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Attendance to Diabetes Clinics is associated with a lower all-cause mortality. A meta-analysis of observational studies.

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ABSTRACT

Objective. The epidemiological explosion of diabetes is a challenge for Health Systems and the identification of the most appropriate models of care are warranted. The inclusion of primary care physicians in the models is unquestioned whereas the role played by secondary and tertiary care (diabetes clinic) is often debated. However, studies focusing on hard endpoints and comparing diabetes clinic attendance vs. no attendance are scant.

Research Design and Methods. In the present paper, we have meta-analyzed 3 large observational cohort studies carried out in Italy, where a network of public diabetes clinics has been operating in the last 40 years. The endpoint was all-cause mortality and a comparison was made between patients attending vs. those not attending diabetes clinics. Attendance was defined by prescriptions and reimbursement of specialist visits by the National Health System.

Results. Overall, 191,847 subjects with diabetes were included in the analysis, and about half of them had at least one visit in the diabetes clinic per year. During the follow-up, ranging 1 to 10 years, 9,653 subjects died. Mortality was remarkably lower in subjects with attendance to diabetes clinic (MH-OR 0.70, 95% CI 0.55-0.88, $p=0.002$). Results were confirmed after adjusting for confounders (MH-OR 0.81, 95% CI 0.69-0.95, $p=0.009$).

Conclusions. The results of the present study suggest that attendance to diabetes clinics is associated with a remarkably lower all-cause mortality. This finding might be instrumental to implement the best models of care for person with diabetes.

Key words: diabetes – mortality – diabetes clinic – care model

Diabetes mellitus has been defined an emergency by several international institutions, including United Nations and World Health Organization, due to the exponential increase of its prevalence worldwide (1). Several hundred millions of subjects suffer from this long-standing chronic disease, which is often complicated by severe and life-threatening target organ damage (2). The economic burden of diabetes is growing and represents a serious challenge for sustainability by individuals, families and societies (3). Most National Health Systems are facing the problem of taking care of millions of patients with diabetes and several models of care were tested and/or proposed (4-15). The involvement of General Practitioners (GPs) in these models of care is unquestioned whereas the contribution of diabetes clinics, with their teams of specialist doctors, dietitians, nurses, psychologists and podiatrists, is often debated. Although the added value of diabetes specialists or diabetes clinics is intuitive, the magnitude of their impact on hard endpoints such as all-cause mortality was formally examined in very few studies. Moreover, some of them are quite old while others were mainly focusing on other aspects of diabetes care, mortality being a secondary one (16-23). Most importantly, the model in which care is shared by GPs and single specialists is substantially different from the model in which care is shared by GPs and diabetes clinics.

A nation-wide network of public diabetes clinics has been established within the frame of the National Health System in Italy several decades ago, starting in the early 1970s. As many as 2 millions of patients with diabetes attend these clinics nowadays, with a variable frequency, depending on the stage of the disease as well as the attitude of their GPs to participate more or less actively in a shared diabetes care. This model of care is peculiar of Italy for its capillary diffusion (as many as 500 outpatient clinics) but in other Countries a sizable proportion of patients with diabetes attend regularly to diabetes clinics or receive care also by specialists (24,25).

Models of care based upon diabetes clinics are currently challenged by the broadening concept that chronic and common diseases, such as diabetes, heart failure, chronic obstructive pulmonary disease, arthritis, and others should be mostly or exclusively managed by GPs. On the other hand, the rapid and continuous progress of medical knowledge, with the subsequent increase in diagnostic tools, available drugs and sophisticated technologies, confutes this concept and supports the idea that diabetes clinics should collaborate with GPs for the care of diabetes in the majority of cases.

This meta-analysis of three observational studies conducted in Italy in the last 30 years explored the association of all-cause death with the attendance/not attendance to diabetes clinics. The meta-analysis does not include the studies conducted in other Countries, in order to avoid the

confounding bias generated by differences across Countries in the organization of primary and secondary care.

METHODS

Data Sources and Searches. All observational cohort studies performed in Italy which assessed all-cause mortality in patients with diabetes were searched. The search was performed on Medline, with the search string “diabetes”, “mortality”, and “Italy” and was limited to human and clinical studies, with an update on June 15th, 2017.

Study Selection. Studies were selected for the meta-analysis when they reported separately data for patients attending or not attending diabetes clinics. Study selection and data extraction were performed independently by two of the authors (E.M., M.M.), and conflicts resolved by a third investigator (E.B.).

Data Extraction. Mortality (crude estimates and adjusted odds ratios) were extracted from the primary publication or by other publications of the studies identified as above.

Data Synthesis and Analysis. The principal outcome of this analysis was the effect of diabetes clinic attendance on all-cause mortality. Crude mortality data were combined to calculate Mantel-Haenszel odds ratio (MH-OR), whereas adjusted odds ratios were combined in a single estimate, weighed for study size. All those analyses were performed using Comprehensive Meta-analysis Version 2. Biostat. (Englewood, NJ, USA). For each study a number needed to treat (NNT) at 10 years was calculated on the basis of crude mortality rates; an overall NNT was calculated weighing each study for the total observation (person*year). In addition, an adjusted NNT was obtained by calculating 10-year cumulative mortality in the patients not attending (control) group, and applying estimated OR (adjusted) in the diabetes clinic group.

RESULTS

Out of 232 studies identified, three studies fulfilling the inclusion criteria specified above were retrieved and used for analysis. The search flow is illustrated in Figure 1, whereas the main characteristics of subjects examined in the selected studies are reported in Table 1. All the three studies enrolled cohorts in Northern Italy: Verona, Veneto Region (17), Casale Monferrato, Piedmont Region (18), and 7 large Local Health Units of the Lombardy Region (19).

The main results of the meta-analysis are summarized in Figure 2. All-cause mortality was significantly lower in patients attending diabetes clinics (MH-OR 0.70 [95% CI 0.55-0.88], $p=0.002$), the difference being statistically significant even in adjusted analyses (OR 0.81 [0.69-0.95], $p=0.009$). Variables used for adjustment in individual studies always included gender and age; the other confounders were insulin therapy and place of residence in the study of Zoppini et al. (17), and duration of diabetes in the study of Bruno et al. (18).

The 10-year number-needed-to-treat (NNT) (i.e. diabetes clinic attendance) was 23, 9, and 11 for Verona, Casale Monferrato, and Lombardy. Overall, estimated 10-year mortality was 23.6 and 31.4% in patients attending and non-attending diabetes clinics, respectively. The calculated 10-year NNT was 13. Considering a reduction of mortality with respect to control group of 19% after adjusting for confounders (see above), the adjusted NNT was 17.

DISCUSSION

Results of this meta-analysis support the conclusion that all-cause mortality is greatly reduced when diabetic people are cared not only by their GPs but also by specialist teams operating in diabetes clinics. Remarkably, data are numerically consistent within the 3 studies included in the meta-analysis and across a time span ranging from 1980-1990 (Verona Diabetes Study)(17) to 1991-2001 (Casale Monferrato Study)(18) and 2012 (Lombardy Study)(19). The conclusion is further supported by the fact that, in two of these studies, the difference in mortality between patients attending or not attending to specialist clinics was confirmed after adjusting not only for age and gender, but also for other potential confounding factors (17,18). Residual confounding due to differences in degree of glucose control or other biochemical risk factors, chronic complications or comorbidities, treatment or monitoring of diabetes cannot be ruled out. In fact, patients attending to diabetes clinics might be different from those not receiving also a specialist care. For example, it

can be argue that patients attending to diabetes clinics have a greater participation to care being aware of its crucial role, or a greater motivation to monitoring and treatment, being aware of risk associated to diabetes, or a higher level of compliance to medical prescriptions, being aware of benefits of good adherence. However, these differences, if any, could be listed among the added values of attending to diabetes clinics and therefore explanations of our findings rather than confounding factors. In other words, the empowerment of patients by specialist teams could be one of the reasons for the lower mortality observed in patients receiving also a specialists care. Also possible differences in goals and targets of treatment, monitoring procedures, access to modern technology and/or drug prescriptions for hyperglycemia and related disorders (e.g., dyslipidemia, hypertension) should be considered an explanation of results rather than a confounding factor.

It is possible that a higher mortality in patients not attending to diabetes clinic is partially explained by a higher prevalence of concurrent conditions (e.g., dementia, severe disabilities, etc.) which represent a relevant barrier for accessing, and which are per se associated with increased mortality rates. On the other hand, it is reasonable to argue that patients attending to diabetes clinics are more likely to have more severe forms of the disease since poor glucose control and advanced chronic complications are usual reasons for specialist referral. Accordingly, patients attending to diabetes clinics were more frequently treated with insulin than those not attending, and showed more frequently high HbA1c, hypertension and coronary heart disease (17,18,26,27). In particular, in some Countries or areas, specialists are only referred sicker patients with more complex metabolic abnormalities and more severe complications, and for such reason more likely to die. Therefore, it seems hard to conclude that the lower mortality of subjects attending to diabetes clinics is biased because they are in better health condition. It is plausible, indeed, that specialists can better manage the greater complexity and severity of the disease with specific skills acquired with their initial and continuous medical education (*the theory*) and their wide experience (*the practice*) in diabetes care. Nowadays, diabetes monitoring and care is based upon dozens of laboratory tests and exams, a vast array of drugs targeting blood glucose, lipids, blood pressure, thrombophilia and target organ damage and sophisticated devices. The experience of using them several times every day, as it happens to a specialist, and not only occasionally, as it happens to a GP, could make the difference in most cases, with a substantial benefit in terms of survival. Accordingly, other studies documented the positive impact of specialists in diabetes care (11, 28-31).

Noteworthy, the estimated 10-year NNT to prevent one death with specialist care is low (less than 20) and quite similar to the one estimated in trials of secondary prevention of CVD with statins (32) or RAS antagonists (33) in diabetes. Since treatment with statins or renin-angiotensin

system antagonists in diabetes is strongly recommended by most credited guidelines, including those of the American Diabetes Association (34), attendance to diabetes clinics could be similarly recommended.

Observational “real world” studies can highlight statistical associations, thus strengthening hypotheses and reinforcing concepts, but they are not definitely probative in terms of cause-effect relationships and potential advantages/disadvantages, even in the presence of a strong clinical plausibility. It is plausible, indeed, that the diabetes clinic team can add value in terms of survival. The results of this meta-analysis provide support to this concept. A randomized large trial with well-matched groups of attending and not attending patients followed for several years could eliminate some residual doubts. This large trial, however, which to our knowledge has never been conducted, would be very difficult to implement because in one arm the attendance to diabetes clinic should be prohibited or strongly discouraged throughout the study period and this would generate ethical and/or legal concerns. In addition, the introduction of specific procedures with the study protocol, and the unavoidable limitation of enrolment to subjects happy to participate and providing an informed consent, would make the results of such a clinical trial not fully applicable to real world. Most probably, this large trial will never be carried out. On the other hand, small trials conducted many years ago reported a lower mortality associated with specialist care (20, 22).

The generalization of these results, collected in Italy, to other Countries with a different organization of care should be made with caution.

In conclusion, this meta-analysis extends and reinforces the concept that attendance to diabetes clinics is beneficial and is associated with a remarkably lower all-cause mortality. This information might be relevant for decision makers (politicians and technicians) working for organizing the best diabetes care at local, regional and national levels.

LEGEND TO FIGURES

Figure 1 – Search flow of studies included in the meta-analysis.

Figure 2 – Mantel-Haenzel odds ratio with 95% Confidence Intervals (MH-OR, 95% CI) for all-cause mortality in each study included in the meta-analysis.

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Table 1 – Main characteristics of the studies included in the meta-analysis.

<i>First author (year)</i>	Enrolment	Follow-up (years)	Patients		Age (years)	Gender		Deaths	
	(year)		(No.)	General Practitioner		(Male,	Insulin (%)	(No.)	
						%)		Specialist	General Practitioner
Zoppini G. 1999 (17)	1986	10	4,047	3,101	67	47	6	1,564	1,332
Bruno G. 2005 (18)	1991	10	1,097	316	69	44	17	502	180
Baviera M. 2017 (19)	2012	1	80,692	102,594	69	57	22	2,016	4,059

Figure 1

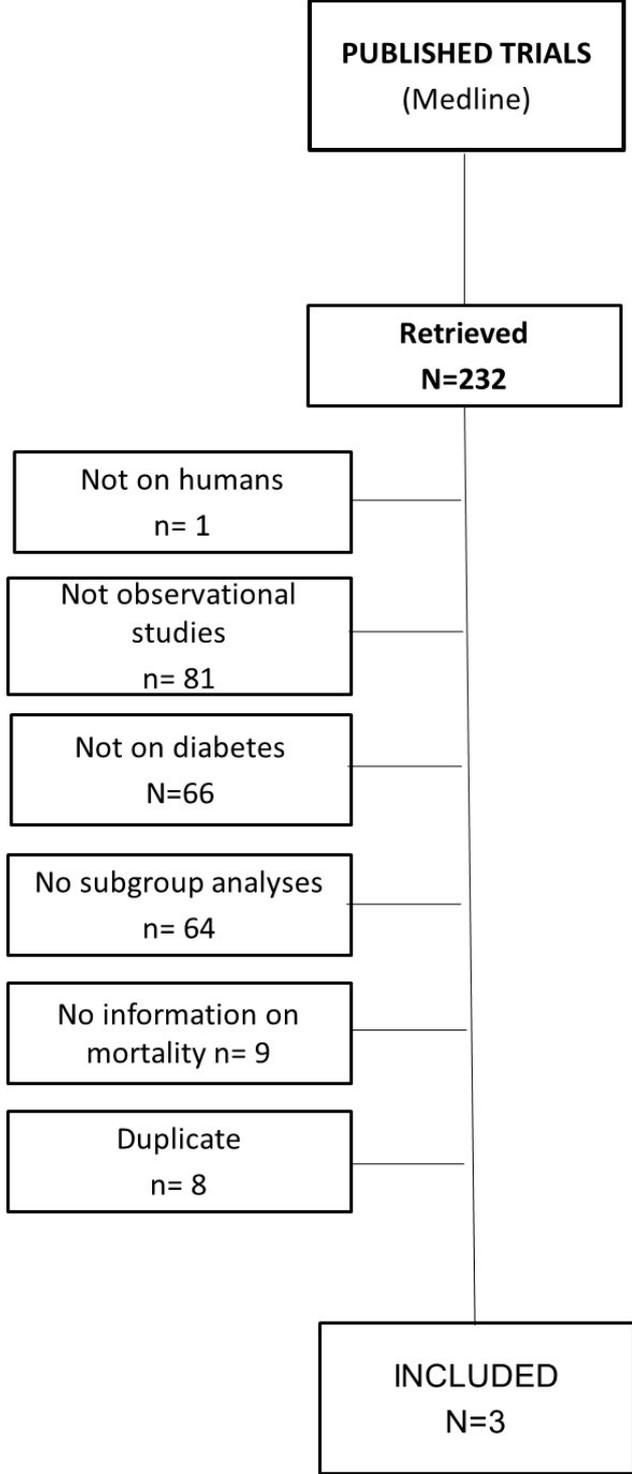


Figure 2

Study (reference)	Statistics for each study <i>MH odds ratio (95%, CI)</i>	p
Baviera M 2017 (19)	0.62[0.59-0.66]	<0.001
Zoppini G 1999 (18)	0.84[0.76-0.92]	<0.001
Bruno G 2005 (17)	0.64[0.49-0.82]	<0.001
Overall MH-OR	0.70[0.55-0.88]	0.002

