=0.12) in the PCI arms. This subgroup differed significantly vs. the remaining trials for death and PCI risk ratios. Thus, PCI may actually be more effective in reducing the risk of death especially in trials where all patients had a relatively recent MI. Longer follow-up and additional data would be useful before making

TABLE 3. Random Effects Risk Ratios (95% Confidence Intervals) for PCI vs. Conservative Medical Management in Subgroup Analyses

Subgroups	Death	Cardiac death or MI	Non-fatal MI	CABG	PCI
Stent availability					
Yes	0.89 (0.33-2.36)	1.28 (0.66-2.48)‡	1.32 (0.81-2.15)	0.99 (0.35-2.77)	1.42 (0.67-3.00)
No	0.99 (0.71-1.39)	1.18 (0.85-1.63)	1.26 (0.84-1.89)	1.06 (0.80-1.40)	1.11 (0.64-1.94)
All patients with recent MI*					
Yes	0.40 (0.17-0.95)	1.01 (0.18-5.60)	1.26 (0.27-5.83)	0.24 (0.04-1.42)	0.42 (0.20-0.91)
No	1.04 (0.78-1.39)	1.31 (1.00-1.73)	1.35 (0.96-1.90)	1.06 (0.82-1.38)	1.41 (0.88-2.24)
Ischemia documented in >80%†					
Yes	0.98 (0.63-1.55)	1.50 (0.88-2.56)	1.13 (0.60-2.14)	1.11 (0.64-1.90)	1.85 (0.87-3.91)
No	0.86 (0.42-1.74)	1.10 (0.71-1.72)	1.33 (0.93-1.91)	1.00 (0.58-1.72)	0.96 (0.56-1.65)

CABG: coronary artery bypass grafting; MI: myocardial infarction; PCI: percutaneous coronary intervention.
* 8 days to 3 months prior to entry to the trial, † based on exercise test with or without scintigraphy
Adapted from Katritsis et al (reference 5).

a strong recommendation for using PCI in this setting, since data are driven largely by a single trial (ALKK).

PROCEDURE-RELATED MYOCARDIAL INFARCTION

We observed a trend for increased risk of MI in patients undergoing PCI. This may reflect also the risk carried by the invasive procedure per se. Data were not consistently available across these trials to separate procedure-related infarctions from subsequent MI. Additionally, micro-infarcts caused in a considerable proportion of patients undergoing PCI may have adverse prognostic importance in the long-term.[22]

CORONARY ARTERY BYPASS GRAFTING

The early literature suggested that PCI may cause an increased need for CABG.[4] We found no evidence for any increased need of CABG in the PCI strategy as compared with the conservative strategy.

INTENSE MEDICAL THERAPY

The included trials did not routinely use the full spectrum of conservative interventions currently available for CAD management. Interestingly, excellent results for the conservative arm were obtained in a trial where special emphasis was placed on exercise, although it should be acknowledged that weekly counselling was also provided to patients in the exercise group.[19] Exercise may be unjustifiably under-utilized in current clinical practice.[23] Moreover, the advent of statins has improved the treatment and outcomes of patients with chronic CAD with or without significant hypercholesterolemia.[24] This potential benefit was not available in any of the early trials. In view of current recommendations the angioplasty-treated group in the AVERT trial had inadequate control of their lipids. Overall, the different and potentially suboptimal medical management across the discussed trials is a limitation for unequivocal conclusions. However, one would expect even better outcomes, if medical management were indeed optimized.

CONCLUSIONS

In patients with chronic coronary artery disease and good left ventricular function, PCI does not confer any clear benefit in terms of hard long-term clinical outcomes, such as mortality, myocardial infarction or the need for subsequent revascularization, as compared with medical conservative treatment. Evidence-based indications of PCI in this setting include relief of symptoms and recent myocardial infarction. At the same time, the early fear of increased need for revascularization after PCI is probably not warranted. By comparing the benefits against cost considerations, it seems that many percutaneous interventions that are currently performed in patients with non-acute CAD are probably not justified.

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