Journal of Clinical and Basic Cardiology

An Independent International Scientific Journal

Journal of Clinical and Basic Cardiology 2001; 4 (2), 149-152

A Practitioner Based Evaluation of Nicorandil on Symptoms and Quality of Life in Patients with Chronic Stable Angina Pectoris

Kiowski W, Riebenfeld D

Indexed in
Chemical Abstracts
EMBASE/Excerpta Medica

Krause & Pachernegg GmbH · VERLAG für MEDIZIN und WIRTSCHAFT · A-3003 Gablitz/Austria

A Practitioner Based Evaluation of Nicorandil on Symptoms and Quality of Life in Patients with Chronic Stable Angina Pectoris

W. Kiowski[1], D. Riebenfeld[2]

Nicorandil is an antianginal agent with unique pharmacological properties combining a nitrate-like action with vasodilation through opening of ATP-potassium channels. The antianginal effects of nicorandil have been carefully studied in mostly small, comparative trials but its usefulness outside of the setting of clinical trials is less well studied. We investigated the antianginal effects (patient diary for angina episodes and nitroglycerin consumption for immediate pain relief) of nicorandil in 200 patients (46 % females, 71.4 ± 9.9 years) followed by 56 primary care physicians in general practice. Nicorandil was started at 2 × 10 mg and, increased after 3 weeks to 2 × 20 mg, if tolerated and judged necessary, for a total of 12 weeks. Nicorandil was given as monotherapy in 22 % and in combination with beta-blockers, calcium antagonists or long-acting nitrates in 78 % of patients. An assessment of quality of life was performed at baseline and at week 12.

Nicorandil was withdrawn in 14 patients (7 %) because of headache and/or flushing and in 10 patients because of acute illnesses unrelated to therapy or administrative reasons. After 12 weeks, nicorandil resulted in small but statistically significant ($p < 0.05$) decreases of systolic (–5.0 ± 14.3 mmHg) and diastolic (–2.4 ± 8.6 mmHg) blood pressure and heart rate (–1.9 ± 9.0 bts/min). Weekly anginal episodes and nitroglycerin consumption decreased markedly by –5 ± 6.3 and –5.6 ± 8.5 ($p < 0.001$) and ratings of quality of life improved for all aspects ($p < 0.001$). Both patients and physicians rated efficacy and tolerability in 80 to 90 % as excellent or good and 169 out of 174 patients opted for long-term nicorandil therapy after 12 weeks.

Thus, nicorandil given alone or in combination proved to be highly efficacious and well tolerated in patients with chronic stable angina pectoris followed by their private physicians in general practice. *J Clin Basic Cardiol 2001; 4: 149–152.*

Key words: nicorandil, angina pectoris, quality of life

Nicorandil is an antianginal agent with unique pharmacological properties. On the one hand, it induces vascular smooth muscle relaxation by stimulation of guanylyl cyclase leading to a nitrate-like action due to increased intracellular cyclic guanosine monophosphate levels [1]. On the other hand, it results in hyperpolarization of vascular smooth muscle cell membrane by opening of ATP-sensitive potassium (K_{ATP}) channels [2, 3], which, in turn, leads to closing of calcium (Ca^{2+}) channels, a reduction in intracellular Ca^{2+} concentration and venous and arterial vasodilation [4–8]. Although nicorandil has a nitrate-like action there is good evidence that opening of K_{ATP} channels contributes significantly to its vasodilatory properties [3]. Trials in patients with chronic stable angina pectoris have demonstrated that nicorandil, 10–20 mg twice daily, is effective and well tolerated and has a similar antianginal and antiischaemic efficacy as compared to nitrates [9, 10], beta-adrenoreceptor blockers [11–13] and calcium channel blockers [14–16]. Interestingly, despite its nitrate-like action clinical tolerance does not appear to be a problem [10, 17, 18]. Although, therefore, the value of nicorandil is undoubted in patients with chronic stable angina pectoris, there is little information about practicability of its use outside of controlled trials. This aspect is important, as results obtained in controlled trials, often performed in specialized centers, need not necessarily reflect efficacy and acceptance by patients and physicians in general practice. Accordingly, we investigated efficacy, tolerability and acceptance of nicorandil therapy for treatment of angina pectoris in patients treated in general practice.

Patients and Methods

The study was conducted in the offices of 56 general practitioners and internists in Switzerland. Two hundred patients with chronic stable angina pectoris agreed to participate in this open label, 12 weeks trial that was approved by the local ethics committees. Exclusion criteria were a recent (< 3 months) myocardial infarction and known intolerance to nicorandil.

After obtaining written informed consent patients were instructed in the use of diaries to record the frequency of angina pectoris episodes and the number of acutely acting nitroglycerin preparations required for pain relief. In addition, an attempt was made to assess patients' quality of life using a scale of 1 (best) to 5 (worst) for the following questions: "How is your general well being?"; "How is your physical capacity?"; "How is your endurance during strenuous physical work?"; and "How much are you bothered by angina pectoris in daily life?". Patients were asked to fill out the questionnaire at the end of each week. Moreover, at the end of the study, patients were asked to judge the efficacy and tolerability of nicorandil as excellent, good, moderate, or poor and physicians were asked to perform the same rating.

Following the baseline visit, patients were started on open label nicorandil 2 × 10 mg daily and were scheduled for a further visit three weeks later. Concomitant therapy was continued. If tolerated and/or judged clinically necessary, nicorandil was increased after three weeks to 2 × 20 mg daily. Down titration to 2 × 5 mg daily was allowed in case of adverse effects. Patients were scheduled for a final visit after 12 weeks when they were given the option to continue nicorandil.

At each visit, seated casual blood pressure (sphygmomanometer), heart rate (radial pulse) and body weight were measured.

Statistics

Paired t-test was used to analyse changes as compared to baseline. Results are presented as means ± standard deviation and proportions as percentages.

Received April 11th, 2001; accepted June 28th, 2001.
For full list of investigators see appendix
From the [1]Division of Cardiology, University Hospital, [2]Medical Department, Merck (Schweiz) AG, Zürich, Switzerland
Correspondence to: Prof. W. Kiowski, MD, Division of Cardiology, University Hospital, CH-8091 Zürich, Switzerland; e-mail: karkiw@usz.unizh.ch

Results

Patient characteristics

Baseline patient characteristics are given in Table 1. Patients were elderly and mildly to moderately symptomatic with a history of prior myocardial infarction on average 7.85 ± 7.9 years earlier in approximately 30 %, coronary artery bypass grafting 7.2 ± 4.4 years earlier in 13.5 %, and percutaneous coronary intervention 3.8 ± 3.4 years earlier in 12.5 % of the patients. Only 14 % of patients were current smokers and antihypertensive drugs other than beta-blockers and calcium antagonists were used in approximately one fourth. Diabetes mellitus was infrequent with 6.5 % of patients using oral hypoglycaemic drugs and only one patient using insulin. Beta-blockers were used most frequently, followed by long-acting nitroglycerin preparations, calcium antagonists and molsidomine. Forty six percent of the patients received one, 24 % two, and 8 % three antianginal agents. Twenty two percent of patients used nitroglycerin tablets or sprays only for pain relief. Interestingly, only 40 % received a platelet inhibitor and only 10 % an HMG-CoA reductase inhibitor. In 27 patients, nicorandil replaced other antianginal therapy (beta-blockers in three, calcium channel blockers in 4, and long-acting nitrates in 20 patients), mostly because of adverse effects of these therapies.

Table 1. Patient characteristics

Age (years)	71.4 ± 9.9
Male/female (%)	54 / 46
Current/previous smoker (%)	14 / 19.5
Angina pectoris NYHA class II/III (%)	74.5 / 25.5
Duration of angina pectoris (years)	4.29 ± 5.2
Previous myocardial infarction (%)	29.5
Percutaneous coronary intervention (%)	12.5
Coronary artery bypass grafting (%)	13.5
β-blockers (%)	44.0
Calcium antagonists (%)	26.0
Long acting nitroglycerin preparations (%)	29.5
Molsidomine (%)	9.5
Platelet inhibitors (%)	39.0
HMG-CoA reductase inhibitors (%)	9.6
ACE-inhibitors, angiotensin receptor antagonists, diuretics (%)	26.5
Oral hypoglycaemic drugs (%)	6.0

Table 2. Haemodynamic and antianginal effects of nicorandil

	Baseline	Nicorandil 3 weeks	Nicorandil 12 weeks
Systolic blood pressure (mmHg)	141.8 ± 18.5	137.4 ± 17.9*	136.5 ± 16.4**
Diastolic blood pressure (mmHg)	82.3 ± 9.1	80.3 ± 9.7	79.8 ± 8.7
Heart rate (bts/min)	72.8 ± 9.9	72.0 ± 9.7	71.2 ± 8.6*
Weight (kg)	74.5 ± 13.4	74.4 ± 13.4	74.0 ± 13.7
Angina pectoris episodes (per week)	6.3 ± 6.4	2.6 ± 3.3**	1.3 ± 2.1**
Nitroglycerin consumption (per week)	6.6 ± 8.9	2.5 ± 3.5**	1.0 ± 1.7**

* $p < 0.05$, ** $p < 0.001$

Patient disposition during study

During the 12 weeks of follow up, 24 patients discontinued nicorandil. In 14 of them (7 %), adverse effects (headaches and/or flush in 13, gastrointestinal disturbances in 1 patient(s)) led to withdrawal of nicorandil within the first three weeks. Lack of compliance (3), administrative reasons (2) and acute illnesses (1 death from cerebral haemorrhage, 1 heart failure decompensation, 2 coronary artery bypass operations and 1 non-cardiac hospitalization) accounted for the other withdrawals from the trial. None of the acute illnesses was considered to be related to study medication by the treating physicians. Thus, 176 patients (88 %) completed the 12 week treatment period as planned. Of these, 121 completed the weekly quality of life questionnaire. The final nicorandil dose was 2 × 5 mg in 3.5 %, 2 × 10 mg in 70.8 %, 2 × 15 mg in 2.9 %, and 2 × 20 mg in 22.8 %.

Clinical effects of nicorandil

Haemodynamic and antianginal effects of nicorandil are summarized in Table 2. On average, nicorandil caused small but significant decreases of systolic (–5.0 ± 14.3 mmHg) and diastolic (–2.4 ± 8.6 mmHg) blood pressure at week 12. Heart rate decreased slightly but significantly (–1.9 ± 9.0 bts/min) while weight was unchanged. Weekly anginal episodes and nitroglycerin consumption decreased markedly by –5 ± 6.3 and –5.6 ± 8.5. Although most of these effects were present at week 3, additional effects were seen at week 12.

Figure 1 shows the average weekly scores for the four questions relating to patients' quality of life. As shown, all scores for the 4 questions improved markedly over time, again with the greater portion of the effect being present after 3 weeks already.

After 12 weeks, physicians rated efficacy and tolerability of nicorandil as excellent or good in 85.4 % and 89.3 % of patients, respectively (Table 3). Likewise, 84.7 % and 89.3 % of patients rated efficacy and tolerability as excellent or good, respectively. Consistently, tolerability was judged as poor in approximately 7 % by patients and physicians, reflecting the number of patients who discontinued the trial because of adverse effects. Finally, 169 patients opted for continuation of nicorandil after 12 weeks.

Table 3. Rating of nicorandil by physicians and patients

	Physicians	Patients
Efficacy (%)		
– excellent	44.8	42.1
– good	40.6	42.6
– moderate	13.5	13.2
– poor	1.0	2.1
Tolerability (%)		
– excellent	54.8	50.8
– good	34.5	38.5
– moderate	3.6	4.1
– poor	7.1	6.7

Rating of efficacy was based on 179 patients and of tolerability on 197 patients

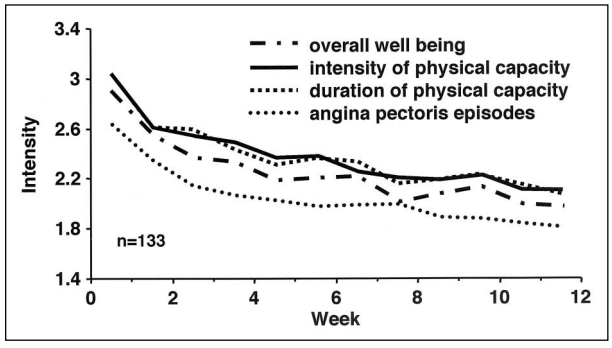

Figure 1. Line graph of averages of weekly assessments of patients' quality of life based upon four questions. A score of 1 was considered best and a score of 5 as worst for the respective questions. Results are presented for those 121 patients who correctly filled out the weekly questionnaire and who completed the 12 week-treatment period

No formal dose comparison was performed but it was interesting to see that the efficacy of the lower dose of 2 × 10 mg/d, which was used in the majority of patients, was similar to that of the highest dose of 2 × 20 mg. Thus, the number of weekly anginal episodes decreased from 5.8 ± 6.2 to 1.3 ± 2.3 ($p < 0.01$) in patients taking 2 × 10 mg/d and from 6.1 ± 7.1 to 1.0 ± 1.8 in patients taking 2 × 20 mg/d. Similarly, weekly nitroglycerin consumption decreased by 5.1 ± 6.2 and 7.1 ± 13.5 in patients taking 2 × 10 and 2 × 20 mg/d nicorandil, respectively.

Discussion

The present study confirms in a large population with chronic stable angina pectoris, that nicorandil is a highly effective antianginal agent [9–16, 19], reducing the number of anginal episodes and use of nitrates for immediate pain relief by approximately 80 %. Expectedly, improved control of anginal pain caused a profound improvement of quality of life, as assessed by a previously used simple questionnaire [16]. These effects were equally found in the 22 % of patients who received nicorandil as monotherapy and the remainder of patients in whom it was added to other antianginal therapy. The starting dose of 2 × 10 mg per day proved to be effective in the majority of patients but antianginal effects were similar after 12 weeks in patients who required the higher dose of 2 × 20 mg. This long-term antianginal efficacy provides further evidence that antianginal and haemodynamic tolerance to nicorandil does not develop to a significant degree [10, 17, 18]. Also, cross-tolerance between nicorandil and nitroglycerin does not seem to occur [20]. Although cross-tolerance was not examined in this study, the finding that the decrease in nitroglycerin consumption paralleled closely that of the reduction in anginal episodes is compatible with this contention. Expectedly, the main adverse effect was headache and/or flushing, which accounted for 13 out of a total of 14 adverse event related treatment discontinuations. Although this incidence (7 %) is somewhat higher than that reported in the prescription-event monitoring study of nicorandil, eg 3.5 % [21] it is still low given the good overall clinical efficacy. Taken together, therefore, nicorandil appears to be an effective and safe drug for the management of these patients in the setting of general practitioners and internists.

Interestingly, these pronounced antianginal effects were achieved with only a small fall of blood pressure, confirming previous results [22, 23]. This finding supports the notion that not only reductions of blood pressure and afterload [24] but also coronary vasodilation with increased oxygen delivery [6, 25] as well as reduced oxygen demand through a reduction in preload [4, 6] are important determinants of nicorandil's antianginal effects. Obviously, it is impossible to determine the relative importance of activating K_{ATP} channels as compared to the nitrate-like effect for the antianginal effects of nicorandil.

Likewise, one could only speculate about the importance of opening K_{ATP} channels for the induction of ischaemic preconditioning. It is of interest, though, that nicorandil, when added to aggressive antianginal treatment for unstable angina, reduced transient myocardial ischaemia compared to placebo suggesting that pharmacological preconditioning through its effect on K_{ATP} channels might be clinically relevant [26]. However, data in patients with chronic stable angina pectoris are missing in that regard. Results from the large (5000 patients) Investigation of Nicorandil in Angina (IONA) study [27] should clarify whether this unique pharmacological effect of nicorandil not only improves symptoms but also reduces ischaemia related cardiac events, eg death, non-fatal myocardial infarction and hospitalization for angina pectoris. Clearly, demonstration of such an effect would place nicorandil at the front of the therapeutic armamentarium for angina pectoris since neither nitrates nor calcium channel or beta-blockers, with the exception of post-infarction patients [28, 29], have a protective effect in chronic stable angina pectoris.

Blood pressure decreased somewhat during nicorandil therapy. Interestingly, heart rate did not increase but decreased also slightly. However, almost half the patients in this trial were taking a beta-blocker, rendering conclusions regarding effects of nicorandil on heart rate difficult. Nevertheless, unchanged heart rate was also found in almost all studies of patients receiving nicorandil [22, 23].

A number of interesting aspects were revealed in this study. Thus, a surprisingly low fraction of patients received antiplatelet agents or HMG-CoA reductase inhibitors even though the value of these agents is established, at least in secondary coronary prevention [30–32]. As 55.5 % of patients either had a previous myocardial infarction or had undergone coronary revascularisation, a much wider or, in the case of platelet inhibitors, a general use would have been expected. This finding clearly shows that further educational efforts are needed to optimize medical therapy of these patients.

There are a number of limitations of this trial. Thus, it was neither randomized nor placebo controlled. Obviously, results from such trials might be biased by patients' as well as physicians' preferences. Also, exercise testing was not performed rendering the evaluation of the antianginal effects of nicorandil purely subjective. However, the efficacy in this trial is not far from what has been found in smaller, placebo controlled or comparative trials of nicorandil [9–16, 19]. Also, 80 % out of a total of 8713 patients in the prescription-event monitoring study of nicorandil [21] reported good efficacy.

Formal dose comparison was not performed making it impossible to draw conclusions regarding the efficacy of 2 × 10 vs 2 × 20 mg dosing regimen. However, it appears that a dose of 2 × 10 mg/d is sufficient for the majority of patients while only approximately one fourth of patients requires a dose of 2 × 20 mg/d to achieve a similar clinical effect. Finally, concomitant therapy was not standardized, making conclusions about the antianginal efficacy in combination with other drugs difficult.

In conclusion, nicorandil given alone or in combination with other antiischaemic drugs proved to be highly efficacious and well tolerated in patients with chronic stable angina pectoris followed by their private physician in general practice. The improvement in quality of life suggests that it should be considered as a therapeutic option for the long-term management of angina pectoris. Whether the effects of nicorandil on K_{ATP} channels will be associated with additional benefit awaits further study.

References:

1. Holzmann S. Cyclic GMP as possible mediator of coronary arterial relaxation by nicorandil (SG-75). J Cardiovasc Pharmacol 1983; 5: 364–70.
2. Kukovetz WR, Holzmann S, Braida C, Poch G. Dual mechanism of the relaxing effect of nicorandil by stimulation of cyclic GMP formation and by hyperpolarization. J Cardiovasc Pharmacol 1991; 17: 627–33.
3. Holzmann S, Kukovetz WR, Braida C, Poch G. Pharmacological interaction experiments differentiate between glibenclamide-sensitive K^+ channels and cyclic GMP as components of vasodilation by nicorandil. Eur J Pharmacol 1992; 215: 1–7.
4. Belz GG, Beermann C. Venodilatory effects of nicorandil in healthy volunteers. J Cardiovasc Pharmacol 1992; 20 (Suppl 3): S57–S58.
5. Richer C, Pratz J, Mulder P, Mondot S, Giudicelli JF, Cavero I. Cardiovascular and biological effects of K^+ channel openers, a class of drugs with vasorelaxant and cardioprotective properties. Life Sci 1990; 47: 1693–705.
6. Treese N, Erbel R, Meyer J. Acute hemodynamic effects of nicorandil in coronary artery disease. J Cardiovasc Pharmacol 1992; 20 (Suppl 3): S52–S56.

7. Muller-Ehmsen J, Brixius K, Hoischen S, Schwinger RH. Inotropic and coronary vasodilatory actions of the K-adenosine triphosphate channel modulator nicorandil in human tissue. J Pharmacol Exp Ther 1996; 279: 1220–8.
8. Kool MJ, Spek JJ, Struyker Boudier HA, Hoeks AP, Reneman RS, van Herwaarden RH, et al. Acute and subacute effects of nicorandil and isosorbide dinitrate on vessel wall properties of large arteries and hemodynamics in healthy volunteers. Cardiovasc Drugs Ther 1995; 9: 331–7.
9. Hayata N, Araki H, Nakamura M. Effects of nicorandil on exercise tolerance in patients with stable effort angina: a double-blind study. Am Heart J 1986; 112: 1245–50.
10. Döring G. Antianginal and anti-ischaemic efficacy of nicorandil in comparison with isosorbide-5-mononitrate and isosorbide dinitrate: results from two multicenter, double-blind, randomized studies with stable coronary heart disease patients. J Cardiovasc Pharmacol 1992; 20 (Suppl 3): S74–S81.
11. Hughes LO, Rose EL, Lahiri A, Raftery EB. Comparison of nicorandil and atenolol in stable angina pectoris. Am J Cardiol 1990; 66: 679–82.
12. Meeter K, Kelder JC, Tijssen JG, Bucx JJ, Henneman JA, Kerker JP, et al. Efficacy of nicorandil versus propranolol in mild stable angina pectoris of effort: a long-term, double-blind, randomized study. J Cardiovasc Pharmacol 1992; 20 (Suppl 3): S59–S66.
13. Di Somma S, Liguori V, Petitto M, Carotenuto A, Bokor D, de Divitiis O, et al. A double-blind comparison of nicorandil and metoprolol in stable effort angina pectoris. Cardiovasc Drugs Ther 1993; 7: 119–23.
14. Ulvenstam G, Diderholm E, Frithz G, Gudbrandsson T, Hedback B, Hoglund C, et al. Antianginal and anti-ischaemic efficacy of nicorandil compared with nifedipine in patients with angina pectoris and coronary heart disease: a double-blind, randomized, multicenter study. J Cardiovasc Pharmacol 1992; 20 (Suppl 3): S67–S73.
15. Guermonprez JL, Blin P, Peterlongo F. A double-blind comparison of the long-term efficacy of a potassium channel opener and a calcium antagonist in stable angina pectoris. Eur Heart J 1993; 14 (Suppl B): 30–4.
16. The SWAN study group. Comparison of the antiischaemic and antianginal effects of nicorandil and amlodipine in patients with symptomatic stable angina pectoris: the SWAN study. J Clin Basic Cardiol 1999; 2: 213–7.
17. Tsutamoto T, Kinoshita M, Nakae I, Maeda Y, Wada A, Yabe T, et al. Absence of hemodynamic tolerance to nicorandil in patients with severe congestive heart failure. Am Heart J 1994; 127: 866–73.
18. Larsen AI, Goransson L, Aarsland T, Tamby JF, Dickstein K. Comparison of the degree of hemodynamic tolerance during intravenous infusion of nitroglycerin versus nicorandil in patients with congestive heart failure. Am Heart J 1997; 134: 435–41.
19. Raftery EB, Lahiri A, Hughes LO, Rose EL. A double-blind comparison of a beta-blocker and a potassium channel opener in exercise induced angina. Eur Heart J 1993; 14 (Suppl B): 35–9.
20. Tabone X, Funck-Brentano C, Billon N, Jaillon P. Comparison of tolerance to intravenous nitroglycerin during nicorandil and intermittent nitroglycerin patch in healthy volunteers. Clin Pharmacol Ther 1994; 56: 672–9.
21. Dunn N, Freemantle S, Pearce G, Wilton LV, Mann RD. Safety profile of nicorandil-prescription-event monitoring study. Pharmacoepidemiology and Drug Safety 1999; 8: 197–205.
22. Knight C, Purcell H, Fox K. Potassium channel openers: clinical applications in ischaemic heart disease—overview of clinical efficacy of nicorandil. Cardiovasc Drugs Ther 1995; 9 (Suppl 2): 229–36.
23. Markham A, Plosker GL, Goa KL. Nicorandil. An updated review of its use in ischaemic heart disease with emphasis on its cardioprotective effects. Drugs 2000; 60: 955–74.
24. Baumbach A, Braun U, Doring G, Haase KK, Voelker W, Karsch KR. Double-blind comparison of the acute effects of two relevant doses of oral nicorandil on central hemodynamics, left ventricular function, and myocardial contractility. Cardiovasc Drugs Ther 1995; 9 (Suppl 2): 213–20.
25. Nakae I, Matsumoto T, Horie H, Yokohama H, Omura T, Minai K, et al. Effects of intravenous nicorandil on coronary circulation in humans: plasma concentration and action mechanism. J Cardiovasc Pharmacol 2000; 35: 919–25.
26. Patel DJ, Purcell HJ, Fox KM. Cardioprotection by opening of the K(ATP) channel in unstable angina. Is this a clinical manifestation of myocardial preconditioning? Results of a randomized study with nicorandil. CESAR 2 investigation. Clinical European studies in angina and revascularization. Eur Heart J 1999; 20: 51–7.
27. Hillis S. IONA – the way forward. Potassium channel openers in cardioprotection: from theory to practice. Satellite Symposium, XXI[st] Congress of the European Society of Cardiology, Barcelona, August 1999.
28. Goldstein S. Beta-blocking drugs and coronary heart disease. Cardiovasc Drugs Ther 1997; 11 (Suppl 1): 219–25.
29. Gibson RS, Hansen JF, Messerli F, Schechtman KB, Boden WE. Long-term effects of diltiazem and verapamil on mortality and cardiac events in non-Q-wave acute myocardial infarction without pulmonary congestion: post hoc subset analysis of the multicenter diltiazem postinfarction trial and the second danish verapamil infarction trial studies. Am J Cardiol 2000; 86: 275–9.
30. Antiplatelet Trialist's Collaboration. Collaborative overview of randomised trials of antiplatelet therapy—I: Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. BMJ 1994; 308: 81–106.
31. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S) [see comments]. Lancet 1994; 344: 1383–9.
32. Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, MacFarlane PW, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. N Engl J Med 1995; 333: 1301–7.

Appendix

List of Investigators:

Dr. med. Battaglia Enrico, Via Stefano Franscini 1, 6900 Lugano
Dr. med. Bieler Magnus, Rorschacherstrasse 19, 9000 St. Gallen
Dr. med. Blanc Jac.-Phil., via alle Scuole, 6946 Ponte Capriasca
Dr. med. Blickenstorfer Heinz, Marktgasse 3, 8600 Dübendorf
Dr. méd. Bourgeois Jean, Chemin du Mont-Blanc 28, 1170 Aubonne
Dr . méd. Bruchez Bernard, Av. de la Gare 17, 1920 Martigny
Dr. med. Brunner Harald, Kernmattstrasse 8b, 4102 Binningen
Dr. med. Bugliani Giorgio, Ackerstrasse 6, 5432 Neuenhof
Dr. med. Cadalbert Andrea, In der Ey 39, 8047 Zürich
Dr. med. Cocco Giuseppe, Marktgasse 1a, 4310 Rheinfelden
Dr. med. Fiori Gabriele, Via Vallemaggia 10, 6900 Locarno
Dr. med. Fleig Stephan, Rosengartenstrasse 30, 8280 Kreuzlingen
Dr. méd. Franzetti André, rte du Collège 13, 1912 Leytron
Dr. med. Frei Alfred, Wilenstrasse 126, 8832 Wilen b. Wollerau
Dr. med. Gerber Andreas, Bassbeltweg 26, 2542 Pieterlen
Dr. méd. Greiner Philippe, St. Jakobstrasse 87, 9000 St. Gallen
Dr. med. Hadinia-Glatt Mahmud, Jakob Eglinstrasse 3, 4132 Muttenz
Dr. med. Hagmann Oscar I., Hasenmattweg 2, 4515 Oberdorf
Dr. med. Hilfiker Max, Mühlegasse 22, 3400 Burgdorf
Dr. med. Husi Friedrich, Oltnerstrasse 500, 4652 Winznau
Dr. méd. Imesch Alain, 28, chemin du Mont-Blanc, 1170 Aubonne
Dr. méd. Jeker Bernard, Place du Midi 40, 1950 Sion
Dr. med. Klein Gerhard, Dorfstrasse 18, 6242 Wauwil
Dr. med. Klenecky-Bühler Milan, Huebwiesenstrasse 33, 8954 Geroldswil
Dr. med. Kozàk Josef, Herrenackerstrasse 28, 8730 Uznach
Dr. med. Kull Hans Ulrich, Obere Heslibachstr. 42, 8700 Küsnacht
Dr. méd. Laurent Antoine, rue de la Gare 6C, 1860 Aigle
Dr. med. Leemann Arnold, Alte Bahnhofstrasse 3, 5610 Wohlen
Dr. med. Lütold Benno E., Dorfstrasse 29/31, 4222 Zwingen
Dr. med. Maurer Hermann, Blumenaustrasse 20, 9000 St Gallen
Dr. med. Mayer Rames, Via Mordasini 12, 6500 Bellinzona
Dr. med. Meile Jean Oscar, Via Pocobelli 15, 6815 Melide
Dr méd. Métrailler Alain, 3971 Chermignon
Dr. med. Müller Robert Alfred, Talgutzentrum, 3063 Ittigen
Dr. med. Nagel Gideon, Burgfelderstrasse 200, 4055 Basel
Dr. med. Nager Gabriella, Freiestrasse 211, 8032 Zürich
Dr. méd. Nguyen Thi, Av. de Chailly 25, 1012 Lausanne
Dr. med. Oswald Norbert, Bahnhofstrasse 14, 7130 Ilanz
Dr. méd. Paratte Jacques, av. du Simplon 21, 1890 St. Maurice
Dr. méd. Piccinin Pascal, av. de la Gare 9, 1890 St. Maurice
Dr. med. Poltéra Alois, Paradiesgärtli, 7130 Ilanz
Dr. méd. Providoli Romeo, Av. Mercier-de-Molin 2, 3960 Sierre
Dr. méd. Reymond Frédéric, rue du Midi 2, 1003 Lausanne
Dr. med. Riek Markus, Schmiedgasse 7, 6430 Schwyz
Dr. med. Saberi Mosar, Binzenstrasse 3, 8733 Eschenbach
Dr. med. Sala Gianmarco, Bahnhofstrasse 35, 6460 Altdorf
Dr. méd. Sandell David, rue des Dents-du-Midi 34, 1868 Collombey
Dr. med. Schneider Thomas A., Riehenstrasse 167, 4058 Basel
Dr. med. Tschurr Enrico, Via Nurtal 1, 7402 Bonaduz
Dr. méd. Valenti Paolo, Av. A. Cortot 7F, 1260 Nyon
Dr. med. Vourtsis Konstantin, Seetalstrasse 20, 6020 Emmenbrücke
Dr. med. Waser Marco, Obergrundstrasse 88, 6005 Luzern
Dr. med. Weber Felix, Marktgasse 5,9000 St. Gallen
Dr. med. Weissenberger Benno, Hardstrasse 111, 4052 Basel
Dr. med. Wimmersberger Walter, Steinmürlistrasse 21, 8953 Dietikon
Dr. med. Zuber Michel, Bahnhofstrasse 8, 5504 Othmarsingen

Mitteilungen aus der Redaktion

Besuchen Sie unsere

zeitschriftenübergreifende Datenbank

☑ **Bilddatenbank** ☑ **Artikeldatenbank** ☑ **Fallberichte**

e-Journal-Abo

Beziehen Sie die elektronischen Ausgaben dieser Zeitschrift hier.

Die Lieferung umfasst 4–5 Ausgaben pro Jahr zzgl. allfälliger Sonderhefte.

Unsere e-Journale stehen als PDF-Datei zur Verfügung und sind auf den meisten der marktüblichen e-Book-Readern, Tablets sowie auf iPad funktionsfähig.

☑ **Bestellung e-Journal-Abo**