CLINICAL RESEARCH

REACH: International prospective observational registry in patients at risk of atherothrombotic events
Results for the French arm at baseline and one year

REACH : Registre observationnel prospectif international chez des patients à risque d’événements athérothrombotiques
Résultats des données françaises à l’inclusion et à un an

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Summary

Introduction. — Atherothrombosis is a systemic, diffuse disease associated with a high risk of cardiovascular morbidity and mortality. It is the main cause of death in Western populations, a major public health concern and its prevalence will further increase in the future.

Objectives. — To evaluate the rate of major vascular events at 1 year in French patients with confirmed atherothrombotic disease, recruited in the REACH international registry.

Methods. — The REACH Registry has recruited 55,000 patients in 44 countries, aged at least 45 years and suffering from established atherothrombotic disease (EAD). In France, 713 investigators selected 3,514 patients with EAD between December 2003 and June 2004. Each investigator had to include 5 to 10 patients presenting after a first documented event of cerebrovascular disease (CVD), coronary artery disease (CAD) or lower limb peripheral arterial occlusive disease (PAD). The patients were followed up for 1 year with collection of major vascular events.

Results. — Among the 3,514 French patients with EAD in the REACH registry, 2,373 (68\%) had documented coronary disease, 778 (22\%) had an ischemic stroke and 923 (26\%) had documented PAD. One quarter of CAD patients, one third of CVD patients and one half of PAD patients had another atherothrombotic disease localization. Follow-up at 1 year was documented for 3,373 patients with EAD. The 1-year event rate in patients who had EAD was a function of the number

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Introduction

It is common knowledge that atherothrombotic disease remains a major public health problem. Cardiovascular diseases cause every year the death of 16,500,000 people worldwide including 4,400,000 from stroke. From an epidemiological point of view, the INTERHEART study and the WHO data are concordant and show that 9 major risk factors are responsible for more than 80% of cardiovascular morbidity and mortality [1, 2].

Randomized studies have allowed a constant and rapid improvement in the management of patients with a high atherothrombotic risk. In this rapidly changing context, it has become urgent to update data on therapeutic management. Moreover, in order to better understand differences in major cardiovascular event rates and patient outcomes in different regions of the world, an international comparison was essential, in order to determine, among other things, if this international heterogeneity was due to different car-

Résumé

Introduction. — L'athérothrombose, maladie globale et diffuse, est associée à un risque élevé de morbi-mortalité cardio-vasculaires. Elle est la principale cause de décès dans la population occidentale, véritable enjeu de santé publique et sa prévalence va augmenter dans les prochaines années.

Objectifs. — Évaluer le taux d'événements vasculaires majeurs à 1 an chez les patients français ayant une maladie athérothrombotique établie, inclus dans le registre international REACH.

Méthodes. — Le registre REACH a inclus 55 000 patients dans 44 pays, âgés d’au moins 45 ans et souffrant d’une maladie athérothrombotique établie (MAE). En France, 713 médecins investigateurs ont sélectionné 3 514 patients avec MAE entre décembre 2003 et juin 2004. Chaque investigateur devait inclure 5 à 10 patients se présentant après un premier événement documenté de maladie coronaire, cérébrovasculaire, ou souffrant d’une artériopathie obliterante des membres inférieurs (AOMI). Les patients ont été suivis pendant 1 an avec recueil des événements vasculaires majeurs.

Résultats. — Parmi les 3 514 patients français ayant une MAE du registre REACH, 2 373 (68 %) avaient une maladie coronaire documentée, 778 (22 %) avaient une maladie ischémique cérébrovasculaire et 923 (26 %) avaient une AOMI documentée. Un quart des coronariens, un tiers des patients avec atteinte cérébrovasculaire et la moitié des artéritiques ont une autre localisation athérothrombotique. Le suivi à 1 an a été documenté chez 3 373 patients ayant une MAE. Le taux d’événements à 1 an chez les patients ayant une MAE est fonction du nombre de localisations athérothrombotiques : le taux de décès vasculaire est de 1,8 % s’il existe une seule localisation athérothrombotique et de 4,1 % s’il y a 2 ou 3 localisations athérothrombotiques, le taux du critère combiné de décès, infarctus et AVC est de 3,8 % et de 7,2 % respectivement et de 11,7 % et 22,3 % respectivement si les hospitalisations sont ajoutées au critère précédent.

Conclusion. — Le nombre d'événements vasculaires majeurs à 1 an est élevé chez les patients avec MAE alors qu’il s’agit de patients suivis en ambulatoire et considérés comme stables. Chez les patients ayant une MAE, il existe une relation étroite entre la fréquence de survenue des événements vasculaires majeurs et le nombre de lits artériels symptomatiques (2 ou 3 localisations). Les patients ayant une atteinte polyvasculaire ont à ce titre un risque d'événements vasculaires majeurs doublé par rapport à ceux qui n’ont qu’une seule atteinte artérielle.

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Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ABI</td>
<td>Ankle-brachial index</td>
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<tr>
<td>ACE</td>
<td>Angiotensin converting enzyme</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index</td>
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<tr>
<td>CAD</td>
<td>Coronary artery disease</td>
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<tr>
<td>CVD</td>
<td>Cerebrovascular disease</td>
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<tr>
<td>EAD</td>
<td>Established artery disease</td>
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<td>MVE</td>
<td>Major vascular event</td>
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<td>MI</td>
<td>Myocardial infarction</td>
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<td>REACH</td>
<td>REduction of Atherothrombosis for Continued Health</td>
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<td>PAD</td>
<td>Peripheral artery disease</td>
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diovascular risk profiles between countries, or to differences in management practices and access to healthcare.

Until now, information available in registries about the characteristics, management and prognosis of atherothrombotic patients or at high risk of atherothrombosis was limited to a single geographical location (North America, Europe, etc.), certain sub-groups of patients (post-infarction, stroke, diabetics...), or inpatients and no outpatients in primary prevention. The setting up of the REACH registry (REduction of Atherothrombosis for Continued Health) worldwide, with collection of data and a rigorous follow-up of patients, answers this need for an updated global view of the management and outcome of high-risk stable patients [3].

This article describes 1) the characteristics of the French patients in the REACH registry with established atherothrombotic disease, 2) the therapeutic strategies implemented, 3) their prognosis, in particular as a function of the number of localizations of atherothrombotic disease at baseline.

Methods

The REACH Registry [3] recruited patients aged at least 45 years, signing an informed consent form, and who presented: 1) either a combination of at least three risk factors and a high cardiovascular risk (man ≥ 65 years or woman ≥ 70 years, currently smoking >15 cigarettes/day with type 1 or II diabetes, hypercholesterolemia, diabetic nephropathy, high blood pressure, ankle-brachial pressure index (ABI) < 0.9, asymptomatic carotid stenosis ≥ 70%, or at least one carotid plaque), 2) or stable established atherothrombotic disease (EAD) after a prior documented event: coronary (stable angina, unstable angina, myocardial infarction, angioplasty/stent bypass), cerebrovascular (ischemic stroke or transient ischemic attack), or lower limbs (peripheral arterial occlusive disease), defined by current intermittent claudication with an ankle-brachial index < 0.9 or a history of surgery for intermittent claudication: angioplasty/stent, peripheral bypass or any other vascular procedure including amputation) [3].

The goal of this registry was to conduct an objective study of a contemporary population of stable patients in different regions of the world in order to:

- describe the characteristics and management of these patients globally and in each sub-group;
- evaluate atherothrombotic events in the total population and each sub-group;
- estimate cross-risks among sub-groups;
- compare outcomes according to patient profiles;
- define predictors of subsequent atherothrombotic events.

Patients

Five to ten consecutive patients complying with the inclusion criteria were recruited in each investigator center. The investigators undertook to enroll all consecutive patients complying with REACH registry selection criteria over the predefined 7-month period. Treatment was left up to the physicians’ choices during the whole of the follow-up period.

To ensure uniform recruitment on a national scale, the coordinators of each country, including France, validated the choice of investigators to ensure that they were representative of French healthcare practices in order to obtain reliable epidemiological data.

The data collected were the patients’ clinical characteristics, risk factors, medical history, clinical examination and laboratory test results. Data collection rules were identical in all the countries; once recorded locally, the data were transferred to the Paris center for data processing and statistical analysis. A rigorous audit was conducted on 10% of the investigator centers in order to ensure the quality of the data obtained.

The body mass index (BMI) was defined as weight in kilograms divided by height (in meters) squared. Patients were considered to be overweight if the BMI was between 25 and 29 kg/m² and obese if the BMI was higher than 30 kg/m², and/or if their waist circumference exceeded 102 cm for men or 88 cm for women [4]. Active smoking was defined by a consumption of at least 5 cigarettes per day during the month before recruitment, and past smoking by discontinuation of tobacco intoxication for more than one month.

Polyvascular involvement was defined as documented involvement of at least two arterial territories (CAD, CVD, or lower limb PAD).

Subjects participating in a clinical trial or likely to have difficulties in respecting the schedule of follow-up visits were excluded.

Follow-up

At baseline, the following data were collected for all patients by the investigator centers: major vascular events (MVE), arterial revascularization procedures, weight and body mass index, adherence to treatments. The same parameters were recorded for follow-up at one year (±3 months). Baseline characteristics were analyzed after database lock in December 2005, and the follow-up results at one year after database lock in June 2006. Initial follow-up was planned at 12 months and 21 months and has recently been extended to 3 and 4 years to obtain exhaustive information.

Clinical events were reported by the investigator centers. Diagnosis of stroke or transient ischemic attack required diagnostic confirmation by a neurologist. Vascular deaths comprised fatal stroke, fatal myocardial infarction and other deaths of vascular origin. Other deaths of vascular origin comprised deaths due to pulmonary embolism, sudden deaths, deaths after vascular surgery, percutaneous revascularization or amputation, secondary to heart failure, or visceral ischemia, and finally all deaths that could not be assigned to a nonvascular cause or to hemorrhage. All deaths occurring during the 28 days after a myocardial infarction or a stroke were considered to be fatal myocardial infarctions or strokes.

Statistics

Continuous variables are expressed in the form of means (with standard deviations), and categorical variables are presented as incidences and percentages. Clinical events are reported in annual event rates, after adjustment for age and sex. Only patients with complete data were included in the calculation of the cumulative event rate. Statistical differences between the incidence of events according to the type or number of atherothrombotic sites were
Results

Data at baseline

The REACH registry recruited a total of 67,888 patients in 5,473 centers in 44 countries on all five continents between December 2003 and June 2004. In France, 713 investigators (543 general practitioners (76.2%), 64 cardiologists (9%), 36 angiologists (5.1%), 23 internists (3.2%), 13 endocrinologists (3.2%), 17 neurologists (2.4%) and 7 other physicians) recruited 4,740 patients. 4,693 of these subjects were enrolled [i.e. 46 ineligible patients (1%) and one withdrawal of consent], including 3,514 patients presenting established atherothrombotic disease (EAD), and 1,226 patients with at least three CV risk factors (who are not analyzed here). The analysis presented in this article only concerns the 3,514 patients with prior EAD.

At baseline, the sample of subjects presented the following clinical characteristics (table 1): average age 69.3 years, 76.5% men, 30.8% diabetics, 71.5% with hypertension, 74.2% with hypercholesterolemia, 14.3% smokers, 49.7% past smokers. 47.3% and 22.6% of patients were overweight and obese respectively.

From the vascular point of view, 81.8% of patients had a single arterial localization: CAD in 53.4% of cases, CVD in 14.9%, and PAD in 13.4% of patients (figure 1). In addition, 18.2% of patients had polyvascular disease including more than half (9.8%) with simultaneous involvement of the coronary arteries and the lower limbs. More than seventy percent of polyvascular patients were affected by lower limb PAD. One quarter of the CAD patients, one third of CVD patients, and more than half of PAD patients had another affected arterial site.

The main cardiovascular medications used are presented in table 2. During the visit, 91.3% of patients with documented hypertension or with high blood pressure, received at least one antihypertensive drug. Likewise, 29.1% of the total EAD patients included 30.8% of diabetics or patients with elevated blood glucose levels, received antidiabetic medication. Treatments with statins and antiplatelet agents, indicated in all patients, were prescribed in 70.1% and 82.6% of subjects, respectively. Although these medications were widely prescribed, treatment goals were

| Table 1 Demographic characteristics of patients recruited in France in the REACH registry. |
|---------------------------------|---------------------------------|
| Established atherothrombotic disease |
| N = 3,514                         |
| Average age (years) (EC)          | 69.3 (10.3)                     |
| Male gender (%)                  | 76.5                            |
| Diabetes (%)                     | 30.8                            |
| Hypertension (%)                 | 71.5                            |
| Hypercholesterolemia (%)         | 74.2                            |
| Excess bodyweight BMI: [25-30] (%)| 47.3                            |
| Obesity BMI > 30 (%)             | 22.6                            |
| Past smoking (%)                 | 49.7                            |
| Current smoking (%)              | 14.3                            |

**Figure 1.** Prevalence of polyvascular involvement in patients with documented atherothrombotic disease recruited in France in the REACH registry (n=3,514).
rarely achieved as 73% of the patients had a blood pressure equal to or higher than 140/90 mmHg, 53% had a total cholesterol above 2 grams per liter, and 19% of patients smoked > 5 cigarettes per day.

**Patient data at one year**

In France, 96.2% (n=4514) of the patients recruited were followed up at one year. In all, 226 patients (4.8%) were lost to follow-up: 138 patients (2.9%) did not come to the follow-up visit, and 41 patients (0.9%) were excluded because of the withdrawal of the center.

The cumulative major vascular event rates at one year for patients with EAD (table 3) were 2.3% for vascular deaths, 4.5% for the primary composite endpoint (vascular deaths, nonfatal MI, nonfatal stroke), and 13.7% for the secondary composite endpoint (vascular deaths, nonfatal MI, nonfatal stroke, hospitalization for an atherothrombotic event).

The primary endpoint was 4.7% in CAD patients, 3.8% in PAD patients and increased to 5.8% in CVD patients respectively because of the high incidence of recurrences of non-fatal stroke in this population (3.4% of recurrences). If hospitalizations were added to this composite endpoint, the event rate concerned nearly one patient out of 7 for the population presenting an EAD, and up to 1 out of 5 for patients with peripheral arterial occlusive disease. All comparisons were statistically significant.

These rates increased with the number of localizations of atherothrombotic disease (table 4). For cardiovascular deaths, the annual incidence ranged between 1.8% in subjects with an isolated vascular lesion and 4.1% for subjects with 2 vascular lesions or more. For the primary composite endpoint, these figures were 3.8% and 7.2% respectively (p<0.001). For the secondary composite endpoint, these annual rates were 11.7% and 22.3% respectively (p<0.001).

The main reasons for hospitalization during follow-up were the occurrence of unstable angina (4%), transient ischemic attack (0.9%), another ischemic arterial event (2.8%), or chronic heart failure (3.6%) (table 3). The occurrence of a hemorrhage (requiring hospitalization or transfusion) was only reported in 0.6% of patients.

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**Tableau 2  Treatments at baseline of patients recruited in France in the REACH registry.**

<table>
<thead>
<tr>
<th>No. of patients with diagnosed hypertension or elevated blood pressure at initial examination (n)</th>
<th>Established atherothrombotic disease N=3,514</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients with history of diabetes or elevated blood glucose at initial examination (n)</td>
<td>1083</td>
</tr>
</tbody>
</table>

*Percents base on total EAD population.
Discussion

The REACH registry is the first worldwide epidemiological study on a population of atherothrombotic patients [3]. The French patients in this registry represent a large cohort permitting valid statistical analysis. Several fundamental points may be made after examining the French registry data.

Patients’ characteristics

French patients with established atherothrombotic disease (EAD) have a classic risk profile. Comparative analysis with previous French epidemiological data, in the pooled analysis of the ECLAT, APRES and PRISMA studies, conducted in 1999-2000 by V. Bongard et al. [3] in 14,544 patients with a
history of an atherothrombotic event, showed that the profile of risk factors has changed in a few years: The percentages of diabetics, hypercholesterolemic subjects, obese or smokers (active or previous) has increased. One of the explanations of this increase in the number of patients with risk factors could be improved screening and/or changes in diagnostic cut-offs in particular for hypercholesterolemia, high blood pressure or diabetes.

The profiles of French patients in the REACH registry [6] are similar to those of patients recruited in Europe (West or East), but also on other continents (North America, Latin America, Asia, Middle East), with a few slight differences, expect for diabetes which is more marked in North America and Asia. These data confirm the results of recent epidemiologic studies [1, 2] which underline the predominant role of major risk factors (smoking, hypertension, dyslipidemia, type 2 diabetes, abdominal obesity) in the genesis of major vascular events, and confirm the universal nature of the risk factors.

Cardiovascular morbidity and mortality in EAD

The number of vascular events is high in EAD patients although these patients were followed up on an outpatient basis and are considered to be stable. The 1-year major vascular event rate for French patients was high, since it was 3.5% for all-cause mortality, and higher in CAD or PAD patients (4.1% and 4% respectively) compared to CVD patients (2.9%). Usually the all-cause mortality rate is higher in PAD patients than the over EAD population; the small number of patient in the REACH France PAD group could explain this unexpected finding. In the worldwide registry data we observe the usual increase of all-cause mortality between CAD, CVD and PAD patients [6]. The major vascular event rate for the composite endpoint (vascular deaths, MI and stroke) was also high at one year. If hospitalizations were added to this composite endpoint, the event rate concerned nearly one patient out of 7 for the population presenting an EAD, and up to 1 out of 5 for patients with peripheral arterial occlusive disease. For polyvascular patients near one patient out of 4 present a vascular event or hospitalization for ischemic reason at one year follow-up. This data is all the more worrying as earlier French epidemiological data from the APRES study [7], in a similar population of patients with a history of at least one atherothrombotic event (documented MI, non-embolic ischemic stroke or peripheral arterial occlusive disease), seen by general practitioners between 1999 and 2000, gave a 1-year event rate (MI, ischemic stroke and cardiovascular death) of 3.8%, with a cardiovascular death rate of 1.3% (versus 4. 5% and 2.3% in the REACH registry France).

A geographical analysis shows that the major vascular event rate for the composite endpoint in France was similar to that observed in Western Europe, North America, and Australia. It was lower than event rates noted in Eastern Europe and Latin America, and higher than that observed in Japan. These differences may be explained by geographical differences in lifestyle, but also by differences in healthcare systems and health policies. An improvement in therapeutic management of patients in France also seems to be necessary, since 73% of hypertensive patients did not achieve target blood pressure values, 50% of dyslipidemic patients still had total cholesterol levels higher than 2 g/l, and 14.3% of patients continued to smoke. The causes of the unsatisfactory control of risk factors are undoubtedly multifactorial and inherent to some extent to the patients themselves (adherence, concomitant diseases, resistance factors to treatment), but are also probably related to a certain “therapeutic inertia” noted during other French epidemiologic studies [8, 9] and also internationally, since in our French registry, antiplatelet agents and statins were not prescribed in 17 and 30% of patients respectively, whereas insulin treatment was only used in 9.2% of diabetics with EAD.

Polyvascular involvement consequences

Polyvascular involvement was frequent, since it concerned a quarter of CAD patients, one third of CVD patients, and half the PAD patients. More than seventy percent of polyvascular patients are PAD patients. This polyvascular involvement conditioned patient outcomes. The event rate increased linearly according to the number of atherothrombotic sites. It could reinforce the importance of polyvascular diagnosis by the detection of PAD patients.

This French data on the prognostic role of polyvascular involvement is confirmed by the worldwide results of the REACH registry, which showed that in patients with an EAD, there was a quasi-linear relation between the incidence of vascular events and the number of symptomatic arterial beds [3,4,6].

Whereas patients in secondary prevention have traditionally been considered globally, with no stratification of risk, this new data provides invaluable information and a real change of paradigm, by showing the heterogeneity of risk level in patients with EAD, directly correlated with the number of symptomatic vascular beds.

These innovative data should help us refine therapeutic strategies and objectives in order to intensify the management of certain groups of patients at increased risk.

Type of vascular event and EAD topography

Another important finding of the REACH registry is that for these EAD patients, recurrences during the first year generally occurred in the initially affected arterial bed (acute coronary syndromes after myocardial infarction, recurrence of stroke during secondary prevention of ischemic stroke). The short time between the initial event and the recurrence of the ischemic event probably explains why these events have the same localization, though recurrences of stroke were nevertheless more frequent than recurrences of MI in the population of patients with EAD. In the Oxford Vascular Study [10] which was a population-based survey, the incidence of stroke was at least as high or even higher than the incidence of MI. The relative incidence of stroke compared to MI was 1.1 to 1.2. corresponding to 10 to 20% more events.

PAD patients have a high risk of vascular death. Two complementary physiopathological mechanisms may explain this result: PAD patients are very often polyvascular patients; paradoxically these patients often benefit from fewer validated treatments and/or less frequently achieve blood pressure, lipid or glucose goals. In these PAD patients, 7.3% presented a worsening of their claudication
requiring hospitalization, contrasting with previously documented epidemiological data on arteritis patients.

The global risk of hemorrhage requiring hospitalization or transfusion was low (0.6%), with a benefit-risk ratio which seems all the more positive as the absolute vascular risk of these patients was high.

**Study limitation**

Despite the quality data collection, the REACH registry is not a prevalence study and these results cannot be extrapolated to the whole population of French atherothrombotic patients. The desire of certain physicians to take part in the study may have lead to the selection of patients receiving the best treatment and follow-up, though this would have led to an underestimation of risk, which is already high in our registry. On the other hand, it is a partial geographic analysis of a global registry which can explain some statistical issue. No sample size calculation was performed for the French population. Finally, no conclusion may be about why the recommended treatments for patients with EAD were underutilized. This may have been due to therapeutic inertia and/or the presence of co-morbidities or concomitant diseases contra-indicating the use of these therapies.

**Conclusion**

The French REACH registry data showed that there is a high one-year major vascular event rate in stable outpatients with established atherothrombotic disease. This event rate is similar to the rates observed in other areas of the world, in particular in Western Europe and North America. Polyvascular involvement is frequent and constitutes a potent risk marker of vascular morbidity and mortality, since it doubles the risk of major vascular events compared to involvement of a single arterial bed. The number of arterial beds is therefore a better predictor of outcome than the type of arterial bed initially affected. Patients with established atherothrombotic disease have a heterogeneous level of risk requiring optimization of their management with an essential stepping up of validated treatments. This must go hand in hand with optimization of the control of the main cardiovascular risk factors. The use of antiplatelet agents is all the more effective when the vascular risk is high. All these epidemiological data confirm the validity of the global approach to atherothrombosis, and not its segmentation according to the initially affected arterial bed.

**References**


