The constitutive procoagulant and hypofibrinolytic state in patients with intermittent claudication due to infrainguinal disease significantly improves with percutaneous transluminal balloon angioplasty

Simon D. Hobbs, MBChB, Tim Marshall, MSc, Chris Fegan, MD, Donald J. Adam, MD, and Andrew W. Bradbury, MD, Birmingham, United Kingdom

Background: Patients with intermittent lower limb claudication (IC) exhibit a prothrombotic diathesis that is acutely exacerbated by exercise. This may occur because of ischemia/reperfusion injury within the leg muscles during walking and may contribute to the increased risk of thrombotic vascular events in this group of patients. This randomized study compared the effect of lower limb revascularization by percutaneous transluminal balloon angioplasty (PTA), supervised exercise, and best medical therapy (BMT) alone on this prothrombotic state.

Methods: Twenty-three patients (16 men and 7 women; median age, 67 years; range, 57-77 years) with IC due to infrainguinal disease were randomized to receive BMT alone (n = 7), BMT plus PTA (n = 9), or BMT plus supervised exercise (n = 7) as part of the Health Technology Assessment–funded EXercise vs Angioplasty in Claudication Trial (EXACT). Patients were assessed at baseline and at 3 and 6 months. Thrombin-antithrombin complex (TAT) was determined as a marker of thrombin generation, and plasminogen activator inhibitor (PAI) antigen was determined as a marker of fibrinolysis. Increased TAT indicates a procoagulant state, and increased PAI antigen indicates a hypofibrinolytic state.

Results: At 6 months, subjects randomized to BMT plus PTA demonstrated a significant improvement in ankle-brachial pressure index (P = .013) and maximal walking distance (P = .008), a significant decline in resting thrombin generation (median [interquartile range] TAT, 6.4 µg/L [2.7-13.5 µg/L] to 1.5 µg/L [0.3-2.9 µg/L]; P = .038), and an improvement in resting fibrinolysis (median [interquartile range] PAI-1, 10.0 ng/mL [1.0-20.5 ng/mL] to 1.0 ng/mL [1.0-14.8 ng/mL]; P = .043). There was no significant change in any of these parameters in patients randomized to BMT plus supervised exercise or to BMT alone.

Conclusions: The addition of lower limb revascularization by PTA to BMT in patients with IC due to infra-inguinal disease results in a medium-term improvement in the resting procoagulant and hypofibrinolytic state. This may translate into a reduction in morbidity and mortality from thrombotic vascular events in this group of patients. (J Vasc Surg 2006; 43:40-46.)

Intermittent claudication (IC) is a common condition that affects 5% of the middle-aged (55-74 years old) white population and is a common cause of immobility, social exclusion, and impaired health-related quality of life. Patients with IC have an annual mortality rate that is three to four times higher than that of an age- and sex-matched nonclaudicant population. Most of this excess mortality is due to thrombotic vascular events—namely, myocardial infarction, ischemic stroke, and critical limb ischemia. Previous work from this institution has demonstrated that exercise in individuals with IC is associated with a prothrombotic response characterized by excessive thrombin generation and relative hypofibrinolysis. It has been postulated that the repeated ischemia/reperfusion injury (IRI) occurring in the lower limb of the exercising claudicant contributes to this prothrombotic diathesis and may, in turn, expose the individual to an increased risk of thrombotic vascular events. We hypothesized that lower limb revascularization by percutaneous transluminal balloon angioplasty (PTA), in addition to best medical therapy (BMT), would reduce the IRI, thus resulting in an attenuation of the prothrombotic response. The aim of this study, therefore, was to compare the effects of BMT only, BMT plus supervised exercise, and BMT plus infrainguinal PTA on coagulation and fibrinolysis in subjects with IC due to infrainguinal disease entered into the UK Health Technology Assessment (HTA)-funded multicenter EXercise vs Angioplasty in Claudication Trial (EXACT).
METHODS

Exercise vs angioplasty in claudication trial. EXACT was a UK HTA program multicenter randomized controlled trial comparing the adjuvant benefits of supervised exercise and PTA over BMT in patients with mild to moderate IC (defined as an absolute claudication distance [ACD] of 50-500 m on a treadmill) due to infrainguinal disease. Briefly, suitable patients were those who (1) had clinically and hemodynamically confirmed mild to moderate IC due to infrainguinal disease as their exercise-limiting diagnosis and (2) were suitable for unilateral infrainguinal PTA and participation in a dedicated, trial-funded, supervised exercise class. Subjects were excluded if they had significant aortoiliac disease, equally severe bilateral symptoms (and, therefore, were unsuitable for unilateral angioplasty), or previous ipsilateral infrainguinal intervention or were unable to exercise to ACD on the treadmill (eg, limited by shortness of breath).

All patients underwent a standard vascular examination, including measurement of ankle-brachial pressure index (ABPI) and a treadmill test (speed 3 km/h at a fixed 10% gradient) to ACD. The diagnosis of IC was confirmed by using the Edinburgh claudication questionnaire combined with a finding of a resting ABPI <0.9 or a significant decrease in ABPI after the treadmill test in the affected leg. Patients with confirmed IC due to atherosclerotic peripheral arterial disease (PAD) were stabilized on BMT, as previously described, for 3 to 6 months before consideration for trial entry.

All patients deemed suitable for EXACT at their first visit were further assessed with duplex ultrasonography (Philips ATL HDI-5000; Philips Medical Systems, Reigate, UK) by an experienced vascular technician. Duplex findings were discussed in a multidisciplinary meeting attended by vascular surgeons and interventional radiologists. All TransAtlantic Inter-Society Consensus femoropopliteal category A and B lesions were considered appropriate for PTA. Certain category C lesions were also considered appropriate in the absence of a flush superficial femoral artery occlusion or diffuse superficial femoral artery disease. After 3 to 6 months of stabilization on BMT, all potentially eligible patients were reassessed to monitor progress and to determine compliance with BMT. At this point, patients were invited to take part in EXACT if they

1. Remained, in the patient’s opinion, “unacceptably symptomatic.”
2. Still had an ACD of 50 to 500 m on treadmill assessment.
3. Had infrainguinal disease amenable to unilateral PTA.
4. Were suitable for enrollment within the supervised exercise program.

Subjects underwent central randomization to continue with BMT alone, to receive BMT plus supervised exercise, or to receive BMT plus PTA. Those randomized to supervised exercise were enrolled in a 12-week course of twice-weekly 1-hour structured exercise sessions led by a vascular nurse specialist and a physiotherapist, and subjects randomized to PTA underwent the procedure within 12 weeks of randomization.

Between September 2002 and July 2004, 372 patients referred by their primary care physicians for investigation and treatment of suspected claudication were screened for entry into EXACT. Of these, 23 (6%) patients gave fully informed written consent to be randomized into the present study (Table 1). The main reasons for excluding willing patients were one or more of the following: incorrect diagnosis in primary care, equally severe bilateral symptoms (patients were therefore judged inappropriate for unilateral PTA), significant aortoiliac disease, maximum claudication distance less than 50 m or more than 500 m (outside EXACT trial limits), no lesion suitable for PTA on duplex scan, and previous ipsilateral intervention. Nine subjects were randomized to receive BMT plus PTA; seven, to receive BMT plus supervised exercise; and seven, to remain on BMT alone. Subjects in the three treatment groups were well matched for age, smoking status, diabetes, lipid profile, antiplatelet therapy, statin therapy, angiotensin-converting enzyme inhibitor therapy, ABPI, initial claudication distance (ICD), ACD, and the TransAtlantic Inter-Society Consensus category of the target lesion. However, subjects randomized to supervised exercise were significantly more likely to be receiving anti-hypertensive medication than those randomized to PTA (P = 0.034; Fisher exact test). Subjects who underwent PTA had the procedure performed a median of 39 days (interquartile range [IQR], 28-77 days) after randomization. One subject in the supervised exercise group withdrew from the study shortly after randomization; the remainder completed their 3- and 6-month follow-up assessments.

Exercise program. The exercise program was devised by the Faculty of Health and Exercise at University College Worcester to include group activity and a personalized exercise prescription. Although there is some evidence that thrice-weekly sessions are superior to twice-weekly sessions, the evidence is not particularly strong because of the small number of trial participants in the assessed studies. It was therefore believed that a twice-weekly program would offer the optimal balance between therapeutic benefit and, importantly, compliance with the regimen. The 1-hour exercise program encouraged subjects to perform exercise of moderate intensity in accordance with the American College of Sports Medicine guidelines and has been validated for use in subjects with IC. After a 5-minute warm-up, subjects underwent a circuit sequence of exercises. This sequence involved a shuttle walk at moderate to hard pace; paired toe raising to heel raising, with chair support for balance; continuous sitting and standing from chair; spot marching with high knees, swinging arms; arm exercises from the upright sitting position (side arm raising, alternate arm vertical pushing, and side bent-arm lift); shuttle walk at moderate to hard pace; knee bends with chair support for balance; alternate heel raising (left/right) with chair support for balance; step-ups on bench or stairs; and arm exercises from the upright sitting position (straight side arm small backward circling, double arm vertical pushing, and...
side bent-arm lift, alternating arms). Subjects underwent 3 minutes of activity at each station followed by 2 minutes of rest. On days when not attending the supervised sessions, subjects were asked to perform the exercise program unsupervised at home. Training logs were kept to detail the number of repetitions performed and the maximal heart rate at each station to ensure an adequate training effect.

**Studies of coagulation and fibrinolysis.** After local ethics approval, subjects randomized into EXACT at our center were additionally enrolled into this substudy assessing the effects of adjunctive treatment on coagulation and fibrinolysis. Subjects were assessed immediately after randomization and at 3 and 6 months after randomization. Before each visit, subjects were asked to refrain from smoking or eating a heavy meal and to avoid unaccustomed exercise in the preceding 24 hours. All visits took place between 8:30 and 9:00 AM, and subjects were transported to the hospital by taxi and then transferred to the Vascular Investigation Unit by wheelchair to avoid walking. Subjects rested for 60 minutes before undergoing venipuncture from an antecubital fossa vein without tourniquet. Blood was collected into sodium citrate tubes and was immediately centrifuged at 4°C for 15 minutes at 2000 g. The resultant plasma was stored at −80°C for later batch analysis. ABPI was measured in both legs by using a Mini Dopplex with an 8-MHz probe (Huntleigh Diagnostics, Cardiff, UK). For each leg, the highest recorded pressure from the three ankle vessels (anterior tibial, posterior tibial, and perforating peroneal) was used to determine the ABPI. Subjects then exercised with a standard treadmill exercise test (3 km/h at 10% incline) to their ACD or to 1000 m (at follow-up visits), whichever was soonest. The distance when claudication pain was first perceived was recorded as the ICD. A further venipuncture was performed 3 minutes after completion of the treadmill test from an antecubital vein different from that used for the first venipuncture, and the plasma was extracted and stored as described previously.

Thrombin generation cannot be directly measured because, under pathologic conditions, less than 1% of circulating prothrombin is transformed to thrombin, and it is rapidly inactivated by antithrombin III. Thrombin generation can, however, be measured indirectly by measuring the amount of inactivated thrombin, namely, the thrombin-antithrombin (TAT) complex.11 Plasma levels of TAT (Dade-Behring, Marburg, Germany) were determined by enzyme-linked immunosorbent assay (ELISA) on the resting and postexercise samples at baseline and 6 months. The analysis was manual except for the reading, which was performed on an ELISA workstation (Triturus, Grifols, Cambridge, UK). Samples were analyzed as one batch, and the intra-assay coefficient of variation was <5%.

Fibrinolytic function can be examined by measuring plasminogen activator inhibitor (PAI)-1 antigen levels. A hypofibrinolytic state is associated with increased PAI-1 antigen levels. Because our previous studies had not demonstrated an acute change in fibrinolysis with exercise, PAI antigen levels (Technoclone, Vienna, Austria) were determined by ELISA on the resting samples only, at baseline and 3 and 6 months. TAT and PAI-1 antigen were chosen for this study because our pilot studies have shown these to be significantly increased in claudicants when compared

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Figures represent the number of cases or median values (interquartile range).

**BMT,** Best medical therapy; **SE,** supervised exercise; **PTA,** percutaneous transluminal balloon angioplasty; **NS,** not significant; **ACE,** angiotensin-converting enzyme; **TASC,** TransAtlantic Inter-Society Consensus.

*Analysis of variance.
†Fisher exact test.
with both smoking and nonsmoking controls.\textsuperscript{5} PAI activity was not measured because we were unable to find an activity assay that produced reproducible results in our hands. All assays were performed by a UK National Health Service–accredited laboratory.

**Sample size calculation and statistical analysis.** For the study to support the working hypothesis described previously, it needed to have the power to be able to show significant improvements in thrombin formation and fibrinolysis in patients undergoing PTA. On the basis of pilot data, 21 subjects (7 per group) were required to detect a 75% reduction in TAT in the treatment groups with 80% power and a $P$ value of $<.05$. Data were analyzed with SPSS version 11.0.1 for Windows (SPSS Inc, Chicago, Ill). Groups were compared at baseline by using the analysis of variance (ANOVA) test for continuous data and the Fisher exact test for categorical data. Changes over time were analyzed by using the Wilcoxon signed rank test. A $P$ value of $\leq .05$ was considered statistically significant.

**RESULTS**

**Change in disease severity**

**Ankle-brachial pressure index.** Over the 6-month study period, there was a significant improvement in ABPI in the target leg in the group as a whole. Subgroup analysis showed that the only subjects to demonstrate an improvement were those in the BMT plus PTA group. Subjects in the BMT-alone and BMT plus supervised exercise groups had no significant changes in ABPI (Table II).

**ICD and ACD.** There was a significant improvement in ICD and ACD for the subjects as a whole over the 6-month study period. However, on subgroup analysis, the only subjects to demonstrate significant improvements in walking distance were those randomized to BMT plus PTA.

**Thrombin generation: TAT**

There were no significant differences in TAT levels among the three groups at baseline ($P = .16$; ANOVA). Resting TAT levels correlated with ICD (Spearman coefficient, 0.486; $P = .022$) but no other clinical parameter. Taking the study population as a whole, a significant acute increase in TAT after exercise to ACD was observed at baseline and 3 and 6 months (median [IQR] TAT: baseline, 3.1 $\mu$g/L [1.8-9.3 $\mu$g/L] to 4.8 $\mu$g/L [2.6-15.8 $\mu$g/L], $P = .006$; 3 months, 2.8 $\mu$g/L [1.3-4.7 $\mu$g/L] to 4.3 $\mu$g/L [0.9-12.9 $\mu$g/L], $P = .019$; 6 months, 1.2 $\mu$g/L [0.1-4.1 $\mu$g/L] to 2.4 $\mu$g/L [0.1-12.4 $\mu$g/L], $P = .004$; Fig 1). These data are consistent with the results of our previous study.\textsuperscript{5} Overall, resting TAT decreased over the time course of the study, becoming significantly lower by 6 months ($P = .004$).

On subgroup analysis, there was a significant fourfold reduction in resting TAT levels over the 6-month study period in subjects randomized to BMT plus PTA (median [IQR] TAT, 6.4 $\mu$g/L [2.7-13.5 $\mu$g/L] to 1.5 $\mu$g/L [0.3-2.9 $\mu$g/L]; $P = .038$). There was no significant reduction in TAT in either the BMT-alone group (median [IQR] TAT, 1.9 $\mu$g/L [1.8-11.5 $\mu$g/L] to 1.8 $\mu$g/L [0.5-6.9 $\mu$g/L]; $P = .138$) or the BMT plus supervised exercise group (median [IQR] TAT, 2.4 $\mu$g/L [0.9-4.0 $\mu$g/L] to 1.6 $\mu$g/L [0.1-3.5 $\mu$g/L]; $P = .249$; Fig 2). In the BMT plus PTA group, the improvements observed in TAT showed a significant correlation with the improvement in ABPI (Spearman coefficient, 0.676; $P = .045$).

In addition to reduced resting TAT levels, there was a positive trend toward reduced postexercise TAT levels over the 6-month period in the BMT plus PTA group (median postexercise [IQR] TAT, 10.2 $\mu$g/L [3.5-13.8 $\mu$g/L] to 8.7 $\mu$g/L [0.8-6.7 $\mu$g/L]; $P = .066$). No change in postexercise TAT levels was observed in either the BMT-
alone group (median postexercise [IQR] TAT, 16.1 µg/L [2.4-39.5 µg/L] to 16.2 µg/L [2.8-29.6 µg/L]; P = .500) or the BMT plus supervised exercise group (median postexercise [IQR] TAT, 7.4 µg/L [2.2-11.0 µg/L] to 6.2 µg/L [0.1-9.7 µg/L]; P = .345).

Fibrinolysis: PAI-1 antigen

No correlation between baseline PAI-1 antigen levels and disease or symptom severity was found. There was no significant difference in baseline PAI-1 antigen levels among the three groups (P = .21; ANOVA). On subgroup analysis, a significant reduction in PAI antigen levels was observed in subjects in the BMT plus PTA group (median [IQR] PAI antigen, 10.0 ng/mL [1.0-20.5 ng/mL] to 1.0 ng/mL [1.0-14.8 ng/mL]; P = .043) at 6 months compared with baseline. This reduction in PAI antigen levels showed a significant correlation with the percentage improvement in ACD (Spearman coefficient, 0.696; P = .039) and the improvement in ABPI (Spearman coefficient, 0.856; P = .003). There were no significant changes in PAI antigen levels in the BMT group (median [IQR] PAI antigen, 20.0 ng/mL [3.0-34 ng/mL] to 16.5 ng/mL [7.3-42.5 ng/mL]; P = .686) or in the BMT plus supervised exercise group (median [IQR] PAI antigen, 15.0 ng/mL [2.5-20.5 ng/mL] to 9.5 ng/mL [1.0-18.8 ng/mL]; P = 1.00).

DISCUSSION

The UK HTA-funded prospective randomized controlled EXACT has demonstrated—to our knowledge, for the first time—that lower limb revascularization by PTA in patients with mild to moderate unilateral IC due to infranigual disease results in an improvement in the resting procoagulant and hypofibrinolytic state as demonstrated by a reduction in TAT levels and PAI-1 antigen levels in the medium term. Furthermore, these changes correlate well with the observed improvement in ABPI and ACD. Because similar changes in TAT and PAI-1 antigen were not observed in patients randomized to continue with BMT alone or to receive BMT plus supervised exercise, we believe that these novel data support the working hypothesis. Specifically, they suggest that PTA, but not BMT or BMT plus supervised exercise, leads to an improvement in the procoagulant diathesis observed in this patient group because it alone leads to an improvement in resting leg blood flow and a reduction in calf muscle ischemia/reperfusion on exercise.

It is well established that PAD is associated with a procoagulant and hypofibrinolytic state, as demonstrated by increased levels of fibrinogen, d-dimer, prothrombin fragment 1 and 2, TAT, PAI-1 antigen, and tissue plasminogen activator antigen and that the severity of this hypercoagulable state may correlate with disease severity. In response to moderate to heavy exercise, normal controls demonstrate activation of coagulation that is well balanced by activation of the fibrinolytic system. Previous work from our group has shown that this exercise-induced activation of coagulation is exacerbated in patients with IC, with increases in TAT detectable immediately after exercise to ACD. This results in significantly higher postexercise TAT levels compared with age- and sex-matched controls. These findings that are similar to those shown in other studies of subjects with other cardiovascular diseases. Although our previous study failed to demonstrate an improvement in fibrinolysis, several other studies have suggested that fibrinolysis may be enhanced after acute exercise. This disparity may be due to the different intensity and duration of exercise in these studies.
The reasons why patients with cardiovascular disease—in particular, PAD—have a prothrombotic tendency are not well understood. One possible explanation in patients with IC is based on the important observation that when such patients walk (and then rest because of pain), they experience IRI of the leg muscles, which, in turn, leads to an acute increase in inflammatory markers. It has been suggested that IRI and the inflammatory response within the leg muscles during exercise leads to endothelial cell activation and injury, as demonstrated by increased levels of endothelial products such as von Willebrand factor. This in turn leads to the activation of the coagulation system. Exercise training may lead to an attenuation of some elements of this systemic inflammatory response in healthy individuals and patients. The effect of exercise training, however, on thrombin production in subjects with coronary heart disease is equivocal and has not been evaluated in PAD. With regard to fibrinolysis, only one nonrandomized study has demonstrated enhanced endogenous fibrinolysis after 6 months of exercise training.

Successful PTA in patients with IC has been shown to be associated with an immediate increase in fibrin turnover, most probably secondary to endothelial cell activation. However, no study to date has examined the medium- and long-term effects of PTA on coagulation and fibrinolysis in patients with IC. One study assessing the effect of surgical revascularization on coagulant activity demonstrated no change in the preoperative coagulation and fibrinolytic defects. It is important to note, however, that all subjects in the study had critical limb ischemia, and follow-up was performed only to 30 days.

The findings of this study provide novel insights into the pathophysiology of cardiovascular risk in patients with IC. Patients randomized to remain on BMT or to BMT plus participation in a 12-week supervised exercise program showed no significant improvement in their resting procoagulant diathesis. In contrast, subjects randomized to BMT plus PTA demonstrated a significant improvement in their thrombotic tendency that was associated with clear evidence of improved limb perfusion and symptoms. Furthermore, BMT plus PTA seemed to attenuate the acute hypercoagulable response observed after treadmill testing to ACD when compared with BMT alone or BMT plus supervised exercise. This attenuation occurred despite the almost fourfold improvement in ACD observed in the BMT plus PTA group.

The data from this study strongly support, but do not prove, the working hypothesis that both the chronic constitutive and acute postexercise procoagulant state observed in patients with IC are a consequence of reduced lower limb perfusion and the resulting IRI developed upon walking and then resting. The most likely underlying mechanism would seem to be endothelial cell damage and activation. This hypothesis is supported by the observation that compared with healthy controls, patients with PAD demonstrate activation of coagulation that is associated with endothelial cell activation and disease severity. Treatments such as PTA (and, presumably, also surgery) that restore (nearly) normal perfusion obtund this IRI and thus attenuate both the resting procoagulant diathesis and the response to acute exercise. In contrast, other treatments such as (supervised) exercise and specific pharmacotherapy—which, although effecting symptomatic improvement through as yet incompletely defined mechanisms, do not alter the underlying hypoperfusion and IRI—may not affect the acute on chronic procoagulant diathesis observed in these patients.

This study failed to show significant symptomatic improvements in subjects randomized to supervised exercise. Although this may be a consequence of the design of the exercise program, its twice-weekly nature (augmented by unsupervised home exercise), and its 12-week duration, pilot data show that the intensity of exercise and the training effect observed should have been sufficient to produce improvements in walking distance. Indeed, these pilot studies and other clinical data have shown improvements of up to 94% in ACD after this exercise program. The lack of an observed treatment effect of BMT plus supervised exercise may, therefore, be an example of a type II statistical error, especially because this science study, nested within a larger clinical trial, was not aimed at or powered to consider walking distance as an end point. Although this study has demonstrated a significant benefit of PTA, we have not been able to fully establish the effect of supervised exercise and BMT on the resting procoagulant state. Although these did not reach significance, we observed a positive trend for both thrombin production and fibrinolysis with BMT plus supervised exercise and, to a lesser extent, with BMT alone. Although it is clear that the magnitude of this change is significantly less than that observed with PTA, it is possible that a larger study would confirm a positive benefit for supervised exercise on the prothrombotic diathesis. Indeed, a larger nonrandomized study by Killewich et al previously demonstrated a significant 23% improvement in PAI activity after 6 months of supervised exercise. The effect of supervised exercise and pharmacotherapy on thrombin production and fibrinolysis is currently the subject of an ongoing randomized controlled study.

Building on the observational platform provided by the present original data, further studies will be aimed at confirming or refuting the original hypothesis. By improving the acute or chronic prothrombotic diathesis, PTA has the potential not only to improve walking distance, but also to reduce morbidity and mortality due to thrombotic vascular events. However, these longer-term clinical benefits and the durability of the benefits already observed will need to be established in much larger prospective longitudinal studies comparing treatments that do (surgery or angioplasty) and do not (pharmacotherapy or supervised exercise) revascularize the limb.

Firm conclusions from this randomized study are limited by the small numbers of patients and require corroboration in a larger cohort. However, if confirmed, they suggest that a more aggressive approach to IC due to infragenital disease may have a positive effect on cardio-
vascular risk and symptomatic status in this group of patients.

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AUTHOR CONTRIBUTIONS

Conception and design: SDH, CF, DJA, AWB
Data collection: SDH
Analysis and interpretation: SDH, CF, DJA, AWB
Writing the article: SDH
Critical revision of the article: CF, DJA, AWB
Final approval of the article: SDH, TM
Statistical analysis: SDH, TM
Obtained funding: SDH, CF, AWB
Overall responsibility: SDH

REFERENCES


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