Cardiovascular risks in type 2 diabetes and secondary cardiovascular prevention

P Ducimetière

SUMMARY
In order to emphasize the necessity of treating aggressively the main cardiovascular risk factors (hypertension, hypercholesterolemia, smoking) in diabetics, it was proposed in 1998 to assimilate their absolute risk level to that of non diabetics with a history of myocardial infarction. In this short review, it is recalled that diabetics (and coronary patients as well) constitute heterogeneous groups and the results of such comparisons depend heavily on the selection of the two groups as shown by published works on this topic since 1998. Anyway, the treatment of the main risk factors in true diabetics should be strict and new preventive approaches by treating the disease itself are awaited.

Key-words: Type 2 diabetes · Cardiovascular risk · Risk factors · Secondary prevention · Epidemiology.

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RÉSUMÉ
Risques cardiovasculaires du diabète de type 2 et prévention cardiovasculaire secondaire
Afin d’insister sur la nécessité de traiter agressivement les principaux facteurs de risque cardiovasculaire (hypertension artérielle, hypercholestérolémie, tabagisme) chez les diabétiques, il a été proposé en 1998 d’assimiler leur niveau de risque absolu à celui des sujets non diabétiques qui avaient un antécédent d’infarctus du myocarde. Dans cette courte revue il est rappelé que la population des diabétiques (comme celle des coronariens d’ailleurs) est très hétérogène et que les résultats d’une telle comparaison dépendent étroitement de la sélection des deux groupes de sujets ainsi que le montrent les travaux publiés sur ce thème depuis 1998. Quoi qu’il en soit, le traitement des facteurs de risque chez les diabétiques avérés doit être strict et de nouvelles approches préventives par le traitement de la maladie diabétique sont attendues.

Mots-clés : Diabète de type 2 · Risque cardiovasculaire · Facteurs de risque · Prévention secondaire · Épidémiologie.
In 1998, Haffner et al. [1] raised a challenging question concerning the status of type 2 diabetes as a risk factor (among others) for coronary heart disease and death or as a particularly high risk condition which should be put in the same category as having a prior history of coronary disease (a previous myocardial infarction for example).

The issue is of importance because treating aggressively risk factors in subjects with prior disease (secondary prevention) is a key statement of all public health recommendations and is now widely accepted among clinicians, whether they are cardiologists or not. The rationale for the statement is straightforward: these patients are at high absolute risk of a new coronary episode (for instance 15% in 5 years) and prevention trials, confirming purely observational data, have shown that the number of subjects to be treated (for one or more risk factors) in order to prevent one event during that period is particularly low (some dozens as an order of magnitude).

In their observational study, Haffner et al. showed that the risks of diabetics in primary prevention are of the same order of magnitude as those of non-diabetics and, consequently, the same type of public health recommendations should apply.

In this short review, we first discuss the nature and determinants of cardiovascular risks among diabetics, emphasizing the heterogeneity of this condition, then we examine some further published data on Haffner’s paradigm and propose a conclusion.

Cardiovascular risks associated with type 2 diabetes

More than twenty years ago, the Framingham Study [2] clearly demonstrated that in “clinically defined” diabetics, the risk of cardiovascular events was increased by a factor of about 2 in men for many cardiovascular endpoints including congestive heart failure, intermittent claudication and cardiovascular death for which the associated relative risk was even higher (> 3) in women. The order of magnitude of these risks held while adjusted on the other main risk factors (so called the “classic” ones): high blood pressure, cigarette smoking, hypercholesterolemia and, also, presence of left ventricular hypertrophy on the ECG, all factors which carried out relative risks of a magnitude more or less comparable to that associated with diabetes. Risks attributable to diabetes, however, (defined as the proportion of events that would not be observed if the factor was suppressed) were relatively low due to its low prevalence. In addition to the subjects medically treated for diabetes at entry, only those with two casual blood glucose higher than 150 mg/dl and who proved to be diabetic after further clinical examinations were included, yielding a prevalence of 2-6% in men and women aged 45-74.

The same type of results were observed in most cohort studies when comparable restrictive definitions of type 2 diabetes were used, for instance in the Paris Prospective Study [3] where only men who declared at entry being diabetic according to their doctor were included. On the opposite, no such risk excess was observed in unknown diabetic subjects with fasting hyperglycaemia recorded at one occasion only, even though some elevation had been proven [4]. The inclusion of subjects with one measurement higher than 126 mg/dl in the definition of diabetes, which is now adopted by most authors, increases its prevalence in the population and, as a corollary, decreases the risk for cardiovascular events in diabetics during a 5-15 year period after the discovery.

If the definition of the disease is, as such, a major determinant of the risk of clinical complications, other sources of heterogeneity exist and should be taken into account. As an illustration, in the WHO collaborative work on vascular diseases in diabetes [5], the duration of type 2 diabetes (though difficult to determine with precision) was a definite marker of risk, independently of age. Compared to the general population of the corresponding countries, all-cause standardized mortality ratios (SMRs) increased from 180 to 300 in men (190 to 440 in women) when diabetes duration less than 6 years increased to more than 14 years. In parallel, the degree of renal involvement as judged by an existing proteinuria, carried out higher SMRs which reached 500 in men and 800 in women when it was accompanied by hypertension.

Needless to say, combinations of these simple determinants might identify groups of diabetics belonging to the same population who presented very contrasted levels of absolute risk of clinical complications. As a corollary, the protocol to include diabetic subjects in a study might give rise to highly selected groups with indeed very different risk levels.

Evidently, the same remarks apply as well when patients with prior coronary disease should be recruited. Among the multiple factors of heterogeneity, the date of recruitment is obviously important, due to the dramatic improvement in the prognosis of acute coronary disease in the last twenty years [6].

Compared cardiovascular risk in diabetics without history of coronary disease and non diabetics with myocardial infarction?

Previous remarks gave some indication that this question is not adequately formulated and, very likely, does not correspond to any defined scientific problem. The ultimate goal of Haffner et al.’s work was of another nature and, pragmatically, it might be useful to check whether their findings could have been reproduced or not. Another form of
selection, namely publication-bias, is however operating and it is by no means sure that the few papers published since which directly addressed that question were not highly selected.

In the Finnish study [1], diabetics were identified from a social insurance registry and were probably validated cases. The very high absolute risks in diabetics with history of myocardial infarction in the population during the 80’s should be noted (table I).

On the opposite, prevalent disease cases were declared at entry in the US Male Physicians cohort study [7], only newly discovered diabetics were included in the Tayside cohort study [8] and glycaemia criteria at screening were used in the ARIC study [9]. In these studies, higher event rates were observed in the non diabetic myocardial infarction group than in the diabetic non coronary group (table II). The same conclusion was also reached in a cohort study of elderly in Australia [10] with a risk ratio of 1.7.

### Conclusion

There is now a lot of evidence that “classic” coronary factors are strong determinants of risk in diabetics as well in non diabetics. The core facts are illustrated in figure 1 which shows, among the population of more than 300,000 men who were screened for the MRFIT intervention trial [11], the absolute risk of cardiovascular death (/10,000 person-years) according to the number of risk factors associated or not with diabetes defined by medication taking.

From this figure, we see that prevention in diabetics should in fact take two directions: treating risk factors intensively on the one hand, treating specifically the diabetic state on the other hand. It is not necessary to compare artificially the risks entailed by non coronary diabetics vs coronary non diabetics to know that true diabetics are at high cardiovascular risk and should be treated accordingly as now fully demonstrated [12, 13]. The possibility, however, of slowing down the diabetic process and as a conse-

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### Table I

Annual incidence rate of myocardial infarction, stroke and cardiovascular death according to presence of type 2 diabetes and/or history of myocardial infarction (MI) [1].

<table>
<thead>
<tr>
<th></th>
<th>Non diabetics No MI</th>
<th>Diabetics No MI</th>
<th>MI non diabetics</th>
<th>MI and diabetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>1304</td>
<td>890</td>
<td>69</td>
<td>169</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0.5*</td>
<td>3.2</td>
<td>3.0</td>
<td>7.8</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.3</td>
<td>1.6</td>
<td>1.2</td>
<td>3.4</td>
</tr>
<tr>
<td>CV death</td>
<td>0.3</td>
<td>2.5</td>
<td>2.6</td>
<td>7.3</td>
</tr>
</tbody>
</table>

* events/100 person-years.

### Table II

Relative risks for various endpoints in subjects with history of myocardial infarction but without diabetes compared to diabetic subjects without myocardial infarction (MI).

<table>
<thead>
<tr>
<th>Study – endpoint</th>
<th>Diabetics without MI</th>
<th>MI without diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lotufo et al. [7]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary heart disease deaths</td>
<td>1.0* (89)</td>
<td>1.86 (445)</td>
</tr>
<tr>
<td>Evans et al. [8]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All deaths</td>
<td>1.0 (1196)</td>
<td>1.35 (2596)</td>
</tr>
<tr>
<td>Cardiovascular deaths</td>
<td>1.0 (222)</td>
<td>2.93 (1077)</td>
</tr>
<tr>
<td>Hospital MI</td>
<td>1.0 (142)</td>
<td>3.10 (656)</td>
</tr>
<tr>
<td>Lee et al. [9]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MI and Coronary heart disease deaths</td>
<td>1.0 (141)</td>
<td>1.75 (59)</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.0 (88)</td>
<td>1.05 (17)</td>
</tr>
<tr>
<td>Cardiovascular deaths</td>
<td>1.0 (110)</td>
<td>1.82 (35)</td>
</tr>
</tbody>
</table>

*relative risk (number of cases).
sequence obtaining a further preventive effect on macrovascular and not only microvascular disease has only received partial answers [14] and much research is now going on in this direction.

References

4. DECODE Study Group. Is the current definition for diabetes relevant to mortality risk from all causes and cardiovascular and noncardiovascular diseases? Diabetes Care 2003;26:688-96