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Contrasting mortality risks among subgroups of treated hypertensive patients developing new-onset diabetes

Stefanie Lip†, Panniyammakal Jeemon†, Linsay McCallum, Anna F. Dominiczak, Gordon T. McInnes, and Sandosh Padmanabhan*

Institute of Cardiovascular and Medical Sciences (ICAMS), University of Glasgow, Glasgow G12 8TA, UK

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Aims Hypertension and diabetes mellitus (DM) frequently cluster together and synergistically increase cardiovascular risk. Among those who develop DM during treatment for hypertension (new-onset diabetes, NOD), it is unclear whether NOD reflects a separate entity associated with increased risk or merely reflects accelerated presentation of DM.

Methods and results We analysed data on 15 089 hypertensive patients attending the Glasgow Blood Pressure Clinic. The date at first hospital encounter either with diagnosis of diabetes or prescription of anti-hyperglycaemic medication were considered as the onset of diabetes. Cox proportional hazard models (including propensity score matching) were employed to study associations between diabetes status, early and late NOD (diagnosis <10 years or >10 years from first clinic visit) and cause-specific mortality. There were 2516 patients (16.7%) with DM, of whom 1862 (12.3%) had NOD [early NOD = 705 (4.6%); late NOD = 1157 (7.6%)]. The incidence rate of NOD was 8.2 per 1000 person-years. The total time at risk was 239 929 person-years [median survival: 28.1 years (inter-quartile range: 16.2–39.9)]. Compared with non-diabetic individuals, prevalent DM [hazard ratio (HR) = 1.8, 95% confidence interval (CI): 1.4–2.2] and time varying NOD status (HR: 1.09, 95% CI: 1.06–1.17) were associated with increased adjusted all-cause mortality. Early NOD (HR: 1.39, 95% CI: 1.2–1.6) was associated with increased in mortality risk, but not late NOD (HR: 0.92, 95% CI: 0.83–1.01). Results were consistent in the propensity score matched analyses.

Conclusion Although 1-in-8 hypertensive patients develop NOD, mortality is increased only in the 1-in-20 who develop early NOD. Further studies are warranted to determine if early identification of such individuals should provide an alert for intensification of therapeutic interventions.

Keywords New-onset diabetes mellitus • Hypertension • Mortality • Pre-diabetes

Introduction

There is unequivocal evidence that prevalent diabetes at diagnosis of hypertension is associated with increased mortality risk,[1] and the co-existence of diabetes and hypertension is associated with a two- to three-fold higher risk of cardiovascular disease (CVD).[2–5] However, there are conflicting data regarding the risk associated with the development of diabetes in hypertensive patients who were initially non-diabetic at diagnosis of hypertension—designated new-onset diabetes (NOD).[4,6–12]

Compared with normotensive individuals, non-diabetic hypertensive patients have increased prevalence of insulin resistance and risk of developing diabetes.[10–12] The reported incidence of NOD in middle-aged male and elderly hypertensive individuals is 1.3 and 1.5% per year, respectively.[1,13] In general, a pre-diabetic stage, with relatively higher levels of baseline glucose and body mass index (BMI), is associated with development of NOD.[7,11,12,14–17] *Post hoc* analyses of hypertension clinical trial data suggest that antihypertensive therapy with both diuretics and beta-blockers increases the risk of developing NOD[7,15,18] and recent guidelines

* Corresponding author. Tel: +44 141 330 2228, Fax: +44 141 330 6997, Email: sandosh.padmanabhan@glasgow.ac.uk
† These authors contributed equally.

do not recommend beta-blockers or thiazides in hypertensive patients at high risk of developing diabetes.[19] It is unclear whether NOD reflects a separate entity associated with increased risk or merely reflects accelerated presentation of diabetes mellitus (DM) in individuals destined to develop DM. In this study, we propose to clarify the issue in a large treated hypertensive cohort followed-up for 40 years.

Materials and methods

Study setting and study population

The Glasgow Blood Pressure Clinic (GBPC) provides secondary and tertiary level service for patients with hypertension. More details on the study population and measurements are described elsewhere[20] and in the Supplementary material online, *Methods section*. The West of Scotland Research Ethics Service of the National Health Service has approved the study of the GBPC database (11/WS/0083).

New-onset diabetes mellitus

The definition of diabetes was based on hospital record of diabetes or any diabetes-related diagnosis or prescription of anti-hyperglycaemic drug or diabetes monitoring material. The date of first relevant hospital encounter was considered as the onset of diabetes. Individuals were classified as having NOD if their diabetes diagnosis was made at least 2 years after their first visit to the blood pressure clinic. We used the 2-year cut-off primarily to minimize bias from reverse causality. We classified those who were diagnosed with diabetes in the first 2 years as prevalent diabetes rather than NOD reflecting pre-existing diabetes diagnosed late. New-onset diabetes were classified into early and late (diagnosis <10 or >10 years from first clinic visit). As the classification into DM categories was based on all the entire hospital and prescription data on these patients (not just BP clinic data), the likelihood of ascertainment or surveillance bias is minimal.

Outcome assessment

Records kept by the General Register Office for Scotland ensured notification of a subject's death (provided that it occurred in the United Kingdom) together with the primary cause of death according to the International Classification of Diseases, 10th Revision, Version for 2007 (ICD-10), codes. We considered cardiovascular death as ICD-10 codes ranging from I00-I99 (CV mortality). Deaths not due to these conditions were classified as non-CV death. Mortality data were collected up to April 2013.

Statistical analysis

The categorical variables are presented as proportions, and continuous variables as means with standard deviation (SD) or as median with interquartile range (IQR). The characteristics of the study population across groups based on diabetes status were compared using independent '*t*' test or 'χ^2' test as appropriate. Univariate survival analysis for DM status was performed using Kaplan–Meier survival plots and log rank tests. Multivariable Cox proportional hazard (Cox-PH) models were employed to study the risk of NOD and cause-specific mortality. Similarly, extended Cox-PH models were employed to study the associations between time varying NOD status and cause-specific mortality. The multivariable models included baseline age, gender, epochs (a variable on year of first visit strata), BMI, total cholesterol, smoking status (never vs. ever), systolic BP, alcohol use, baseline ischaemic heart disease, and chronic kidney disease (CKD) status (eGFR $=60$) as covariates (variables that are clinically relevant and associated with diabetes status in the bi-variate analyses are included). The Cox-PH model for predictors of NOD also included baseline glucose level. Since we observed a time-dependent effect of NOD status on mortality, the Cox-PH models were repeated after stratifying the NOD group into early and late NOD. In order to exclude any potential competing risk introduced due to the long follow-up period, the follow-up start date was also considered from the date of diagnosis of DM and the Cox-PH models were repeated. Propensity scores for DM risk based on baseline risk factors were generated for each individual. The generated propensity score was used for identifying matched non-diabetic hypertensive patients (nearest neighbour approach) for each individual with NOD or prevalent diabetes. The Cox-PH models were again repeated in the propensity score matched pairs. Finally, a regression spline Cox-PH model was used to assess the relationship between 'time to development of diabetes' from the first BP clinic visit and mortality outcomes among prevalent DM and NOD individuals after adjustment for all variables as in the multivariable model mentioned earlier.

Results

Baseline demographics

Diabetes status and baseline demographic variables were available in 15 089 (women $=7975$) individuals. The results presented are restricted to this group. The study population was middle aged (mean $\pm$ SD: 50.9 $\pm$ 14.7 years) and overweight (BMI: 27.8 $\pm$ 5.8 kg/m^2). Prevalence of smoking and alcohol use of >5 units per week was 44 and 59%, respectively (Supplementary material online, *Table S1*).

Of the patients presenting to the GBPC 4.3% had prevalent diabetes mellitus (PrevDM). In individuals without PrevDM, 12.9% progressed to develop NOD. The mean age of onset of NOD was 63.7 years (SD $=11.9$). The incidence of NOD per 1000 person-years was 8.2 [95% confidence interval (CI): 7.8–8.5], higher in men (9.3, 95% CI: 8.8–9.9) than in women (7.1, 95% CI: 6.7–7.6). Patients with PrevDM were older (mean $\pm$ SD: 59 $\pm$ 14 years) and with NOD were younger (mean $\pm$ SD: 50 $\pm$ 12 years) in comparison with non-diabetic mellitus (NonDM) (mean $\pm$ SD: 51 $\pm$ 15 years) individuals. Both PrevDM and NOD had higher BMI at presentation and higher plasma glucose (Supplementary material online, *Table S1*). Prevalent diabetic patients had higher baseline prevalence of CKD and ischaemic heart disease compared with NOD and NonDM subjects. Both BP and cholesterol at presentation were lower in PrevDM and higher in NOD when compared with NonDM patients (*Table 1*).

Of the NOD patients, 38% developed early NOD. Early NOD patients were older with a higher BMI and plasma glucose, lower blood pressure, lower prevalence of alcohol use, and higher prevalence of CKD in comparison with individuals with late NOD (Supplementary material online, *Table S2*).

Predictors of new-onset diabetes

Significant predictors of NOD were, in descending order, blood glucose, BMI, history of smoking, systolic BP, and age (Supplementary material online, *Table S3*). Alcohol users and women had a lower risk. In the subgroup analyses among individuals with prescription data available (from 2004), anti-hypertensive drug use or number of anti-hypertensive drugs taken were not different in NOD in

Table 1 Characteristics of study population in prevalent diabetic, new-onset diabetic, and non-diabetic individuals

Variables	DM (n = 654)	NOD (n = 1862)	NonDM (n = 12 573)	P-Value[a]	P-Value[b]
Age in years, mean (SD)	59.25 (14.03)	49.78 (12.02)	50.65 (14.93)	0.016	<0.001
Age at NOD in years, mean (SD)	–	63.73 (11.90)	–		
Time to NOD in years, median (IQR)	–	12.74 (7.56–19.70)	–		
Women, n (%)	313 (47.86)	883 (47.42)	6779 (53.92)	<0.001	0.002
Body mass index in kg/m^2, mean (SD)	31.50 (6.29)	30.41 (6.23)	27.19 (5.56)	<0.001	<0.001
Smoking, n (%)	221 (45.85)	837 (45.27)	5046 (44.12)	0.358	0.455
Alcohol use, n (%)	157 (35.20)	1040 (57.46)	6643 (60.10)	0.033	<0.001
Systolic blood pressure in mmHg, mean (SD)	160.06 (27.14)	164.55 (27.11)	162.57 (28.71)	0.005	0.031
Diastolic blood pressure in mmHg, mean (SD)	89.51 (14.62)	98.20 (14.46)	96.62 (20.57)	0.001	<0.001
Plasma glucose, mmol/L	9.51 (4.83)	6.87 (3.43)	5.44 (1.21)	<0.001	<0.001
CKD (eGFR < 60), n (%)	187 (40.56)	340 (20.13)	2382 (23.07)	0.007	<0.001
Ischaemic heart disease, n (%)	115 (22.42)	377 (20.30)	1895 (16.17)	<0.001	<0.001
Total cholesterol in mmol/L, mean (SD)	5.32 (1.44)	6.11 (1.33)	5.91 (1.47)	<0.001	<0.001

DM, diabetes mellitus; NOD, new-onset diabetes; NonDM, non-diabetic mellitus; SD, standard deviation; IQR, inter-quartile range; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease.
[a]NOD vs. NonDM.
[b]DM vs. NonDM.

comparison with NonDM patients (Supplementary material online, *Table S4*). Age at baseline, BMI, blood glucose, CKD, ischaemic heart disease, alcohol use, and gender were associated with development of early NOD (Supplementary material online, *Table S5*) with age, BMI, and blood glucose the top predictors by Wald statistic. Both BMI (Supplementary material online, *Figure S1*) and random blood glucose (Supplementary material online, *Figure S2*) were higher in the early NOD and prevalent diabetes groups compared with non-diabetic participants.

Survival analyses

There were 5220 deaths (52% from cardiovascular causes) over a 40-year follow-up period. The total time at risk was 239 799 person-years with a median survival time of 28.05 years (IQR: 16.2–39.9). In the Kaplan–Meier analyses, the overall NOD status was not associated with all-cause mortality (*Figure 1*). However after stratification by time to NOD, individuals with early NOD had shorter survival time and higher incidence of mortality (log rank $P < 0.001$) (*Figure 2*). The median survival time in individuals with early NOD was 18.6 years in comparison with the median survival time of 28.4 years in NonDM.

In the simple Cox-PH model, overall NOD status was not associated with all-cause, cardiovascular, and non-cardiovascular mortality outcomes (*Table 2*). In the extended Cox-PH model, the time varying NOD status was associated with increased all-cause mortality (HR = 1.09, 95% CI: 1.06–1.13). Prevalent diabetes status increased the all-cause and cardiovascular mortality risk by >80% (HR = 1.84, 95% CI: 1.55–2.20 and HR = 1.81, 95% CI: 1.42–2.29, respectively). In the stratified analyses, early NOD status increased the all-cause (HR = 1.39, 95% CI: 1.21–1.60), cardiovascular (HR = 1.29, 95% CI: 1.06–1.57), and non-cardiovascular (HR = 1.52, 95% CI: 1.26–1.85) mortality risk by 39, 29, and 52%, respectively (*Table 3*). However, late NOD was not associated with all-cause mortality (*Table 3*). Results were consistent in the propensity score matched analyses (*Tables 4* and *5*) and in the analyses with mortality risk estimated from onset of diabetes (Supplementary material online, *Table S6*). In the regression spline Cox-PH model, we find a linear decrease in mortality risk with increase in the 'time to diagnosis of diabetes' (*Figure 3*) for both all-cause (*A*) and CVD (*B*) mortality.

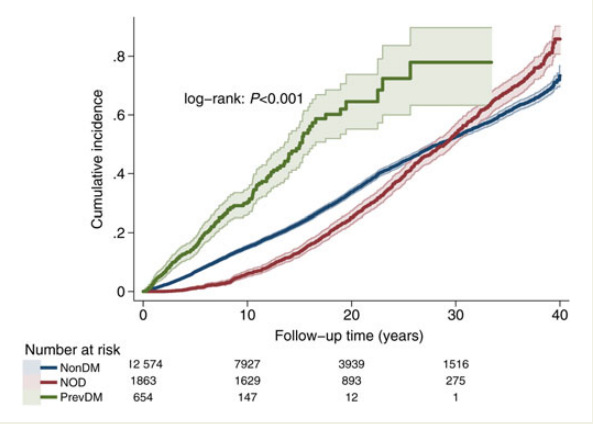

Figure 1 Survival analysis (time to all-cause mortality) of hypertensive patients with PrevDM, NOD, and NonDM. PrevtDM, prevalent diabetes mellitus; NOD, new-onset diabetes; NonDM, non-diabetic mellitus.

Discussion

In this study of 15 089 treated hypertensive patients followed-up for 40 years by the GBPC, 12.9% of patients who were non-diabetic at first presentation developed NOD during follow-up, with 37% of

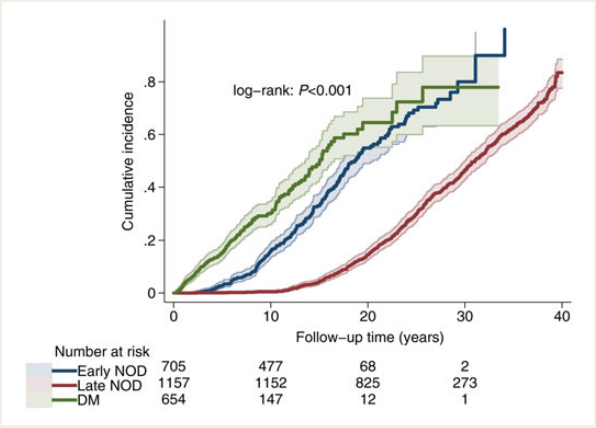

Figure 2 Survival analysis (time to all-cause mortality) of early and late NOD. NOD, new-onset diabetes; early NOD, those who developed diabetes within the first 10-year follow-up; late NOD, those who developed after completion of 10-year follow-up.

them developing NOD within 10 years. The early NOD group despite not having diabetes at baseline had a 40% higher mortality risk (similar to those with prevalent DM at baseline) compared with non-diabetic patients and those with late onset NOD. The most significant predictors of early NOD at baseline were random blood sugar and BMI offering a simple inexpensive clinical stratification test to target a subgroup of hypertensive patients, either at first presentation or in the early period after commencing anti-hypertensive treatment, for more intensive investigation and interventions to improve survival.

In contrast to previous studies, we analysed early and late NOD as two distinct entities. We reasoned that individuals developing early NOD were more likely to have a higher baseline risk for DM, longer duration of DM, and overall higher cardiovascular risk in comparison with those who develop late NOD. The risk of developing early NOD increased with increasing age, BMI, and random blood glucose in keeping with findings from previous studies.[17] Smoking, CKD, and male gender also increased the risk of early NOD, with a 30% lower risk of NOD in regular alcohol users. In our population, the mortality risk (from first presentation at the blood pressure clinic) associated with diabetes (PrevDM and early

Table 2 Cox model for diabetes status and cause-specific mortality compared with non-diabetic hypertensive patients

Variables	ACM (n = 4211)	CVM (n = 2149)	Non-CVM (n = 2062)
NOD	1.04 (0.96–1.13)	0.97 (0.86–1.09)	1.11 (0.99–1.26)
Prevalent DM	1.84 (1.55–2.20)*	1.81 (1.42–2.29)*	1.90 (1.47–2.45)*

NOD, new-onset diabetes; ACM, all-cause mortality; CVM, cardiovascular disease mortality; Non-CVM, non-cardiovascular disease mortality.
*$P < 0.05$.

Table 3 Cox model for early and late onset diabetes and cause-specific mortality in comparison with non-diabetic hypertensive patients

Variables	ACM (n = 4211)	CVM (n = 2149)	Non-CVM (n = 2062)
Early NOD	1.39 (1.21–1.60)*	1.29 (1.06–1.57)*	1.52 (1.26–1.85)*
Late NOD	0.92 (0.83–1.01)	0.85 (0.74–0.99)*	0.98 (0.85–1.13)

NOD, new-onset diabetes; ACM, all-cause mortality; CVM, cardiovascular disease mortality; Non-CVM, non-cardiovascular disease mortality.
*$P < 0.05$.

Table 4 Propensity score matched Cox model for diabetes status and cause-specific mortality compared with non-diabetic hypertensive patients

Variables	ACM (n = 2494)	CVM (n = 1344)	Non-CVM (n = 1150)
NOD (propensity score matched)	1.05 (0.95–1.16)	0.89 (0.77–1.03)	1.27 (1.01–1.46)*
Prevalent DM (propensity score matched)[a]	1.66 (1.36–2.02)*	1.48 (1.13–1.93)*	1.96 (1.46–2.64)*

NOD and Prevalent DM are matched separately for NonDM controls.
NOD, new-onset diabetes; ACM, all-cause mortality; CVM, cardiovascular disease mortality; Non-CVM, non-cardiovascular disease mortality.
[a]ACM = 1688, CVM = 932, and Non-CVM = 736.
*$P < 0.05$.

Table 5 Propensity score matched Cox model for early and late onset diabetes and cause-specific mortality in comparison with non-diabetic hypertensive patients

Variables	ACM (n = 2494)	CVM (n = 1344)	Non-CVM (n = 1150)
Early NOD (propensity score matched)[a]	1.43 (1.19–2.05)*	1.24 (1.01–1.53)*	1.71 (1.37–2.13)*
Late NOD (propensity score matched)[a]	0.91 (0.81–1.03)	0.76 (0.65–0.90)*	1.12 (0.95–1.32)

NOD, new-onset diabetes; ACM. all-cause mortality; CVM, cardiovascular disease mortality; Non-CVM, non-cardiovascular disease mortality.
[a]NOD is matched for NonDM controls.
*$P < 0.05$.

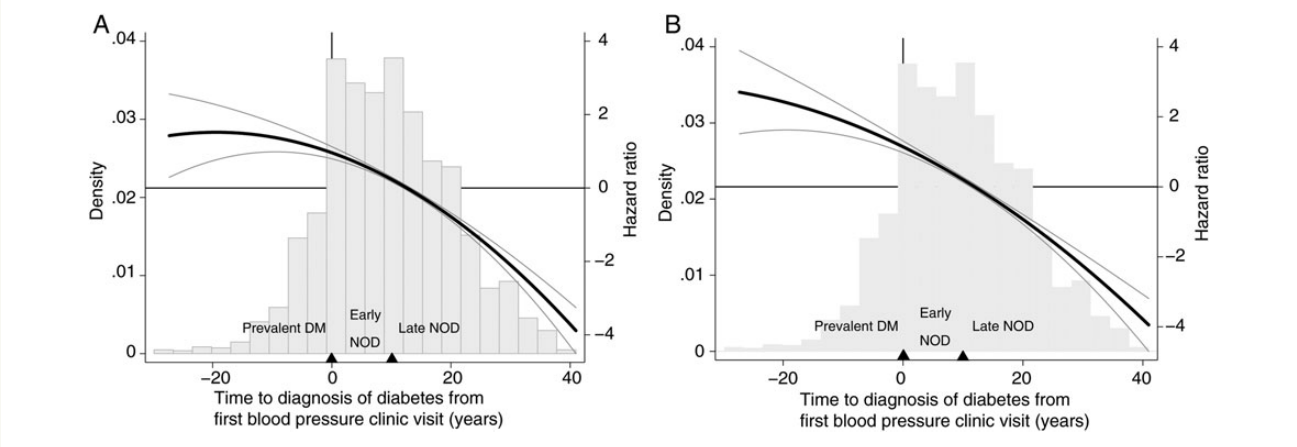

Figure 3 Regression spline Cox proportional hazard model for time to diabetes and mortality. (*A*) All-cause mortality and (*B*) cardiovascular disease mortality. NOD, new-onset diabetes; early NOD, those who developed diabetes within the first 10-year follow-up; late NOD, those who developed after completion of 10-year follow-up. The histogram describes the distribution of 'time to diagnosis of diabetes' from first blood pressure clinic visit. The hazard ratios are given on the secondary *Y*-axis. The thick line represents the point estimate (HR) for all-cause mortality from 'time to diagnosis of diabetes' and the light grey lines above and below this line represents the upper limit and lower limit of the confidence interval. The panels clearly depicts that as the 'time to diagnosis of diabetes' from first blood pressure clinic visit increases the mortality risk decreases linearly.

NOD) was higher than in NonDM patients, but there was no mortality difference between NonDM and late NOD patients. However, early NOD status was clearly associated with a significantly increased all-cause and cardiovascular mortality compared with those who were non-diabetic or developed late NOD, and this risk was similar to those PrevDM. As the duration of diabetes will have an impact on any outcome analysis, we analysed the mortality risk estimated from the time to onset of diabetes (in subjects with PrevDM and NOD) and again this confirmed an increased mortality risk with early NOD and PrevDM but not for late NOD. Late NOD was associated with a 53% lower risk of cardiovascular death suggesting a possible survivorship bias among these individuals. When we analysed mortality risk associated with 'time to diagnosis of diabetes from first BP clinic visit', we demonstrated the earlier that diabetes was diagnosed from the first BP clinic visit, the greater the mortality risk. This implies that the subgroup of hypertensive patients who proceed to develop diabetes within 10 years of presentation to the BP clinic, already exhibit at baseline the same excess risk as those with prevalent diabetes. The baseline demographic differences of the predictors of NOD indicate a healthy cohort effect in late NOD patients. To ensure that the lower risk associated with late NOD was not due to survivorship bias, we performed the analysis in a subset of the population who had a minimum of 11-year follow-up and the results were no different. Indeed our analysis of late NOD subjects suggests that the baseline risk at presentation (which may also reflect latent DM) is the predominant predictor of mortality rather than the development of diabetes during follow-up. This potentially renders the debate over the risk posed by anti-hypertensive therapy-induced diabetes largely academic. Though we found no difference in the exposure to different anti-hypertensive drug classes in the NOD and NonDM group, our sample size for drug data was small and this cohort is not the ideal cohort to test the risk posed by drugs.

As hypertensive patients who develop early NOD are at a significantly higher mortality risk, this group can be categorized as 'hypertensive pre-diabetes'. Though evidence for interventions to prevent or retard progression to diabetes is limited,[21–26] we propose that this subgroup of patients should be specifically targeted for early screening and lifestyle interventions. Whilst current screening for DM at our clinic is a baseline random blood sugar, our findings

indicate that more detailed screening for DM would be a useful addition to the hypertension investigation panel. There is clear evidence from clinical trials that raised glucose level is a modifiable risk factor for ischaemic heart disease and intensive glycaemic control reduces macrovascular complications like myocardial infarction.[27,28] This warrants further prospective studies to test whether these patients should be started on anti-hyperglycaemic medication or whether diabetic screening at initial presentation is effective to identify individuals who are 'hypertensive pre-diabetes' early.

On average, hypertensive patients who develop early NOD lose 10 years of life (estimated from the median survival time) in comparison with those who do not develop diabetes. Of the estimated 1.43 million hypertensive patients in Scotland based on the hypertension prevalence in adult (>16 years),[29] if no preventive or risk management measures are taken, Scotland would lose 715 000 life years in the hypertensive population due to NOD in the next 10 years. In the diabetes prevention programme, intensive lifestyle education and simple metformin therapy reduced the diabetes incidence risk by 58 and 31% in high-risk pre-diabetes individuals, respectively. If we assume the same efficacy in the hypertensive patients at high-risk early, these two strategies could potentially save 414 700 and 221 650 life years in Scotland, respectively. From our data, simple measurements of random blood glucose and BMI in all hypertensive patients at first diagnosis would be enough to stratify a subset of 71 500 patients who are at high risk of development of early diabetes in Scotland for preventive interventions.

We summarize the important strengths and limitations of our study and questions that need further resolution in future studies. The main strengths of our study include the large cohort size conducted in real life settings with global healthcare records obtained through electronic linkage; long duration of follow-up; large number of mortality events; longitudinal clinic and laboratory measurements; and availability of refill prescription data. The limitations include the following—the patients in our cohort are confined to a secondary care hypertension clinic in the West of Scotland and therefore the extent of generalizability of our findings is unknown. We do not have data on oral glucose tolerance test, fasting blood glucose, medication adherence, or lifestyle behaviours. Most of the patients were on multiple anti-hypertensive drugs which limited our ability to analyse drug effects. Our study highlights the priorities for future research in this area—Does hypertension accelerate transition to diabetes in those who develop early NOD? Is there any difference in the cumulative exposure to combinations of beta-blockers, thiazides, and renin angiotensin aldosterone system (RAAS) blockers on risk of early and late NOD? Is there an interaction between beta-blockers, thiazides, and RAAS blockers with baseline blood glucose or BMI on risk of development of early NOD? Will detailed baseline metabolic profiling incrementally improve risk prediction of NOD over and above baseline blood sugar and BMI? Will screening for risk factors and early treatment of hyperglycaemia delay development of early NOD and consequently will this delay in NOD improve cardiovascular mortality?

Conclusion

Although 1-in-8 hypertensive patients develop NOD, mortality is increased only in the 1-in-20 who develop NOD early. Our findings suggest that in the management of hypertension, early detection and management of hyperglycaemia irrespective of its origins should be a priority. Whether early screening and treatment for diabetes at first presentation of hypertension is effective in improving outcomes in hypertensive patients requires further investigation in prospective trials.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Authors' contributions

P.J. and S.P.: performed statistical analysis. S.P.: handled funding and supervision. L.M., A.F.D., G.T.M., and S.P.: acquired the data. S.P., G.T.M., and S.L.: conceived and designed the research. S.L., P.J., L.M., and S.P.: drafted the manuscript. A.F.D., G.T.M., and S.P.: made critical revision of the manuscript for key intellectual content.

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Conflict of interest: none declared.

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