French medical practice in type 2 diabetes: The need for better control of cardiovascular risk factors

C. Marant a, I. Romon a,*, S. Fosse a, A. Weill b, D. Simon c, d, E. Eschwège d, M. Varroud-Vial c, A. Fagot-Campagna a

a Institut de veille sanitaire, 12, rue du Val-d’Osne, 94415 Saint-Maurice, France
b Caisse nationale d’assurance maladie, 75019 Paris, France
c Association nationale de coordination de réseaux diabètes, 91230 Montgeron, France
d Institut national de la santé et de la recherche médicale U780, 94800 Villejuif, France

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Abstract

Aims. – In type 2 diabetes (T2D), to describe treatments to prevent cardiovascular disease, to compare current practice to French guidelines, and to identify factors associated with recommended treatments.

Methods. – In the Échantillon National Témoin Représentatif des Personnes Diabétiques (ENTRED) study, 10,000 adults treated for diabetes (any type) were randomly selected from the French National Health Insurance System database. Deliveries during the last quarter of 2001 of treatments to prevent cardiovascular disease were extracted. Questionnaires were mailed to these people and their care providers. Final populations included 3324 people with T2D and their 1553 care providers.

Results. – Overall, 18% reported coronary heart disease (CHD) and 44% were classified as having a high cardiovascular risk; 68% received one or more antihypertensive treatment: ACE inhibitor/angiotensin receptor blocker (ARB), 44%; diuretic, 35%; calcium channel blocker, 25%; beta-blocker, 24%. Among those receiving antihypertensive treatment, 59% had blood pressure greater than 130/80 mm Hg. Overall, 42% received a hypolipidaemic treatment: statin, 25%; fibrate, 18%. About half the people with a high cardiovascular risk had LDL cholesterol greater than 1 g/L, but only 32% were given a statin. Among people with an abnormal albumin/creatinine ratio (11%), 59% received an ACE inhibitor/ARB. Among those with CHD, 35% received the two treatments recommended in 1999 (beta-blockers and antiplatelet agents); in multivariate analyses, this two-treatment delivery was positively associated with male gender, self-reported hypertension and consulting a cardiologist.

Conclusion. – Cardiovascular risk profiles reported by providers in T2D people are high. Despite recent progress, there is a need for major improvement in practices intended to prevent cardiovascular disease in these people, especially in those at greatest CHD risk.

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Résumé

Prise en charge médicale du diabète de type 2 en France : nécessité d’améliorer le contrôle des facteurs de risque vasculaire.

Objectifs. – Chez les personnes atteintes de diabète de type 2, décrire l’utilisation des traitements préventifs à visée cardiovasculaire, la comparer aux recommandations de bonne pratique et identifier les facteurs associés à l’utilisation des traitements recommandés.

Méthodes. – Pour l’échantillon national témoin représentatif des personnes diabétiques (Entred), 10 000 adultes traités pour diabète (quel que soit le type) ont été tirés au sort dans les bases de données de l’Assurance maladie. Les médicaments préventifs à visée cardiovasculaire délivrés au cours du dernier trimestre 2001 ont été extrait de ces bases. Des questionnaires ont été envoyés aux personnes diabétiques et à leurs médecins. La population d’étude finale inclus 3324 personnes diabétiques de type 2 et leurs 1553 médecins.

Résultats. – Globalement, 18 % des personnes ont déclaré une complication cardiovasculaire et 44 % ont été classées comme étant à haut risque cardiovasculaire ; 68 % ont reçu un ou plusieurs traitements antihypertenseur : IEC/ARA, 44 % ; diurétique, 35 % ; inhibiteur calcique, 25 % ; bétabloquant : 24 %. Parmi les personnes recevant un traitement antihypertenseur, 59 % avaient une pression artérielle supérieure à 130/80 mm Hg. Globalement, 42 % des personnes ont reçu un traitement hypolipémiant : statine, 25 % ; fibrate, 18 %. Près de la moitié des personnes classées à haut risque vasculaire avaient des concentrations plasmatiques de LDL supérieures à 1 g/L, mais seulement 32 % d’entre elles ont reçu une statine.

* Corresponding author.

E-mail address: i.romon@invs.sante.fr (I. Romon).

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1. Introduction

Diabetes increases the risk of cardiovascular disease (CVD) two- to fourfold, and CVD is given as the underlying cause of death in half the death certificates mentioning diabetes [1,2]. The standardized death rate for ischaemic heart disease in the general French population in 2001 was 48 per 100,000 [3]. In France, the prevalence of treated diabetes is estimated to be about 3.8%, which ranks among the lowest in European countries, although medical insurance data show that this is increasing by 5.7% every year [4]. Reducing the frequency and severity of cardiovascular complications in people with diabetes has been given high priority in the French public-health agenda [5], and specific French guidelines published in 1999 [6] and in 2006 [7] have emphasized the need for preventing or tightly controlling cardiovascular risk.

The subgroup of 3324 individuals with type 2 diabetes (T2D) from the Échantillon National Témoin Representatif des Personnes Diabétiques (ENTRED) study has been analysed to:

- define the frequency of preventative treatments for cardiovascular diseases in T2D people in 2001, as well as the trends from 2001 to 2003;
- identify the factors associated with adequate preventative treatment in 2001.

2. Research, design and methods

2.1. ENTRED study

The ENTRED study described the health status of people with diabetes living in France and the quality of healthcare they received. For the study, 10,000 adults who had claimed reimbursement for at least one delivery of an oral hypoglycaemic agent (OHA) or insulin from October to December of 2001 were randomly drawn from the database of the main National Health Insurance System (NHIS). This insurance system covers all active and retired employees and their relatives, about 70% of the population living in France.

First, all claims for medical care, clinical measurements and drug reimbursements were obtained for the 10,000 people sampled for the years 2001–2003. Questionnaires were mailed to these 10,000 people and a medical questionnaire was mailed to the care providers of the people who gave their permission to do so. The ENTRED study was approved by the French National Ethics Committee.

2.2. Study population and databases

We included all the individuals who responded to the detailed patient questionnaire (n = 3646). We further selected those classified as having T2D (n = 3324; 91%), using an epidemiological algorithm based on age at diagnosis (threshold: 45 years) and insulin treatment (threshold: two years since diagnosis). Diabetes duration, weight and height were self-reported in the patient questionnaire, and coronary heart disease (CHD) was defined as self-reported myocardial infarction, angina or coronary revascularization. Overweight was defined as BMI greater or equal to 25 kg/m² and less than 30 kg/m², and obesity as BMI greater or equal to 30 kg/m².

Medical data reported by the care providers were available for a subset of 1553 people with T2D. The last available measurements of their systolic and diastolic blood pressures (BP) were reported for 96%, urinary albumin excretion for 57%, LDL cholesterol for 61% (calculated using the Friedwald formula [8]), HbA1c for 92% and triglycerides (TG) for 85%. Hypercholesterolaemia was defined, as in the 2006 French guidelines, as LDL cholesterol greater or equal to 1.3 g/L plus TG greater or equal to 2 g/L [7]; hypertriglyceridaemia as TG greater or equal to 2 g/L plus LDL cholesterol less than 1.3 g/L; and combined dyslipidaemia as LDL cholesterol less than 1.3 g/L plus TG greater than 2 g/L [7]. People were considered to have a high cardiovascular risk on the basis of the algorithm from the 2006 French guidelines that used age, gender, smoking, previous CHD, hypertension, HDL cholesterol and albumin excretion [7]. Provider satisfaction with the cardiovascular risk control was also covered by the questionnaire.

To confirm that the subsamples of people and care providers were representative of the original sample, the characteristics and cardiovascular preventative treatments of those who responded to the detailed questionnaire were compared with those who did not, using the 2001 administrative data available for all of these people.
2.3. Preventative treatments for cardiovascular disease

Based on the Anatomical Therapeutical Chemical (ATC) classification system, European Pharmaceutical Marketing Research Association (EphMRA) and Club InterPharmaceutique (CIP) codes, four types of treatment were determined: antihypertensive, hypolipidaemic, kidney-protective, and antithrombotic. We analysed all the drugs delivered during the last quarter of 2001, one delivery being considered to constitute treatment. To identify treatment trends, deliveries were also extracted for the second quarter of 2003, and compared with those of 2001 for the subset of 3163 people for whom data were available for both periods (95% of the original sample: 43 people had died; 118 were lost to follow-up and may have been insured by another insurance scheme or were living abroad). Treatments were described according to French official guidelines. The 1999 guidelines [6] in place when ENTRED was carried out were updated in 2006 [7]. Data were analysed according to both 1999 and 2006 guidelines to evaluate:

- the 2001 practices and recommendations;
- the gap between the 2001 situation and the updated recommendations.

2.4. Statistics

Descriptive procedures included frequencies and their 95% confidence intervals (CI). Pearson’s chi-squared tests and trend tests were used to compare frequencies. Data were age-adjusted using Mantel–Haenszel tests. Stepwise ascending logistic-regression models were used to determine the factors associated with adequate preventative treatments for cardiovascular disease in people with existing CHD. One model tested sociodemographic data (such as age, gender, educational level, occupation), another model added health-status data (such as microvascular complications, coronary revascularization, smoking, age at diabetes, type of hypoglycaemic treatment), and the third and final model added care indicators (such as at least one visit to a cardiologist or endocrinologist, examination of the fundus of the eye, and three HbA1c measurements, every year).

3. Results

3.1. Representativeness of the ENTRED participants

The individuals who took part in the detailed patient survey were somewhat younger (64 years versus 65 years, \( P < 0.01 \)) and more often male (54% versus 46%, \( P < 0.01 \)) than those who did not; they were also more frequently treated with insulin (23% versus 19%, \( P < 0.01 \)) and less frequently with a single OHA (55% versus 61%, \( P < 0.01 \)). In addition, they were less frequently treated with at least one preventative treatment for CVD — 79% versus 81%, \( P = 0.03 \) (diuretics, 33% versus 40%, \( P < 0.01 \); beta-blockers, 23% versus 25%, \( P = 0.01 \)) — except in the case of statins (24% versus 22%, \( P < 0.03 \)). No other differences were found between people whose care providers responded to the medical survey and those whose care providers did not.

The prevalence of CHD, weighted for the characteristics of non-participants (to take into account age, gender and treatment characteristics), was similar to the crude estimate (17%) [9].

3.2. Description of the population

The mean age of the 3324 participants with T2D was 65 years, and the mean duration of diabetes was 11 years; 54% were men; 10% were treated with insulin only, 7% with insulin plus OHA and 83% with OHA alone. At least one hospitalization was recorded in 2001 in 27%, one endocrinology visit in 10%, and one cardiology visit in 32%; 80% benefited from a waiver of co-payment for a chronic disease (diabetes or some other disease), which is dependent on provider request.

Among all participants with T2D, 18% reported at least one CHD in 2001, 56% reported hypertension and 53% dyslipidaemia; 41% were classified as overweight and 36% as obese, based on self-reported weight and height; 14% were current smokers.

Among those whose medical data were available from their provider reports (\( n = 1553 \)), 40% had an HbA1c level of less than 7%, about one-quarter (26%) had a value of 7–8%, 21% had a value of 8–10%, and 5% had a value of 10% or more. The care provider did not provide information for 8%.

3.3. All preventative cardiovascular treatments

Table 1 shows the frequency of delivery of four classes of preventative cardiovascular treatments overall and by age group. Overall, 82% received at least one treatment during the last quarter of 2001: antihypertensive treatment, 68%; hypolipidaemic treatment, 42%; antithrombotic treatment, 33%.

In people whose data were available for both 2001 and 2003 (\( n = 3163 \)), the frequency of at least one treatment delivery during a three-month period increased over time for statins (+6%), antithrombotics (+6%), ACE inhibitors/ARBs (+5%) and diuretics (+5%). The frequency remained fairly stable for fibrates (−2%), for both alpha and central antihypertensives (+1%), for calcium channel blockers (+1%), and for beta-blockers (+1%).

3.4. Antihypertensive treatments

The target set in people with T2D by the 1999 French guidelines was a BP level less or equal to 140/80 mm Hg; beta-blockers, diuretics and ACE inhibitors were recommended [6]. In 2006, the threshold was lowered to 130/80 mm Hg, and the recommended treatments included beta-blockers, thiazide diuretics, ACE inhibitors/ARBs and calcium channel blockers [7].

During the last quarter of 2001, 32% of the ENTRED participants received no antihypertensive treatment, 26% received one class, 23% received two, 13% three, and 6% four. ACE inhibitors/ARBs (44%) and diuretics (35%) were the most commonly used drugs (Table 1). Among those who received two classes of antihypertensive, the most frequent combinations were ACE inhibitors plus diuretics (25%) or ACE inhibitors plus calcium
<table>
<thead>
<tr>
<th>Treatment for cardiovascular risk factors</th>
<th>Overall n = 3324</th>
<th>&lt; 55 years n = 640</th>
<th>55–64 years n = 883</th>
<th>65–74 years n = 1174</th>
<th>≥75 years n = 627</th>
</tr>
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<tr>
<td>%</td>
<td>CI95%</td>
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<tr>
<td>Resin</td>
<td>0.4 [0.2–0.6]</td>
<td>0.5 –</td>
<td>0.2 –</td>
<td>0.5 –</td>
<td>0.3 –</td>
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<tr>
<td>Heparin</td>
<td>2 [1.1–2.0]</td>
<td>0.8 –</td>
<td>0.7 –</td>
<td>2 [1–3]</td>
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channel blockers (12%). Choices were concordant with the official recommendations: cardioselective beta-blockers were more likely to be used than non-selective ones (19% versus 5%); alpha and central antihypertensive treatments were rarely used (9%) except in cases of high BP; thiazide diuretics were used more often than non-thiazides (20% versus 16%), with furosemide accounting for half of the latter.

Whatever the class of drug, the frequency of at least one antihypertensive treatment delivered over a three-month period increased with the BP level ($\chi^2_{\text{trend}}, P < 0.01$). Both the frequency of at least one delivery of any antihypertensive treatment and the number of antihypertensive treatments combined also increased with age ($\chi^2_{\text{trend}}, P < 0.01$) and diabetes duration ($\chi^2_{\text{MH}}, P < 0.01$). A quarter of people under 55 years of age, and 56% of those over 75 years, received at least two classes of agents. For the same achieved BP level, older people were more likely to have received several antihypertensive treatments. Women were more frequently treated with antihypertensive treatments than men, even after adjusting for age (72% versus 65%,$\chi^2_{\text{MH}}, P < 0.01$).

However, Table 2 shows that many people with high blood pressure could benefit from introducing or adding a hypertensive treatment.

### 3.5. ACE inhibitors/ARBs

The 2006 French guidelines for T2D recommend the use of ACE inhibitors or ARBs to treat people who have abnormal albumin excretion, with the addition of thiazide diuretics in those with excess albumin excretion.

During the last quarter of 2001, 44% of the ENTRED participants received at least one delivery of ACE inhibitor/ARBs (Table 1). This frequency increased with age, from 31% in those less than 55 years of age to 51% in those over 75 years ($\chi^2_{\text{trend}}, P < 0.01$), with no significant gender difference. Whatever the age, ACE inhibitors were more frequently delivered than ARBs (30% versus 15%). Table 2 shows that only 8% of people not taking ACE inhibitors/ARBs would have benefited from the treatment. This is due to the large proportion of such people (46%) whose level of albumin excretion is unknown. Even among those with diagnosed abnormal albumin excretion, only half were treated with ACE inhibitors or ARBs.

### 3.6. Hypolipidaemic treatments

The 1999 and 2006 French guidelines for T2D recommend treating people who have a high cardiovascular risk and/or isolated hypercholesterolaemia or mixed dyslipidaemia with a statin [6,7]. The use of fibrates alone is recommended for T2D people with isolated hypertriglyceridaemia and fibrates combined with a statin for those with combined dyslipidaemia.

During the last quarter of 2001, 42% of the ENTRED participants received at least one delivery of hypolipidaemic treatment (Table 1). This frequency increased in those up to 70 years of age (47%) and subsequently fell to 21% in people over 85. After adjusting for age, treatment was not associated with either gender or diabetes duration. A statin was more often used than a fibrate (25% versus 18%), and the use of a resin was marginal (0.4%), as was any combination of treatments. Lipid levels are shown in Table 4 by type of hypolipidaemic treatment delivered. Only 24% of people not taking hypolipidaemic treatment had normal lipid levels, while 46% had no LDL levels measured.

In people with LDL values below 1 g/L (13%), between 1 and 1.3 g/L (22%), between 1.3 and 1.6 g/L (18%), and above 1.6 g/L (8%), 41, 29, 24 and 29%, respectively were treated with a statin.

### 3.7. Antithrombotic treatments

The 1999 and 2006 French guidelines for T2D recommend the use of antithrombotic therapies to treat people with existing CHD, and to prevent cardiovascular disease in those at risk.
During the last quarter of 2001, a third of the ENTRED participants (33%) received at least one delivery of antithrombotic treatments, which included antiplatelet agents (analgesic aspirin included) (28%), antivitamin K (5%) and heparin (2%). The frequency of antithrombotic treatments is shown by age in Table 1. When controlled for age, treatment was more frequent in men than in women (38% versus 27%, \( \chi^2_{MH} P < 0.01 \)) and in those who had diabetes of longer duration \( (\chi^2_{MH} P < 0.01) \). Of the people with CHD (18%), of those at risk of CHD (64%; people without CHD, but with hypertension, hypercholesterolaemia or who were smokers) and of the others (18%), 75, 25 and 17%, respectively received an antithrombotic drug.

### 3.8. Combinations of treatments among people with CHD

Among the ENTRED participants with CHD (18%), 35% received the two treatments recommended in 1999 [6]: beta-blockers and antiplatelet agents. In a multivariate analysis of sociodemographic factors, people aged 55–70 years and men were more often treated with the two recommended treatments. After adjustment for health-status indicators, people with a history of coronary revascularization (OR = 2.2 [1.5–3.2]), those with self-reported hypertension (OR = 1.7 [1.1–2.5]) and those of male gender (OR = 1.7 [1.1–2.6]) were more often treated with the two recommended treatments. No significant age effect was reported. After adjustment for medical-care procedures, people without coronary revascularization who consulted a cardiologist were more often treated with the two recommended treatments (OR = 2.9 [1.6–5.3]), whereas this difference was not significant among people with a history of revascularization.

In 2006, the guidelines recommend, for people with T2D and CHD, a combination of four treatments: beta-blockers (or verapamil or diltiazem); statins; ACE inhibitors/ARB and antiplatelet agents [7]. Among those with CHD and whose data were available for 2001 and 2003 (17%), 49 and 53%, respectively, received at least three of the four recommended treatments.

### 4. Discussion

This study quantifies medical care practice during 2001–2003 in terms of preventative treatments for CVD in T2D people living in France. In a country with a high level of access to healthcare, our study demonstrates a lack of proper management and poor cardiovascular-risk control in people with T2D, and suggests some ways of improving control.
comparison, 32% of people over age 55 years with at least one cardiovascular risk factor in the HOPE study [13], and 29% of people with previously diagnosed diabetes in the US [14], had microalbuminuria. In the ENTRED study, treatments with demonstrated efficacy in reducing the incidence or aggravation of kidney disease were not often used, with only half of those with diagnosed abnormal urine albumin being treated with ACE inhibitors/ARBs.

People with T2D and existing CHD are a major population group that needs to be targeted for better control of cardiovascular risk factors. In 1999–2000, the EUROASPIRE II study [15] described risk factors and treatments in people hospitalized for CHD who were aged 70 years or under in 15 European countries. It included 1086 people with diabetes and showed levels of risk factors similar to those of the ENTRED participants, although clinical data for ENTRED were not measured but reported by providers: 57% had BP greater or equal to 140/90 mm Hg versus 61% in ENTRED, when restricted to people of similar age with CHD; 18% were current smokers (versus 18%); 44% were obese, according to measured weight and height (versus 44%); and 57% had LDL cholesterol higher than 1.2 g/L (versus 42% among people with a reported value for LDL). However, treatments were more frequent in the hospitalized EUROASPIRE people than in ENTRED: 82% were treated with antiplatelet agents (versus 65%); 66% with beta-blockers (versus 50%); 52% with ACE inhibitors (versus 39%); and 57% with statins (versus 45%). This may demonstrate the lack of intensive treatment outside highly specialized centres or long after the coronary event. In contrast, in ENTRED in 2001, a visit with a cardiologist and existing coronary revascularization were considered to be important determinants of adequate prevention. Other determinants were male gender and self-reported hypertension. Similar disparities according to gender have been previously reported [16], with women with T2D being less often or less aggressively treated for cardiovascular risk factors than men.

While considerable effort is still required to improve the cardiovascular profile of people with T2D, some positive trends can already be observed. During 2001–2003 and over only 18 months, the use of statins, antithrombotic treatments, ACE inhibitors/ARBS and diuretics increased by 5–6% in people with existing CHD.

The present study has several important limitations. First, the results may not be fully representative of France as a whole, as the study included only patients insured through the main NHIS (70% of the total French population) and those receiving pharmaceutical treatment for diabetes. Biases linked to participation (only 36% of people filled in the detailed questionnaire) are a common limitation of mailed surveys that include elderly people. The retrospective and self-reporting nature of the data is also an obvious limitation. Non-responders may have poorer health than the responders, which could lead to an underestimation of the prevalence of the self-reported cardiovascular complications (myocardial infarction, angina or coronary revascularization). Moreover, LDL-cholesterol and albuminuria values were frequently missing in the reports from care providers and, as a result, the proportion of people with clinical abnormalities is probably underestimated, especially in elderly people. However, reimbursement data added important and objective information, with only slight differences found in the frequency of treatment in the people who responded compared with those who did not respond.

We classified people as having been treated if they received just one delivery during a three-month period, and this may have overestimated the frequency of treatment and use of combination treatments. It was also not possible to determine the medical indication for which the treatments were prescribed (beta-blockers, ACE inhibitors/ARBS).

5. Conclusion and perspectives

In France, the medical follow-up of people with T2D is usually provided by general practitioners (86%) [17]. Although 70% of the medical providers surveyed stated that they were satisfied with the cardiovascular risk control of their people with diabetes [9], the ENTRED study demonstrates an urgent need to improve the control of cardiovascular risk factors in people with T2D. The first requirement is to improve the quality of BP measurement, and the frequency of LDL-cholesterol and albumin-excretion measurements. Improving the control of risk factors also calls for more frequent initiation of antihypertensive treatments and use of combinations, and a wider use of statins. Finally, specific people subgroups could be targeted. In particular, a recent report shows that those with diabetes and multiple risk factors have a 10-year cumulative incidence of CHD that is equivalent to that of people without diabetes and with previous CHD [18]. However, our present study demonstrates a lack of adequate preventative treatment in that same subgroup, which underscores the need to specifically target people with diabetes and existing CHD or multiple risk factors.

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