Articles

Coronary angioplasty versus medical therapy for angina: the second Randomised Intervention Treatment of Angina (RITA-2) trial

*RITA-2 trial participants**

Summary

Background The role of percutaneous transluminal coronary angioplasty (PTCA) in the management of patients with angina remains controversial, particularly in patients whose symptoms are adequately controlled by medical treatment.

Methods RITA-2 is a randomised trial comparing the long-term effects of PTCA and conservative (medical) care in patients with coronary artery disease considered suitable for either treatment option. 1018 patients were recruited from 20 cardiology centres in UK and Ireland. The 504 randomised to PTCA were intended to have dilatation within 3 months. The 514 assigned to medical treatment received antianginal drugs; those whose symptoms were not controlled by optimum medical therapy could cross-over to myocardial revascularisation. The primary endpoint was the combined frequency of death from all causes and definite non-fatal myocardial infarction.

Findings This report covers a median 2·7 years' follow-up. At randomisation 53% of patients had grade 2 or worse angina, and 40% had two or more diseased coronary arteries. 93% of patients randomised to PTCA had this procedure carried out, within a median of 5 weeks. Death or definite myocardial infarction occurred in 32 patients (6·3%) treated with PTCA and in 17 patients (3·3%) with medical care (absolute difference 3·0% [95% CI 0·4–5·7%], p=0·02). This difference was mainly due to one death and seven non-fatal myocardial infarctions related to the randomised procedures. There were 18 deaths (11 PTCA, seven medical) of which ten were not due to heart disease. Of the patients in the PTCA group, 40 (7·9%) required coronary artery bypass grafting (CABG), including nine instead of PTCA and seven emergencies following unsuccessful PTCA. 56 other PTCA patients (11·1%) required further non-randomised PTCA. In the medical group 118 patients (23·0%) underwent a revascularisation procedure during follow-up, mostly because of worsening symptoms. Angina improved in both groups, but more so in the PTCA group. There was a 16·5% absolute excess of grade 2 or worse angina in the medical group 3 months after randomisation (p<0·001), which attenuated to 7·6% after 2 years. Total exercise time (Bruce protocol) also improved in both groups, again with a treatment difference in favour of PTCA: mean advantage of 35 s at 3 months (p<0·001). These benefits of PTCA were greater in patients with more severe angina at baseline, judged by high initial grade of angina and short initial exercise-time.

Interpretation In patients with coronary artery disease considered suitable for either PTCA or medical care, early intervention with PTCA was associated with greater symptomatic improvement, especially in patients with more severe angina. When managing individuals with angina, clinicians must balance these benefits against the small excess hazard associated with PTCA due to procedure-related complications.

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Introduction

For patients with angina who require revascularisation, randomised trials comparing the long-term effects of coronary angioplasty and coronary artery bypass surgery[1–3] have provided important information for clinical management. Randomised trials are also needed to determine whether patients in whom myocardial revascularisation is not essential should be treated by early angioplasty, or can have revascularisation deferred. The Veterans Administration Angioplasty Compared to Medicine trial[4] is relevant but had limited power to detect clinically important differences.

The second Randomised Intervention Treatment of Angina (RITA-2) trial was designed to compare the effects of initial strategies of coronary angioplasty and conservative (medical) care over at least 5 years' follow-up in patients deemed suitable for either treatment. We present the interim results of RITA-2 after a median 2·7 years' follow-up.

Patients and methods

Patients

Patients were recruited at 20 centres in the UK and Ireland. The ethics committee of each centre approved the protocol. Patients with coronary artery disease proven arteriographically were considered if the supervising cardiologist thought that both continued medical therapy and coronary angioplasty were acceptable alternatives. All eligible patients had a significant stenosis in at least one major epicardial vessel that appeared technically amenable to balloon dilatation. Patients had to be over 18 years of age, but there was no upper age limit and patients of either sex were considered. Patients were not required to have current symptoms but patients with severe symptoms were potentially eligible if they would consider an initial

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strategy of conservative therapy. Patients with multivessel disease, occluded coronary arteries, or impaired left ventricular function were eligible. Patients with recent unstable angina could also be included; this was defined as an episode of ischaemic chest pain associated with electrocardiographic changes with admission within the preceding 90 days, but entry was restricted to those whose most recent episode was at least 7 days before randomisation and who had not developed new pathological Q waves or increases in serum cardiac enzymes to twice normal.

Patients in whom early myocardial revascularisation (coronary angioplasty or coronary bypass surgery) was considered necessary for symptom relief or for prognostic benefit and patients with previous myocardial revascularisation, left main stem disease, or haemodynamically significant valve disease were not eligible. Patients with life-threatening non-cardiac disease likely to limit survival or have a major influence on compliance were not eligible.

During the recruitment phase, patients undergoing coronary arteriography under the care of the participating cardiologists were entered into a log. The main purpose of the log was to identify eligible patients, but since the log was not completely maintained in all centres we can only give estimated numbers screened and eligible. Across all centres, around 70 000 patients underwent coronary arteriography for any reason during the trial recruitment phase (figure 1). Of these, around 2750 were considered eligible for RITA-2, of whom 1018 (37%) were randomised. Clinician's subjective choice was inevitably a major contributor to deciding whether patients were eligible and whether to randomise or not. This may be the principal reason why recruitment was low. Of course, myocardial revascularisation is mandated on prognostic or symptomatic grounds for many patients who have undergone coronary arteriography. In addition, patients' refusal was the documented reason for about half the eligible patients who were not randomised. For all patients undergoing arteriography, the consequent planned treatment was declared to be medical (35%), percutaneous transluminal coronary angioplasty (PTCA) (19%), coronary artery bypass grafting (CABG) (35%), other (6%), or unknown (4%).

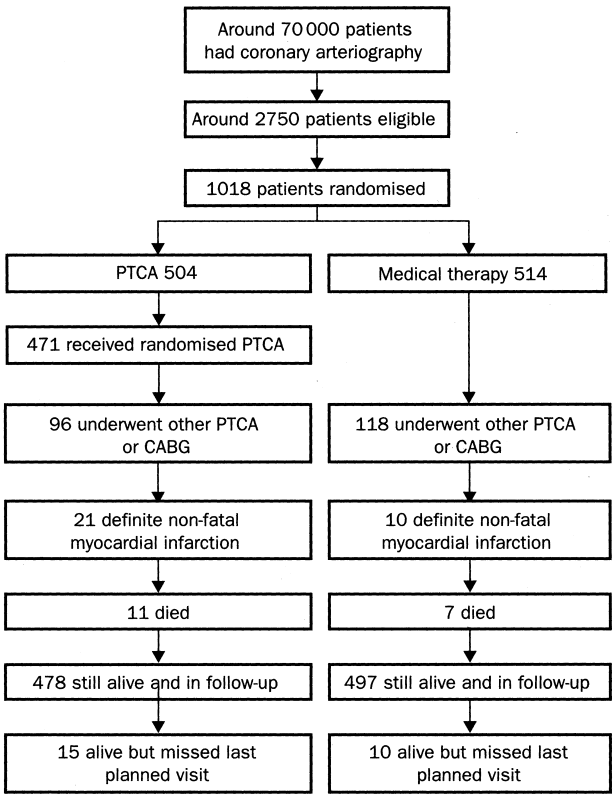


Figure 1: **Trial profile**

Before randomisation the coronary arteriograms of eligible patients were reviewed by an interventional cardiologist who identified at least one significant coronary lesion in a major epicardial vessel which would be dilated if the patient were assigned to treatment by angioplasty. A significant coronary lesion was defined as a 50% or greater diameter stenosis in at least two radiographic projections or 70% diameter stenosis in one projection. Major coronary vessels were defined as the left anterior descending artery or large diagonal branches, the circumflex artery or large obtuse marginal branches, and a balanced or dominant right coronary artery.

Patients who satisfied the eligibility criteria and provided informed consent to participate in the trial were randomised by telephone call to the Royal Free Hospital's coronary care unit. The randomisation used permuted blocks within strata defined by centre, by extent of disease (single vessel or multivessel), and whether the patient had had recent unstable angina.

Treatment

The protocol required that patients assigned to coronary angioplasty underwent dilatation of the prospectively identified stenosis or stenoses within 3 months of randomisation. Methods for PTCA were not standardised between centres but all angioplasty procedures had to be carried out by experienced operators, usually consultant interventional cardiologists or occasionally fully-trained senior cardiac registrars. There was no requirement for all coronary stenoses to be dilated, but multivessel dilatation could be staged over more than one procedure. In all cases the intended strategy was based on conventional balloon dilatation, but stents and other coronary interventional techniques (eg, coronary atherectomy) were permissible if the initial angioplasty result was unsatisfactory. Angioplasty of a coronary stenosis was considered successful if there was a reduction in stenosis severity of at least 20%, with less than 50% residual stenosis and good distal flow on the final arteriogram. Following intervention, medication was determined by individual clinical circumstances, but clinicians were encouraged to discontinue antianginal drugs for patients without angina. During follow-up, coronary arteriography and additional intervention procedures were carried out when indicated, with the objective of detecting and treating patients with restenosis. The trial did not reimburse centres for costs related to intervention procedures.

Patients assigned to initial medical therapy were prescribed antianginal medication for symptom relief. During follow-up, coronary arteriography was repeated only for compelling clinical reasons, and the indications for a change from the assigned non-interventional strategy were recorded on a cross-over form. The protocol required that myocardial revascularisation procedures were reserved for patients whose symptoms were not adequately controlled by optimal medical therapy, which usually included a β-adrenoceptor blocker, with a calcium antagonist and/or long-acting nitrate in maximally tolerated doses.

During the study all patients were treated with aspirin unless contraindicated. Patients were recruited before the results of randomised trials of the clinical effects of hydroxy-methyl-glutaryl co-enzyme A (HMG Co-A) reductase inhibitors were published,[5] and lipid-lowering drugs were prescribed at the discretion of the supervising clinician.

Data collection

Patients were assessed at baseline, and at 3 months, at 6 months, and yearly after randomisation. Demographic information, risk factors, and coronary arteriographic data were recorded at baseline. Left ventricular function was assessed from a right anterior oblique contrast left ventricular angiogram with a wall-motion score.[6] Contraction was scored on a six-point scale (normal=1, mild/moderate hypokinesia=2, severe hypokinesia=3, akinesia=4, dyskinesia=5, aneurysmal=6) for each of five left ventricular segments (anterobasal, anteroapical, apical,

inferoapical, and inferobasal). The sum of the scores (ranging from 5–30) provided an index of overall left ventricular function.

The primary endpoint was defined as the combined frequency of death (from all causes) and definite non-fatal myocardial infarction. An independent event-validation committee reviewed all deaths and reported myocardial infarcts, blind to the patient's assigned treatment. The cause of death was classified as cardiac or non-cardiac. Definite myocardial infarction was diagnosed if new pathological Q waves (>30 ms in duration) appeared on an electrocardiogram within 7 days of any myocardial revascularisation procedure (procedure-related infarction) or during subsequent follow-up. Definite myocardial infarction was also diagnosed if a convincing clinical history was associated with electrocardiographic changes compatible with non-Q-wave infarction and the serum activities of at least two cardiac enzymes were above twice normal. Possible myocardial infarction was diagnosed within 7 days of any myocardial revascularisation procedure or in association with a convincing clinical history if changes consistent with a diagnosis of non-Q-wave myocardial infarction appeared on a follow-up electrocardiogram or if the serum activities of at least two cardiac enzymes were above twice normal.

All major cardiovascular events and hospital admissions were documented. Unstable angina was defined as admission for ischaemic cardiac pain associated with electrocardiographic signs of myocardial ischaemia, but without elevation of serum cardiac enzymes or the appearance of new Q waves. Stroke was defined as a sudden focal disturbance of brain function of presumed vascular origin persisting longer than 24 hours. For transient stroke the clinical syndrome persisted less than 24 hours. Patients were considered to have developed cardiac failure if they required new maintenance drug therapy for heart failure. An arrhythmia occurring after randomisation was considered significant if the patient required new maintenance antiarrhythmic drug therapy or permanent pacemaker implantation.

Angina was assessed with the Canadian Cardiovascular Society classification,[7] and by documentation of antianginal drug use. Breathlessness and physical activity were assessed by ordinal scales.[2] Symptom-limited treadmill tests (Bruce protocol[8]) were carried out at 3 and 6 months and at 1 and 3 years after randomisation. Interim analyses were reviewed by the data-monitoring committee about every 6 months, each time with a recommendation that the trial continue as planned.

Statistics

The accrual target of 1400 patients was calculated on the basis of previous reports[9–12] which suggested that the combined 5-year rate of death and definite non-fatal myocardial infarction in the trial would be around 15%. A trial of this size would have 80% power to detect a one-third reduction in the event rate in one treatment arm compared with the other at (two-sided) 5% significance. The recruitment rate was slower than anticipated, largely because the treatment policies were distinct, which makes the clinician's willingness and patient's consent to randomisation no easy matter. 1018 patients were randomised from July, 1992, to May, 1996, when accrual was terminated to avoid extension of recruitment beyond 4 years. Our trial has substantial power to provide precise comparison of the two treatment strategies for symptoms and exercise tolerance. All data were analysed according to the original treatment assignment (intention-to-treat).

Results

1018 patients were randomised to coronary angioplasty (504) or continued medical treatment (514). This report concerns follow-up to Nov 30, 1996, which was complete for 98% of patients. Minimum and median follow-ups were 6 months and 2·7 years respectively.

Baseline comparability

	PTCA (n=504)	Medical (n=514)	All patients (n=1018)
Diseased vessels			
1	311	300	611 (60%)
2	163	175	338 (33%)
3	30	39	69 (7%)
Recent unstable angina	47	52	99 (10%)
Angina grade			
None	103	97	200 (20%)
1	116	157	273 (27%)
2	180	154	334 (33%)
3	62	61	123 (12%)
4	43	43	86 (8%)
Antianginal drugs			
None	24	47	71 (7%)
1	217	195	412 (41%)
2	188	193	381 (37%)
3	74	79	153 (15%)
Current medication			
β-blocker	344	335	679 (67%)
Calcium antagonist	238	273	511 (50%)
Long-acting nitrate	233	210	443 (44%)
Aspirin	439	447	886 (87%)
Lipid-lowering drug	70	60	130 (13%)
ACE inhibitor	46	56	102 (10%)
Age (years)			
<50	101	106	207 (20%)
50–59	180	197	377 (37%)
60–69	190	181	371 (37%)
⩾70	31	29	60 (6%)
Women	93	90	183 (18%)
Previous myocardial infarction	235	236	471 (47%)
On diabetic treatment	48	42	90 (9%)
Left ventricular score			
5	276	269	545 (54%)
6–9	194	201	395 (39%)
⩾10	27	36	63 (6%)

ACE=angiotensin-converting enzyme.

Table 1: **Patients' characteristics at randomisation**

Overall, there was close similarity between patients randomised to PTCA and medical treatment (table 1). The median age was 58 years and 18% were women. Angina grade 3 or worse (marked limitation of ordinary physical activity) was present in 21% of patients. A fifth of patients reported no anginal symptoms at the time of randomisation but since all patients had undergone coronary arteriography most would have had symptoms earlier. During the 3 months before randomisation 16% had been admitted with angina. A previous myocardial infarction had occurred in 47% of patients, 22% of these being within the previous 3 months.

Randomised PTCA

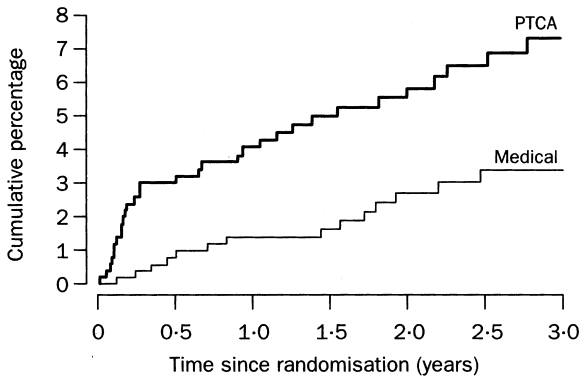
The intended randomised PTCA was performed in 471 (93%) of patients in the PTCA group. Reasons for not undergoing PTCA in the other 33 were: lesion regression (12), symptomatic improvement (four), disease progression (ten, of whom nine underwent CABG), patient refused (seven).

The median time from randomisation to PTCA was 5 weeks; 5% of PTCAs were done within a week and 91% within 12 weeks of randomisation. In total, angioplasty was attempted in 642 vessel segments of which 93% were successfully dilated. A single-vessel segment was treated in 335 patients with 92% success. 107 and 29 patients, respectively, had two and three or more vessel segments treated, with all segments successfully dilated in 86% and 90% of such patients, respectively. Dilatation was

	PTCA	Medical
Deaths		
All causes	11	7
Cardiac	5	3
Non-cardiac	6	4
Definite non-fatal myocardial infarctions*		
Total	21	10
Related to randomised PTCA	7	—
Related to other intervention	3	2
Other	11	8
Possible non-fatal myocardial infarctions*		
Total	3	5
Related to randomised PTCA	1	—
Related to other intervention	1	1
Other	1	4
Patients with primary endpoint (death or deinite myocardial infarction)	32	17
Subsequent interventions		
Non-randomised PTCA	62	101
CABG	40	30
Coronary arteriography	133	92

*Each patient is included only once.

Table 2: **Deaths, myocardial infarctions, and new interventions during median 2·7 years' follow-up**



Number of patients

PTCA	504	488	437	390	324	254	181
Medical	514	509	468	411	345	276	209

Figure 2: **Cumulative risk of death or definite myocardial infarction**

attempted in 65 occluded vessels with 69% success.

Patients' recruitment began before the widespread use of coronary stents, which were used during 12 (4%) of the 311 randomised PTCAs during 1992–94 compared with 32 (20%) of the 160 randomised PTCAs during 1995–96.

PTCA was complicated by emergency CABG in seven patients (1·5%), including two in whom stents were inserted. Another patient underwent elective CABG before discharge from hospital. The median length of hospital stay for the group randomised to angioplasty was 3 days, with 15% staying only 1 day and 8% over a week.

Death and myocardial infarction

During follow-up, 18 patients have died: 11 (2·2%) in the PTCA group and seven (1·4%) in the medical group (table 2, p=0·32).

The five cardiac deaths in the PTCA group included a randomised-procedure-related death from severe haemorrhagic complications of standard-dose heparin, a death due to complications of CABG following non-randomised PTCA, two sudden deaths 12 weeks and 2 years after PTCA, and a death from myocardial infarction 46 weeks after randomisation in a patient not undergoing PTCA because of lesion regression. The three cardiac deaths in the medical group were sudden in two and followed myocardial infarction in one patient.

There were 21 and ten definite non-fatal myocardial infarctions in the PTCA and medical groups, respectively, this difference being largely explained by the seven randomised-procedure-related infarcts in the PTCA group (for two of whom stents were inserted). Three of the other definite infarcts in the PTCA group were related to later non-randomised PTCA or CABG.

During follow-up, death or definite myocardial infarction occurred in 32 PTCA patients (6·3%) and 17 medical patients (3·3%) (figure 2, table 2). The relative risk was 1·92 with 95% CI 1·08 to 3·41 (p=0·02). The absolute treatment difference in risk of death and myocardial infarction was 3·0% (95% CI 0·4–5·7%).

Subsequent interventions

Since randomisation, 40 patients randomised to PTCA (7·9%) and 30 patients randomised to medical treatment (5·8%) had a CABG (table 2). This includes the seven emergency CABGs following the randomised PTCA and the nine CABGs performed instead of the intended randomised PTCA mentioned earlier. Three patients (two PTCA, one medical) underwent a second CABG. Figure 3 shows the accumulating risk of death, myocardial infarction, or CABG for patients randomised to PTCA

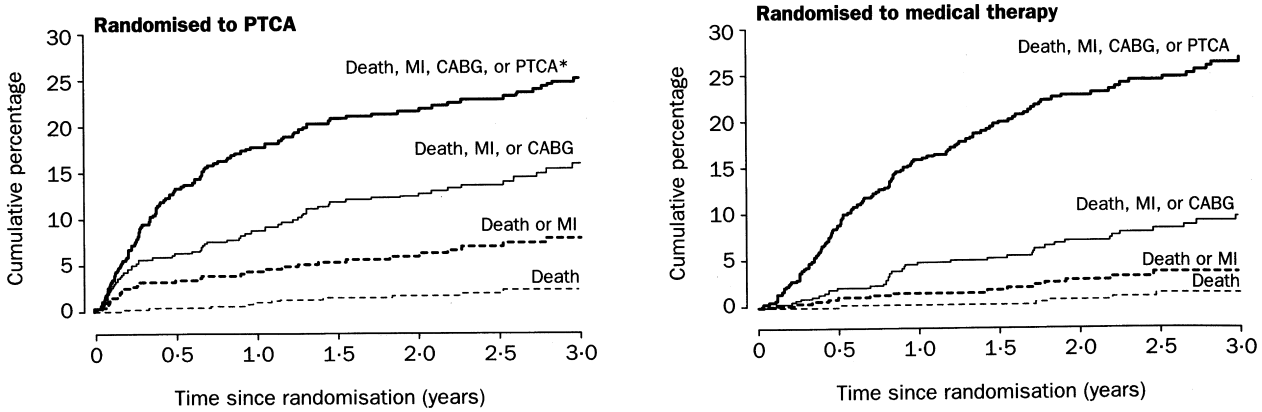


Figure 3: **Cumulative risk of PTCA, CABG, myocardial infarction (MI), or death**

*In addition to randomised PTCA.

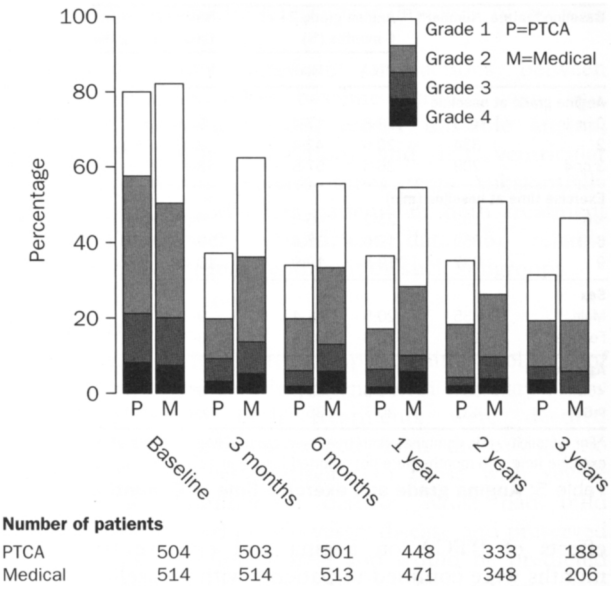


Figure 4: **Percentage with angina**

and medical treatment. The combined risk after 2 years' follow-up was 12·3% and 7·1% in the PTCA and medical groups, respectively. Additional non-randomised PTCA has been required in 62 patients randomised to PTCA of whom six also had CABG. The estimated life-table risk of requiring repeat PTCA or CABG within a year of the initial randomised PTCA was 14·9%.

In the medical group, 101 patients subsequently underwent PTCA of whom 13 also needed CABG. The accumulating risks of PTCA together with death, myocardial infarction, and CABG are also shown in figure 3. The risk of requiring PTCA or CABG within a year of randomisation was 15·4%. Most of the medical group "cross-overs" to PTCA or CABG were because the patient's angina was not adequately controlled by medical therapy. Of the 117 medical group patients who have undergone revascularisation, 75% had grade 3 or 4 angina and 83% were taking two or more antianginal drugs at the time of change in treatment strategy.

As for the randomised procedures, the use of coronary stents during non-randomised PTCA increased by calendar year: 9/95 (9%) in 1993–94, 16/59 (27%) in 1995, and 15/32 (47%) in 1996.

Event	Total	Time since randomisation		
		Within 3 months	3 months to 1 year	Over 1 year
Unstable angina				
PTCA	50	18	20	21
Medical	47	14	20	21
Cardiac failure				
PTCA	8	3	5	1
Medical	15	5	5	6
Arrhythmia				
PTCA	15	5	6	4
Medical	7	1	7	3
Stroke				
PTCA	1	1	0	0
Medical	6	2	3	4
Transient stroke				
PTCA	1	0	0	1
Medical	5	0	0	5

*Entry in each cell refers to number of patients experiencing event in that period.

Table 3: **Secondary events during follow-up***

Time since randomisation	Number	Number of antianginal drugs			
		None	1	2	3
3 months					
PTCA	501	99 (20%)	218	132	52 (10%)
Medical	508	36 (7%)	184	195	93 (18%)
6 months					
PTCA	499	115 (23%)	223	122	39 (8%)
Medical	508	37 (7%)	170	206	95 (19%)
1 year					
PTCA	144	112 (25%)	199	100	33 (7%)
Medical	466	45 (10%)	155	193	73 (16%)
2 years					
PTCA	328	101 (31%)	136	66	25 (8%)
Medical	343	43 (13%)	111	137	52 (15%)
3 years					
PTCA	188	68 (36%)	73	36	11 (6%)
Medical	203	28 (14%)	67	78	30 (15%)

Table 4: **Antianginal medication**

Secondary events

The occurrence of other clinical events is shown overall and in three time bands: first 3 months, rest of the year, and beyond a year since randomisation (table 3). The pattern of unstable angina was similar in both randomised groups (9·5%). Cardiac failure was slightly more common in the medical group (p=0·15) while arrhythmias were more frequent in the PTCA group (p=0·08). The incidence of stroke and transient stroke was low, each with a non-significantly greater rate in the medical group.

Angina and breathlessness

Throughout follow-up there was a substantial improvement in reported angina in both groups, but this improvement was significantly greater in the PTCA group (figure 4). This treatment difference was greater early on (figure 5), with a 16·5% excess of grade 2+ angina in the medical group 3 months after randomisation (p<0·001). After 2 years' follow-up, the medical group had only a 7·6% excess of grade 2+ angina (p=0·02), which represents a significant attenuation in the treatment difference over these 21 months (p=0·05).

This trend can be partly explained by the fact that patients with worsening symptoms underwent cardiac interventions subsequently in both treatment groups. For instance, in the medical group, of the 68 patients reporting grade 2+ angina at 3 months who improved to less than grade 2 at 2 years, 26 (38%) underwent PTCA and/or CABG in the intervening 21 months. Similarly, in the PTCA group, of the 42 patients experiencing the same improvement, 12 (29%) had had a coronary intervention meantime.

Centres differed in the baseline rate of angina grade 2 or more (heterogeneity test, p<0·001), which reflects differences in attitude as to what severity of angina was appropriate for inclusion in RITA-2. However, there was no evidence of between-centre heterogeneity in the treatment difference in angina frequency at 3 months (p=0·12), although such a test inevitably lacks statistical power.

Patients in the medical group had greater use of antianginal drugs during follow-up compared with patients in the PTCA group (table 4). Even so the use of triple-drug therapy never exceeded 20% in the medical

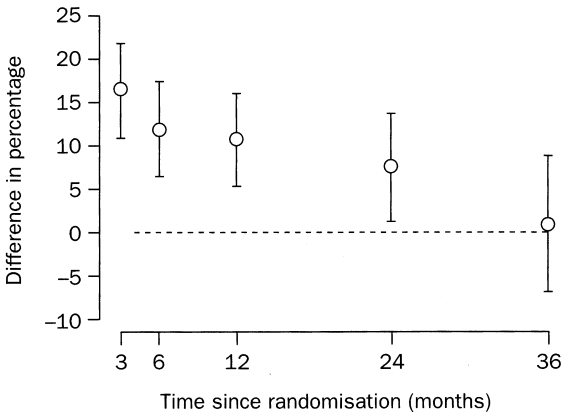


Figure 5: **Difference in percentage with grade 2 or worse angina**

Medical minus PTCA, 95% CI.

Baseline feature	Number*	Angina grade 2+ at 6 months (%)		Mean (SE) exercise time at 6 months	
		PTCA	Medical	PTCA	Medical
Angina grade at baseline					
0 or 1	473	13·8	17·4	9·16 (0·18)	9·25 (0·19)
2	334	20·6	42·4	8·79 (0·21)	7·86 (0·23)
3 or 4	209	36·5	57·8	8·44 (0·29)	7·45 (0·29)
Exercise time at baseline (min)					
⩽6	263	23·2	45·5	6·85 (0·24)	5·87 (0·20)
6–9	359	19·6	35·4	8·88 (0·17)	8·15 (0·15)
9	332	19·5	19·9	10·49 (0·17)	10·92 (0·18)
Sex					
Male	835	20·5	31·4	9·34 (0·13)	8·90 (0·15)
Female	183	22·8	39·8	6·72 (0·25)	6·52 (0·26)
Age (years)					
<60	584	20·9	31·0	9·54 (0·16)	9·19 (0·17)
⩾60	431	20·7	35·7	8·04 (0·18)	7·48 (0·20)

*For simplicity, this combines both treatment groups. Angina grade at 6 months and exercise time at 6 months were not reported for 9 and 118 patients, respectively.

Table 5: **Angina grade and exercise time at 6 months**

group, and over two-thirds of PTCA patients were still taking at least one antianginal drug after 2 years' follow-up. There was no difference between the two treatment groups in the use of aspirin or lipid-lowering drugs during follow-up.

During follow-up, breathlessness was reduced in the PTCA group (42% at 3 months *vs* 57% in the medical group, p<0·001). Similarly, severe breathlessness (defined as breathless when walking at own pace, washing, dressing, or at rest) was less common in the PTCA group compared with the medical group at 3 months (13% *vs* 17%, p=0·04) but these differences became less marked over time.

There was no significant difference in reported physical activity. Also the rates of unemployment due to coronary disease did not differ between the PTCA and medical groups, staying at around 25% for men aged under 65 at randomisation throughout 2 years' follow-up.

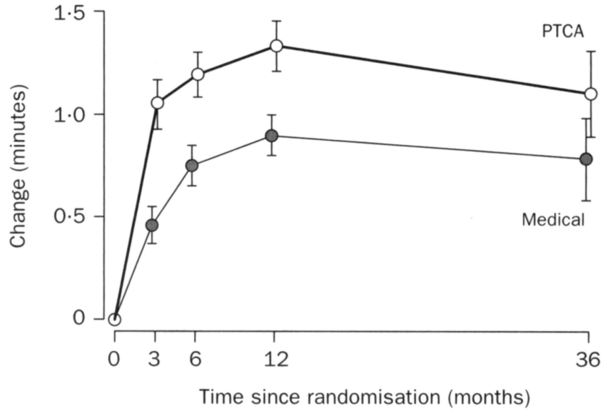
Exercise testing

The Bruce test was performed in about 90% of patients at each follow-up. At baseline, the mean exercise time was 7 min 41 s in both groups (SD 2 min 47 s). Figure 6 shows the mean changes in exercise time in relation to baseline. After 3 months the PTCA group had a larger improvement in exercise time compared with the medical group, mean difference 35 s (95% CI 20–51 s), but this attenuated (non-significantly) to 25 s (7–42 s) by 1 year. At 3 months, the numbers of patients who improved their exercise time by over 2 min compared with baseline were 124 (30%) and 74 (17%) in the PTCA and medical groups, respectively.

Subgroup analyses

The most striking findings are the strong influences of baseline grade of angina and baseline exercise time on the treatment differences (table 5). For patients with baseline angina grade 2 or more there was a marked benefit of PTCA at 6 months with a 20% lower frequency of angina and a 1-min longer mean exercise time than in the medical group patients. By contrast, for patients with no angina or grade 1 angina at baseline, there was negligible difference between PTCA and medical policies (interaction tests for angina and exercise outcomes, respectively, p=0·03 and p=0·01). Similarly the beneficial effects of PTCA on angina and exercise times at 6 months were confined to patients with a baseline exercise time of 9 min or less (interaction tests for angina and exercise outcomes, respectively, p=0·007 and p<0·001).

We simultaneously analysed the influences of angina grade and exercise time at baseline on these treatment differences at 6 months. The benefits of PTCA over medical treatment were largely concentrated in patients with both severe angina and poor exercise time at baseline. For the 366 patients with both angina grade 2 or more and exercise time of 9 min or less at baseline, the frequency of angina grade 2 or more at 6 months was 27·6% greater in the medical group than in the PTCA group. By contrast, for the 183 patients with both angina grade 0 or 1 and exercise time over 9 min at baseline, the medical group had 1·6% fewer patients with angina grade 2 or more at 6 months. For patients in an intermediate situation (either angina grade 2 or more at baseline or exercise time of 9 min or under at baseline), the medical group had 8·0% more patients with angina grade 2 or more at 6 months. A similar pattern of differential treatment effects emerged when we analysed mean exercise time at 6 months by baseline exercise time and baseline grade of angina. These results were confirmed by multiple logistic regression analysis of angina outcome and quantitative multiple-regression analyses of exercise



Number of patients

PTCA	469	418	425	369	154
Medical	485	446	436	399	177

Figure 6: **Changes in Bruce exercise times**

Mean and SE.

time outcome.

There were no significant interactions between treatment and six other baseline features: age, sex, number of diseased vessels, recent unstable angina, previous myocardial infarction, and left ventricular abnormality. Mean exercise times were substantially lower in women and older patients in both treatment groups. There were insufficient data for reliable evaluation of the primary endpoint by such subgroups.

Discussion

RITA-2 was designed to compare initial policies of PTCA and medical care in patients with coronary artery disease in whom both treatments were deemed acceptable. Our patients ranged from those with no angina and single-vessel disease to those with severe symptoms and multivessel disease. Most had mild symptoms, one-vessel or two-vessel disease and preserved left-ventricular-function scores, and would be predicted to be at low cardiovascular risk.[6,13,14] The patients were therefore not representative of all patients undergoing percutaneous coronary intervention, but represented a substantial group for whom medical therapy or angioplasty appear appropriate and for whom optimal treatment has been uncertain.

After 2·7 years, the PTCA group had a significantly greater risk of death or non-fatal infarction, the main endpoint. Even so, the absolute risk was low in both groups (3·3% in the medical arm versus 6·3% in the PTCA arm), and most of this difference occurred within 3 months of randomisation.

The randomised PTCA procedures were carried out with high success and low complication rates, with one procedure-related death (0·2%). RITA-2 lacks statistical power to detect small but potentially important differences in long-term mortality. Indeed, having recruited fewer patients than intended, we had reduced power for the main endpoint, which was nevertheless statistically significant.

RITA-2 patients were not systematically screened for myocardial infarction, and small procedure-related infarcts, which may be associated with increased cardiovascular risk,[15] were not included in the main endpoint. The true infarct rate in RITA-2 may therefore have been underestimated.

The excess risk of definite non-fatal infarction in the PTCA group was mainly due to procedure-related events but might also be partly explained by closer supervision of the PTCA patients. We doubt that this inevitable difference in follow-up could result in substantial bias. The risk of unheralded myocardial infarction in the medical group was low, although all patients had a significant coronary stenosis in a major epicardial artery. These data are consistent with evidence that myocardial infarction is often not due to pre-existing flow-limiting stenoses.[16,17] To date, the RITA-2 results provide no evidence to support the widely held belief that successful PTCA of a severe coronary stenosis reduces the risk of myocardial infarction. We await the long-term survival effects of the excess of non-fatal infarcts among PTCA patients, but a detrimental effect on prognosis is plausible.

The prognostic advantage of revascularisation by PTCA or CABG in ACIP[18] may reflect the fact that the patients were at higher cardiovascular risk, as judged by age and disease severity, than our patients. Moreover, 41% of patients assigned to revascularisation underwent coronary bypass surgery, which has prognostic advantages in particular groups.[13,14]

We demonstrated that PTCA improves symptoms (angina and breathlessness), reduces the requirement for antianginal medication, and improves exercise tolerance compared with medical therapy. These differences attenuated over 2–3 years' follow-up, partly because the patients with severe symptoms in the medical group eventually underwent myocardial revascularisation. Symptomatic improvement in the medical group may also be partly due to modification of antianginal therapy, disease regression, development of coronary collaterals, and regression to the mean. In the PTCA group the initial decrease in the occurrence of angina was maintained over 3 years, but during this period additional revascularisation procedures were carried out in over a fifth of these patients.

Subgroup analyses indicated that the beneficial effects of PTCA on angina and exercise tolerance are greatest in patients with severe symptoms or limited exercise tolerance at baseline; these findings have important implications for management. Patients without severe angina initially did not gain substantial symptomatic benefit from PTCA, and one might argue that in these patients revascularisation may reasonably be deferred unless more severe symptoms supervene. Moreover, exercise tolerance did not improve appreciably in patients with good exercise tolerance at baseline, and since these patients are at low cardiovascular risk[19,20] they are unlikely to gain major prognostic advantage from coronary angioplasty. For patients with more severe symptoms or impaired exercise tolerance, PTCA seems more warranted, but the beneficial effects must be balanced against the small procedure-related hazard. These observations suggest that the current clinical enthusiasm for early PTCA in low-risk cohorts in some countries needs to be reappraised.

Other small trials have also compared the effects of PTCA and medical treatment.[4,21–23] None has sufficient power to compare the two strategies for risk of death or myocardial infarction, but their results could be combined with RITA-2 in a meta-analysis.

Since RITA-2 began in 1992 there have been important advances in the medical and interventional treatment of patients with coronary artery disease. HMG CoA reductase inhibitors reduce cardiovascular risk in patients with coronary artery disease,[5,24] and the use of these drugs increased during RITA-2. Nevertheless, more aggressive use of lipid-lowering therapy in both groups might have resulted in better prognosis with fewer additional revascularisation procedures. Glycoprotein IIb/IIIa receptor blockers[25,26] and coronary stents[27–30] improve the acute and long-term results of coronary interventions. The use of stents increased during RITA-2 reflecting routine clinical practice in the UK and other countries. In some centres, stents are used in 50–70% of percutaneous coronary interventions, but the long-term implications of such a policy are unknown.

By addressing the balance between symptomatic benefit and procedure-related risk, RITA-2 has helped to define optimal treatment strategies for an important subgroup of patients with angina.

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