

Total Ischaemic Burden European Trial (TIBET)

Effects of ischaemia and treatment with atenolol, nifedipine SR and their combination on outcome in patients with chronic stable angina

H. J. Dargie*, I. Ford*, K. M. Fox† on behalf of the TIBET study group

*University of Glasgow, Glasgow, U.K.; †Royal Brompton Hospital, London, U.K.

Objectives To study the relationship between presence or absence of ischaemic events on Holter monitoring and occurrence of a hard or hard+soft endpoint.

Design A randomized double-blind parallel group study of atenolol, nifedipine and their combination, with ambulatory monitoring off-treatment and after 6 weeks of randomized treatment and prospective follow-up of 2 years on average.

Setting Europe.

Subjects 682 men and women with a diagnosis of chronic stable angina and who were not being considered for surgery.

Main outcome Hard endpoints were cardiac death, non-fatal myocardial infarction and unstable angina; soft endpoints were coronary artery bypass surgery, coronary angioplasty and treatment failure.

Results The study showed no evidence of an association between the presence, frequency or total duration of ischaemic events on Holter monitoring, either on or off treatment, and the main outcome measures. There was a non-significant trend to a lower rate of hard endpoints in the group receiving combination therapy. Compliance, as measured by withdrawal from trial medication, was clearly poorest in the nifedipine group with similar withdrawal rates in the atenolol and combination therapy groups.

Conclusion The recording of ischaemic events in 48 h Holter monitoring failed to predict hard or hard+soft endpoints in patients with chronic stable angina. (Eur Heart J 1996; 17: 104–112)

Key words: Ischaemia, Holter monitoring, beta-blocker, calcium channel blocker.

Introduction

The dual aims of treatment in patients with coronary heart disease (CHD) are to relieve symptoms and to improve outcome by preventing or postponing serious cardiac events, including mortality. In patients with CHD in whom the dominant symptom is exertional angina, both those aims are achieved by coronary bypass surgery in selected groups of patients^[1–3]. Anti-anginal medication also reduces the frequency and severity of chest pain to a variable extent but has never been shown conclusively to improve the prognosis^[4,5]. In patients with angina, ischaemia can be provoked in a number of ways but most commonly by symptom-limited exercise testing, while ischaemia occurring during daily life is readily detectable in about half of those

patients presenting for investigation of chronic stable angina by the technique of ambulatory monitoring of the ST segment of the ECG. Since both medical treatment and CABG can abolish or substantially reduce evidence of myocardial ischaemia demonstrated by both these non-invasive techniques^[6,7], and since the presence and severity of ischaemia is closely and directly related to outcome^[8,9], it is reasonable to suggest that medical reduction of ischaemia might also improve survival.

The Total Ischaemic Burden European Trial (TIBET) was set up, firstly to address the hypothesis that the frequency and duration of ischaemia in daily life, as detected by ambulatory monitoring of the electrocardiogram, would be predictive of clinical outcome as assessed by the frequency of cardiac death, non-fatal myocardial infarction (MI), unstable angina, revascularization, treatment failure and the necessity for withdrawal from prescribed treatment. In addition, we aimed to determine any trends in prognosis from which power calculations could be made on which to base a larger

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Correspondence: Professor H. J. Dargie, West Medical Building, University of Glasgow, Glasgow G12 8QQ, U.K.

appropriately powered trial of the impact of medical treatment on mortality.

Patients and methods

Design

The design, patient selection and methods have been described in detail elsewhere^[10], but, briefly, the plan was as follows: Patients with chronic stable angina, whose symptoms were well enough controlled on medical therapy so that they were not immediately being considered for revascularization, were entered into a randomized double-blind clinical trial of three commonly used treatments. These were the beta-blocker atenolol, the calcium channel blocker nifedipine (slow release formulation), and their combination. In order to be randomized, patients were required, during a 2-week placebo run-in period, to have at least 1.5 mm ST segment depression during a symptom-limited exercise tolerance test at a workload of less than 10 METS. Although a central analysis was carried out on all exercise tests at a later date to ensure uniformity of interpretation, the results of the central analysis were, necessarily, unavailable to the investigators at that visit. Randomization, therefore, took place on the basis of the analysis of the pre-randomization test by the investigators themselves. In order to minimize withdrawal due to side-effects, patients had to demonstrate their tolerance to a 2-week treatment period with the full dose of the combination treatment of atenolol and nifedipine. Ambulatory ECG recording was carried out during the placebo run-in period and, together with a further exercise test, after 6 weeks on randomized treatment. At the 6-week visit, there was an opportunity to increase the doses of nifedipine in the monotherapy and combination arms from the starting doses of 20 mg twice daily to 40 mg twice daily. The dose of atenolol remained at 50 mg twice daily throughout the study in both arms. Exercise testing could be performed either on a treadmill using the Bruce protocol or on a bicycle ergometer at a starting workload of 30 watts which increased by 30 watts every 3 min. All patients were followed regularly at the out-patient clinic for an average of 2 years or until death had occurred. Withdrawal from trial therapy occurred if unblinding of medication was required for any reason or in the presence of severe side-effects or adverse reactions.

Primary endpoints

The predetermined endpoints of the study were designated 'primary' or 'secondary'. The primary endpoints were as follows:

- (1) Cardiac mortality. For a diagnosis of 'acute fatal myocardial infarction' to be recorded, this diagnosis either had to be stated in the death certificate or, in

the event of the death certificate diagnosis being uncertain, macroscopic or microscopic myocardial necrosis had to be demonstrated at the autopsy. 'Sudden cardiac death' was recorded if the patient died within 24 h of the onset of symptoms in the absence of extracoronary causes of death.

- (2) Myocardial infarction — 'silent' or 'symptomatic'. A 'silent' myocardial infarction was defined as the appearance of pathological Q waves in the ECG without a history of chest pain. Patients with silent myocardial infarction could be withdrawn from randomized treatment for further investigation depending on the clinical situation. 'Symptomatic' myocardial infarction was defined according to the following three criteria, at least two of which had to be fulfilled: (a) Central chest pain of more than 30 min duration with onset during the previous 48 h, pulmonary oedema without previously known valvular disease, or shock without suspicion of acute hypovolemia of intoxication. (b) Transient elevation of aspartate transaminase (AST/SGOT) to values above the normal limits for the laboratory and with a maximum approximately 24 h after the estimated onset of infarction, combined with less pronounced or no elevation of alanine transaminase (ALT/SHPT); or if AST and ALT tests were not routinely performed, transient elevation of creatine phosphokinase to values above the normal limits for the laboratory and with a maximum approximately 24 h after the estimated onset of infarction. (c) The development of pathological Q waves and/or the development or disappearance of localized ST-segment elevation combined with the development of T-wave inversion in at least two of the 12 routine standard leads (I, II, III, aVR, V₁, V₂, V₃, V₄, V₅ and V₆).
- (3) Unstable angina defined as chest pain of increasing frequency and severity, occurring at rest, requiring hospitalization of the patient and not associated with the development of new Q-waves on the ECG or a rise in cardiac enzymes. Patients who developed unstable angina were withdrawn immediately to facilitate urgent treatment and further investigation.
- (4) CABG and/or angioplasty.
- (5) Treatment failure. Where symptoms persisted on high dose trial therapy plus prophylactic short-acting nitrate therapy, patients were considered to be 'treatment failures'. When treatment was withdrawn, the patient was followed-up wherever possible as if he/she were continuing in the trial. Details of additional investigations, treatment, and subsequent outcome were recorded for the duration of the study.

Cardiac mortality, myocardial infarction, and unstable angina were regarded as 'hard' endpoints, whilst CABG, angioplasty, and treatment failure were considered to be 'soft'. The primary endpoints were verified by the Endpoints Committee which comprised three non-participating clinicians, together with the

TIBET coordinator whose function it was to collect and make available all data required by the Committee. The committee members audited and confirmed all primary endpoints by reference to original documentation, including case records, electrocardiograms, cardiac enzyme results, autopsy reports and death certificates.

Secondary endpoints

The secondary endpoints of the study were as follows: (1) Time to onset of angina or significant ischaemia (1.00 mm ST depression) during a standard exercise test. (2) Total duration of exercise (exercise test). (3) Number and duration of ischaemic episodes defined as 1 mm ST segment depression (48 h Holter).

Ischaemic episodes included painful (symptomatic) and silent (asymptomatic) ischaemia, thereby constituting the total ischaemic burden (TIB).

Statistical methods

The time until the occurrence of an endpoint was taken to be the response variable for statistical analysis. Comparisons among sub-groups of patients (for instance split on the basis of presence/absence of ischaemia on Holter monitoring) were assessed by the logrank test. Analyses involving adjustment for covariates were based on the Cox proportional hazards model. Since patients could have more than one event in any category (for instance, non-fatal MI followed by cardiac death in the hard endpoint category), the time until the first endpoint in the category was used in the analysis. In the analyses involving Holter monitoring, patients were excluded from the analysis if they did not have at least 23 h of analysable tape from the 48 h monitoring period. Otherwise, all analyses have been carried out on an intention to treat basis with the status of all patients having been obtained at trial completion. Survival curves and withdrawal curves were estimated using the Kaplan-Meier approach. Tests of association between categorical variable were based on standard chi-squared statistics.

Analyses were carried out for the full randomized set of patients (682) and for the sub-set (608) who met the trial entry criteria on central analysis of the baseline exercise test ECG. Results are reported only for the full set of 682 patients. Those for the smaller group were very similar.

Results are reported for the composite events (i) hard endpoints and (ii) hard+soft endpoints.

Results

Secondary endpoints

Nine hundred and sixteen patients were entered into the study, 682 eventually being randomized (74.4%). The

Table 1 Baseline characteristics of the TIBET subjects (n=682), age, sex and clinical history

	Atenolol (n=226)	Nifedipine (n=232)	Combination (n=224)
Age [mean(SD)]	58.8 (7.6)	60.0 (7.7)	59.7 (7.9)
Males	196	191	198
Previous MI	77	71	77
Previous heart failure	2	4	1
Hypertension	52	54	47
Diabetic	10	7	18
Current smokers	39	30	44
Previous angiogram	67	62	64
Previous PTCA	4	5	5
Previous CABG	14	12	9

patients were drawn from 69 centres in nine European countries. The baseline characteristics of the 682 subjects are given in Table 1. The central analysis carried out after randomization indicated that 608 patients (89%) satisfied the inclusion criteria of having a valid exercise test with 1.0 mm ST segment depression on central analysis during the placebo exercise test. The results reported in this paper have been analysed separately for the total population randomized and for those fulfilling the entry criteria.

The secondary endpoint data are described in detail in an accompanying paper in this issue^[1], but, briefly, the results were as follows: atenolol, nifedipine and their combination were equally effective in markedly and significantly reducing all markers of reversible ischaemia both during exercise testing and ambulatory monitoring. This included total exercise time, time to the development of angina and of 1 mm ST segment depression, maximum ST segment depression, and the percentage of patients with episodes of ambulatory ischaemia (as defined) in the 48 h recording period.

Heart rate was similarly lowered on atenolol and the combination. These changes were significantly different than that obtained on nifedipine, which caused a slight increase in heart rate. Atenolol and nifedipine also reduced systolic and diastolic blood pressure equally and significantly while the combination lowered it to a significantly greater extent [mean reductions being 12.9/7.3, 12.5/6.7 and 20.6/11 mmHg respectively (SBP/DBP), see Fig. 1]. These values are for sitting, those for standing being virtually identical.

Primary endpoints

(1) Frequency of endpoints: 124 subjects had a total of 163 trial endpoints (13 cardiac death, 38 non-fatal MI, 26 unstable angina, 30 CABG, four angioplasty and 52 treatment failure). The duration of follow-up ranged from 1 to 3 years (mean 2 years). Table 2 contains the distribution of the most 'severe' trial endpoint incurred by the trial subjects, split by the three randomized treatment groups (atenolol,

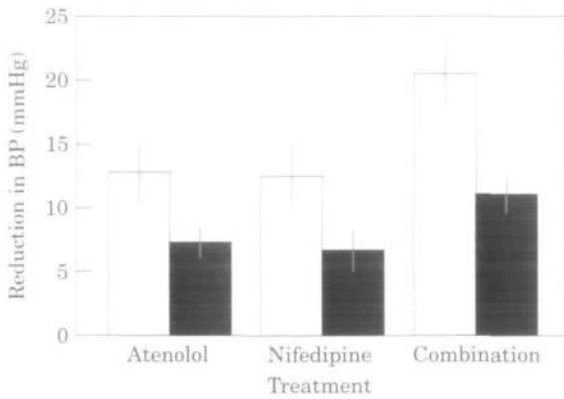


Figure 1 Reductions in systolic (□) and diastolic (■) blood pressure after 6 weeks of randomized treatment for atenolol, nifedipine and their combination. Data displayed are mean reductions and 95% confidence intervals.

Table 2 Distribution of the 682 subjects by treatment group and severest endpoint

Severest endpoint	Atenolol	Nifedipine	Combination	Total
Cardiac death	3	6	4	13
Non-fatal MI	14	15	7	36
Unstable angina	12	4	8	24
CABG	7	6	4	17
PTCA	1	0	0	1
Treatment failure	10	15	8	33
No endpoint	179	186	193	558
Total	226	232	224	682

nifedipine, and their combination). The ranking of the endpoints in decreasing order of severity was taken to be cardiac death, non-fatal MI, unstable angina, CABG, angioplasty and treatment failure.

(2) Relationships with presence of ischaemia on Holter monitoring Table 3: For hard and hard+soft endpoints, the distribution of subjects with and without an endpoint is cross-tabulated with the presence or absence of at least one ischaemic event on Holter separately for off- and on-treatment visits. For the off-treatment Holter data in the group of subjects

Table 3 Cross-tabulations of subjects by presence/absence of an endpoint and presence/absence of one or more ischaemic events on Holter monitoring off treatment and on treatment, for each of the combinations of Hard and Hard+Soft Endpoints with Holter outcome. Results are for subjects with at least 23 h of analysable Holter tape at the visits considered in each sub-table

		Off treatment Event on Holter		On treatment Event on Holter	
		Yes	No	Yes	No
Hard Endpoint	Yes	33	30	23	40
	No	265	299	183	383
		<i>(P=0.42)</i>		<i>(P=0.50)</i>	
Hard+Soft Endpoint	Yes	58	51	41	71
	No	240	278	165	352
		<i>(P=0.19)</i>		<i>(P=0.34)</i>	

with ischaemic episodes 11% (20%) of subjects had a hard (hard+soft) endpoint in comparison to 9% (16%) for subjects who had no ischaemic attacks. For the on-treatment Holter data, the corresponding event rates were 11% (20%) for those with ischaemic events and 9% (17%) for those with no ambulatory ischaemic events. None of these comparisons achieved statistical significance when the 'time to event' data were analysed by the logrank test.

Tables 4 and 5, respectively, contain corresponding distributions of trial endpoints by the number of ischaemic events and by their duration on Holter monitoring. There was no evidence of any association between the frequency or duration of ischaemic events at Visit 3 or Visit 5 and the risk of a hard or hard+soft endpoint.

The relationship between times until trial endpoint data and presence of ischaemic events were also analysed using a Cox proportional hazards model adjusting for randomized treatment and age. The relationships with the on-treatment Holter data were, in addition, adjusted for presence/absence of ischaemic attacks at the off treatment visit. None of

Table 4 For both on and off treatment data, the table contains a breakdown of the patient group by the number of ischaemic episodes (silent or symptomatic) recorded on Holter monitoring and by the occurrence of a Hard (Hard+Soft) endpoint. Only patients with at least 23 h of analysable tape are included. Chi-squared test P values were calculated after re-grouping the number of episodes into four groups (0, 1, 2, 3 or 4, ≥5 events)

Number of events		0	1	2	3	4	≥5	Total
Off treatment	Patients with an endpoint	30(51)	10(17)	6(14)	4(5)	2(2)	11(20)	63(109)
	All patients	329	89	56	38	18	97	627
		<i>[P=0.95(0.30)]</i>						
On treatment	Patients with an endpoint	40(71)	7(16)	7(10)	4(6)	1(1)	4(8)	63(112)
	All patients	423	76	37	29	20	44	629
		<i>[P=0.33(0.37)]</i>						

Table 5 For both on and off treatment data, the table contains a breakdown of the patient group by the total duration of ischaemic episodes (silent or symptomatic) recorded on Holter monitoring and by the occurrence of a Hard (Hard+Soft) endpoint. Only patients with at least 23 h of analysable tape are included. Chi-squared test *P*-values were calculated after re-grouping the duration of episodes into 3 groups (0, 1–30 and >30 min)

Duration of events (min)		0	1–30	31–60	61–120	>120	Total
Off treatment	Patients with an endpoint	30(51)	14(27)	7(8)	5(14)	7(9)	63(109)
	All patients	329	112	69	63	54	627 [<i>P</i> =0.59(0.11)]
On treatment	Patients with an endpoint	40(71)	6(14)	12(17)	3(6)	2(3)	63(111)
	All patients	423	90	58	36	21	628 [<i>P</i> =0.19(0.30)]

these analyses revealed evidence of a relationship between the presence/absence of ischaemic on Holter monitoring (on or off treatment) and subsequent patient outcome (as defined by presence/absence of a hard or hard+soft endpoint).

- (3) Relationship with treatment: From Table 2 it can be seen that 12.8% (20.8%) of subjects on atenolol, 11.2% (19.8%) of those on nifedipine, and 8.5% (13.8%) of those on the combination had a hard (hard+soft) endpoint. Comparison of the times to event among the three treatments, using the logrank test, did not achieve statistical significance (*P*=0.32 for hard endpoints, *P*=0.14 for hard+soft endpoints). However, there is a non-significant trend to fewer events on the combination treatment. The estimated survival curves for the three treatment groups are given in Fig. 2(a) (hard endpoints) and (b) (hard+soft endpoints).

Withdrawals

During the active follow-up phase of the study, 217 patients withdrew from study medication. The breakdown of these subjects by treatment and their percentage in relation to the numbers randomized to each group are 60 (27%) for atenolol, 93 (40%) for nifedipine, and 64 (29%) for their combination. These percentages are significantly different (*P*=0.001) when time until withdrawal is analysed using the logrank test. There is clear evidence of a higher withdrawal rate in the nifedipine group, due to side-effects, with the rates for atenolol and the combination therapy being similar. Kaplan–Meier plots of the withdrawal patterns are displayed in Fig. 3 for each of the three treatments.

Discussion

The main aim of the TIBET study was to investigate the prognostic importance of the total ischaemic burden, defined as the total number of episodes of myocardial ischaemic occurring during 24 h; this was quantified by recording the number of episodes of significant ST

depression (greater than or equal to 1 mm) and lasting for at least 1 min during a 24 h period of ambulatory ECG monitoring. In the present study, about 50% of patients at baseline had significant ambulatory ischaemia which is consistent with most other studies in patients with chronic stable angina^{6,7}. Of those with ischaemic changes 60% had only silent episodes, 10% painful episodes and 30% had both silent and painful episodes. The results of the TIBET study do not support the hypothesis that episodes of myocardial ischaemia as

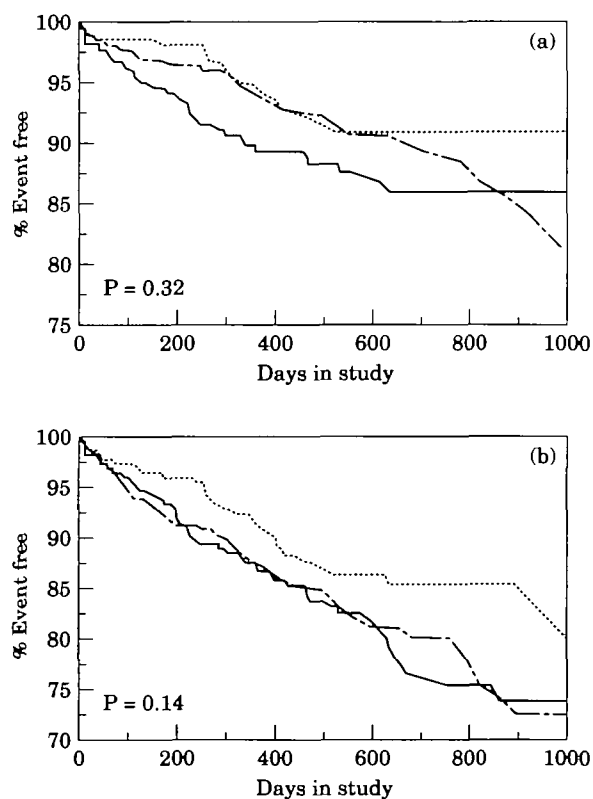


Figure 2 Kaplan–Meier survival curves showing percentage of subjects event free by days in study, for the three treatment arms, for Hard Endpoints (a) and Hard+Soft Endpoints (b). — = atenolol; - - - = nifedipine; . . . = combination.

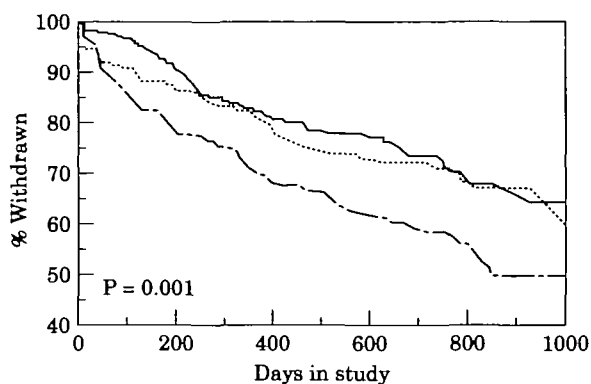


Figure 3 Kaplan-Meier survival curves showing percentage of subjects still on randomized treatment by days in study for the three treatment arms. — = atenolol; - - - = nifedipine; - · - · = combination.

detected by ambulatory monitoring predict outcome either in terms of failure of medical treatment, requirement for revascularization or the development of important cardiac events such as cardiac death, non-fatal myocardial infarction or unstable angina. Even when those patients who had five or more episodes during 24 h were considered separately, no prognostic impact of ambulatory ischaemia could be determined, nor was there a definite trend.

The prognostic importance of ambulatory ischaemia has been well established in patients with unstable coronary disease and especially in those with unstable angina^[12,13]. However, previous studies in patients with chronic stable angina have been conflicting. In one small study in 40 patients followed up for a median time of 28 months silent ischaemia had no prognostic value^[14]; conversely in another report of 86 patients followed up for 1 year the presence of silent ischaemia identified a high risk group for the development of cardiovascular events^[7]. In a third study of 107 patients, silent ischaemia was an independent predictor of mortality^[15].

It would not be surprising that the identification of myocardial ischaemia by whatever mechanism would predict outcome. Ambulatory ischaemia, therefore, might have been a stronger prognostic factor in TIBET had this been an inclusion requirement such that all patients in the study displayed this phenomenon. However, our patients were a relatively unselected group of patients with chronic stable angina who were not at the time of recruitment being considered for revascularization and in whom only about half had evidence of ambulatory ischaemia.

In the absence of a control group, the lack of an association between the presence of myocardial ischaemia and outcome can only be applied to medically treated patients. The relationship may well be different in untreated patients as suggested in the ASIST study in which atenolol reduced ambulatory ischaemia and the risk of adverse cardiac events^[16]. By univariate analysis, the absence of ischaemia after 4 weeks of treatment

was significantly associated with a reduced event rate. By multivariate analysis, however, this was no longer significant. Hence, the ASIST study is inconclusive in establishing whether the reduction in silent ischaemia by atenolol was responsible for the improvement in outcome.

The ASIST population was an unusual one in that patients were either asymptomatic or minimally symptomatic and, therefore, not reflective generally of patients with chronic stable angina. In clinical practice, therefore, the most useful information is whether ambulatory ischaemia can predict outcome in previously or currently symptomatic patients on treatment; the TIBET study strongly suggests not.

The ACIP study confirmed the beneficial effects of both medical and surgical treatment on ischaemia but, as a pilot study, was insufficiently powered to investigate prognosis. It was suggested that a large trial to determine the efficacy of a symptom or ischaemia guided management strategy was feasible^[17].

Since myocardial ischaemia on ambulatory monitoring is more likely to develop in patients with severe coronary disease^[18] perhaps our patients, who were not being considered for revascularization, constituted a rather mild group. In fact, the TIBET population in terms of cardiac mortality is comparable with other large scale survival studies; in 1083 medically treated patients with ischaemic heart disease and who were followed up for a mean period of 66 months in Italy^[19], the cardiac mortality rate was 1.4% as compared with 1.08% in the TIBET study group. Both these populations showed a lower mortality than in the CASS study where the total annual mortality was 1.6%^[3]. In the CASS study, however, patients were being actively considered for revascularization and might therefore have been expected to be a more severe group.

A further objective of the TIBET study was to take advantage of the long-term medical follow up to investigate the impact of standard medical therapy on outcome.

The TIBET endpoints were divided into 'hard' endpoints which were cardiac death, myocardial infarction and unstable angina and 'soft' endpoints which included treatment failure and the need for revascularization. It can be seen that there was no statistically significant effect of either nifedipine, atenolol or their combination on hard or in a combination of hard and soft endpoints; there was, however, a definite trend in favour of the combination.

At the outset, we elected to include unstable angina as a hard endpoint since the underlying pathology is thought to be similar to that of acute myocardial infarction. Interestingly, there were 12 cases of unstable angina on atenolol and only four on nifedipine with the combination occupying the intermediate position with eight cases. Whether these differences are in any way meaningful is, of course, speculative, and difficulty in the diagnosis of unstable angina might have led to these patients forming a rather heterogeneous group.

Other major studies of outcome have adopted the more conventional combined endpoint of cardiac death and non-fatal myocardial infarction. Looking at the data in this way, it can be seen that, while 21 cardiac deaths or nonfatal myocardial infarctions occurred on nifedipine and 17 on atenolol, only 11 such events occurred on the combination. This represents a reduction of 48% in these end points on the combination as compared with nifedipine and 35% as compared to atenolol alone.

The TIBET dosing regimen was chosen to try to reflect current clinical practice. Thus increase in nifedipine and placebo was allowed but the dose of atenolol was held constant. This was because atenolol 50 mg twice daily was considered to be the maximum dose of atenolol in usual clinical practice; the initial dose of nifedipine 20 mg twice daily was, however, lower than that often prescribed and so the opportunity to increase that to a higher dose was provided. This may have led to the greater number of withdrawals in the nifedipine arm. Interestingly, there was no such trend in the combination group.

To what extent the 74 patients with ≤ 1 mm ST during the placebo phase could have influenced the overall conclusions is uncertain but is likely to be minimal. Firstly, over 80% of them were men with a clinical presentation sufficiently convincing to lead to a diagnosis of coronary heart disease by an experienced cardiologist; and, secondly, all had significant ST depression on their pre-inclusion screening exercise test, as assessed by their cardiologist. Thirdly, as noted in the text, statistical analysis with or without these patients had no impact on the overall conclusions.

Since the frequencies of endpoints on each treatment are not statistically different it may be considered speculative even to suggest that there might have been a reduction on the combination; but there does seem to be a definite trend which could only be investigated further in a larger scale study.

Since all treatments equally reduced evidence of myocardial ischaemia either on exercise or on ambulatory monitoring, any favourable trend on the combination could not be attributed to the reduction in ischaemia. However, the occurrence of endpoints such as myocardial infarction and cardiac death may be closely related to acute events such as plaque dissection and rupture than to chronic myocardial ischaemia^[20,21]. The factors leading to plaque rupture and dissection are as yet unclear but it is possible that the highly significant greater reduction in blood pressure on the combination than on monotherapy could provide at least part of the explanation^[22].

It is important to consider the underlying severity of ischaemia in the TIBET population given the low rate of serious cardiac endpoints. As has been stated previously, these patients were not being considered actively for revascularization and so clearly their symptoms were not severe enough to limit their lifestyle to the extent that revascularization was indicated for the relief of symptoms. In contrast, their performance on the

exercise test was relatively poor since the average maximum ST segment depression was at least 2 mm and the total mean exercise time was approximately 7 min, or only 1 min into the third stage of the Bruce protocol. By current recommendations these patients would therefore be regarded by most as suffering ischaemia of at least moderate severity and by some as being at high risk^[23,24]. Nevertheless, despite this impressive degree of ischaemia at a relatively low workload, only 13 cardiac deaths occurred during a total of 1300 patient years giving an annual mortality of 1%. Only 30 patients underwent coronary artery bypass surgery and four patients underwent angioplasty. There were 38 non-fatal myocardial infarctions which is a rate of 3% per annum. These data certainly raise the issue of whether it is reasonable to intervene by means of revascularization for prognostic reasons in patients with mild symptoms but with evidence of significant reversible myocardial ischaemia. The TIBET data would suggest that this was not necessary in view of the very low rate of serious cardiac endpoints.

The TIBET study, therefore, has shown that the presence of ambulatory myocardial ischaemia does not predict outcome in an unselected group of patients with chronic stable angina who have mild symptoms but who have evidence of exercise-induced ischaemia. Moreover, the outcome in the TIBET study suggests that such patients may be safely followed medically and that the principal indication for intervening by revascularization would be the development of more severe symptoms. The patients in the TIBET study were not actively being considered for revascularization because their symptoms, as judged by their cardiologist, did not justify it. Since policy on invasive investigation and revascularization varies widely throughout Europe, it is possible that the good outcome in the TIBET population could, or should, have implications for the clinical practice of those cardiologists with a lower threshold for angiography than that of the TIBET investigators.

In patients with more severe symptoms, the combination of beta-blockers and calcium channel blockers has been shown to be superior to monotherapy in terms of symptom reduction and exercise and ambulatory ischaemia^[25,26]. In such patients, therefore, the prescription of such a combination is a logical element of clinical practice. Are the results of the TIBET study in patients with milder symptoms sufficiently convincing to recommend combination therapy on prognostic grounds? A much larger study would have been required to have sufficient power to demonstrate whether the apparent trend in favour of the combination treatment with a beta-blocker and calcium antagonist seen in the TIBET study does in fact confer greater freedom from serious cardiac events than treatment with either agent alone. Until such a study is carried out, it would be premature to suggest such a course of action despite its mechanistic plausibility.

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Appendix I

TIBET investigators

Dr J. Aberg, Sundsvall; Dr S. Aallam, Verdun; Dr M. Arstilla, Turku; Dr P. C. Barnes, Manchester; Dr J. Bayliss, St Albans; Dr A. Blanc, Bayonne; Dr R. L. Blandford, Worksop; Dr J. Bour, Saint Avoild; Dr G. Camilleri, Lille; Dr X. Chanudet, Saint Mandé; Prof A. Cherchi, Cagliari; Prof Chiariello, Naples; Dr P. Crean, Dublin; Dr K. Daly, Eire; Dr P. Dambrine, Merlebach; Dr A. Davies, Middlesbrough; Dr C. Davidson, Brighton; Dr C. Davidson, Rochdale; Dr M. Gil de la Pena, Santiago; Dr W. Fennel, Cork; Prof Y. Frances, Marseille; Dr T. Fyfe, Glasgow; Dr A. Gabriel, Freyming; Dr J. M. Garcin, Saint Mandé; Dr G. Habib, Marseille; Dr S. Hansen, Eksjo; Dr M. Harkonen, Porvoo; Dr A. Harley, Liverpool; Dr W. C. Hendry, Amersham; Dr P. Hourdebaigt, Paris; Dr U. Idanpaan-Heikkila, Espoo; Dr S. Jagerholm, Porvoo; Dr K. Jensen, Eksjo; Dr O. Johnson, Umea; Dr S. Juul-Moller, Malmo; Dr A. C. F. Kenmure, Aberdeen; Dr A. Kohvakka, Helsinki; Dr F. Labaki, Freyming; Prof P. Larroque, Saint Mandé; Dr J. Lawrence, Dunsfries; Dr D. M. Lawrie, Kirkcaldy; Prof R. Luccioni, Marseille; Dr O. J. Luurila, Helsinki; Dr J. O. Magnusson, Eksjo; Dr P. Maiolino, Cittadella; Dr M. Marquet, Gap; Dr A. McLeod, Poole; Dr G. McNeill, Dundee; Dr D. N. S.

Malone, *Dunfermline*; Dr M. W. Miller-Craig, *Derby*; Dr T. Mooe, *Umea*; Dr N. Naqvi, *Wigan*; Dr P. Nicol, *Koping*; Dr E. S. Niewendijk, *Amsterdam*; Assoc Prof G. Nilsson, *Vasteras*; Assoc Prof H. Nilsson, *Fagersta*; Assoc Prof O. Nilsson, *Norrkoping*; Dr D. Oakley, *Sheffield*; Dr M. Palmieri, *Monfalcone*; Dr D. Patterson, *London*; Dr T. H. Peirce, *Limerick*; Prof Piccolo, *Mestre VE*; Dr G. Pinelli, *Bologna*; Prof J. C. Pony, *Rennes*; Dr J. P. Queney, *Sarreguemines*; Dr B. Rask, *Porvoo*; Dr G. Rasmanmis, *Stockholm*; Dr C. Ringqvist, *Sundsvall*; Prof I. Ringqvist, *Umea*; Dr A. Rozkovec, *Bournemouth*; Dr F. Rusticali, *Forli*; Prof L. Ryden, *Stockholm*; Prof A. Sanchez Cascos, *Madrid*; Dr J. E. Sanderson, *Taunton*; Dr J. Silas, *Liverpool*; Dr R. Sipila, *Espoo*; Dr T. Skjaerpe, *Trondheim*; Dr D. J. Smithard, *Rochdale*; Dr P. A. Sullivan, *Mallow*; Dr B. J. van den Berg, *Rotterdam*; Dr R. van Nieuwenhuizen, *Arhem*; Dr W. A. M. Vedt, *Alkmaar*; Dr C. M. J. Vitdehaag, *Doetinchem*; Dr A. Westheim, *Oslo*; Dr E. G. Weyers, *Gouda*; Dr P. Wilkinson, *Ashford*; Dr P. Zardini, *Verona*.

Appendix II

TIBET Executive Committee: Prof Henry Dargie (Chairman), Western Infirmary, *Glasgow*; Dr Kim Fox,

National Heart Hospital, *London*; Prof Ian Ford, University of Glasgow, *Glasgow*; Mrs Mona Archibald (Secretary), Western Infirmary, *Glasgow*.

TIBET Steering Committee: Dr Kim Fox (Chairman), National Heart Hospital, *London*; Prof Henry Dargie, Western Infirmary, *Glasgow*; Prof Ivar Ringqvist, Central Hospital, *Vasteras*; Prof Lars Ryden, Medicinska Kliniken, *Stockholm*; Prof Arend Jan Dunning, Academisch Medisch Centrum, *Amsterdam*; Prof Pentti Siltanen, HYKS/Sydanasema, *Helsinki*; Dr P Sellier, Hopital Broussais, *Paris*; Prof A L'Abbate, Fisiologia Clinica del CNR, *Pisa*; Prof Ian Ford (statistician), University of Glasgow, *Glasgow*; Dr Julie Charlesworth (Committee Secretary), ICI, *UK*.

TIBET Safety Committee: Prof J Lubsen, Thorax Center, *Rotterdam*; Prof D. Julian (Chairman), British Heart Foundation, *London*; Prof L. Wilhelmsen, Ostia House CK Plan 2, *Gottenburg*; Dr T. B. Hart, ICI, *UK*.

TIBET Endpoint Committee: Dr I. Findlay, Royal Alexandra Hospital, *Paisley*; Dr R. Hall (Chairman), University Hospital of Wales, *Cardiff*; Dr J. McLenachan, Western Infirmary, *Glasgow*; Prof Henry Dargie, Western Infirmary, *Glasgow*.