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Trans-Atlantic Conference on Clinical Trial Guidelines in PAOD (Peripheral Arterial Occlusive Disease) Clinical Trial Methodology

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Introduction

Chronic peripheral arterial occlusive disease (PAOD) can be regarded as a marker of generalised atherosclerosis. Patients with intermittent claudication must be considered a high-risk population for the development of clinical manifestations of cardiovascular disease. From a medical and socio-economic point of view, the major goals are reduction of cardiovascular morbidity and mortality, improvement of PAOD symptoms, normalisation of mobility, and prevention of amputation. Concurrent illness, life style, and life expectancy all influence initial treatment decisions for intermittent claudication. Current treatment recommendations are generally conservative and focus on symptomatic relief through risk-factor modification, exercise and, if efficacious, drug treatment. Percutaneous transluminal angioplasty (PTA) and/or bypass surgery may be appropriate in selected cases.

In patients with critical limb ischaemia, invasive vascular intervention is the treatment of choice. However, for patients who are not eligible for vascular reconstruction and patients with a critical-risk profile, pharmacological-treatment options may be important.

Over the years, a number of guidelines for the clinical development of drugs for the treatment of peripheral vascular disease were developed by specialist vascular societies and national health authorities. Recently, the European Regulatory Agency issued guidelines, aiming at a harmonisation of the drug development process at least within the countries of the European Union. In North America, no such guidelines have been promulgated over the last decade. However, with increasing globalisation, transatlantic cooperation in drug research and development is crucial. Guidelines by definition are not static documents, but should reflect the current knowledge. In order to stimulate this discussion process and to facilitate joint U.S.A./European development programmes, a conference was held in Basel, Switzerland on 15–17 November 1997, to discuss the scientific background of PAOD guidelines based on published evidence and the extensive knowledge of clinical investigators and experienced regulators.

The conference was organised by Prof. William R. Hiatt, University of Colorado Health Sciences Center, Denver, CO, U.S.A., Prof. John A. Dormandy, Department of Vascular Sciences, St George's Hospital, London, U.K., Prof. Kurt A. Jaeger and Dr. Karl-Heinz Labs, Department of Angiology, University of Basel Medical School, Basel, Switzerland, and Dr. Claus-Steffen Stuerzebecher, Berlin, Germany. Fifty-two experts from the U.S.A. and Europe, including representatives from Regulatory Authorities, participated.

The following text summarises the conclusions of the meeting. It was composed by the Organising Committee of the meeting and based on the transcript of the meeting's discussion sessions. However, it must be emphasised that, although the manuscript was circulated to and accepted by the participants, the content of the paper may not necessarily reflect the opinion of all individuals. It is hoped that this paper may serve as a reference for the development of future transatlantic guidelines for the evaluation of pharmacotherapy in PAOD.

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Part A: Peripheral Arterial Occlusive Disease: Fontaine Stage II (Intermittent Claudication)

Study design

General design

Phase III clinical trials should generally follow a randomised, double-blind, parallel-group study design. Crossover designs should be the exception and may only be acceptable for short trials with short-acting drugs, e.g. pharmacokinetic or pharmacodynamic phase I or II studies, but not for phase III trials.

Placebo control versus active-drug control

Phase III clinical trials in patients with intermittent claudication with the walking distance as the primary outcome measure should generally be placebo-controlled. Active-drug-controlled trials without a placebo arm will be the exception and may only be considered if the comparator drug has consistently shown superiority over placebo in several trials and the magnitude of the drug effect has been widely accepted by the medical community. The aim of clinical trials using an active-therapy control may be to demonstrate superiority or non-inferiority of the experimental drug. An appropriate statistical approach for the study aim chosen should be determined *a priori*.

Duration of treatment and follow-up

The duration of treatment will depend on the aim of the study and the endpoint(s) chosen.

Claudication trials. For claudication studies, a period of approximately 6 months is generally accepted and is in agreement with the guidelines of the European Union (Committee for Proprietary Medicinal Products, CPMP).[1] The length of exposure to the drug should be sufficient to ensure that tolerance (if expected) will not develop.

The duration of the post-treatment follow-up period will also depend on the study goals. With respect to efficacy in claudication trials, a short follow-up period (e.g., not less than 4 weeks) is regarded as sufficient to demonstrate that no sudden loss in claudication distance (rebound) occurs.

With respect to safety, long-term experience is required to demonstrate that the clinical benefit of the compound outweighs the risks. This holds particularly true for PAOD patients, with their high risk of cardiovascular events (i.e. myocardial infarction, ischaemic stroke). If there is any evidence of drug toxicity, the follow-up should be performed in a double-blind, controlled rather than an open-label manner.

Prevention trials. CPMP guidelines suggest a minimum trial duration of $\geq$12 months for long-term endpoints, such as cardiovascular morbidity and mortality or progression of atherosclerosis.[1] However, in order to obtain sufficient event rates and clinical relevance of the results, a treatment period of $\geq$24 months is strongly recommended.

Recommendation: Trial design

Claudication trials

- PAOD trials aiming at the claudication distance should have a randomised, double-blind, placebo-controlled, parallel-group design.
- A treatment period of approximately 6 months is generally considered sufficient.
- To exclude a sudden rebound effect, a post-treatment follow-up period of not less than 4 weeks should be considered.
- To obtain appropriate safety information the total study time (treatment phase and follow-up phase) should not be less than 12 months in an appropriate number of patients.
- If there is evidence of drug toxicity, the follow-up should be performed in a double-blind, controlled rather than in an open-label manner.

Prevention trials

- For trials aiming at the cardiovascular morbidity and mortality or at the progression of atherosclerosis a treatment period of $\geq$24 months is recommended.

Stratification

Uneven distribution of potential but unknown confounders, such as cardiovascular risk factors, haemodynamic parameters, demographic variables, and others can usually be avoided by an appropriate randomisation process and an adequate sample size.

Stratification reduces the risk of an imbalance between study groups and may bias results and diminishes the need to adjust data *post hoc*. However, these gains may be modest in comparison with the disadvantages of complicating both patient recruitment and data analysis. In general, a prerandomisation stratification is recommended: (a) if the hypothesis whether a drug is particularly efficacious in an identifiable subgroup of patients is to be tested, or (b) if one or more of the patient background characteristics are known to be strong independent predictors of outcome.

The occurrence of slight imbalances in the dataset can be handled by *post hoc* (analytic) adjustment, provided that the adjustment for the effects of predefined and covariables is prospectively planned and specified in the study protocol.

However, in claudication trials, there is usually no need for stratification. The clinical suspicion that claudicants with diabetes mellitus respond to drug treatment differently to those without diabetes has not been substantiated in clinical trials; thus, stratification is not required even for diabetics, as long as patients with clinically severe diabetic neuropathy are excluded; the latter is required, as this complication interferes with the assessment of the claudication distances ACD (=absolute claudication distance) and ICD (=initial claudication distance).

In prevention trials the situation is different. There is evidence from studies using antiplatelet agents in patients with diabetes mellitus and vascular disease that less (rather than more) man-years of treatment are required to prevent fatal cardiovascular events than for non-diabetic patients with vascular disease.[2,3] Thus, stratification for diabetes mellitus (or separate trials for diabetics) is recommended.

Recommendation: Stratification

- Present knowledge does not indicate that stratification in clinical trials in intermittent claudicants is usually required, unless there is strong evidence that independent predictors of outcome (other than the trial endpoint) exist, or if a hypothesis that the drug is efficacious only in specific patient subgroups is being tested.
- For prevention trials diabetics should be stratified or tested in a separate study.

Run-in phase and testing for baseline stability

(Note: The following sections, up to and including *Physical training*, refer to claudication trials only)

It is commonly known that walking distance may vary with mood, motivation, temperature, and other environmental factors. The larger this "background noise", the more difficult it will be to demonstrate drug efficacy, particularly for only moderately effective compounds. In order not to unduly inflate the size of the patient sample needed, European Union (CPMP) guidelines[1] recommend that patients with pronounced baseline variability in claudication distance be excluded (the absolute claudication distance should not vary by more than 25% when tested twice on a treadmill over a three- to six-week run-in period).

However, there is no published evidence that variability prior to entry translates into higher variability during and at the end of the study. Insistence on the stability of the absolute claudication distance (ACD) at baseline results in a loss of $\geq$20% of patients otherwise fulfilling the study inclusion criteria, and also conflicts with the rule that the study sample should be representative of a general PAOD stage II population (study sample representativity).

It is recommended: (a) to include only patients in whom the diagnosis of stage II PAOD is established for $\geq$6 months, (b) to exclude patients who have a recognised potential for instability (differences in claudication distances between days, recent phases of deterioration or improvement, recent surgical or endovascular intervention), and (c) to limit the study run-in phase to two or three treadmill tests for the purpose of treadmill test familiarisation.

However, a counter-argument was proposed to maintain the treadmill variability $\leq$25% as an entry criterion. This would ensure a more reproducible measure of ACD, which would in turn require fewer patients to reach statistical significance in a clinical trial. The decision to define criteria for baseline treadmill-test variability should be left to the investigators and the sponsors responsible for a particular trial. The issues are the anticipated magnitude of drug effect, the variability of the treadmill methodology, and the stability of the population enrolled in the study. All of these issues will affect sample size.

Regarding other variables potentially influencing the claudication distance, therapeutic strategies should be set and not changed during the course of the study. These variables include lipid-lowering therapy, anticoagulation, smoking, exercise, changes in body weight, and others. However, there is no good reason

for withholding life-style counselling from patients (particularly on smoking, even if smoking is stopped after initiation of the trial).

Recommendations: Stability of baseline claudication distance

- Patients who by history have a recognised potential for instability should be excluded, and factors potentially influencing the claudication distance should be kept constant during the course of the study.
- Testing for stability of claudication distance during a study run-in phase should not be mandatory; the question of whether to include stability testing or not should be left to the decision of investigators and sponsors of a particular trial. To include stability testing will increase the precision, reduce the baseline variance and decrease the sample size; to omit stability testing will increase the enrolment of patients and improve the generalisability of the study results.

Selection of patients

Inclusion and exclusion criteria should warrant that the patient sample is representative of a general PAOD population.

Inclusion criteria

Inclusion criteria for PAOD stage II trials are broadly accepted and are well described in the current European Union (CPMP) guidelines.[1] Claudication should be stable and should have been present for $\geq$6 months, the diagnosis of PAOD established and confirmed by haemodynamic measurements (ankle–brachial pressure index, ABPI <0.90); the location of the lesion(s) should be documented by duplex sonography or angiography. Patients with a recognised potential for claudication instability should be excluded (see *Run-in phase and testing for baseline stability* section, on page 255). In trials aiming at the claudication distance there is usually no reason for prerandomisation stratification of the patient sample (see *Stratification* section, on page 254). European Union guidelines[1] stipulate that the ACD range at baseline should be limited to 100–300 m, the reason for the lower limit being that the clinical prognosis of patients with more severe disease may differ from that of patients with a lesser degree of PAOD. There are a number of variables which are associated with the prognosis, including peripheral haemodynamics such as the ankle pressures and the ABPI.[4–8] However, these variables correlate poorly with the patient's walking ability.[9–13] Consequently, there is little scientific justification for defining a lower end of a claudication distance range. Still, further clinical-trial data on the behaviour of these markedly disabled patients with claudication would be desirable.

The reason for the upper limit (300 m) relates to the increased frequency of a walking-through phenomenon known to occur with longer claudication distances.[15] However, this is a problem specifically related to constant-workload treadmill protocols. With graded treadmill protocols, workload is increased until the maximum walking capacity is reached; thus, walking-through phenomena are avoided.[15,16]

Physical training

The therapeutic value of a structured, organised, and supervised physical training programme cannot be doubted.[14,17] However, there are few such programmes available, and there is published evidence that the willingness of patients to participate is limited.[18] Patients already participating or intending to enrol in a supervised physical-group-training class should be excluded from clinical trials unless the study protocol defines that all patients from both groups will participate.

The value of non-supervised physical training is less clear. As with all other factors potentially influencing the claudication distance (see *Run-in phase and testing for baseline stability* section, on page 255), decisions should be made and strategies should be set prior to initiation of a clinical trial, and these should not be changed during the course of the study. It may also be recommended that in order to allow for a potentially necessary adjustment for different levels of physical activity, the type, frequency and intensity of any home-based training may be documented in the case record form.

Recommendation: Selection of patients

- The diagnosis of PAOD must be established clinically and confirmed haemodynamically, and the location of lesions should be documented.
- Intermittent claudication should be stable and should have been present for at least 6 months.
- Patients participating or intending to enrol in structured, organised, supervised physical training programmes should be excluded unless the protocol defines that all patients from both groups will participate.
- Strategies for a home-based training programme should be set prior to enrolment into a clinical trial and should not be changed during the course of the study. This also applies to all other factors that may potentially influence the patient's walking performance.

Outcome measures

Primary endpoints

Since the key symptom of PAOD stage II is intermittent claudication, claudication distance on the treadmill should be the primary endpoint. The decision to use treadmill testing for the assessment of claudication distances is merely related to a non-acceptable variance of results from other possible alternative testing methods. It should, however, be emphasised in this context that treadmill-test results markedly underestimate the patient's walking ability under daily-life conditions.

Cardiovascular morbidity and mortality represent the main risk associated with stage II PAOD.[4,5,19–21] Prevention studies represent an entirely different category of clinical trials and thus require an entirely different study design. From a clinical and an economical point of view, this type of study may even be more important than trials, merely focusing on the patient's walking ability.

Initial claudication distance versus absolute claudication distance

European Union guidelines[1] recommend the use of the initial claudication distance (ICD) or both the initial and the absolute claudication distance (ACD) as primary endpoints in claudication trials. In the U.S.A., ACD is preferred over ICD. This is because the ACD is felt to define the maximal exercise capacity of the patient. Treatment of claudication should improve the maximum physical capacity of the patient and therefore would serve as the endpoint. From a clinical point of view, ICD may be the more important variable, since patients seldom force themselves to the extreme of ACD. On the other hand, ICD is more subjective. In addition to the question of clinical relevance (the answer to which may remain open), the reproducibility of ICD and ACD is an issue. There is published evidence that the reproducibility of the two parameters varies with the treadmill protocol used.[15,16,22–27] With constant-load treadmill protocols, the reproducibility of ICD and ACD is similar, whereas with graded protocols ACD is superior to ICD. Consequently, ACD may be given preference over ICD as the primary endpoint; this decision would allow it to be independent of the treadmill protocol but is mandatory if a graded test is used.

Assessment of the claudication distance: Constant-workload versus graded-workload treadmill testing. The preferred method to assess claudication distances is treadmill testing. There are two internationally accepted treadmill protocols, i.e. the constant-workload protocol using a constant speed and grade (mostly 2 mph = 3.2 km/h; and 12% grade), and the graded test where the speed is kept constant but the grade is varied, starting horizontally but then increasing in predefined steps (e.g. 2%) at predefined intervals (e.g. 2 min).

The two tests differ, in that the relationship between workload and walking time follows a linear function with the constant test but a curvilinear function with the graded test.[15,28] This curvilinear relationship explains the main advantages of the graded test: (a) a low workload in the early test phase allows proper differentiation of patients with differing highly limited walking distances and (b) the continuously increasing workload in late test stages avoids the occurrence of a walking-through phenomenon.

The reproducibility of the two tests is comparable, except with rather short claudication distances (e.g. $\leq$100 m, as measured with the constant load test). In these cases, the graded test is superior to the constant load test.[28] Both tests can be equally recommended for use in clinical trials, although, if either very short or rather long claudication distances are to be tested, the graded test should be preferred. However, at present there is still limited experience with the analysis of graded-treadmill data, particularly regarding the non-linear relationship of cumulative workload applied and the outcome measure that is the claudication distance or the time walked on the treadmill. It is also known that both types of treadmill tests are highly reproducible when performed in laboratories that have

expertise in treadmill testing in a PAOD population. The reproducibility will be worse in centres with less familiarity with this form of exercise-testing.

Prevention studies: morbidity and mortality. The main risk for PAOD patients is related to ischaemic cardiovascular events. An adequate endpoint in prevention studies is a composite endpoint comprising non-fatal ischaemic stroke, myocardial infarction, cardiovascular death, and potentially coronary and carotid revascularisation and major amputation, whichever occurs first. In order to clarify the terminology, reference is made to the WHO criteria for the diagnosis of coronary events and strokes (fatal and non-fatal). In the optimal case, total mortality may be the most relevant clinical endpoint; however, this poses problems of feasibility because of the need for large patient numbers. Combining non-fatal cardiovascular morbidity with all-cause mortality reflects a comparison of unequal entities, and inclusion of non-cardiovascular morbidity renders clinical trials rather difficult. A combination endpoint using cardiovascular morbidity and cardiovascular mortality has been criticised, because survival, irrespective of the cause of death, is what ultimately matters. Such a concern may be mitigated if it can be proved that results for the primary composite endpoint are statistically significant, that in the optimal case cardiovascular mortality is significantly reduced and that the change in cardiovascular mortality also favourably influences all-cause mortality.

Regarding background treatment with platelet-aggregation inhibitors, reference is made to the section *Background treatment*, on page 261 of this article.

Secondary endpoints

Secondary endpoints should focus on clinically relevant data supporting the study aim. These data may include variables describing the haemodynamics of PAOD (such as data on peripheral flow and pressure) or markers for thrombotic events (such as platelet-aggregation and other tests of thrombosis and atherogenesis) which, due to the fact that they are poorly correlated to the patient's walking performance, are not suitable as primary endpoints.[9,13,29] If the primary endpoint is a composite endpoint, the components of this composite endpoint should be evaluated as individual secondary endpoints.

In claudication trials with the walking distance as the primary endpoint, data on morbidity and mortality must also be collected for safety reasons.

Quality of life as an endpoint

PAOD represents just one (peripheral) manifestation of a generalised atherosclerotic process. Usually, affected patients have multiple morbidities, and the assessment of quality of life (QoL) may give a more representative picture of the patient's perception of health than the exclusive measurement of walking performance. Thus, QoL may be a good primary endpoint for clinical trials in patients with intermittent claudication. Multiple QoL instruments have been used in PAOD patients. These include specific scales such as the Peripheral Arterial Disease – Walking Impairment Questionnaire (PAD–WIQ), the Peripheral Arterial Disease – Physical Activity Recall Questionnaire (PAD–PAR), the Claudication Scale (CLAU-S), and the Periphere Arterielle Verschlusskrankheit 86 Scale (PAVK 86), but also non-specific instruments such as the Medical Outcome Study SF 36 (MOS-SF36), the Nottingham Health Profile (NHP), the McMaster Health Index Questionnaire (MHIQ), or the European Quality of Life Scale (EuroQol). At present, a number of unsettled questions prevent the use of QoL as a primary endpoint. Problem areas include choosing the most appropriate instrument, proper validation of scales, potential composition of endpoints, and the definition of what magnitude of change with a specific QoL scale may be considered clinically relevant. At present, QoL should be assessed as a secondary endpoint.

Statistical significance versus clinical relevance

The question of statistical significance versus clinical relevance for changes in claudication distance has been a matter of debate for a long time, without a consensus ever being reached. This statement also holds for the Basel conference. Consequently, ongoing discussions in the medical community on the clinical relevance of study results seem to be inevitable. This dilemma may be resolved by including a responder analysis, where a certain (predefined) percentage of patients must reach a (predefined) level of improvement. If a clinically non-relevant margin can be defined this non-relevant difference should not be included within the 95% confidence interval (CI) for the difference of group means[30] (e.g. if a difference of group means of 5% is considered clinically non-relevant, 5% should not be included within the 95% CI for the difference of group means). This concept is currently under discussion with international regulatory authorities; however, no final consensus has yet been reached.

For prevention trials any statistically significant difference for the primary (composite) endpoint, in the optimal case a significant reduction in the

cardiovascular mortality, coupled with evidence that all-cause mortality is also positively influenced but definitely not increased, should be acceptable as being clinically relevant.

Recommendations: Outcome measures

- The primary endpoint will depend on the aim of the study. For walking-performance studies, the absolute claudication distance (ACD), measured by treadmill testing, is recommended. Treadmill testing may be performed using a constant-workload or a graded-workload-treadmill protocol, except at the extremes of walking distance where the graded test should be preferred. For the constant-load test it is of advantage to use internationally accepted settings, e.g. a speed of 2 mph (3.2 km/h) and a grade of 12%. The treadmill protocol and treadmill settings must not be changed during the course of the trial; also, environmental and all other factors influencing the test result (room temperature, timing etc.) and staff members performing the test should be kept constant.
- For prevention studies, a composite endpoint including cardiovascular mortality and cardiovascular morbidity, i.e. fatal and non-fatal myocardial infarction and stroke (as defined by the respective WHO criteria) is appropriate. Convincing study results would demonstrate that significant changes in the primary endpoint occur, that in the optimal case cardiovascular mortality is significantly reduced, and that all-cause mortality is also favourably influenced.
- Secondary endpoints should focus on additional clinically relevant data supporting the study aim. If ACD is used as the primary endpoint, ICD should serve as a secondary endpoint. If walking distance is used as the primary endpoint, information on cardiovascular morbidity and cardiovascular mortality as well as all-cause mortality should be included for safety reasons.
- Theoretically, QoL could be used as a primary endpoint. However, a number of questions on validation, sensitivity, and clinical relevance of results are still unsolved. At present, QoL should be assessed only as a secondary endpoint.
- The question of the clinical relevance of claudication distance changes remains unresolved. The definition of a clinically unimportant margin, which should not be included into the 95% confidence interval for the difference of group means, may be potentially useful.

Part B: Peripheral Arterial Occlusive Disease: Fontaine Stages III and IV (Critical Limb Ischaemia, CLI)

For the purpose of PAOD guidelines, only the chronic but not the acute form of CLI will be considered.

Definition of PAOD stages III and IV/critical limb ischaemia and CLI-related risk

Most vascular specialists in continental Europe use the Fontaine classification to categorise the most severe forms of limb ischaemia. The original Fontaine classification was based on clinical information only. The need for a more objective definition of Fontaine stages III and IV (or its Anglo-American equivalent "critical limb ischaemia") became evident when it was shown that these patients carry an excessively high risk of cardiovascular events, amputation, and mortality. The lack of uniform criteria in reporting the results of studies in CLI precludes the acquisition of reliable data and prevents the comparison of efficacy of different therapeutic strategies. Thus, in order to clarify, specify, and homogenise the definition of PAOD stages III and IV, a consensus document was devised with the input of eight European vascular specialist societies.[31,32] CLI in both diabetics and non-diabetics was defined by either of two criteria: persistent recurrent distal-extremity pain at rest requiring analgesics for more than 2 weeks, with an ankle systolic pressure of ≤ 50 mmHg and/or a toe systolic pressure ≤ 30 mmHg; or ulceration or gangrene of the foot or toes in combination with the haemodynamic criteria listed above. Furthermore, variables describing the comprised microcirculation (such as a $tcpO_2 \leq 20$ mmHg) were included, particularly to be applied in patients with unreliable pressure readings. The justification of the criteria used was based on the correlation between impaired peripheral haemodynamics and the increased risk of cardiovascular events and amputation.[4–7]

Recent studies have raised doubts as to whether the ankle- or toe-pressure cut-off points have been correctly chosen and whether the threshold values were too low.[33,34] There is published evidence indicating a comparable incidence of a combined endpoint of amputation and cardiovascular death in placebo-treated patients with peripheral pressures below 50 mmHg and those with peripheral pressures below 60 mmHg and/or an ABI <0.60.[33] Comparable findings regarding ulcer-healing and amputation were reported elsewhere.[35,36] Conversely, patients with peripheral pressures clearly below CLI threshold who did

not experience pain at rest or ischaemic skin lesions have been described in the literature.[37]

There is undoubtedly a general association between cardiovascular risk, amputation and peripheral pressures. It is of primary value to describe the population at risk with the highest possible sensitivity and specificity. The second CLI Consensus Conference[32] used a pressure cut-off of 50 mmHg for this purpose which, as shown by recent experience,[33,34] may be doubted. The problem is that the optimal cut-off is not known and that the best at present is to give a pressure range (50–70 mmHg). The higher the pressure cut-off chosen the higher will be the sensitivity, but the lower the specificity, for the description of risk. For clinical trials using the upper end of the range will increase the study's inclusivity and thus the availability of patients, but will decrease the cardiovascular-event rate as well as the amputation rate. Using the lower end of the range will result in a narrower (exclusive) set of study criteria with high patient-sample homogeneity and a higher event rate, but reduced patient enrolment. Some reasons for the uncertainty of the correct choice of the right pressure cut-off are related to problems with the accuracy of measuring peripheral pressures non-invasively, particularly in diabetics, chronic renal patients, patients with chronic steroid treatment, and the elderly (>80 years). Under these circumstances it remains an open question whether one fixed cut-off point can be defined at all. At present, reflecting the above discussion and until further data are available, regulators suggest stratifying CLI patients with respect to pressure ranges (e.g. ankle pressure $\leq$50 mmHg versus 50 mmHg $\leq$ankle pressure $\leq$70 mmHg; or alternatively toe pressure $\leq$30 mmHg versus 30 mmHg $\leq$toe pressure $\leq$50 mmHg), and to report the results of clinical trials accordingly.

Recommendation: Definition of critical limb ischaemia

- Recent studies suggest that the haemodynamic threshold values used in the CLI consensus document may have to be reconsidered; final agreement on this issue has not yet been reached.
- At present, it is suggested that the CLI patient sample be stratified according to baseline pressure ranges (i.e. ankle pressure $\leq$50 mmHg versus 50 mmHg $\leq$ankle pressure $\leq$70 mmHg; or alternatively toe pressure $\leq$30 mmHg versus 30 mmHg $\leq$toe pressure $\leq$50 mmHg), and to report study results accordingly.

Study design

Due to the nature and progression of the disease, only double-blind, randomised, parallel-group trials are appropriate (cross-over designs are not acceptable). Proper randomisation will ensure an equal distribution of risk factors and patient background characteristics between the treatment groups. The treatment of concomitant diseases should be continued throughout the trial; a protocol-defined standard regimen for the treatment of concomitant diseases is not feasible, particularly in multicentre, multinational trials. However, such standardisation of a concomitant medication regimen is not required if an appropriate randomisation procedure is used.

Duration of treatment and follow-up

The duration of treatment will be determined by the pharmacological and toxicological profile and the mode of action of the drug under investigation. The overall duration of the trial will also depend on the endpoint(s) selected. While a total of $\leq$6 months may be appropriate as a treatment and follow-up period for ulcer healing, the assessment of limb salvage rates requires a longer period of time (i.e. $\geq$12 months).

A short run-in phase of 3–4 days should provide evidence that the disease is roughly stable (i.e. that there is no rapid improvement or deterioration). In the majority of cases, a wash-out period is not considered necessary; however, if the previous treatment included a drug prohibited by the study protocol, a short wash-out period (of 2–3 days) is recommended.

Stratification

Special stratification procedures are generally not required. The exception may be diabetes mellitus. There is no clear evidence from the literature that diabetics react differently to drug treatment than do non-diabetics.[38–40] On the other hand, it may be argued that the pathophysiology of diabetic PAOD (where microangiopathy and neuropathy potentially play a major role) differs from PAOD caused solely by atherosclerosis. In view of these differences in pathophysiology, and in agreement with European Union guidelines,[1] it is suggested that diabetics and non-diabetics should be stratified, particularly if the study endpoint includes the limb salvage rate, cardiovascular morbidity and mortality, and/or quantification of the progression of atherosclerosis.

Placebo-controlled versus active-therapy-controlled trials

Based on the European Union guidelines,[1] a double-blind, placebo-controlled trial design is a standard requirement. However, if there is a comparator drug which has consistently been proven to be superior to placebo and has shown convincing efficacy, an active-therapy-controlled trial may be considered. The aim of clinical trials using an active-therapy control may be to demonstrate superiority or non-inferiority of the experimental drug. An appropriate statistical approach for the study aim chosen should be predetermined.

Background treatment

The conference considered the conditions under which antiplatelet background treatment (in particular with acetylsalicylic acid) should be accepted in studies of other investigational drugs, if the cardiovascular-event rate is the primary outcome. The effects of antiplatelet agents in preventing cardiovascular morbidity and mortality in PAOD patients have not been evaluated. However, meta-analyses of antiplatelet drugs in PAOD patients in combination with those suffering from MI and stroke have shown a significant reduction in the frequency of cardiovascular events during the study observation period.[41,42] Thus, and due to the fact that PAOD patients are multi-morbid patients with a high prevalence of coronary heart disease,[19,20] there is justification to use antiplatelet drugs as background therapy in both treatment groups (drug and placebo). If antiplatelet agents were used as background therapy in a trial aiming at cardiovascular morbidity and mortality, there is no general need to later use the investigational drug in combination with the background medication. The question on the value of the combination of the investigational drug and background therapy could only be answered with the help of a third study arm of drug + placebo, but without background treatment.

Recommendations: Study design

- CLI trials should have a randomised, double-blind, parallel-group design. Cross-over trials are not recommended.
- The duration of treatment will differ between trials and will depend on the pharmacological and toxicological profile and the mode of action of the study drug.
- For trials in ulcer healing, a cumulative treatment/follow-up period of ≤ 6 months may be appropriate, whereas trials on limb-salvage rates require a longer period of time (i.e. ≥ 12 months).
- Run-in phases may be as short as 3–4 days and should provide some evidence of disease stability.
- Wash-out periods are normally not required, but a short wash-out of 2–3 days may be advisable if patients had previously received a drug prohibited by the study protocol.
- With the exception of diabetes, prerandomisation stratification is not required if appropriate randomisation procedures are applied. Minor imbalances resulting from potential but unknown confounders in the final dataset can be handled by adjustment of effects of covariables, if covariables were prospectively specified and adjustment procedures were prospectively planned and defined in the study protocol.
- Active-drug control may be considered if the comparator drug has consistently been shown to be superior to placebo, and if the magnitude of its effect is generally accepted by the medical community.
- Antiplatelet drugs should be accepted as background therapy for both the active and the placebo study arm.

Patient selection

In principle, all patients with proven CLI (see **Definition of PAOD stages III and IV**, on page 259) in whom there is no sudden improvement or deterioration (see *Duration of treatment and follow-up* section, on page 260) are eligible for CLI trials. European Union guidelines[1] stipulate that only those patients who are ineligible for vascular reconstruction should be included. Although understandable for ethical reasons, this requirement will result in a selection of end-stage cases in whom it is highly unlikely that clinical efficacy of any therapeutic measure would be demonstrated. A compromise could be to accept patients eligible for reconstruction in clinical trials, as long as the trial design warrants that surgical or endovascular procedures are not withheld or unduly delayed; the special design of these types of studies must be accounted for in the statistical analysis plan. A lower age-limit of 45 years may help to exclude patients suffering from Buerger's disease rather than from chronic atherosclerotic disease. It is recommended that the distribution of atherosclerotic lesions be documented by

duplex sonography or angiography, since these investigations are required for the work-up of CLI patients and are available in the vast majority of cases.

Recommendations: Patient selection

- The diagnosis of CLI must be established clinically and confirmed haemodynamically.
- Patients eligible for surgical reconstruction can be included, provided that the study design ensures that reconstructive and/or endovascular measures are not withheld or unduly delayed.

Endpoints

Primary endpoints

CLI patients may suffer from pain at rest, may have ischaemic lesions, may require amputation, and will have an increased risk for cardiovascular morbidity and mortality. Thus, the CLI patient should be evaluated in a comprehensive fashion. The primary endpoint may focus on pain at rest, ulcer healing, or amputation, but all other variables (including cardiovascular and total mortality) should also be considered, at least as secondary endpoints. The primary endpoint may be single, composite or may be based on response criteria.

Single endpoints

Pain at rest. If pain intensity is chosen as a primary endpoint, it should be assessed objectively, preferably by using visual analogue scales. Pain at rest remains a soft endpoint influenced by variables such as mood, motivation, and environmental and other factors. Pain assessment should always be done by the same assessor at the same time of the day, preferably at the time of trough plasma levels of the drug under investigation. Since analgesia is difficult to quantify and the type and dose of analgesics are likely to change during the course of the trial, pain relief must be defined as "complete relief of pain while off analgesics".

Ulcer-healing. To ensure clinical relevance, ulcer-healing must be defined as healing of all ulcers of both legs (all ulcers epithelialised as assessed by an independent physician; photographic documentation, even if standardised, is considered insufficient). Only patients with "flat surface" or "transdermal" ulcers should be admitted. Ischaemic cracks between the toes or on the heel cannot be used as measurable endpoints. The ulcer status at baseline may be documented by measuring the cumulative total ulcer area, e.g. using a dual acetate technique.[43] Partial ulcer-healing or only healing of a reference ulcer is of doubtful clinical relevance and should not be used as a clinical endpoint.

Amputation. The rate of major amputation (through or above the ankle) can be considered as a primary endpoint or part of a primary endpoint (see also *Composite endpoints*, below). The amputation rate is usually considered to be one of the "hardest" endpoints in CLI trials. However, as the criteria for performing amputation may vary, particularly in multicentre and multinational studies, the interpretation of study results may be limited. Existing guidelines[1] recommend that amputation criteria be predefined in the study protocol. Even if adhering to this recommendation, rules may sometimes be broken, because the decision to amputate is highly individual and depends on the patient's individual risk pattern, general condition, and other factors. Thus, guidance included in a protocol will be of limited value and may introduce a level of pseudo-accuracy not in line with a real-life situation.

Because the underlying cause of CLI is generalised atherosclerosis, both legs (and not only the index leg) must be considered for the assessment of amputation rates.

Composite endpoints

Mortality alone, whether cardiovascular or total, is rarely used as a single primary endpoint in CLI studies. In addition to the prevention of death, the status of the leg is of primary concern. Thus, a composite endpoint, e.g. amputation and death; or amputation, systemic morbidity (such as ischaemic stroke and myocardial infarction) and death should be preferred over mortality alone.

Response-based endpoints

The trial endpoint may be based on response criteria and a responder definition applied to both the treatment and the placebo/comparator groups, with

optimal response defined as the patient being alive, having both legs, having no wound or pain, and being off analgesics. This endpoint concept would allow us to consider both the time to response as well as the duration of response, before the inevitable late-failure process will occur. As a measure it is suggested to count the number of "good days", i.e. the time period for which the response criterion applies in a given follow-up period. Such an approach may be a conceptual step forward.

Secondary endpoints

Secondary endpoints should focus on clinically relevant data supporting the study objective. Whatever the primary endpoint, information on cardiovascular morbidity and mortality, as well as on all-cause mortality, must be collected over a sufficiently long period of time (in view of the generally pessimistic prognosis of CLI patients, this will rarely exceed 12 months). If there is legitimate concern that a treatment may increase mortality, the study must be powered appropriately to allow for a second estimation of the drug's effect on mortality. If the primary endpoint is a composite endpoint, the components of this composite endpoint should be evaluated individually as secondary endpoints.

Quality of life as an endpoint

As with intermittent claudication, the assessment of QoL would provide a good tool to quantify a patient's well-being if sufficiently validated scales were available. QoL instruments have been used in CLI patients and results were published for CLI-related domains including pain, anxiety, depression, functional activity, life style, and mobility. Instruments used include the Burford visual analogue scale for pain (Burford pain thermometer), the Hospital Anxiety and Depression Scale, the Barthel ADL (activity of daily living) Index, the Frechay Activity Index, the Environmental Scoring System, and the Schedule for Evaluation of Individual Quality of Life. The limitations of QoL assessments discussed in the context of PAOD stage II patients (see *Quality of life as an endpoint* section, on page 258) also apply to CLI patients. Furthermore, QoL cannot yet be regarded as an established endpoint in CLI trials; continued evaluation of QoL instruments is important to define appropriate QoL measures in CLI patients. At present QoL may be considered as a secondary endpoint in CLI trials.

Recommendations: Endpoints

- Conventional primary endpoints acceptable for clinical trials in CLI include the assessment of pain at rest (complete relief of pain, off analgesics), ulcer-healing (complete healing of all ulcers of both legs), and amputation rates.
- A composite primary endpoint, including cardiovascular morbidity, amputation and all-cause mortality may be superior to single primary endpoints focusing only on CLI symptoms.
- If not used as primary endpoints, cardiovascular morbidity and mortality as well as total mortality should be assessed individually as secondary endpoints to ensure the collection of appropriate safety information.
- A new endpoint concept based on an optimal response definition takes into account the recovery after treatment and the inevitable late failure and may focus on the number of "good days" after recovery (patient alive, both legs, no wound, no pain, off analgesics).
- In contrast to intermittent claudication the assessment of QoL is not yet an established endpoint in CLI trial; however, continued evaluation of quality of life instruments is important to define appropriate QoL measures in CLI patients. At present the assessment of QoL may be considered as a secondary endpoint.

Statistical significance versus clinical relevance

The question of clinical relevance is less problematic in CLI than in intermittent claudication. Generally, a statistically significant difference in total ulcer-healing, amputation rate, and/or mortality is considered clinically relevant if shown for the intention-to-treat population. For mortality, the same argument applies as made for PAOD stage II cardiovascular prevention trials: a statistically significant difference in cardiovascular mortality between groups, which also favourably influences all-cause mortality, should be acceptable.

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