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Supplementary Materials

Specialist Advice Does Not Modify the Risk of Death of Diabetic 2 Patients

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ABSTRACT

Context: A recent meta-analysis (Bonora and coll.) reports benefits on death-risk for Italian diabetic patients mainly followed by the diabetic clinics of the National Health Service.

Aims: A) to do a critical appraisal of the meta-analysis by Bonora and coll. B) to verify its results conducting a controlled cohort study based on clinical records of a primary care setting.

Methods: (A) We evaluated the meta-analysis by Bonora through AMSTAR II checklist and the trials recruited in the review through ROBINS-I tool. (B) We analysed a cohort of diabetes 2 patients living in Veneto (Italy) and followed from 1/1/2009 to 12/31/2017 to compare the risk of death of a control group (i.e. never followed by specialists) with that of another two groups (i.e. respectively, followed by one specialist visit or by at least two visits in the last three years). We used a time-to-event approach (Cox model) for the main analysis; complementary designs were also tested (Restricted design and Matched design). Statistical adjustments were made both through Multivariate Cox regression and Propensity score. For the adjustments, the covariates considered were: age, sex, severity of diabetes, comorbidity, laboratory values, duration of diabetes and drugs use.

Results: (A) The meta-analysis by Bonora shows to be affected by serious pitfalls (B) A cohort of 6530 diabetic patients (none visit: n=3441; one visit: n=947; two or more visits: n=2142) was followed for a mean of 7.32y. Main multivariate analysis was not able to demonstrate any difference in mortality between groups exposed or not exposed to specialist advice: one visit HR=1.01 (0.98-1.03); two or more visits HR=1.12 (0.88-1.43). These results were confirmed by all other analytical approaches.

Conclusion: Mortality in diabetes2 is not influenced by specialist consultant. Our results differ by those reported by the meta-analysis because of our better adjustment for prognostic and confounding factors. Most of diabetes 2 patients should be entrusted with confidence to primary care facilities.

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APPENDIX A: EVALUATION OF BONORA'S META-ANALYSIS TROUGH AMSTAR II[8] CHECK-LIST.

TABLE A1 - AMSTAR'S ITEMS	judgment	comment
1. Was an 'a priori' design provided? The research question and inclusion criteria should be established before the conduct of the review.	□ Yes X No □ Can't answer □ Not applicable	None protocol was published
2. Was there duplicate study selection and data extraction? There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.	X Yes □ No □ Can't answer □ Not applicable	Study selection and data extractions were performed independently by two authors
3. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.	□ Yes X No □ Can't answer □ Not applicable	Was explored Only MEDLINE; the search strategy used only three free-text keyword; were considered only published data (none research in the grey literature, none personal communication with the authors of the researches that were recruited; none handsearching)
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language etc.	X Yes □ No □ Can't answer □ Not applicable	In Supplmentary Table 2 the authors state that were included in their research only individual researchs studies
5. Was a list of studies (included and excluded) provided?	□ Yes X No	The authors provide only a list of the included studies

A list of included and excluded studies should be provided.	□ Can't answer □ Not applicable	
6. Were the characteristics of the included studies provided? In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analyzed e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.	X Yes □ No □ Can't answer □ Not applicable	Table 1 reports some characteristics of the studies that were included
7. Was the scientific quality of the included studies assessed and documented? 'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.	X Yes □ No □ Can't answer □ Not applicable	Supplementary table 3s illustrates the analysis of the quality of the included studies based on Newcastle-Ottawa quality assessment scale for observational cohort studies
8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.	□ Yes X No □ Can't answer □ Not applicable	The authors limited themselves to compiling the checklist used for the evaluation of the quality of individual studies without commenting on the extreme lack of adjustments for prognostic and confounding factors. In no way did the quality of the studies influence the discussion of the results of the meta-analysis
9. Were the methods used to combine the findings of studies appropriate? For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi-squared test for homogeneity, I^2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?).	□ Yes X No □ Can't answer □ Not applicable	The authors have pooled results using both adjusted and unadjusted efficacy measures. The latter do not make any sense in a meta-analysis of observational studies because their weighted average will present unpredictably distorted results because of the bias burdening the individual researchs. The authors applied publication bias search techniques with insufficient statistical power (the meta-analysis only had three studies while at least ten were needed [Higgins 2011, Cochrane Handbook]). The meta-analysis considered in the same pooling efficacy results expressed both as odds ratio and as the risk ratios. The two measures do not express the same effect when the endpoint, as in this case, is not a rare or very rare event (the basal mortality rates of the Zoppini[5]'s study, for example, correspond to 6.08 per cent person-years). Finally, authors imputed an errata RR [RR=0.87 (0.73-1.04)]

		for the results of Bruno[6], because they were confused by the table 1 of that publication, in which are illustrated mortality Risk Ratios *only* adjusted for age, sex and duration of diabetes. In main text of that article are instead well explained the results of *another more complex analysis*, i.e. of a multivariate model adjusted for age, sex, hypertension, smoking, ldl-cholesterol , triglycerides, Ghb , microalbuminuria , fibrinogen , antidiabetic and antihypertensive treatments , where was produced a mortality Risk Ratio of RR=0.81 (0.67-0.98).
10. Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).	□ Yes □ No □ Can't answer X Not applicable	This item of quality is not applicable because the analysis of publication bias does not be appropriate in presence (as is case) of a too small number of studies included in the meta-analysis
11. Was the conflict of interest stated? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.	X Yes □ No □ Can't answer □ Not applicable	

APPENDIX B: RISK OF BIAS OF TRIALS RECRUITED BY BONORA'S META-ANALYSIS EVALUATED TROUGH ROBINS-I[9] METHOD.

TABLE B1: ZOPPINI[5]'S RESEARCH

	Signalling questions	**Description**	**Response options**
1. Bias due to confounding			
	1.1 Is there potential for confounding of the effect of intervention in this study? **If N/PN to 1.1:** the study can be considered to be at low risk of bias due to confounding and no further signalling questions need be considered	We consider as main confounders: a) severity of the diabetes disease , in that can influence both the outcome (death) and "to have be sent to specialist consultation" b) comorbidity status of the patient, a pre-intervention prognostic factor that can influence also the exposition (the more the patient is ill, the less he is sent by the specialist). Note: the latter, being a pre-intervention covariate, must be considered into the Confounding bias domain (=not into the Selection bias domain)[8]. Authors did not make these adjustments.	YES
	If Y/PY to 1.1: determine whether there is a need to assess time-		

	varying confounding:		
	1.2. Was the analysis based on splitting participants' follow up time according to intervention received? **If N/PN**, answer questions relating to baseline confounding (1.4 to 1.6) **If Y/PY**, go to question 1.3.	The exposition to insulin was recorded in basal condition, that is in the cross-sectional phase of the Verona Diabetes Study[20]. So, the analysis can be considered as an ITT-like observational approach[8]	NO
	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome? **If N/PN**, answer questions relating to baseline confounding (1.4 to 1.6) **If Y/PY**, answer questions relating to both baseline and time-varying confounding (1.7 and 1.8)	-	NA
	Questions relating to baseline confounding only		
	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	Authors did adjust their analysis by Multivariate Cox regression for "to be exposed to insulin" but they have not consider in the same model any indicator of comorbidity	NO
	1.5. **If Y/PY to 1.4**: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	See above; YES for insulin exposition; NA for the comorbidity-indicator (lacking)	NA
	1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	No	NA
	Questions relating to baseline and time-varying confounding		
	1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?		NA
	1.8. **If Y/PY to 1.7**: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?		NA
	Risk of bias judgement	At least one know important domain was not appropriately controlled for	**SERIOUS**
	Optional: What is the predicted direction of bias due to confounding?		-

2. Bias in selection of participants into the study			
	2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? **If N/PN to 2.1:** go to 2.4	The Cochrane tool classifics into that domain of bias only selections of the participants made after the exposition[8]. The analysis of mortality in Zoppini[5]'s research started from the diagnosis of diabetes made in the Verona Diabetes Study[20]. In that research the cohort was represented by persons diagnosed as diabetics a) by general practitioners b) by the diabetic clinics c) from drugs use (i.e. from administrative datasets). In Zoppini[5]'s research the exposition to specialist consultant was definied by "to have been diagnosed as diabetic patient by the diabetic clinics". In that manner the selection of partecipants have regarded patients already exposed to specialist consultant (*prevalent users-like design*): the selection of diabetics that don't haved the outcome have so excluded the patients prematurely deceased.	YES
	2.2. **If Y/PY to 2.1**: Were the post-intervention variables that influenced selection likely to be associated with intervention? 2.3 **If Y/PY to 2.2**: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?		NA
	2.4. Do start of follow-up and start of intervention coincide for most participants?	The exposition was recorded in basal conditions. In fact the authors examined the cohort of Verona Diabetes study[20], being identified as 'exposed' the 4047 diabetic patients originally identified by the diabetic clinics (ITT –like observational approach). Start of intervention predates so start of follow-up (prevalent users design[29]), being the exposed patients a potentially more resistant group to fatal endpoints	NO
	2.5. **If Y/PY to 2.2 and 2.3, or N/PN to 2.4**: Were adjustment techniques used that are likely to	None done	NA

	correct for the presence of selection biases?		
	Risk of bias judgement	Selection into the study was related both the intervention and to outcome	**SERIOUS**
	Optional: What is the predicted direction of bias due to selection of participants into the study?		
3. Bias in classification of interventions			
	3.1 Were intervention groups clearly defined?	Authors state that '4047 patients regularly attended the diabetes centres' but they they do not explain what this means. In others terms, some patients can be followed both by the general practitioners and by the diabetic clinic.	No
	3.2 Was the information used to define intervention groups recorded at the start of the intervention?	Yes (see above)	Y
	3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	The intervention status was classified ex post (see above): so that was not possible	NO
	Risk of bias judgement	We judge the risk of bias low in that the definition of the intervention practically coincides with a dichotomous variable, being also the approach ITT-like (see above). Despite the classification of the intervention is not clear, we don't have reasons for to suspect a differential misclassification (i.e.: affected by knowledge of the outcome or risk of the outcome)	Low
	Optional: What is the predicted direction of bias due to classification of interventions?		
4.Bias due to deviations from intended interventions			
	If your aim for this study is to assess the effect of assignment to intervention, answer questions 4.1 and 4.2		
	4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	It cannot be know if patients followed by specialists were better cured for other comorbidity than diabetes respect to patients followed by the general practitioners because none information is available.	NI
	4.2. **If Y/PY to 4.1**: Were these deviations from intended		NA

	intervention unbalanced between groups *and* likely to have affected the outcome?		
	If your aim for this study is to assess the effect of starting and adhering to intervention, answer questions 4.3 to 4.6		
	4.3. Were important co-interventions balanced across intervention groups?		NA
	4.4. Was the intervention implemented successfully for most participants?		NA
	4.5. Did study participants adhere to the assigned intervention regimen?		NA
	4.6. **If N/PN to 4.3, 4.4 or 4.5**: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?		NA
	Risk of bias judgement		**NO INFORMATION**
	Optional: What is the predicted direction of bias due to deviations from the intended interventions?		
5. Bias due to missing data			
	5.1 Were outcome data available for all, or nearly all, participants?	446/7148 patients that were recruited (6.2%) was lost to follow-up	NO
	5.2 Were participants excluded due to missing data on intervention status?	The 446 patients lost to follow-up were not excluded by analysis in that authors did in practice a analysis type " best scenario ". In fact they were considered alive (= no having the outcome) at the end of the study. Authors don't explain how many of these patients were in the exposition arm and how many in the control arm.	NI
	5.3 Were participants excluded due to missing data on other variables needed for the analysis?	It can not be know	NI
	5.4 **If PN/N to 5.1, or Y/PY to 5.2 or 5.3**: Are the proportion of participants and reasons for missing data similar across interventions?	It can not be know (see above)	NI
	5.5 **If PN/N to 5.1, or Y/PY to 5.2 or 5.3**: Is there evidence that results were robust to the presence of missing data?	It does not simple understand if a loss of follow-up of 6.2% of the recruited cohort was able to seriously distort the results of that research. In fact[30] while for continuous endpoints it is unlikely	PY

		that a notable bias will result from missing data less than 5% of outcome data, for dichotomous endpoints the proportion requires is directly linket to the risk of the event, that is in this case not trivial (MR=5.339 for 100py for the entire cohort). So, it appears unlikely that the analysis have removed the risk of bias arising from the missing data, despite that in this case was present a not very high proportion of missing outcome-data.	
	Risk of bias judgement	The authors should have done a sensitivity analysis considering both "best case scenarios" and "worst case scenarios" in both arms in order to evaluate the robustness of their conclusions.	**MODERATE**
	Optional: What is the predicted direction of bias due to missing data?		-
6.Bias in measurement of outcomes			
	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	Outcome death was recorded by record linkage with administrative databases	NO
	6.2 Were outcome assessors aware of the intervention received by study participants?		NA
	6.3 Were the methods of outcome assessment comparable across intervention groups?	See above	YES
	6.4 Were any systematic errors in measurement of the outcome related to intervention received?	no	NO
	Risk of bias judgement		**LOW**
	Optional: What is the predicted direction of bias due to measurement of outcomes?		
7.Bias in selection of the reported result			
	Is the reported effect estimate likely to be selected, on the basis of the results, from...		
	7.1. ... multiple outcome *measurements* within the outcome domain?	No, authors report both all-cause and specific-cause deaths	NO
	7.2 ... multiple *analyses* of the intervention-outcome relationship?	No, authors based their mains results only on the results by a multivariate Cox model , the main analysis	NO

	7.3 ... different *subgroups*?	No, authors analysed the whole cohort	NO
	Risk of bias judgement		**LOW**
	Optional: What is the predicted direction of bias due to selection of the reported result?		-
Overall bias			
	Risk of bias judgement	The study is judged to be at serious risk of bias in two important domain (selection bias and confounding bias) , being for the other domains at low risk (classification of interventions , measurement of outcomes , selection of the reported result) or at moderate risk (missing data) and being not possible judge it for the deviations from intended interventions because of lack of information	**SERIOUS**
	Optional: What is the overall predicted direction of bias for this outcome?		

TABLE B2: BRUNO[6]'S RESEARCH.

	Signalling questions	**Description**	**Response options**
1.Bias due to confounding			
	1.1 Is there potential for confounding of the effect of intervention in this study? **If <u>N/PN</u> to 1.1:** the study can be considered to be at low risk of bias due to confounding and no further signalling questions need be considered	We consider as main confounders: a) severity of the diabetes disease in that can influence both the outcome (death) and "to have be sent to specialist consultation" b) comorbidity status of the patient, a pre-intervention prognostic factor that can influence also the exposition (the more the patient is ill, the less he is sent by the specialist). Note: the latter, being a pre-intervention covariate, must be considered into the Confounding bias domain (=not into the Selection bias domain)[8]. Authors did not make these adjustments. Having a lot of clinical data, the authors should have correct for other important confounders as well , as education level, insitutionalization and education	YES

	If Y/PY to 1.1: determine whether there is a need to assess time-varying confounding:		
	1.2. Was the analysis based on splitting participants' follow up time according to intervention received? **If N/PN**, answer questions relating to baseline confounding (1.4 to 1.6) **If Y/PY**, go to question 1.3.	No, the exposition to specialist advice was recorded only at baseline	NO
	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome? **If N/PN**, answer questions relating to baseline confounding (1.4 to 1.6) **If Y/PY**, answer questions relating to both baseline and time-varying confounding (1.7 and 1.8)	-	NA
	Questions relating to baseline confounding only		
	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	The exposition to insulin was not considered as single covariate (at pg. 429 authors[6] cite to have generically adjusted 'for antidiabetic drugs in secondary analysis); nevertheless Ghb values were used in Cox model both as baseline and time-varying confounder: so, authors show to have adjusted for the severity of the diabetic disease. Nevertheless (see later) based on the ITT-observational approach of their research they should not made adjustments using that covariate also as a time dependent variable (as instead done). <u>Authors did not consider in the same model any indicator of overall comorbidity</u>. They considered in fact as covariates only some classical CHD risk factors (age, sex, hypertension, smoking, Ghb, microalbuminuria, fibrinogen, LDL-CL and TG – pg. 429[6]).	<u>NO</u>

	1.5. **If <u>Y/PY</u> to 1.4**: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	See above; YES for the severity of the diabetes; NI for the comorbidity-indicator (lacking)	NA
	1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	Authors considered Ghb values also as variable time-dependent: this does not be appropriate, because it represent a post exposition adjustment for a factor can be influenced by the same exposition	Yes
	Questions relating to baseline and time-varying confounding		
	1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?		NA
	1.8. **If <u>Y/PY</u> to 1.7**: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?		NA
	Risk of bias judgement	At least one know important domain was not appropriately controlled (that is: the level of comorbidity)	**SERIOUS**
	Optional: What is the predicted direction of bias due to confounding?		-
2.Bias in selection of participants into the study			
	2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? **If <u>N/PN</u> to 2.1:** go to 2.4	The Cochrane tool classified into that domain of bias only selections of the participants made after the intervention[8]. In that study 1565 patients with know diabetes were included as study population (source of the ascertainment: diabetes clinic, general practitioners, hospital discharges, prescriptions and sale records[6]). The study *has not a new-users design*, so start of follow up and start of intervention do not coincide. In this *prevalent-users approach* may have been exposed patients more resistant to fatal	YES

		outcomes because not yet dead.	
	2.2. **If Y/PY to 2.1**: Were the post-intervention variables that influenced selection likely to be associated with intervention? 2.3 **If Y/PY to 2.2**: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?		NA
	2.4. Do start of follow-up and start of intervention coincide for most participants?	The intervention was recorded in basal conditions (ITT –like observational approach)*	YES
	2.5. **If Y/PY to 2.2 and 2.3, or N/PN to 2.4**: Were adjustment techniques used that are likely to correct for the presence of selection biases?		NO
	Risk of bias judgement	Selection into the study was related to intervention and outcome	**SERIOUS**
	Optional: What is the predicted direction of bias due to selection of participants into the study?		
3.Bias in classification of interventions			
	3.1 Were intervention groups clearly defined?	Authors declare (pg. 429) that the control group was represented by people cared exclusively by their general practitioners.	Yes
	3.2 Was the information used to define intervention groups recorded at the start of the intervention?	Yes (see above)	Y
	3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	The intervention status was classified only according the source of the ascertainment of the diabetic disease (see above): so that was not possible	NO
	Risk of bias judgement	We judge the risk of bias be low in that the definition of the intervention practically coincides with a dichotomous variable, being also the intervention defined by ITT-observational approach (see above)	**LOW**
	Optional: What is the predicted direction of bias due to		

	classification of interventions?		
4.Bias due to deviations from intended interventions			
	If your aim for this study is to assess the effect of assignment to intervention, answer questions 4.1 and 4.2		
	4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	It cannot be know if patients followed by specialists were better cured for other comorbidity than diabetes respect to patients followed by the general practitioners because none information is available. The author adjusted only for antidiabetic and antihypertensive treatments in a secondary analysis –pg. 426[6]	NI
	4.2. **If Y/PY to 4.1**: Were these deviations from intended intervention unbalanced between groups *and* likely to have affected the outcome?		NA
	If your aim for this study is to assess the effect of starting and adhering to intervention, answer questions 4.3 to 4.6		
	4.3. Were important co-interventions balanced across intervention groups?		NA
	4.4. Was the intervention implemented successfully for most participants?		NA
	4.5. Did study participants adhere to the assigned intervention regimen?		NA
	4.6. **If N/PN to 4.3, 4.4 or 4.5**: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?		NA
	Risk of bias judgement		**NO INFORMATION**
	Optional: What is the predicted direction of bias due to deviations from the intended interventions?		
5.Bias due to missing data			
	5.1 Were outcome data available for all, or nearly all, participants?	Only 1/565 patients that were recruited was lost to follow-up (0.6 for thousand)	YES
	5.2 Were participants excluded due to missing data on intervention status?	If so, it would be trivial	PN
	5.3 Were participants excluded due to missing data on other variables needed for the analysis?	If so, it would be trivial	PN
	5.4 **If PN/N to 5.1, or Y/PY to 5.2**	Only one patients was lost to	NA

	or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?	follow-up (arm not know)	
	5.5 **If PN/N to 5.1, or Y/PY to 5.2 or 5.3**: Is there evidence that results were robust to the presence of missing data?	Securely	YES
	Risk of bias judgement	Data are complete	**LOW**
	Optional: What is the predicted direction of bias due to missing data?		-
6.Bias in measurement of outcomes			
	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	Outcome death was recorded by record linkage with administrative databases	NO
	6.2 Were outcome assessors aware of the intervention received by study participants?		NA
	6.3 Were the methods of outcome assessment comparable across intervention groups?	See above	YES
	6.4 Were any systematic errors in measurement of the outcome related to intervention received?	no	NO
	Risk of bias judgement		**LOW**
	Optional: What is the predicted direction of bias due to measurement of outcomes?		
7.Bias in selection of the reported result			
	Is the reported effect estimate likely to be selected, on the basis of the results, from...		
	7.1. ... multiple outcome *measurements* within the outcome domain?	No, authors reports both all-cause and CV-specific deaths	NO
	7.2 ... multiple *analyses* of the intervention-outcome relationship?	No, the mains result comes from the main analysis	NO
	7.3 ... different *subgroups*?	No, authors analysed the whole cohort	NO
	Risk of bias judgement		**LOW**
	Optional: What is the predicted direction of bias due to selection of the reported result?		-
Overall bias			
Risk of bias judgement		The study is judged to be at serious	**SERIOUS**

	risk of bias in two important domain (confounding bas and selection bias) , being for the other domains ad low risk (classification of interventions , missing data, measurement of outcomes , selection of the reported result) being finally not possible to judge it for the deviations from intended interventions because of lack of information	
Optional: What is the overall predicted direction of bias for this outcome?		

TABLE B3: BAVIERA[7]'S RESEARCH.

	Signalling questions	**Description**	**Response options**
1.Bias due to confounding			
	1.1 Is there potential for confounding of the effect of intervention in this study? **If N/PN to 1.1:** the study can be considered to be at low risk of bias due to confounding and no further signalling questions need be considered	We consider as main confounders: a) severity of the diabetes disease in that can influence both the outcome (death) and "to have be sent to specialist consultation" b) comorbidity status of the patient, a pre-intervention prognostic factor that can influence also the exposition (the more the patient is ill, the less he is sent by the specialist). Note: the latter, being a pre-intervention covariate, must be considered into the Confounding bias domain (=not into the Selection bias domain)[8]. Authors did not make these adjustments.	YES
	If Y/PY to 1.1: determine whether there is a need to assess time-varying confounding:		
	1.2. Was the analysis based on splitting participants' follow up time according to intervention received? **If N/PN**, answer questions relating to baseline confounding (1.4 to 1.6) **If Y/PY**, go to question 1.3.	No, the exposition to specialist advice was recorded only in a cross design trough a logistic regression model	NO
	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome? **If N/PN**, answer questions relating to baseline confounding (1.4 to 1.6) **If Y/PY**, answer questions relating to both baseline and time-varying	-	NA

	confounding (1.7 and 1.8)		
	Questions relating to baseline confounding only		
	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	No adjustment was made: neither for the severity of the diabetes disease nor for the concomitant co-morbidity	NO
	1.5. **If Y/PY to 1.4**: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	No	No
	1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	No	No
	Questions relating to baseline and time-varying confounding		
	1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?		NA
	1.8. **If Y/PY to 1.7**: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?		NA
	Risk of bias judgement	For at least two know important domain was not appropriately controlled for (that is: for the severity of the disease and for the level of comorbidity); the study, adjusted only for age and sex, appears too problematic to provide any useful evidence of the effects of the exposition	**CRITICAL**
	Optional: What is the predicted direction of bias due to confounding?		-
2.Bias in selection of participants into the study			
	2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? **If <u>N/PN</u> to 2.1:** go to 2.4	The Cochrane tool classified into that domain of bias only selections of the participants made after the intervention[8]. In that study the analysis is cross-sectional based (was used an logistic models for data recorded in year 2012). The study has so (obviusly) not a *new-users* design but a *prevalent-user* design, so start of follow up and start of intervention do not coincide. In this prevalent-users approach may have been exposed the patients more resistant to fatal	YES

		outcomes because not yet dead.	
	2.2. **If Y/PY to 2.1**: Were the post-intervention variables that influenced selection likely to be associated with intervention? 2.3 **If Y/PY to 2.2**: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?		NA
	2.4. Do start of follow-up and start of intervention coincide for most participants?	Cross-sectional design	NA
	2.5. **If Y/PY to 2.2 and 2.3, or N/PN to 2.4**: Were adjustment techniques used that are likely to correct for the presence of selection biases?	This item is not applicable because the study is probably lacking of selection bias	NA
	Risk of bias judgement	Selection into the study was related both the intervention and to outcome	**SERIOUS**
	Optional: What is the predicted direction of bias due to selection of participants into the study?		
3.Bias in classification of interventions			
	3.1 Were intervention groups clearly defined?	Authors declare that the control group was represented by people not followed by diabetic clinics	Yes
	3.2 Was the information used to define intervention groups recorded at the start of the intervention?	Item not applicable in a cross sectional design	NA
	3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	No	NO
	Risk of bias judgement	We judge the risk of bias low in that the definition of the intervention practically coincides with a dichotomous variable based on secure data (administrative dataset)	**LOW**
	Optional: What is the predicted direction of bias due to classification of interventions?		
4.Bias due to deviations from intended interventions			
	If your aim for this study is to assess the effect of assignment to intervention, answer questions 4.1 and 4.2		
	4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	Item not applicable in a cross-sectional design	NA
	4.2. **If Y/PY to 4.1**: Were these deviations from intended intervention		NA

	unbalanced between groups *and* likely to have affected the outcome?		
	If your aim for this study is to assess the effect of starting and adhering to intervention, answer questions 4.3 to 4.6		
	4.3. Were important co-interventions balanced across intervention groups?		NA
	4.4. Was the intervention implemented successfully for most participants?		NA
	4.5. Did study participants adhere to the assigned intervention regimen?		NA
	4.6. **If N/PN to 4.3, 4.4 or 4.5**: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?		NA
	Risk of bias judgement		**NO INFORMATION**
	Optional: What is the predicted direction of bias due to deviations from the intended interventions?		
5.Bias due to missing data			
	5.1 Were outcome data available for all, or nearly all, participants?	Item not applicable in a cross-sectional design	NA
	5.2 Were participants excluded due to missing data on intervention status?	Item not applicable in a cross-sectional design	NA
	5.3 Were participants excluded due to missing data on other variables needed for the analysis?	Item not applicable in a cross-sectional design	NA
	5.4 **If PN/N to 5.1, or Y/PY to 5.2 or 5.3**: Are the proportion of participants and reasons for missing data similar across interventions?	Item not applicable in a cross-sectional design	NA
	5.5 **If PN/N to 5.1, or Y/PY to 5.2 or 5.3**: Is there evidence that results were robust to the presence of missing data?	Item not applicable in a cross-sectional design	NA
	Risk of bias judgement	Data are complete	**NOT APPLICABLE**
	Optional: What is the predicted direction of bias due to missing data?		-
6.Bias in measurement of outcomes			
	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	Outcome death was recorded by record linkage with administrative databases	NO
	6.2 Were outcome assessors aware of the intervention received by study participants?		NA
	6.3 Were the methods of outcome assessment comparable across intervention groups?	yes	YES
	6.4 Were any systematic errors in measurement of the outcome related to	no	NO

	intervention received?		
	Risk of bias judgement		Low
	Optional: What is the predicted direction of bias due to measurement of outcomes?		
Bias in selection of the reported result			
	Is the reported effect estimate likely to be selected, on the basis of the results, from...		
	7.1. ... multiple outcome *measurements* within the outcome domain?	No, the fatal endpoint was recorded into a subgroup of a research organised for other purposes (to compare many outcome between diabetic and not diabetic people)	NO
	7.2 ... multiple *analyses* of the intervention-outcome relationship?	No, the main results comes from the main analysis into a subgroup of a research organised for other purposes (to compare many outcome between diabetic and not diabetic people)	NO
	7.3 ... different *subgroups*?	No, authors analysed the whole cohort into a subgroup of a research organised for other purposes (to compare many outcome between diabetic and not diabetic people)	NO
	Risk of bias judgement		**LOW**
	Optional: What is the predicted direction of bias due to selection of the reported result?		-
Overall bias			
Risk of bias judgement		The study is judged to be at critica risk of bias in one important domain (confounding bias) and at serious risk for another (selection bias) , being for the other domains ad low risk (classification of interventions , measurement of outcomes , selection of the reported result) being not possible judge it for the deviations from intended interventions because of lack of information and being not applicable the evaluation of the missing data.	**CRITICAL**
Optional: What is the overall predicted direction of bias for this outcome?			

TABLE B 4: OUTCOME MORTALITY – OVERALL RISK OF BIAS EVALUATION TROUGH ROBINS-I[8] CHECK LIST.

DOMAINS	ZOPPINI[5]	BRUNO[6]	BAVIERA[7]
1.Bias due to confounding	Serious	Serious	Critical
2.Bias in selection of participants into the study	Serious	Serious	Serious
3.Bias in classification of interventions	Low	Low	Low
4.Bias due to deviations from intended interventions	No information	No information	No information
5.Bias due to missing data	Moderate	Low	Not Applicable
3.Bias in measurement of outcomes	Low	Low	Low
7.Bias in selection of the reported result	Low	Low	Low
OVERALL JUDGMENT OF RISK OF BIAS	SERIOUS	SERIOUS	CRITICAL

All observational researches recruited in Bonora's meta-analysis are burdened by serious/critical pitfalls; our judgment is based on rigorous respect of ROBIN-I[8] recommendations

APPENDIX C – THE MILLEINRETE DATASET

MilleinRete[3] is a database which collects clinical data of patients assisted by 69 doctors from Veneto (Italy).
All doctors are members of SIMG (Italian Society of General Medicine and Primary Care) and users of the same professional software (Millewin®).
On 12/31/2017 MilleinRete contains 152510 electronic medical records.
All doctors are connected electronically and automatically with a database physically located in Florence and managed by the company Dedalus / Millennium https://www.millewin.it/
All patients assisted by these doctors have given to their General Practitionier and in accordance with Italian law the consent to anonymously manage their clinical data for research or clinical audit purposes. In Italy, researches on datasets of anonymised historical data do not require the prior approval of an Ethics Committee.
MilleinRete is managed by the scientific organization SvEMG (Scuola Veneta di Medicina Generale www.svemg.it) and the scientific responsible of data analysis is the corresponding author of this article, which has competences developed into academic field in terms of epidemiological research and statistical analysis (AB).
MilleinRete has collaborated with the Regional Epidemiological Service of the Veneto region (within the framework of the National Health System) for investigations about the prevalence of chronic diseases and for researches financed by the Public Structure.
The technical aspects of anonymized data extraction relevant to the variables necessary for the research initiatives organized by SvEMG are entrusted by SvEMG to the company Genomedics https://www.genomedics.it/ , which interfaces with Dedalus/Millennum to organize the extraction. The anonymized data is then sent electronically to SvEMG in .dta format.
SvEMG then independently carries out the statistical processing relevant to the research and audit initiatives carried out from time to time.

The Appendix C Table 1 briefly illustrates the type of variables currently available in MilleinRete.

Appendix Table 1: MilleinRete dataset data - summary information.

Data class	<date> variables	Other variables	Notes
General patient data	date of birth ,date of first contact with the doctor (lifetime), date of the doctor's revocation, date of death, date of the last contact with the doctor in the index year	Sex, living habits, education, type of employment, exemption from the medical ticket for pathologies or low income, main data on family history	anonymized
Chronic diseases	date of first onset of the disease		ICD9 codes available

Drug consumption	Not available	Number of packages prescribed in the index year	ATC codes available
Laboratory data	Not available	Number of analyses prescribed in the index year Average value recorded in the index year and / or last value recorded in the index year	codifications of the Veneto Region available
Instrumental examinations	Not available	Number of examination prescribed in the index year	codifications of the Veneto Region available
Specialist advices	Not available	Number of advices prescribed in the index year	codifications of the Veneto Region available

APPENDIX D – VARIABLES USED IN OUR ANALYSES

Table D1: Variables that we used in our models of analysis.

Variable	definition	type of data	Period of analysis	notes
All cause death	outcome	Date of death	From 1/1/2009 to 31/12/2017	Outcome
Specialist advice	exposure	At least one visit in 3 last years	From 1/1/2006 to 31/12/2008	Exposition (basal variable in a ITT-like approach)
		Number of visits in 3 last years	From 1/1/2006 to 31/12/2008	Basal variable
Age	covariate	Years	From birth to 06/30/2008	Basal variable
Sex	covariate	Male/Female		Basal variable
Insulin	covariate	At least one prescription ATC A10A%	From 1/1/2008 to 31/12/2008	Basal variable
statins	covariate	At least one prescription ATC C10AA% C10B%	From 1/1/2008 to 31/12/2008	Basal variable
metformin	covariate	At least one prescription ATC A10BA02	From 1/1/2008 to 31/12/2008	Basal variable
Ghb	covariate	Mean values registred in index year (%)	From 1/1/2008 to 31/12/2008	Basal variable
LDL-CL	covariate	Mean values registered in index year (mg/dl)	From 1/1/2008 to 31/12/2008	Basal variable
TG	covariate	Mean values registered in index year (mg/dl)	From 1/1/2008 to 31/12/2008	Basal variable
Charlson score	covariate	Comorbidity data	From 1/1/2008 to 31/12/2008	Basal variable
Diabetes duration	covariate	years	From date of onset to 31/12/2008	Basal variable

APPENDIX E – ANALYSIS OF THE GOODNESS OF FIT OF COX MODELS 1 AND 3, ADJUSTED WITH ALL COVARIATES

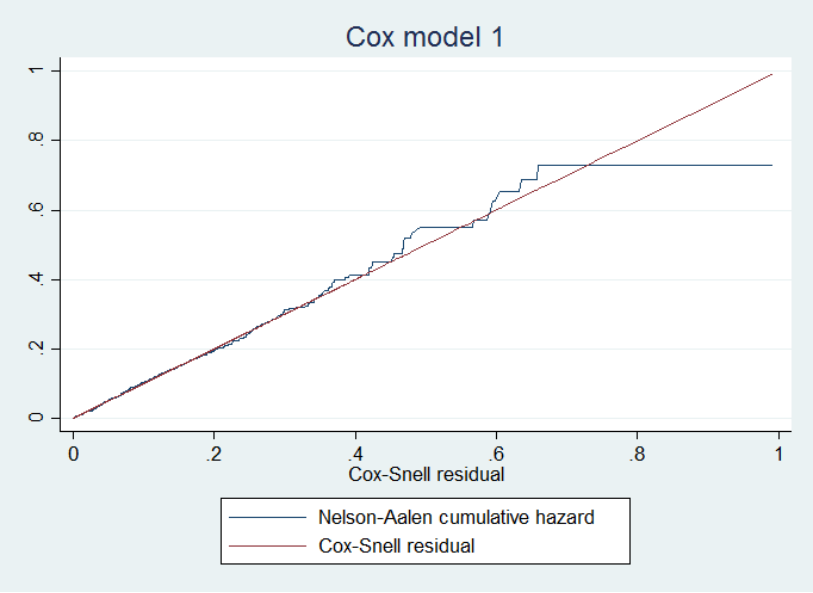

Figure E1- Cox Model 1: (N= 2686 diabetics without missing data i.e. 41.1% of the whole sample): the Nelson-Aalen cumulative hazard estimator is plotted for Cox-Snell residuals[15]. Under optimal conditions the two lines should overlap; nevertheless some variability about the 45 grade line can still be expected, particularly in the right tail of the graph; this is due to the reduced effective sample caused by prior failures and censoring. In overall the graph schows a pretty good goodness of fit [See also the example pg 193 figure 11.8 in: Cleves MA, Gould WW and Gutierrez R: An introduction to survival analysis using StataR –Stata Press 2004 ISBN 1-881228-84-3]

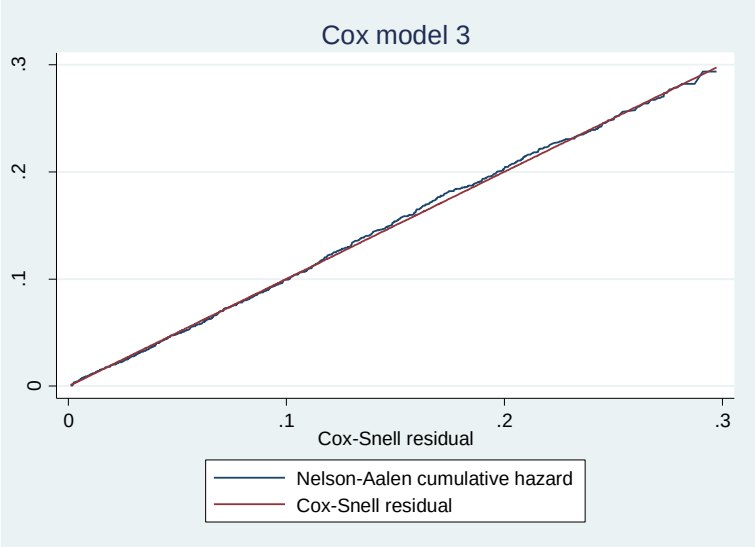

Figure E2- Cox Model 3: (N=5797 diabetics i.e. 88.8% of the whole sample): the Nelson-Aalen cumulative hazard estimator is plotted for Cox-Snell residuals[15]. Under optimal conditions the two lines should overlap. The graph shows so an excellent goodness of fit.

APPENDIX F- ANALYSIS OF PATIENTS EXCLUDED BY THE COX MODEL 1 BECAUSE OF MISSING DATA

Table F1: Values of the covariates in the patients excluded and respectively included in the Multivariate Cox Regression of Table 1 of main text.

	Diabetic Patients excluded by the Multivariate Cox model one	Diabetic Patients included by the Multivariate Cox model one	All Diabetic Patients
Number (n)	3844	2686	6530
Deceased n (%)	697 (18.13%)	395 (14.71%)	1092 (16.72%)
Aged65+ n (%)	2488 (64.72%)	1713 (63.78%)	4201 (64.33%)
Male n (%)	2003 (52.20%)	1504 (56.04%)	3507 (53.78%)
Treated with insulin n (%)	578 (15.04%)	367 (13.66%)	945 (14.47%)
Treated with statins n (%)	1073 (27.91%)	1261 (46.95%)	2334 (35.74%)
Treated with metformin n (%)	923 (24.01%)	1122 (41.77%)	2045 (31.32%)
Glycosylated Hemoglobin n (mean value express in pc)	1342 (7.28 pc value)	2686 (7.10 pc value)	4028 (7.16 pc value)
LDL-Cholesterol n (mg/dl mean value)	744 (117.3 mg/dl)	2686 (113.5 mg/dl)	3430 (114.3 mg/dl)
Triglycerides n (mg/dl mean value)	1086 (162.2 mg/dl)	2686 (138.7 mg/dl)	3772 (145.5 mg/dl)
To have a Charlson score≥4 n (%)	1165 (30.31%)	742 (27.62%)	1907 (29.2 %)
Duration of diabetes n (years)	3111 (13.69 years)	2686 (13.93 years)	5797 (13.80 years)
Having been sent to none specialist visit n (%)	2316 (60.25%)	1125 (41.88%)	3441 (52.70%)
Having been sent to one specialist visit n (%)	499 (12.98%)	448 (16.68%)	947 (14.50%)
Having been sent to two or more specialist visits n (%)	1029 (26.77%)	1113 (41.44%)	2142 (32.80%)
Number of contacts with the practitioners in 2008 n (mean)	3844 (18.2)	2686 (22.19)	6530 (19.8)
Number of ospedalizations in geriatric setting in 2008 n (mean)	3844 (0.012)	2686 (0.004)	6530 (0.009)
Number of ospedalizations in medical setting in 2008 n (mean)	3844 (0.051)	2686 (0.023)	6530 (0.039)

Three thousand eight hundred forty four patients were automatically excluded by the Multivariate Cox Regression model 1 (see Table 2 of main text) because lacking of some of the covariates used in that model (i.e.: results of laboratory analyses).

So, it appear important to indagate about their general characteristics.

In that group were observed more deaths and less specialist advices than patients analyzed by the *Cox model 1*; they also appear less treated, sicker and characterized by a worse metabolic control. The mean number of annual contacts with the general practitioner shows to be lower but the number of hospitalizations show be higher respect to patients that were analyzed.

We cannot exclude that many of these diabetics characterized by a lower number of analyses could be institutionalized people, having so a lower probability that their data are registered in their medical records

We addressed the problem of missing patients by analyzing these trough some alternative adjustment-approaches, ie by calculating a propensity score and using then it in matched ATE analyzes .In the calculation of the propensity score we excluded in fact the laboratory analyzes, thus limiting the number of patients excluded from the Cox Model 1 for missing data

*See **Appendix G** for the ATE PS-matched analyses made on the whole sample and **Appendix H** for the same analysis restricted to patients insulin-treated. For the alternative Cox models adjusted trough Propensity Score : see the main text for the analyses made on the whole sample and **Appendix H** for those restricted to patients insulin-treated)*

APPENDIX G- ANALYSES BASED ON PROPENSITY SCORE CALCULATION

A propensity Score defines in our study the probability to be exposed to specialist advice.

We have calculate the Propensity Score[17] for each diabetic patient trough a logistic regression model in which the outcome was the logodds of be

exposed to specialistic visit and the covariates were: be aged 65+, be sick (Charlson score ≥4), have been exposed to insulin in year 2008, have been exposed to metformin in year 2008, have been exposed to statins in year 2008, the duration of diabetes disease (number of years) (SEE tables G1 and G2). The number of covariates used for this calculation is lower than that used for the adjustments in the Cox Model 1 and in the Cox Model 3 and laboratory values was excluded in that have been excluded laboratory values. This allowed to extend the analysis to a group of patients greater than the one considered in the two Cox models, in which the subjects with missing laboratory data were automatically dropped

We used Propensiy scores in two analytical approaches

A-Propensity Score used in a matched analysis based on Average Treatment Effect (ATE)[16]

Propensity-score matching (PSM) estimators impute the missing potential outcome for each subject by using an average of the outcomes of similar subjects exposed to the other treatment level.

A potential outcome (or counterfactual for that subject) is calculated for every not exposed subject and corresponds to the value that it should have if it were exposed to treatment. The "similarity" between subjects is based on the estimate for each patient the probability of be treated, known just as Propensity Score. The Average Treatment Effect (ATE)[16] is computed by taking the average of the difference between the observed and potential outcomes for each subject.

We matched every exposed patient to one control (=not exposed) characterized by a similar Propensity Score (Propensity Score tolerance: 0.00001).

Table G1 and G2 illustrate the goodness of the balancing in covariates between the matched patients; Fig G1 illustrates the goodness of the respective balancing in values of Propensity Scores.

Finally we calculated trough 11594 matched comparisons an Average Treatment Effect.

Must be noted that an ATE analysis conducted trough a "Propensity Score matching" creates a surrogate of the randomization[17], making the two groups strictly comparable for the values of the know covariates.

Our ATE analysis does not demonstrate any effect of the exposition to specialist consult on mortality risk (see main text)

Table G1: Matched Propensity Score Analysis – raw data Number of observations = 5797.

	Means		Variances	
	None specialist visit in the last three years (not exposed =controls)	Almost one specialist visit in the last three (exposed)	None specialist visit in the last three years (not exposed =controls)	Almost one specialist visit in the last three years (exposed)
N	3146	2651	3146	2651
To be aged65+	0.6697394	0.5767635	0.2212589	0.2441995
To have a Charlson score≥4	0 .2860776	0 .2719728	0.2043021	0 .1980783
To be treated with insulin	0 .0451367	0.2131271	0.0431131	0.1677672
To be treated with statins	0.2692308	0.4511505	0.1968081	0 .2477072
To be treated with metformin	0.2209154	0.4319125	0.1721665	0.2454567
Duration of diabetes	13.58401	14.05942	11.07956	12.37498

Table G1 illustrates the raw data (mean and variances) of the values of the selected covariates. Must be noted that 5797/6530 diabetic persons were recruited in that analysis (i.e. 88.8% of the whole sample). In the some analysis lacked 733 patients whose duration of diabetes disease was not know.

Table G2: Matched Propensity Score Analysis – analysis of the distribution of the values of the covariates Number of observations = 5797; Number of matched comparisons= 11594.

Table G2 – Matched Propensity Score Analysis – analysis of the distribution of the values of the covariates Number of observations = 5797; Number of matched comparisons= 11594				
	Standardized mean Differences (SMD) between exposed and not exposed		Variances Ratio (VR)	
	Raw	Matched	Raw	Matched
To be aged65+	-0.192728	-0.0289536	1.103682	1.015817
To have a Charlson score≥4	-0.0314457	0.0030775	0.9695363	1.003042
To be treated with insulin	0.5173466	-0.0099104	3.891332	0.97777
To be treated with statins	0.3858793	0.0025336	1.258623	1.00161
To be treated with	0.4617416	-0.0040796	1.425693	0.996785

metformin				
Duration of diabetes	0.1388254	0.0090322	1.11692	1.039707

Table G2 illustrates the Standardized Mean Differences (SMDs) and the ratios of the variances (VRs) between exposed and not exposed subjects in the raw and matched analysis respectively. The goodness of the balancing in the matched analysis is usually expressed by a SMD<0.10 and by a VR near to one. We can so seen that the balancing of the covariates shows be of excellent quality.

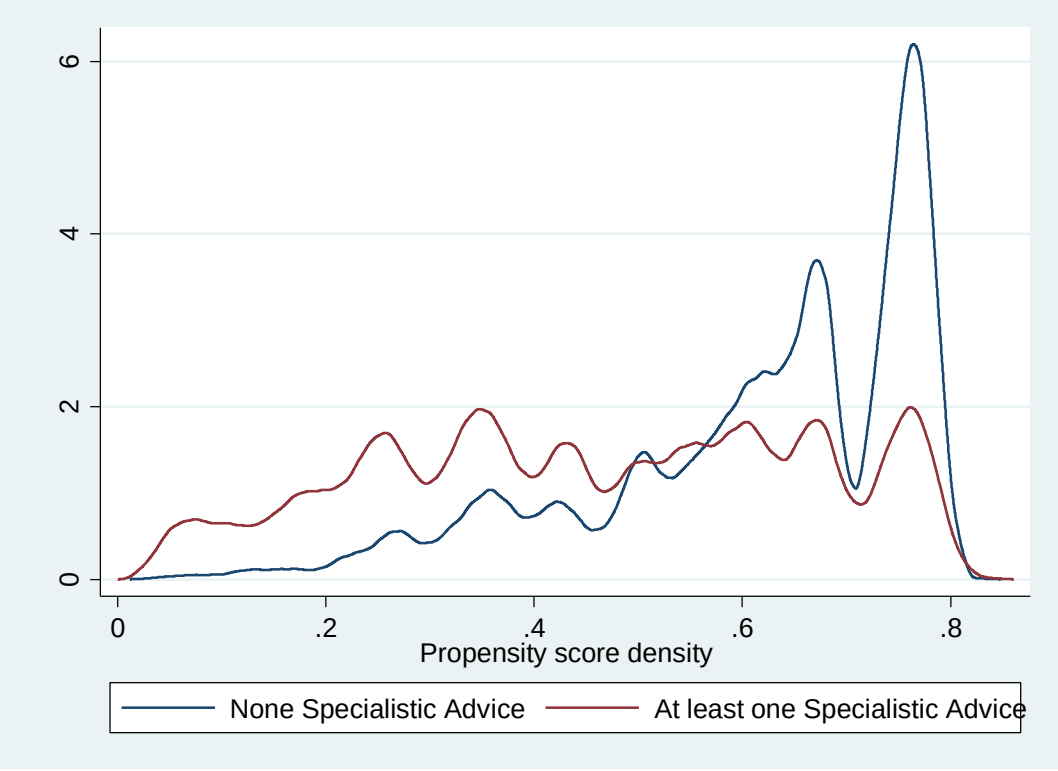

Figure G1: Distribution of the values of the Propensity Score between the exposed (=At least one Specialist Advice in the three last years) and the not exposed (=None Specialist Advice in the three last years).
The graph shows a good distribution. Neither of the two plots shows too much probability mass near 0 or 1. Thus there is no evidence that the overlap assumption is violated.
(see example on https://www.stata.com/manuals13/teteffectsoverlap.pdf)

We also used the same ATE approach in patients treated with insulin alone (see appendix H below)

B-Propensity Score used as covariate of a Cox model

We also used quantiles of propensity scores[17] as adjustment-covariate in classical Cox Models (Table 1B and 2B - see main text) . These models were bivariate analyses in which the duration of diabetes was not considered in the calculation of the propensity score but was instead added to the model as an independent covariate. This was justified by statistical requirements related to the search of the optimal "goodness of fit".

APPENDIX H: ANALYSES DONE ON A RESTRICTED DESIGN

We explored the relationship between to be exposed to specialist advice and risk of death also in a restricted analysis (see main text) i.e. in a cohort of insulin-treated patients.

In the cohort of diabetic patients treated with insulin alone (restricted design) we launched three types of analysis: A) a Cox model (Cox model 3) adjusted with all the covariates used in main analysis (Cox model 1 - see main text) B. a Cox model (Cox model 4) adjusted with propensity score (see main text) C) a. Matched analysis based on Average Treatment Effect (ATE) using Propensity Score as matching-covariate

A.Cox Model 3 (all covariates – adjusted in a restricted design) (Table 1 2A)

Table H1 illustrates the results of the Cox Model launched with the same covariate used in the Model 1

Table H1 – Cox model 3 : Analysis restricted to 367 diabetics assuming insuline

Covariates[2]	Hazard Ratio (CI 95%)	p
To be aged65+	**3.57 (1.71-7.49)**	**0.001**
To be male	-	-
To be treated with insulin	na	na
To be treated with statins	**0.61 (0.40-0.94)**	**0.026**
To be treated with metformin	**0.47 (0.28-0.80)**	**0.005**
Glycosylated Hemoglobin (for each 1% of increment)	1.01 (0.87-1.18)	0.830
LDL-Cholesterol (for each mg/dl of increment)	0.99 (0.99-1.00)	0.514
Triglycerides (for each mg/dl of increment)	-	-
To have a Charlson score≥4	**6.2 (2.63-14.5)**	**<0.0001**
Duration of diabetes (for each additional year)	1.03 (0.97-1.08)	0.247
Having been sent to one specialist visit	0.79 (0.34-1.81)	0.589
Having been sent to two or more specialist visits	0.82 (0.45-1.49)	0.518
Interaction (be aged65+)#(have a Charlson score≥4)	**0.20 (0.07-0.53)**	**0.001**

In Cox model 3 were analyzed only 367/954 insulin-treated diabetics for the same reasons descripted above (587 of these, i.e. 61.5% were lacking of laboratory values in different combinations). Also that model does not demonstrate any association between to be exposed to specialist advice and the risk of death. In that restricted analysis, instead as in the Cox model one to assume statins shows be a protective condition. The consistency of that model shows be good (Pregibons test z 0.14 p=0.888; Test for Schoenfelds residuals chi2 9.08 df 10 p=0.5248).

B.Cox Model 4 (propensity score adjusted in a restricted design) (Table 1 2B)

A Cox model 4 applied to 707 insulin-treated diabetics using as covariates both the PS values in quintiles[17] and the length of diabetic disease does not demonstrate, again, any association between to be exposed to specialist advice and the risk of death: HR=0.73 (0.53-1.00). It Should be noted nevertheless that the result was this time toward benefit and at limit of the statistical significance; the consistency of the model was also good (Pregibons test z -0.04 p 0.967; Test for Schoenfeld residuals: chi2 8.25 df 6 p=0.2206).

C. Propensity score used as matching-covariate in a matched analysis based in restricted design on Average Treatment Effect (ATE) (Table 1 3B)

In coherency with the reasons illustrated in main text for the main analysis (Cox model 1) we launched also in the restricted design an ATE[16] approach based on a Propensity Score[17] matching. Table H2 and H3 and Figure H1 illustrate the goodness of the balancing obtained in the matching process.

We have calculate the Propensity Score for each diabetic patient trough a logistic regression model in which the outcome was the logodds of be exposed to specialistic visit and the covariates were: be aged 65+, be sick (Charlson score ≥4), have been exposed to insulin in year 2008, have been exposed to metformin in year 2008, have been exposed to statins in year 2008. The duration of diabetes disease was not considered in this calculation because it caused imbalances in the pattern of covariates.

Table H2: Matched Propensity Score Analysis restricted to diabetics insulin-treated – raw data Number of observations = 945

	Means		Variances	
	None specialist visit in the last three years (not exposed =controls)	Almost one specialist visit in the last three (exposed)	None specialist visit in the last three years (not exposed =controls)	Almost one specialist visit in the last three years (exposed)
N	179	766	179	766
To be aged65+	0.7430168	0.618799	0.1920156	0.2361952
To have a Charlson score≥4	0.4636872	0.4138381	0.2500785	0.2428932
To be treated with insulin	NA	NA	NA	NA
To be treated with statins	0.2234637	0.4765013	0.1745025	0.2497739
To be treated with metformin	0.1452514	0.2650131	0.1248509	0.1950358
Duration of diabetes	Excluded	Excluded	Excluded.	Excluded

Table H2 illustrates the raw data (mean and variances) of the values of the selected covariates. Must be noted that in that analysis were recruited 945 /954 diabetic persons insulin-treated (i.e. the 99.0 % of the stratum of insulin-exposed patients). In that analysis lacked 9 patients because of missing data. The covariate *duration of diabetic disease* was excluded because caused some imbalance of the PS values

Table H3: Matched Propensity Score Analysis restricted to diabetics insulin-treated- analysis of the distribution of the values of the covariates -Number of observations = 945; Number of matched comparisons= 1890.

	Standardized mean Differences (SMD) between exposed and not exposed		Variances Ratio (VR)	
	Raw	Matched	Raw	Matched
To be aged65+	-0.2684541	4.63e-16	1.230083	1.0
To have a Charlson score≥4	-0.1004062	2.25e-16	0.9712681	1.0
To be treated with insulin	NA	NA	NA	NA
To be treated with statins	0.5493835	0	1.431348	1.0
To be treated with metformin	0.2994572	-1.29e-16	1.562149	1.0
Duration of diabetes	Excluded	Excluded	Excluded	Excluded.

Table H3 illustrates the Standardized Mean Differences (SMDs) and the Variance Ratios (VRs) between exposed and not exposed subjects in the raw and matched analysis respectively. The goodness of the balancing in the matched analysis is usually expressed by a SMD<0.10 and by a VR near to one. We can so seen that the balancing of the covariates shows be of excellent quality.

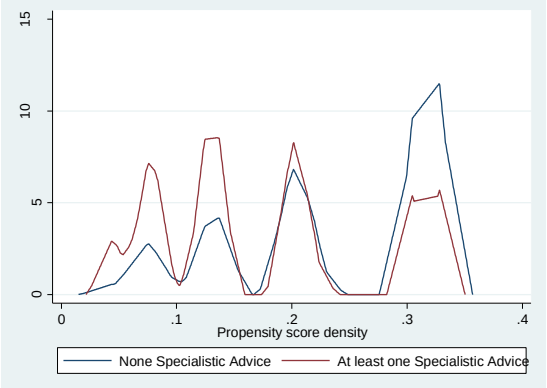

Figure H1: Distribution of the values of the Propensity Score between the exposed (=At least one Specialist Advice in the three last years) and the not exposed (=None Specialist Advice in the three last years) in the analysis restricted to insulin-treated diabetics. The graph shows an excellent distribution. Neither of the two plots shows too much probability mass near 0 or 1, and the two estimated densities have most of their respective masses in regions in which they overlap each other. Thus there is no evidence that the overlap assumption is violated.
(see example on https://www.stata.com/manuals13/teteffectsoverlap.pdf)

APPENDIX I- CALCULATION OF THE SAMPLE SIZE NECESSARY FOR A SPERIMENTAL RESEARCH

Table I1 illustrate the logical steps

If we hypothesize a basic mortality rate of 57.70 cases per 1000py (which corresponds to the basic risk of the Zoppini[5] study), an efficacy equal to RR = 0.81 (as observed by Bonora[1]), a reasonable rate of losses at the follow-up -up of 5%, a 5-year follow-up (reasonable for a mortality study), a 95% confidence, a 20% beta error, and a 70% recruitment compliance, the sample size of this research should coincide with 3254 diabetics. Such a research appears at first sight sustainable; however, the practical difficulties would be enormous. Firstly, it would be very difficult to randomly assign 1762 patients to the intervention group (=regular controls for 5 years at the Antidiabetic Center) and 1762 patients to the control group (=none control for 5 years at the Antidiabetic Center) recruiting prevalent cases of diabetes, given the foreseeable denial of many subjects to renounce the specialist path already in place. One could then think of enrolling only the incident cases, but these correspond (data not shown) to 6 new diagnoses done by the general practitioners every 1000 people a year.

The sample sizes would in that manner be hypertrophied, making it unthinkable to organize also a multi-centered study one.

In fact the population of adult (>14y) persons that in one year (recruitment period) will generate 3254 new cases of diabetes 2 corresponds to 58726 people. Assuming that in the general population the prevalence of ages >14y corresponds to that in Veneto (86.34%) the dimension of the general population able at generate 3254 new cases od diabetes 2 corresponds to 680139 individuals. Assuming a density of one general practitioner every 1500 residents (that is the number required by Italian law), that implies the recruitment of 453 general practitioners. Assuming that in 5 years of follow-up the drop out rate will be 30% the final number of general practitioners required by that RCT should correspond to 647 doctors.

Table I1: Calculations of the sample size of a hypothetical RCT.

				details
A	Follow-up (y)		5	
B	Control event rate (CER)	Death basal rate (cases/1000py)	57.7[5]	
C		Death basal rate (cases/1py)	0.0577	=B/1000
D		Death basal rate (cases/5py)	0.257073319	=1-(1-C)^A
E	Risk Ratio[1]	RR	0.814	
F	Intervention Event rate (IER)	Death basal rate (cases/5py)	0.208229388	=D*E
G	Diabetes 2 incidence	New cases/py*	0.00600059	
H	Theoretical sample size^	n diabetics	2467	
I	Compliance to be recruited	%	70%	
L	Effective sample size (ESS)	n diabetics	3524	=H/(I/100)
M	Adult Population (i.e. >14y) necessary to generate the ESS	n adults	587276	
N	Prevalence od Adults (i.e. >14y) in the general population	n/N	0.863463466	
O	People (i.e.>0 y) necessary to generate the Adult population	N	680139.9516	=M/N
P	Number of patients that can be assisted in Italy by a General Practitioner (GP)	n	1500	
Q	Number of GP theoretically necessary	n	453	=O/P
R	Drop out scheduled for	%	30%	

	doctors in 5 years			
S	Number of GP really necessary	n	647	=Q/(R/100)

* MilleinRete dataset , follow-up from 1/1/2006 to 12/31/2017 (unpublished data)

^Calculated trough Software Pass 2008 admitting:

- a confidence level of 95%
- a error beta of 20%
- a drop-out rate of patients recruited corresponding to 5% during the entire follow-up
- a CER =D
- a IER=F