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Trapidil is as effective as isosorbidedinitrate
for treating stable angina pectoris –
A multinational, multicenter, double-blind,
randomized study

Summary Objective Nitrates have long been used in the treatment of stable angina pectoris. We set out to show that trapidil, a triazolopyrimidine with a mode of action different from that of nitrates, is not inferior to isosorbidedinitrate (ISDN) in the treatment of this clinical syndrome. Patients and Methods We studied the efficacy of 200 mg trapidil (t.i.d.) vs. ISDN (20 mg b.i.d.) in patients with chronic stable angina treated for 12 weeks. The therapeutic effect was measured in terms of responder rate as change in total exercise time (TET) by at least 60 seconds using the bicycle ergometer test. Results A total of 648 patients were included in the study. Responder rates in the Per-Protocol (PP) population (n = 529) were 50.4% (n = 133) in the trapidil group and 52.5% (n = 139) in the ISDN group (p = 0.233). As the lower non-inferiority limit (–15%) was clearly excluded from the 95% CI (pp: –10.6%, + 6.4%; ITT –9.7%, 5.7%), non-inferiority of trapidil compared to ISDN can be concluded. Trapidil 200 mg t.i.d. combined with short-acting NTG prn as rescue medication over 12 weeks in subjects with chronic stable angina pectoris proved to have similar effects on TET and on other clinical endpoints as ISDN 20 mg b.i.d. The secondary efficacy analyses did not reveal any clinically relevant differences between treatment groups, and were not in conflict with the non-inferiority claim. Patients in the ISDN group had significantly more headache (34.1%; n = 110) compared to those taking trapidil (19.3%, n = 62; p < 0.0001). Conclusions Overall results of this study show that both drugs are equally effective and safe for the short-term treatment of patients with chronic stable angina pectoris and that trapidil can be considered as therapeutically equivalent to ISDN.

Key words Chronic angina pectoris – trapidil – ISDN

Introduction
Treatment of chronic stable angina pectoris is directed primarily at reducing the imbalance between myocardial oxygen demand and supply. Besides lifestyle alterations, medical treatment is one of the cornerstones of therapy for chronic stable angina. Nitrates and NO-donors such as ISDN are, among others, accepted as standard therapies for patients who are still symptomatic in spite of treatment with aspirin, beta-blockers and ACE-inhibitors [1–3]. Although the therapeutic value of nitrates and ISDN is generally recognized, side effects limit their use in daily practice [4]. The most common adverse
events are headaches, leading to discontinuation of therapy in 20–30% of patients [5, 6]. Recent findings also reported a partially harmful effect on endothelial function [7]. Caramori [8] and Gori [9] demonstrated endothelial dysfunction in coronary and peripheral arteries. Münzel et al. [10] found that nitrates cause endothelial dysfunction. Nakamura [11] showed in a metaanalysis that treatment of patients with ISDN or ISMN after myocardial infarction could be harmful.

For these reasons, there is a need for alternative anti-ischemic compounds with different modes of action, reducing both the severity of the ischemic episodes and their consequences. Among these compounds, trapidil stands out with its unique mode of action, which involves sensitization processes mediated by intracellular protein kinase II (PKAIi) [12]. In animal experiments trapidil is a potent cardioprotective in ischemia/reperfusion (I/R) models. The substance selectively increases the activity of PKAIi isoforms due to a cAMP-sensitizing activity [13]. Target for trapidil-mediated PKA activation is intracellular phospholamban (PLB) which is phosphorylated by PKA activity. This leads to an enhanced Ca²⁺ uptake which might contribute to its cardioprotective effects in I/R hearts. Through this activation and by influencing further downstream signal transduction pathways the antiischemic action of the substance could be explained [14]. Furthermore, trapidil displays some antiproliferative activities, blocking Raf-Kinase mediated smooth muscle cell growth [15, 16]. Former clinical trials carried out in patients with stable angina pectoris revealed trapidil's favorable side-effect profile [17, 18]. Therefore, we initiated a large-scale clinical trial to investigate the effect of trapidil given for 12 weeks, vs. the reference drug ISDN, on the responder rate measured on a bicycle ergometer.

**Methods**

**Patients**

Patients of either sex in the age range of 30–75 years with chronic stable angina pectoris (Canadian Cardiovascular Society [CCS class I to II]) and documented myocardial ischemia during at least one of the first two exercise tolerance tests (ETTs), i.e. horizontal or downsloping ST-segment depression of ≥1 mm (0.1 mV) in any lead, were included. Subjects had to satisfy inclusion criteria at the initial screening (Visit 1) and additional criteria one week later (Visit 2), after a wash-out period and the second ETT. After Visit 2, patients were randomly assigned to either trapidil or ISDN treatment. Then, 6 weeks and 12 weeks after inclusion patients were subject to control visits (V3; V4) with ETT.

Patients were treated for 12 weeks with trapidil or ISDN in monotherapy. Concomitant anti-anginal medication was withdrawn 2 weeks prior to randomization. As rescue medication a short-acting nitrate was allowed.

Patients had to take study medication three times a day, with the ISDN group receiving a matched placebo for evening intake in order to maintain the nitrate-free interval overnight. The trapidil and ISDN doses chosen were in the recommended range for trapidil (400–600 mg) and in the middle of the range for ISDN (5–80 mg) used for the treatment of stable angina pectoris [19].

**Primary and secondary endpoints**

Primary endpoint was the improvement in an exercise tolerance test (in seconds, after 12 weeks of treatment) measured as responder rate, with a clinical responder having a minimum improvement of 60 seconds.

**Exercise tolerance test**

TET measurements were taken at trough conditions more than 3 hours after a short-acting sublingual nitrate intake and not later than 2 hours before the midday study drug intake. Patients were placed on a bicycle ergometer and subject to exercise testing according to exercise standards [20].

ETT was terminated for safety reasons if one of the following conditions occurred:

(i) Inadequate increase in systolic blood pressure >250 mmHg and/or diastolic blood pressure (DBP) >120 mmHg, or a fall in systolic blood pressure of 20 mmHg or more; (ii) serious rhythm and/or conduction abnormalities, e.g., all types of tachyarrhythmias, paired ventricular extrasystoles, parasystole, SA block, second or third degree AV block, left or right bundle branch block, and intraventricular conduction disturbances; (iii) severe ST-segment shifts (>3 mm ST-depression, >1 mm ST-elevation); (iv) severe fatigue (exhaustion), leg cramps; (v) dyspnea inadequate for the workload applied; (vi) central nervous system symptoms (ataxia, dizziness, or syncope); (vii) signs of poor peripheral perfusion (cyanosis or pallor).

**Secondary endpoints**

Secondary endpoints were time to angina, time to 1 mm segment depression, weekly incidence of anginal