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Revascularization as a means of reducing sudden death

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Introduction

In the preceding contribution arguments have been detailed why the most likely cause for sudden cardiac death in coronary artery disease is related to (bouts of) severe ischaemia. It was also suggested that since recent major trials with antiarrhythmic agents have not shown any reduction in subsequent death rates (while ventricular arrhythmias had in most cases, been markedly reduced), the original tenet that ventricular arrhythmias are the predictors of subsequent cardiac sudden death, could not be maintained any longer. Rather it was shown that the triggering event was often an episode of ischaemia, secondary to thrombotic aggregation with or without spasm which leads to ventricular fibrillation (see Fig. 1). This is often manifest by angina, although it now also has become clear from many studies that 'silent ischaemia' is much more frequent than previously recognized and may cause death without 'warning signs'. Even when ischaemia manifests itself by threatening symptoms such as unstable angina, it has been shown[1,2] that the distinction between a reversible ischaemic state and an already infarcted myocardium cannot clinically be made in many instances. Accordingly, an entire new approach in the prevention of sudden cardiac death would be to strive for early and complete revascularization in all those patients who have been shown in prior contacts with the medical profession to have obstructive coronary artery disease and who are at risk for complete occlusion. Such revascularization may be carried out by coronary artery bypass surgery, percutaneous transluminal coronary angioplasty (PTCA) or thrombolysis for which now a variety of agents have come on the market such as urokinase, streptokinase and most recently tissue plasminogen activators made by the recombinant technique (rt-PA). It is the purpose of this brief review to point towards some recent clinical results which will in part substantiate this strategy for reducing unnecessary cardiac death.

Bypass surgery

Although no randomized trial has been undertaken in patients known to have ischaemia with the express purpose of studying the efficacy of bypass grafting on subsequent deathrates, the results from numerous large scale studies in stable angina have shown an extremely low death rate of approximately 1% per annum, which extend to 10 years after the original surgery. From our own experience at the Thoraxcenter, with 1041 patients followed up for an average of 8 years, it could be shown that the initially low surgical mortality of 1·2% was matched by a similar percentage over the subsequent years (Fig. 2). Thus, at the end of 10 years as many people were alive after bypass surgery as were alive in a comparable group of healthy Dutch citizens. Out of these 1041 only 123 (12%) required in the course of 7·5 years on average a reoperation, which was a PTCA or CABG for recurrent severe angina. In the 89 CABG patients, the operative mortality rose to 6·5% however. Whilst part of the low mortality can be explained by the careful preoperative evaluation of each patient, which excluded those with other severe illnesses, the low mortality figures by themselves indicate that death from cardiac causes has been markedly reduced[3]. It is only reasonable to assume that this is secondary to effective revascularization of obstructive lesions. Even in the series recently published by Berg *et al.*[4] it was shown that when bypass surgery is carried out within hours after the onset of symptoms, in patients known to have an acute infarction, a very low surgical mortality can be achieved in selected cases, which in turn is matched by a very low subsequent mortality.

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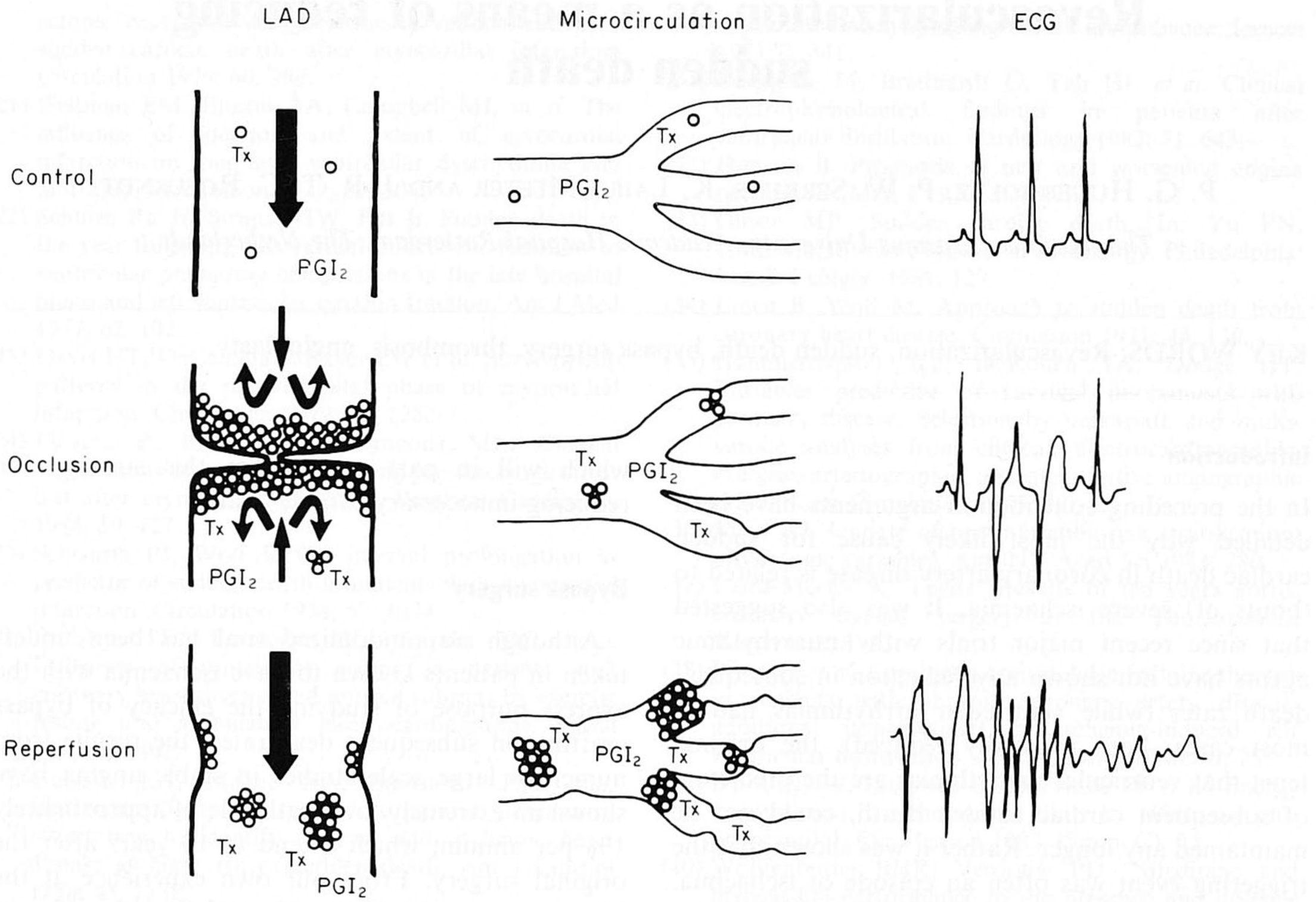

Figure 1 Schematic display of data obtained by Parratt *et al.*[1] in experimental sudden death, caused by sudden interruption of the microcirculation with reperfusion and release of various substances which can induce ventricular fibrillation.

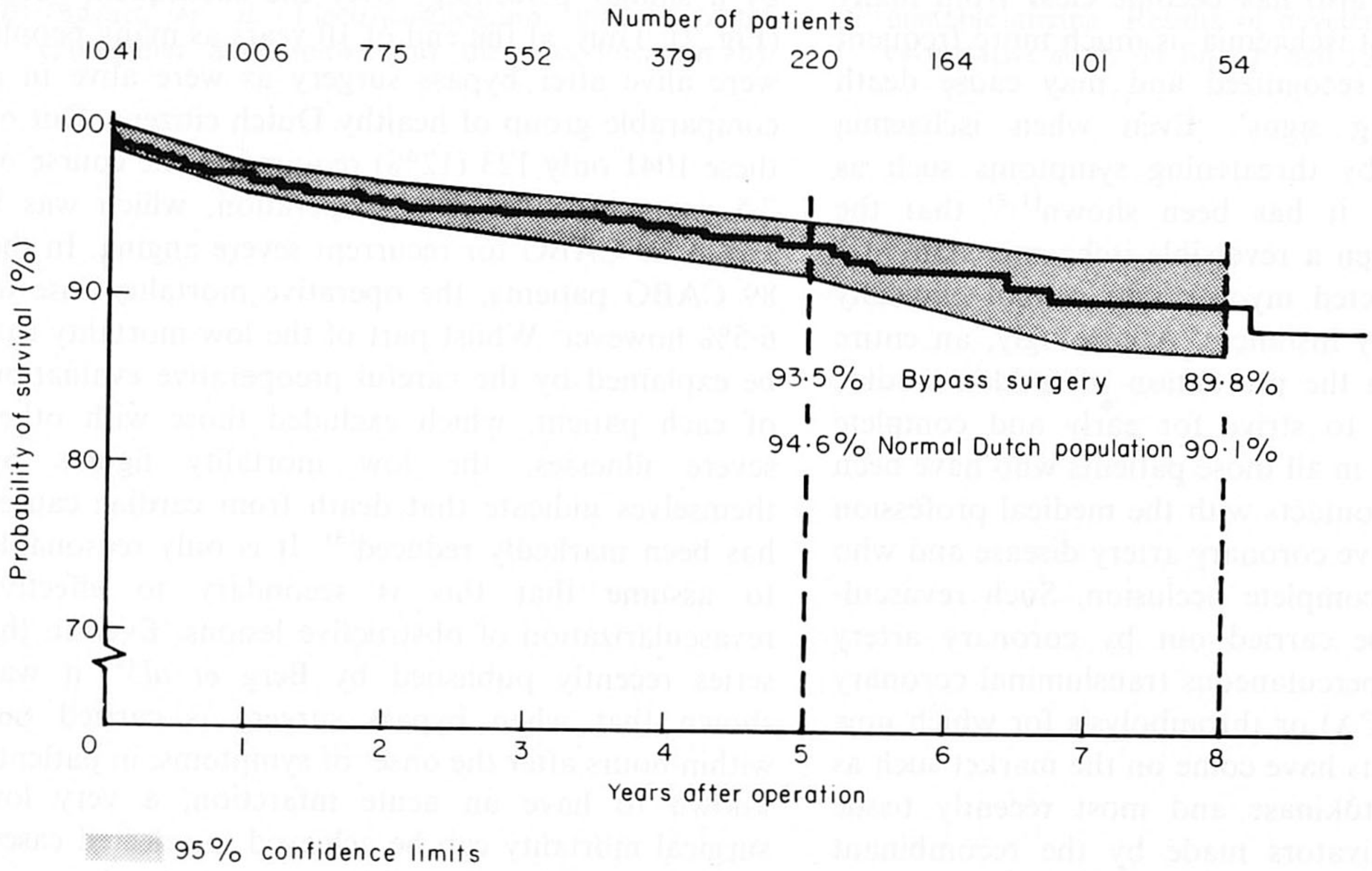

Figure 2 Data obtained during a long-term following of 1041 patients operated on for angina pectoris at our institution[3].

Percutaneous transluminal coronary angioplasty

Now that follow-up studies after PTCA are becoming available it is evident that despite a reocclusion rate of between 15 and 20% at the end of 5 years, mortality in those treated has remained equally low as after successful bypass surgery. Although the procedure heavily favours patients with one vessel disease in whom the mortality is low in any case, increasing numbers of patients with multivessel disease are being treated and similar results observed. Again, the only explanation for the low death rate is the timely revascularization, this time by dilatation of the vessel rather than by bypass. In acute unstable angina it has recently also been shown[5,6] that when medical therapy with beta-blockers, calcium antagonists and nitrates is unsuccessful and patients are deemed refractory, early PTCA (carried out within hours after the pharmacological therapy proved ineffective) had remarkable one year survival rates of 95 to 98%. This is in contrast with data reported in the earlier literature which showed the syndrome of unstable angina, when refractory to initial pharmacological treatment to be associated with death rates up to 20%[7]. Also when angina returns early after an acute myocardial infarction, recent evidence from our laboratory has shown that the previously reported high death rate of $\pm 15\%$ at the end of the first year, can be reduced to a few percent. Again the most likely explanation is adequate revascularization of a region of the myocardium which was at risk of ischaemic episodes and insufficient reperfusion.

Thrombolysis

The most striking circumstantial evidence in favour of the need for early reperfusion comes from recently reported data with streptokinase in acute myocardial infarction. Whilst it is generally accepted that myocardial infarction when treated with conventional methods has a one year mortality ranging from 5 to 15% depending on the region of the infarction and the size of it, the age of the patient and the adequacy of treatment (i.e. availability of CCU etc.), early administration of intravenous streptokinase followed by intracoronary streptokinase with 4 hours after the onset of symptoms, has led to a remarkable reduction in death rates (Table 1). From a recent study[8] it has become evident that when an optimal strategy of early revascularization by means of thrombolysis is followed by balloon dilatation of the residual atheromatous lesion, death rates can be brought down to a few percent in the first year of follow up. In the randomized study reported recently from the Netherlands[8] involving 533 patients with acute myocardial infarction seen at the hospital within the first few hours after symptoms, it was also shown that in the group assigned to a strategy of early reperfusion regardless of the route of administration of streptokinase, the death rate was still half that of the control patients (8·5% *vs* 16·5%—see Fig. 3). In the subset which was given intravenous streptokinase within the first two hours after onset of symptoms as they entered the hospital, and who were subsequently treated in an optimal fashion by

Table 1 533 consecutive patients—onset of symptoms to treatment max 4 hours

	Conventional	Reperfusion	*P* value
Number of patients	264	269	
Cardiogenic shock	24	13	
Ventricular fibrillation	61	38	0·01
Pericarditis	46	19	0·0004
Bleeding	8	53	0·0001
Ejection fraction, %	46	53	0·001
Mortality (14 days)	25	14	0·03
Mortality (8 months)	41 (15·5%)	23 (8·5%)	0·01

Netherlands Interuniversity Cardiology Institute, 1985.
Data reported recently from a large randomized multicenter study[8] in 533 patients with acute myocardial infarction. It is evident that early thrombolytic therapy achieves a halving of the major complications and of the death rate after myocardial infarction.

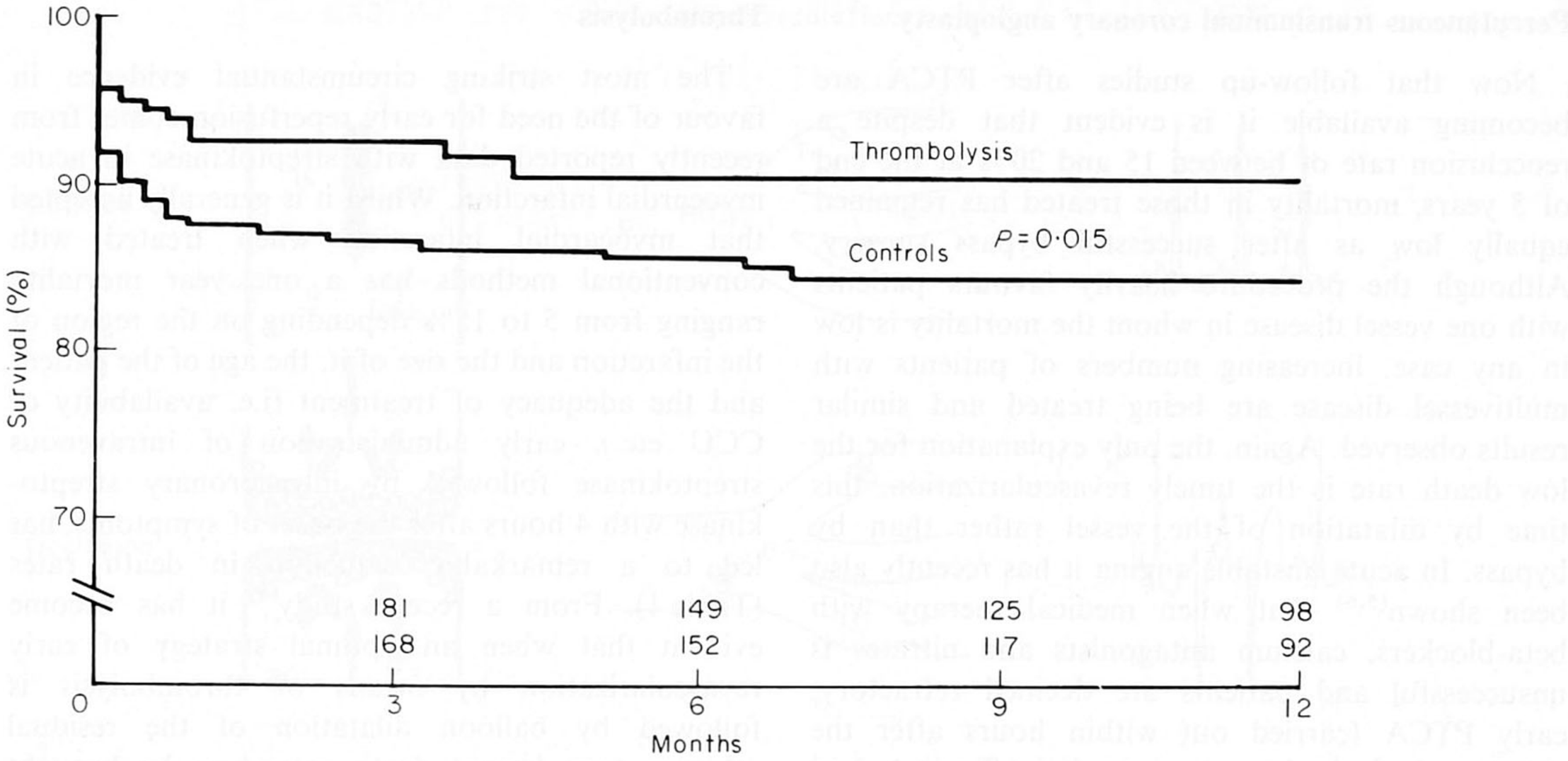

Figure 3 Persistent improvement in survival when thrombolysis was started early after onset of infarction[8].

intracoronary streptokinase and/or PTCA, it could be demonstrated that the one year mortality had declined to just above 1%. Similar data had been reported from the Western Washington Trial conducted by Kennedy, which also revealed a halving of the death rate. Large scale trials with intravenous streptokinase are currently under way, as are trials with the much more promising agent, rt-PA. Since the latter affects the thrombus directly, without depressing the general fibrinogen level, the possibility now becomes quite high that such therapy can be given by the general practitioner when he sees the patients within 1 hour after onset of symptoms. A general policy of early resolution of the obstructing thrombus accompanied by a systematic evaluation of the status of the coronary artery system in those individuals who remain symptomatic and have signs of persisting ischaemia, should enable us to considerably reduce the risk of subsequent infarction and death in patients sustaining their first infartion. With further development of strategies to render the post infarction patient safe from reobstruction it can be anticipated that the incidence of unnecessary cardiac death can be reduced by this means as well.

Other agents

Although many agents have been uncovered which interfere with the clotting process only the recent large scale trial reported by Lewis *et al.*[9] has shown convincingly that the death rate after unstable angina could be reduced by aspirin. In 1266 men the death rate and acute infarction rate combined were reduced by 51%, 31 patients versus 65 patients in the placebo group ($P=0{\cdot}0005$). Recently Cairns[10] has reported an even more impressive proof of the efficacy of aspirin.

Discussion

It is clearly too early to advocate a general strategy at this time. The purpose of this brief review is to redirect the reader towards a rather 'old time' physiological principle, namely reestablishing blood-flow shortly after its interruption to avoid unnecessary loss of myocardial tissue. Since it has now been generally accepted that the degree to which myocardial tissue has been damaged after myocardial infarction, is the sole predictor of subsequent sudden cardiac death, it is only logical to attack this problem by reducing the cardiac damage from the outset i.e. immediately upon presentation of symptoms. As shown in Fig. 4, there is a curvilinear relationship between the function of the left ventricle at the time of discharge after recovery of the acute myocardial infarction event and the one year survival rate. As is evident from that figure, a marked increase in death rate occurs when the ventricular function expressed by the ejection

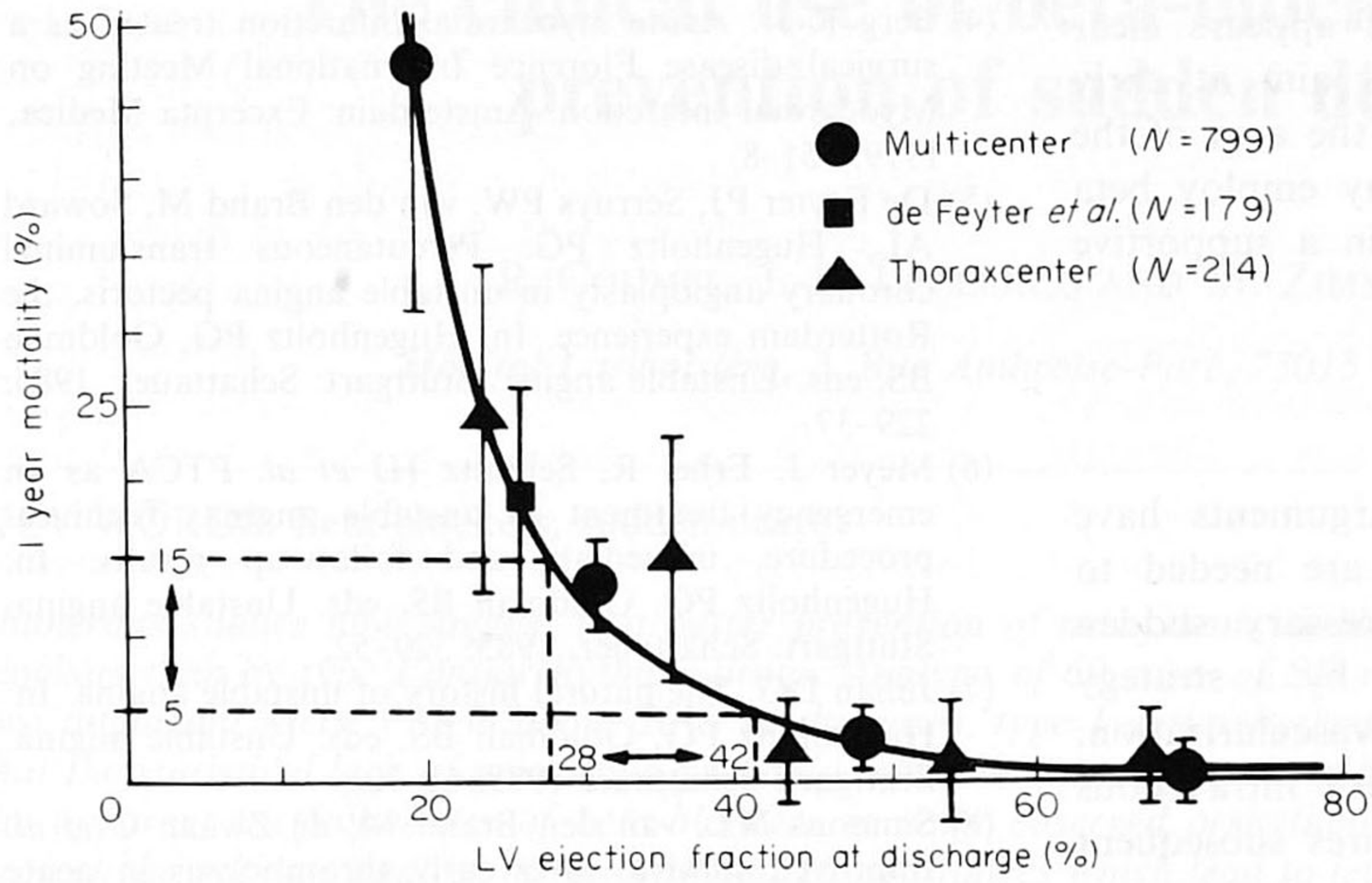

Figure 4 Composite of data reported on 3 studies relating ejection fraction at discharge after acute myocardial infarction with subsequent 1 year survival. It is clear that an improvement in ejection fraction from 28 to 40% would entail a reduction in 1 year mortality from 15 to 5%.

fraction declines below 40%. If therefore, as indicated in that figure a moderate increase in ejection fraction could be achieved by early reperfusion (it was shown in the Netherlands trial to be a mean of 8%), the improvement in left ventricular function by itself, could be held responsible for the improvement in long-term outcome. Again an argument to reestablish blood flow at an early stage.

Whether one talks about stable angina pectoris, unstable angina pectoris, acute myocardial infarction, or angina reoccurring after myocardial infarction, all these clinical states provide clear evidence that the blood supply to the region of the myocardium at risk is impaired. Any strategy aimed at reducing this impairment in coronary blood flow must therefore be judged beneficial and the remaining question becomes now whether or not the cost benefit ratio of these procedures can justify their general application.

In this context the large scale trials with beta blockers and more recently with calcium antagonists, must be mentioned. Whilst in secondary prevention undoubtedly beneficial, in reducing the death rate, the impact of this strategy is less evident when applied early. Large numbers of patients, who are not at risk, must be treated for the demonstration of benefit in just a few. In the most recent and largest reported trial with the beta-blocker metoprolol[11] it was shown that acute treatment (i.e. within the first 12 hours) with intravenous metoprolol could barely influence the mortality figures in the first 14 days. Even the still larger trial carried out with atenolol, involving over 14000 patients could show only a reduction by 14% in overall death rate in the first 24 hours and in order to achieve this effect, 150 patients had to be treated to save one life. No long-term follow up data are available on either the metoprolol or the atenolol trial so that the efficacy of this approach over the first year after the infarction remains still in doubt. When these results and those with the calcium antagonists trials which are even less convincing[13–16] are contrasted with the data shown above for early thrombolysis, the benefits of the latter approach are several orders of magnitude higher.

Admittedly the reperfusion strategy requires a greater initial effort by the medical community, than the simple intravenous injection of a beta-blocker with or without a calcium antagonist, but such therapy can be given only to a subset of those patients offered to the coronary care unit. Most beta-blocker trials had to be restricted by inclusion or exclusion criteria to 40 to 50% of the patients offered and involved usually only those at low risk whilst the thrombolytic reperfusion approach with or without subsequent aspirin can and has been offered to all patients except those showing a haemorrhagic diathesis. Thus, with the promised arrival of more effacious thrombolytic agents with

even fewer complications the road appears clear towards major trials which should aim at early reperfusion of the vessel leading to the area of the myocardium at risk and which may employ beta blockade and calcium antagonists in a supportive fashion.

Summary and conclusion

From this brief overview the arguments have become clear why further studies are needed to verify that the problem of unnecessary sudden cardiac death can best be tackled by a strategy aimed at early and complete revascularization. Whether such a strategy begins with intravenous injection of rt-PA at home or requires subsequent intracoronary manipulation when obstruction persists, whether by thrombolysis with other agents, PTCA or bypass surgery, is in itself a moot point. The main aim should be to offer this strategy as the best chance to reduce the unnecessary sudden death rate which presently accounts for between 25 and 50% of all cardiac deaths. This approach deserves consideration particularly since earlier approaches employing cardioprotective efforts by beta blockade or by anti arrhythmic agents have patently shown that they cannot tackle the problem in a convincing manner.

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