A randomised trial of three counselling strategies for lifestyle changes in patients with hypercholesterolemia treated with ezetimibe on top of statin therapy (TWICE)

Essai randomisé de trois stratégies de conseils de modifications du mode de vie chez des patients hypercholestérolémiques traités par ezetimibe en association à une statine (TWICE)

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Summary
Aims. — To compare the impact of three patient counselling strategies for lifestyle changes and to assess the safety and efficacy of ezetimibe on top of statin therapy in hypercholesterolemic high risk patients.
Methods. — Open, cluster randomized 3-parallel group trial. Physicians were randomized between patient motivation on: diet or physical exercise or both. Counselling was adapted to the patient’s baseline Prochaska stage of change. High cardiovascular risk patients, with LDL-C above or equal to 3 mmol/L despite statin therapy for at least 3 months, were enrolled. Ezetimibe (10mg/day) and patient counselling were started at the same time. Target goal was defined as total cholesterol less than 5 mmol/L and LDL-C above 3 mmol/L.

Results. — Overall 428 physicians enrolled 1496 patients. At baseline, LDL-C was $3.9 \pm 0.9$ mmol/L and total cholesterol was $6.1 \pm 1.1$ mmol/L. LDL-C decreased by $-30.4 \pm 19.3$% and 869 (62%) patients achieved target goal. No difference was shown between randomisation groups. However, improvements in diet consumption patterns were more easily obtained than improvement in physical activity stage of change in non-active patient at baseline.

Conclusions. — The marked short-term impact ($-30\%$) on LDL-C, although similar between the three groups, slightly exceeds usual LDL-C reductions achieved by this dose of ezetimibe. Decreasing fat consumption seems easier than increasing physical activity. This study confirms the good efficacy, short-term tolerability and safety of ezetimibe on top of statins.

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Abbreviations

ALT alanine aminotransferase
AST aspartate aminotransferase
CK creatine kinase
GEE generalized estimating equations
HDL-C high-density lipoprotein cholesterol
HMG-CoA hydroxy-methyl-glutaryl-coenzyme A reductase
LDL-C low-density lipoprotein cholesterol
REML restricted maximum likelihood
TG triglycerides
TWICE ezetimibe together with any statin cholesterol enhancement
ULN upper limit of normal

Background

Diet and physical activity are the key to the treatment of dyslipidemia and prevention of cardiovascular disease, whether used alone or in combination with drug therapy [1,2]. Therapeutic lifestyle changes confer large and usually more than additive benefits in terms of risk reduction [2,3].

Much has been learned during the past two decades about successful modification of diet and lifestyle parameters, using behavioural science [4–7]. For example, the Prochaska and DiClementi [8] “stages of change” model postulates that both cessation of high-risk behaviours and the acquisition of healthy behaviours involve progres-
Results of TWICE trial 725

sion through five stages of change: pre-contemplation, contemplation, preparation, action and maintenance [9]. This transtheoretical model has been shown to generalize across a broad range of problem behaviours (including diet, exercise and weight control) [10–12]. The stage of change was conceived to help or guide planned change efforts. This study was designed to estimate the feasibility of the estimation of stage of change in ambulatory hypercholesterolemic patients and to compare three motivation strategies adapted to the patient baseline stage of change.

Adding ezetimibe to ongoing statin therapy leads to substantial additional reduction in LDL cholesterol levels [13]. Ezetimibe was found to be safe and well tolerated in clinical trials. Post marketing studies allow a better assessment of drug safety in clinical practice. This post-marketing trial therefore provided an opportunity to confirm the safety and efficacy of ezetimibe treatment in co-administration with a statin in routine clinical practice.

Methods

Patients

Patients with primary hypercholesterolemia and low-density lipoprotein (LDL-C) greater or equal to 3 mmol/L (115 mg/dL) currently treated with a statin for at least 3 months and between the ages of 18 and 80 were enrolled. Patients were at high cardiovascular risk: secondary prevention (established cardiovascular organ damage or disease) or in primary prevention with one or more cardiovascular risk factors (diabetes mellitus, sustained arterial hypertension, current smoker, man aged 45 or older, menopause or woman aged 55 or older, family history of premature sudden death or myocardial infarction) other than hypercholesterolemia [2]. A family history of premature event was defined as a sudden death or myocardial infarction in a first degree male relative man before 55 or first degree female relative before 65 [2]. Before starting intervention, it was checked that TG level was below 4.52 mmol/L (400 mg/dL), liver transaminases (ALT, AST) less or equal to 2-fold the ULN, CK less or equal to 2-fold ULN and creatinin clearance (Cockroft formula) higher than 30 ml/min.

Key exclusion criteria included:

• use of other lipid-lowering agents within the last 3 months including HMG-CoA reductase inhibitors other than the current statin, fish oils, cholestyramin, niacin (> 200 mg/day) and fibrates;

• any modification in the statin treatment within the last 6 weeks;

• any contra-indication to statin or ezetimibe treatment;

• myocardial infarction, unstable angina, coronary artery bypass surgery, or angioplasty (coronary or peripheral artery) within the last 3 months;

• any immunosuppressant including cyclosporine;

• uncontrolled hypothyroidism;

• active liver disease including known infection by HBs or HBC virus or known HIV infection.

Study design

This is an open, cluster-randomised, 3-parallel group trial comparing three counselling strategies on lifestyle changes.

Cluster randomisation was used, i.e. the physician was chosen as the unit of randomisation, in an attempt to limit treatment contamination. Physicians were randomised in a 1:1:1 ratio before systematic screening and recruitment between [14,15]:

• motivation on diet (Group 1);

• motivation on physical activity (Group 2);

• both (Group 3).

The trial was approved by the ethic committee and all subjects gave written informed consent before participating. The ClinicalTrials.gov identifier of the trial is NCT00328523.

Intervention

Evaluation of patient stage of change

In all patients, Prochaska stage of change and physical activity were estimated before the start of intervention and at the end of intervention, using a self-administered questionnaire. French translation of validated questionnaires were used. The five stages of change were defined for dietary fat reduction and for a Mediterranean nutrition pattern, with respect to two aspects of a Mediterranean diet: consumption of fish and vegetables. These stages of change reflect participants’ readiness to reduce their dietary fat intake and to adopt a Mediterranean diet [6,7]. The five stages of change were defined for physical exercise using four questions [11,12].

Patient counselling

Patients received a leaflet corresponding to their Prochaska stage of change. The leaflet summarizes counselling given to the patient according to the randomisation group of the physician (counselling based on diet, physical activity or both). The patient leaflets for the various types of Prochaska stage and type of counselling (diet, or physical activity or both) are available online at www.cncardio.org/news00010d08.asp.

Counselling was based on the Second Joint Task Force of European and other Societies on Coronary Prevention [16]. A Mediterranean diet was recommended in this trial as well as the recommendation to reduce fat intake, in order to have a low cholesterol diet. Patients were instructed to eat two or more servings of fruit per day, vegetables once per day at least and to replace red meat by fish twice per week [7,17,18]. Patients were also instructed to reduce butter, cream and cheese consumption [2]. As far as physical activity was concerned, patients were professionally encouraged and supported to increase their physical activity safely to a level associated with the lowest risk of cardiovascular disease. Aerobic exercise (e.g. walking, swimming or bicycling) for 20 min. three times a week was recommended. Physicians emphasized the importance of physical activity in giving the patient a sense of well-being. For the elderly
or poorly conditioned or, people in the pre-contemplation, contemplation or preparation stages of change, any amount of physical activity was recommended such as strolling or gardening with emphasis on the possible benefit.

Physicians were not prevented from giving any other oral counselling on lifestyle changes that they thought might be useful for the patient.

Ezetimibe therapy

Ezetimibe therapy was not part of randomisation and all patients received ezetimibe in addition to the statin they already received. The statin dose was kept unchanged.

Flow of the study

Fig. 1 summarizes the study design. At the end of a run-in period of 1—2 weeks and after counseling have been given, all patients were instructed to take ezetimibe 10 mg once daily in the evening on top of the dose of statin they already received.

Lipid and safety parameters were assessed after 6 to 10 weeks of ezetimibe treatment, in a core laboratory [19]. At the third and last visit in the trial, performed one week after blood sampling, all patients were asked to complete the same self-administered questionnaire in order to estimate physical activity and the stages of change for physical exercise, dietary fat reduction and Mediterranean diet. Information on events and compliance with drug treatment were also recorded.

Statistical analysis

The primary efficacy criterion was the percentage of patients with total plasma cholesterol (TC) less than 5 mmol/L (190 mg/dL) and LDL-C above 3 mmol/L (115 mg/dL) at the end of the trial, 6 to 10 weeks after the start of intervention [1]. The secondary efficacy criteria were:

- the percentage changes in LDL-C, HDL-C and TG from randomization to endpoint after 6–10 weeks of ezetimibe treatment;
- the percentage of patients with LDL-C less than 2.58 mmol/L (100 mg/dL) at the end of the trial;
- the percentage of patients with estimation of stage of change;
- the percentage of patients in a pre-action stage of change (precontemplation or contemplation or preparation stage of change) at baseline having moved to an action stage of change at end of trial.

Safety and tolerability of treatment were secondary criteria.

It was estimated that at most 70% of the patients would achieve target lipid level and that each physician would include three patients [20]. In a conventional randomised trial, without cluster design, 996 patients in every treatment group enabled detection of a difference between two treatment groups of 6% at least, with 80% power, at the 5% significance level [21]. For a cluster-randomised trial, using an intracluster correlation factor of 0.019, the standard sample estimates had to be inflated by a factor of 1.038 [14,22,23]. Therefore, a total of 3102 patients had to be enrolled by 1034 physicians.

The unit of analysis is the patient [14]. Categorical parameters were compared between the three therapeutic strategies using a chi-square adjusted for intracluster correlation, followed by logistic GEE using a model including terms for treatment, baseline LDL-C, age, gender, baseline stage of change and statistically significant interaction terms [14,24]. Percentage change data were expressed as mean or median percentage change (95% CI). Percentage change of LDL-C and other lipid parameters were compared between the three therapeutic strategies using a mixed model REML, with intervention arm and covariates as fixed effects and cluster as random effect [25,26]. Adjustment was done on baseline LDL-C, age, gender, and baseline stage of change. Interaction terms were tested. Intracluster correlation coefficients were estimated from the data. Percentage of patients in a pre-action stage at baseline having improved their stage of change by at least one level at the end of the trial was compared between randomisation groups. However, in order to avoid problems related to multiplicity only evolution of Prochaska stages of change for fat consumption and physical activity were statistically compared and descriptive statistics were used for other Prochaska stages of change: fish and vegetable consumptions. Statistical analysis was based on Intent to Treat, including all patients having received one dose of ezetimibe at least and with one determination of LDL-C before and after start of ezetimibe. All patients having received one dose of ezetimibe at least were included in the safety analysis.

Statistical analysis was conducted using SAS® software Version 8.2 (SAS Institute, Inc., Cary, NC).

Results

Out of 1059 randomised physicians (978 cardiologists and 81 general practitioners [GP]) 506 physicians (438 cardiologists and 68 GP) selected 2232 patients between June 2004 and December 2005. Enrollment, being much lower than anticipated, was stopped after 2232 patients were enrolled by 428 physicians. Of the 2232 patients, 1496 (67%) had received at least one dose of ezetimibe; 1411 (64%) patients were included in the efficacy analysis: 493 patients in Group 1, 490 patients in Group 2 and 428 patients in Group 3.

Patient characteristics

Baseline demographics, medical history and lipid levels were similar between treatment groups (Table 1). Approximately one-third of the patients had a known history of myocardial infarction, and approximately half were treated for hypertension. At baseline, LDL-C was 3.9 ± 0.9 mmol/L (151 ± 35 mg/dL) and total cholesterol was 6.1 ± 1.1 mmol/L (234 ± 39 mg/dL).

Among statins used at baseline, pravastatin was the most commonly used (n = 475 [34%]), followed by atorvastatin (n = 401 [29%]), rosuvastatin (n = 188 [13%]), simvastatin (n = 185 [13%]), and fluvastatin (n = 153 [11%]). The median daily statin dose was 10 mg for rosuvastatin, 20 mg for
Results of TWICE trial

Figure 1. Design of TWICE. Physicians were randomised and trained before starting patients selection.

atorvastatin, pravastatin and simvastatin and 80 mg for fluvastatin.

In general, the three motivation groups were well balanced regarding Prochaska stages of change. At baseline, compliance with dietary guidelines was more frequent than compliance with physical activity guidelines: nearly 60% of the patient reported restriction in fat diet for more than 6 months when only approximately 45% of the patient reported exercising three times or more per week during at least 20 min. for more than 6 months.

After the initial blood sampling and before the start of intervention, irrespective of the motivation randomisation group, most of the patients were motivated on diet and physical exercise. In fact, more than three quarters of the physicians gave oral counselling on lifestyle change not given by randomisation group in addition to the leaflet of their randomisation group (Table 2).

Improvement in stage of change in patients in a pre-action stage at baseline

At the end of the trial, most of the patients in a pre-action stage of change at baseline had improved their Prochaska
Table 1  Baseline characteristics of patients by motivation randomisation groups.

<table>
<thead>
<tr>
<th></th>
<th>Diet n = 493</th>
<th>Physical activity n = 490</th>
<th>Both n = 428</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>60.4 (10.6)</td>
<td>60.5 (11.1)</td>
<td>61.0 (10.7)</td>
</tr>
<tr>
<td>Male</td>
<td>325 (66)</td>
<td>330 (67)</td>
<td>267 (62)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.2 (4.2)</td>
<td>27.2 (4.3)</td>
<td>27.1 (4.0)</td>
</tr>
<tr>
<td>Obesity</td>
<td>105 (21)</td>
<td>115 (23)</td>
<td>91 (21)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>72 (15)</td>
<td>61 (12)</td>
<td>58 (14)</td>
</tr>
<tr>
<td>Treated hypertension</td>
<td>258 (52)</td>
<td>228 (47)</td>
<td>227 (53)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>57 (12)</td>
<td>57 (12)</td>
<td>38 (9)</td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td>11 (2)</td>
<td>11 (2)</td>
<td>11 (3)</td>
</tr>
<tr>
<td>History of coronary artery disease</td>
<td>220 (45)</td>
<td>233 (48)</td>
<td>194 (45)</td>
</tr>
<tr>
<td>History of myocardial infarction</td>
<td>111 (34)</td>
<td>106 (31)</td>
<td>71 (24)</td>
</tr>
<tr>
<td>Lower limb arteriopathy</td>
<td>48 (15)</td>
<td>41 (12)</td>
<td>45 (15)</td>
</tr>
<tr>
<td>Total-C (mmol/L)</td>
<td>6.1 (1.1)</td>
<td>6.0 (1.1)</td>
<td>6.0 (0.9)</td>
</tr>
<tr>
<td>LDL-C (mmol/L)</td>
<td>3.9 (0.9)</td>
<td>3.9 (1.0)</td>
<td>3.9 (0.8)</td>
</tr>
<tr>
<td>HDL-C (mmol/L)</td>
<td>1.4 (0.4)</td>
<td>1.4 (0.4)</td>
<td>1.4 (0.4)</td>
</tr>
<tr>
<td>TG (mmol/L)</td>
<td>1.7 (0.9)</td>
<td>1.6 (0.9)</td>
<td>1.6 (0.8)</td>
</tr>
</tbody>
</table>

Mean (standard deviation) or No. patients (%).

stage of change by at least one level whatever the lifestyle parameter (Fig. 2). Among the 593 patients who were in a pre-action stage of change for physical activity at baseline, 300 (50.6%) patients had improved their stage of change by at least one stage by the end of the trial and most of them had started to exercise at least three times per week for 20 min. This proportion was evenly distributed across physician randomization groups (p = 0.21).

On the other hand, 142/216 (65.7%) patients with no restriction in fat diet at baseline had improved their stage of change by at least one stage at end of trial (Fig. 2). Patients of Group 2 in a pre-action stage of change for fat consumption at baseline were less likely to have started decreasing fat consumption at end of trial than in the two other randomisation groups (Fig. 2, p < 0.001 between groups).

Lipid data at end of trial

The mean duration of ezetimibe treatment was 72 ± 16 days. Overall, 869 (62%) patients achieved target lipid goals (defined as LDL less than 3 mmol/L [115 mg/dL] and total cholesterol less than 5 mmol/L [190 mg/dL]) (95% confidence interval [59%–64%]). No significant difference was shown between groups (p = 0.34 with no adjustment except on cluster, p = 0.50 after adjustment on all covariates) (Fig. 3). In 725 (51%) patients, LDL-C was below 2.58 mmol/L (100 mg/dL) at the end of trial.

The mean effect on LDL-C lowering efficacy was 30.4 ± 19.3% overall and was similar across randomization groups (p = 0.82 with no adjustment except on cluster, p = 0.59 between groups after adjustment on all covariates) (Fig. 4). No significant difference was found between randomisation groups for any of the lipid parameters (Fig. 4). Mean HDL-C did not change and TG slightly decreased (−7.5 ± 35.6%) in all motivation randomisation groups (p = 0.66 between groups with no adjustment except on cluster, p = 0.62 after adjustment on all covariates).

Safety and tolerability of ezetimibe

Elevations in CK ≥ 5 × ULN were observed in one patient at baseline and in two (0.1%) patients after start of ezetimibe. Transaminases ≥ 3 × ULN were observed in four (0.3%) patients at baseline and in one (0.1%) patient on statin and ezetimibe. No rhabdomyolysis (defined as reported by the investigator or CK ≥ 5 × ULN with clinical symptoms or CK ≥ 10 × ULN with or without clinical symptoms) was reported. Myalgia or cramps were recorded in 38 (3%) patients on statin and ezetimibe. Treatment was stopped because of side effects in 50 (3%) patients.

Table 2  Motivation of the patient by the physician by physician randomisation groups.

<table>
<thead>
<tr>
<th>Counselling given by the physician</th>
<th>Randomisation group of the physician</th>
<th>Diet n = 493</th>
<th>Physical activity n = 490</th>
<th>Both n = 428</th>
</tr>
</thead>
<tbody>
<tr>
<td>Counselling on diet</td>
<td></td>
<td>481 (98%)</td>
<td>383 (78%)</td>
<td>402 (94%)</td>
</tr>
<tr>
<td>Counselling on physical activity</td>
<td></td>
<td>359 (73%) a</td>
<td>476 (97%)</td>
<td>403 (94%)</td>
</tr>
</tbody>
</table>

a Oral counselling on lifestyle change not given by randomisation.
Results of TWICE trial

Discussion

This trial is the first to compare patient counselling strategies in patients at risk of cardiovascular disease using the Prochaska transtheoretical model.

It seems easier to make a patient decrease his/her fat consumption than to start or increase physical exercise. In TWICE, compliance with diet guidelines was more often reported at baseline than compliance with physical exercise recommendations and with intervention, stage of change for fat consumption was more likely to improve than stage of change of physical exercise in pre-action patients. This is as odds with a previous study performed in the United States which reported that physical activity was more improved than fat consumption [27]. Country habits might explain this discrepancy.

Within the TWICE study, ezetimibe and lifestyle changes were very effective in achieving LDL targets in high-risk patients with persistently elevated cholesterol levels despite statin monotherapy. LDL-C through the use of statins has been shown to be an extremely effective method for
lowering cardiovascular risk [28]. Within the TWICE study, if the administered statin dose was often lower than the standard statin dose, the 30% LDL-C reduction observed in the present study is more important than what might have been expected after doubling the statin dose and slightly more than the 25–26% expected after addition of ezetimibe in the context of clinical trials [13,29–31]. In another study in 256 patients, treated by statin for at least four weeks, addition of ezetimibe led to a more than 35% LDL-C reduction, however, statin doses were lower than in the present trial [32].

Although the interpretation is limited by intergroup crossover by physicians, a smaller than anticipated trial size and by the absence of a true control group managed conventionally without structured counselling, the almost identical lipid changes observed in the three groups suggest that all motivation strategies have similar and possibly limited short term efficacy on lipids. This is consistent with other published studies [33–35]. In TWICE, counselling was given only once and it cannot be ruled out that repetition of counselling over a longer duration would have impacted more lipid outcomes. Furthermore, long-term changes in lifestyle, including physical exercise and diets high in fruits, vegetables, whole grains, and unsaturated fatty acids are expected to decrease cardiovascular risk per se independently of their effect on conventional risk factors [2].

According to the European guidelines on cardiovascular prevention, moving forward in small consecutive steps is one key to successful long-term change in behaviour [36]. However, results of the present study suggest that counselling on diet and physical activity can be given simultaneously as recommended by the French recommendations on treatment of dyslipidemia updated in 2005 [37]. It is noteworthy that TWICE was started before the release of those recommendations and was based on the European and American guidelines [1,2,16].

We cannot rule out that compliance to lipid-lowering medications also increased with intervention. It is estimated that 60% of individuals prescribed lipid-lowering medications are non adherent and motivation based on the Prochaska transtheoretical model improves adherence [27,38].

In this high-risk population, controlling cholesterol levels is of particular importance and the dramatic LDL-C reduction allows 62% of patients not controlled by statin monotherapy to reach the therapeutic goal. In addition, 51% of the patients had a LDL-C below 2.58 mmol/L (100 mg/dL) at trial end, a level which has been suggested to be an appropriate target for most of the patients at high-cardiovascular risk, according to the updated American and European guidelines; the last ones being made available after the start of TWICE [36,39].

Despite a greater reduction in LDL-C, the percentage of patients at goal in the TWICE study is slightly lower than in an American community-based, double-blind randomized trial of ezetimibe added to statin therapy [13]. However, baseline LDL-C levels (3.2 mmol/L) were lower than in the present study.

The present study confirms the good efficacy on lipid levels and short-term tolerability of ezetimibe added to lifestyle changes and statins.

Conclusions

In conclusion, in the three groups, more than 60% patients met target LDL-C levels. The marked impact (−30%) on LDL-C, although similar between the three groups, slightly exceeds usual LDL-C reductions achieved by this dose of ezetimibe. Decreasing fat consumption seems easier than increasing physical activity. TWICE study confirms the good efficacy on lipid levels and short-term tolerability ezetimibe on top of statins.

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Results of TWICE trial

Jean-Paul 10120 St André-les-Vergers (Cardiologue), BEMU-RAT Latran 33610 CESTAS (Cardiologue), BENITAHI Gérard 66100 PERPIGNAN (Cardiologue), BENITAHI Elie 75010 PARIS (Cardiologue), BENITO Pierre-Olivier 35033 RENNES Cedex 9 (Cardiologue), BERDAGUE Philippe 34500 BEZIERS (Cardiologue), BERDELLOU Thierry 93600 AULNAY S/BOIS (Cardiologue), BERNARD Jean-Pierre 14000 CAEN (Cardiologue), BERNARD Jacques 59000 LILLE (MG), BERNARDEAU Claire 92150 SURESNES (Cardiologue), BEROY Claude 75011 PARIS (Cardiologue), BERTHAUX Xavier 77220 TOURNAEN EN BRIE (Cardiologue), BERTRAND Jean-Henri 84100 ORANGE (Cardiologue), BESSEKRI Abdelkader 67200 STRASBOURG (Cardiologue), BINEAU Bertrand 53950 LOUVENNE (MG), BINET Didier 50700 VALOGENES (Cardiologue), BLACHE Eric 13500 MARTIGUES (Cardiologue), BLANC Emile 20200 BASTIA (Cardiologue), BLANCHARD Benoît 76600 LE HAVRE (Cardiologue), BLISCAUX Pascale 57500 St AVOLD (Cardiologue), BODUR Gokhan 68100 MULHOUSE (Cardiologue), BOISSY Jean-Claude 83700 St RAPHAEL (Cardiologue), BOITTIN Philippe 14400 BAYEUX (Cardiologue), BOLTE François 82000 MONTAUBAN (Cardiologue), BONNAFFE Benoît 44600 ST NAZAIRE (Cardiologue), BORFICA Jean-François 85180 CHATEAU d’OLONNE (Cardiologue), BOUCHAYA Toni 82000 MONTAUBAN (Cardiologue), BOUCHET Gérard 84200 CARPENTRAS (Cardiologue), BOUCHUT Gilles 84800 L’Isle Sur la Sorgue (Cardiologue), BOUCY Jean-Marc 59330 HAUTMONT (MG), BOUKHALIL Charles 72200 LA FLECHE (Cardiologue), BOURAS Yahya 90000 BELFORT (Cardiologue), BOURDON Catherine 13009 MARSEILLE (Cardiologue), BOURJAIU Michel 53950 LOUVENNE (MG), BOURNAZEL Vincent 49800 ANGERS (Cardiologue), BOSIQUIT Jean-Pierre 13009 MARSEILLE (Cardiologue), BOUTAUD Philippe 86000 POITIERS (Cardiologue), BOUTON BROCHET Sophie 92250 La Garenne Colombes (Cardiologue), BOUVIER Eric 64300 ORTHEZ (Cardiologue), BRAL Michel 93000 STAIN (Cardiologue), BRAUT François 53200 CHATEAU GONTIER (MG), BREVYSE Hervé 13300 SALON De PROVENCE (Cardiologue), BROI N Patrick 74703 SALLANCHES (Cardiologue), BROUSSON Pierre 78990 ELAN-COURT (Cardiologue), BRUJON Thierry 59530 LE Quesnoy (Cardiologue), BURGGRAF Christian 25200 MONTBELIARD (Cardiologue), BUSERI Jean-Louis 74100 ANNEMASSE (Cardiologue), CADILHON Jean-Claude 33120 ARCADHON (Cardiologue), CAILLAT Muriel 92100 Boulogne Billancourt (Cardiologue), CAILLAUX Bruno Xavier 21000 DIJON (Cardiologue), CARETTE Bernard 51100 REIMS (Cardiologue), CASTER Luc 31400 TOULOUSE (Cardiologue), CAUDONT Sébastien 59410 ANZIN (Cardiologue), CAUET Jacques 59100 ROUBAIX (Cardiologue), CAYOL Claude 13160 Châteauneuf (Cardiologue), CAVIER Jean-Yves 76100 ROUEN (Cardiologue), CESARINI Joël 91150 ETAMPES (Cardiologue), CHALTEL Maurice-Gérard 38000 GRENOBLE (Cardiologue), CHANTRELLE Alain 31400 TOULOUSE (Cardiologue), CHARRAD Rafik 91160 LONGJUMEAU (Cardiologue), CHARRUAU Rémy 49800 TRELAZÉ (MG), CHEMIN Philippe 33200 BORDEAUX (Cardiologue), CHEVALIER Dominique 13010 MARSEILLE (Cardiologue), CHOPRA Soeb 78990 ELAN-COURT (Cardiologue), CLARET-MONTE CATTINI Philippe 20220 L’ILE ROUSSE (Cardiologue), COHEN Alain 13002 MARSEILLE (Cardiologue), COIGNARD Elisabeth 93120 LA COURNEUVE (Cardiologue), COLIN Remy 83000 TOULON (Cardiologue), CONDOMINES Hervé 82000 MONTAUBAN (Cardiologue), CONDOURET Pierre 75009 PARIS (Cardiologue), CORBEL Claude 56110 GOURIN (Cardiologue), CORBIN André 22100 DINAN (Cardiologue), CORDAINE Bernard 03300 CUSSET (Cardiologue), CROSSE Stephane 34500 BEZIERS (Cardiologue), COSTE LEENHARDT Corinne 13100 Aix En Provence (Cardiologue), COUDRAY Nicolas 06800 CAGNES SUR MER (Cardiologue), COUFFIN Jean-Pierre 78250 MEULAN (Cardiologue), COURIER Guy 68100 MULHOUSE (Cardiologue), COURTALAT Alain 31700 CORNÉBARIEU (Cardiologue), CRESPY Richard 34000 MONTPELLIER (Cardiologue), DAFFOS Nicolas 93190 Sevrain (Cardiologue), DAFFOS Catherine 93800 Epinay-Sur-Seine (Cardiologue), DAGRAN Olivier 13500 MARTIGUES (Cardiologue), DAHAN Simon Robert 67000 STRASBOURG (Cardiologue), DAHAN Jean-Maurice 06800 CAGNES SUR MER (Cardiologue), DAHAN Albert 31000 TOULOUSE (Cardiologue), DAILET Etienne 84110 Vaison-la-Romaine (Cardiologue), DANELY Dominique 33390 BLAYE (Cardiologue), DANY François 87000 LIMOGES (Cardiologue), DASSE Alain 53200 CHÂTEAU GONTIER (MG), DASSONVILLE Bernard 75014 PARIS (Cardiologue), DAVID Jean-Michel 53000 LAVAL (MG), DE ROQUEFEUIL Florence 75016 PARIS (Cardiologue), DEBOMY Alain 59000 LILLE (MG), DEHAIN Jean- Claude 02000 LAON (Cardiologue), DELBECQUE Danièle 59200 TOURCOING (MG), DELHOMME Claire 66000 PERPIGNAN (Cardiologue), DELOY Pierre-Philippe 84400 APT (Cardiologue), DELPLACE MAURY Christelle 37000 TOURS (Cardiologue), DELPONT Maurice 31240 ST JEAN (Cardiologue), DELUCHE Laurent 87100 LIMOGES (Cardiologue), DEMASLES Christian 65100 LOURDES (Cardiologue), DEMATTEO Philippe 50700 VALOGENES (Cardiologue), DENIS Lucien 42400 ST CHAMOND (Cardiologue), DEQUEKER Jean-Luc 64100 BAYONNE (Cardiologue), DEQUIDT Bernard 76106 ROUEN (Cardiologue), DESRUES Hervé 53000 LAVAL (MG), DESTOBES François 59940 ESTAING (Cardiologue), DESTRUBE Bernard 44240 LA CHAPELLE SUR ERDRE (MG), DEVOUASSOUX Charles 26400 CREST (Cardiologue), DIEBOLD Hervé 75116 PARIS (Cardiologue), DISY Jean-François 44600 ST NAZAIRE (Cardiologue), DOMEREGO Jean-Jacques 06000 NICE (Cardiologue), DUC Philippe 94120 Fontenay Sous Bois (Cardiologue), DUCHENE Pierre 49460 FENEU (MG), DUCOS Cécile 33240 St André De Cubzac (Cardiologue), DUCOUDRE Michel 64200 BIARRITZ (Cardiologue), DUMORTIER Daniel 59800 LILLE (Cardiologue), DUPONT Thierry 59530 Le Quesnoy (Cardiologue), DURAFOURG Luc 11000 CARCASSONNE (Cardiologue), DURANDET Philippe 17000 LA ROCHELLE (Cardiologue), DUYROY Christian 53000 LAVAL (MG), ELAHE Abdoul 06150 Cannes La Bocca (Cardiologue), ELIAKIM Agnès 77270 VILLEPARISIS (Cardiologue), EOECH Roger 44300 NANTES (MG), ESCARGUEL Didier 11000 CARCASSONNE (Cardiologue), ETLINGER Philippe 75009 PARIS (Cardiologue), EYMARD Claude 47000 AGEN Cedex (Cardiologue), FALK Claudine 92230 GENEVILLIERS (Cardiologue), FALQUIER Jean-François 24100 BERGERAC (Cardiologue), FARAH Bruno 31076 TOULOUSE Cedex 3 (Cardiologue), FARGES Jean-Louis 62400 BETHUNE (Cardiologue), FAURE Olivier 11000 CARCAS- SONNE (Cardiologue), FAVREAU Bernard 49300 CHOLET (MG), FEDOROWSKY Alan 78800 HOUILLES (Cardiologue), FELDMANN Israel 67500 HAGUENEAU (Cardiologue), FERRER Jean-Claude 13150 TARASCON (Cardiologue), FERRINI Marc 69006
Results of TWICE trial

733

(MG), TRAINEIL Gilles 59000 LILLE (Cardiologue), TRICOIRE Jacques 31000 TOULOUSE (Cardiologue), TRICOT Catherine 17000 LA ROCHELLE (Cardiologue), TRUONG MINH KY Bernard 64000 Pau (Cardiologue), TUBIANA Marie 06110 LE CANNET (Cardiologue), TURMEL Jacques 79000 NIORT (Cardiologue), URBINA Jean-Charles 59224 THIANT (MG), VACOSSIN Christian 51200 EPERNAY (Cardiologue), VAIS-LIC Claude 78150 LE CHESNAY (Cardiologue), VALIN Marc 53001 Laval (MG), VASSEUR Philippe 62100 CALAIS (Cardiologue), VERSCHUURREN Philippe 77130 Montreuil Faute Yonne (Cardiologue), VERPIN Pierrick 78600 MAISONS LAFITTE (Cardiologue), VIAL Hubert 13008 MARSEILLE (Cardiologue), VIEL Christophe 17000 LA ROCHELLE (MG), VIGNE Jean-Marc 59600 MAUBEUGE (Cardiologue), VIOLET Thibaud 74000 ANNECY (Cardiologue), VIRCOULON Bernard 33220 Ste Fey La Grande (Cardiologue), VITOUX Jean-François 92000 NANTERRE (Cardiologue), VITTECOQ Bruno 91240 St Michel Sur Orge (Cardiologue), VOGEL Jacques 59170 CROIX (MG), VOGEL Marc 59390 TOUFLERS (MG), VOGLitMacci Michel 65000 TARBES (Cardiologue), WALCH Jean-Michel 93600 Aulnay-Sous-Bois (Cardiologue), WATTEAU Damien 44000 (Cardiologue), WAZANA Michel 67000 STRASBOURG (Cardiologue), WEILL Didier 88100 St Die (Cardiologue), WIND Pierre 47200 MARMANDE (Cardiologue), WONG Olivier 84130 LE PONTET (Cardiologue), WORINGER Philippe 34800 Clermont l’Hérault (Cardiologue), ZARTARIAN Serge 06140 VENCE (Cardiologue), ZEITOUNI Roland 94250 GENTILLY (Cardiologue), ZITOUN Jacques 83200 TOULON (Cardiologue), ZYLBERBERG Michel 12200 Villefranche De Rouergue (Cardiologue).

References


