Khunti Kamlesh (Orcid ID: 0000-0003-2343-7099)

Xue Charlie (Orcid ID: 0000-0001-6937-9088)

Paul Sanjoy (Orcid ID: 0000-0003-0848-7194)

Title: Therapeutic inertia in the management of dyslipidaemia and hypertension in incident type 2 diabetes and the resulting risk factor burden: real-world evidence from primary care.

Short running title: Therapeutic Inertia and Risk Factor Burden

Joanna Z.J. Ling, MSc[1,2], Olga Montvida, PhD[1], Kamlesh Khunti, PhD[3], Anthony L. Zhang, PhD[2], Charlie C. Xue, PhD[2], and Sanjoy K. Paul, PhD[1,2]

[1]Melbourne EpiCentre, University of Melbourne and Melbourne Health, Melbourne, Australia

[2]School of Health and Biomedical Sciences, RMIT University, Melbourne, Australia

[3]Department of Health Sciences, University of Leicester, Leicester, UK

Corresponding Author:

Professor Sanjoy Ketan Paul

University of Melbourne

The Royal Melbourne Hospital – City Campus | 7 East, Main Building

Grattan Street, Parkville Victoria 3050

Email: sambhupaul@hotmail.com

Phone: +61 3 93428433

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/dom.14364

Keywords: Therapeutic inertia, dyslipidaemia, hypertension, young-onset type 2 diabetes, risk factor control failure.

Word Count, Abstract: 261

Word Count, Main Body: 3847

Number of Tables: 3

Number of Figures: 2

Supplemental Tables: 2

Supplemental Figures: 2

Number of References: 39

ABSTRACT

Objective: The trends in prevalence of hypertension and dyslipidaemia in incident type 2 diabetes (T2DM), time to antihypertensive (AHT) and lipid lowering (LLT) therapy, and the association with SBP/lipid control, are not known.

Research Design and Methods: Using THIN UK primary care database, 254,925 people with incident T2DM and existing dyslipidaemia/hypertension were identified. Among those without atherosclerotic cardiovascular disease (ASCVD) history and not on AHT/LLT at diagnosis, adjusted median months to initiating an AHT/LLT, and the probabilities of high SBP/lipids over 2-years in people initiating therapy within/after 1-year were evaluated by high and low ASCVD risk status.

Results: At diabetes diagnosis 66/66% had dyslipidaemia/hypertension. During 2005-2016, dyslipidaemia prevalence increased by 10% in people aged <60 years, while remained stable for hypertension in all age groups.

Among those with high ASCVD risk-status in the 18-39, 40-49 and 50-59 years-groups, median months (95% CI) to initiate therapy were 20.4 (20.3-20.5), 10.9 (10.8-11.0) and 9.5 (9.4-9.6) months in dyslipidemia sub-cohort; and 28.1 (28.0-28.2), 19.2 (19.1-19.3) and 19.9 (19.8-20.0) in hypertension sub-cohort.

Among people with high and low ASCVD risk status, compared to early LLT initiators, those who initiated LLT after 1-year had 65.3–85.3% and 65.0–85.3% significantly higher probability of failing lipid control over 2-years follow-up, while late AHT initiators had 46.5–57.9% and 65.0–40.0–58.7% significantly higher probability of failing SBP control.

Conclusions: Significant delay in initiating cardioprotective therapies was observed, time to first prescription was similar in primary prevention people irrespective of ASCVD risk status across all T2DM diagnosis age groups, resulting in poor risk factor control over 2-years follow-up.

Hypertension and dyslipidemia are major causes of premature death worldwide, with more than 50% with hypertension not achieving blood pressure control [1-3]. The burden of these conditions is especially high in people with diabetes [2,3], with growing interest in generating population level evidence on the patterns of multimorbidity in people with type 2 diabetes (T2DM). While some recent studies based on cross-sectional data have evaluated the cardiometabolic multimorbidity in people with established T2DM [4-6], there is paucity of epidemiological data on trends of prevalence of hypertension and dyslipidemia at the time of diabetes diagnosis and their management.

International guidelines for treatment of T2DM suggest maintaining tight cardiometabolic risk factor control from diagnosis by active titration of combinations of medication, as well as lifestyle interventions as appropriate [7-9]. The guidelines primarily target a systolic blood pressure of 130/140 mmHg and LDL cholesterol of 1.8/2.6 mmol/L (with recent guidelines introducing tighter targets of 1.4/2.5 mmol/L) in patients with T2DM at high /moderate cardiovascular risk [7,10]. However, a meta-analysis has suggested that only 29/49/58/62% of people with T2DM achieve guideline-based targets for blood pressure/LDL/HDL/triglyceride control respectively [11]. Also, an US electronic medical record (EMR) based study reported that 55% of people on cardioprotective medications consistently failed to maintain clinically acceptable blood pressure and lipid control over 2 years post therapy initiation or intensification [3]. One of the reasons for suboptimal cardiometabolic risk factor control or persistent risk factor burden is the failure or delay in providing appropriate treatment intensification (therapeutic inertia, TI) [12,13]. The concerns regarding persistent existence of TI and the associated consequences are reflected by a recent launch of “Addressing Therapeutic Inertia in 2020 and Beyond: A 3-Year Initiative of the American Diabetes Association” [14] and multiple reviews [15,16].

While several studies have evaluated TI and its consequences in terms of glucose control in people with T2DM [11-13], only a few studies have reported TI for blood pressure management in people with hypertension [17,18], and there is lack of data on TI for blood pressure and lipid control simultaneously in incident T2DM. There is emerging global evidence on the cardiometabolic risk factor burden in people with hypertension [19], dyslipidaemia [20], and particularly the increasing proportions of younger adults below 50 years being less likely to be taking AHT [19,21], resulting in significantly higher life-time cardiovascular and mortality risk compared to older people with hypertension [22]. While few studies have discussed the effect of hypertension [23] and dyslipidaemia [24,25] management as a cause of cardiovascular risk control failure, we are not aware of any population level study that has evaluated the treatment patterns, delay in therapy initiation when needed, and associated medium term impact on systolic blood pressure (SBP) and lipid control from the time of diagnosis of diabetes. With the emerging evidence on the cardiometabolic multimorbidity burden in people with T2DM, there is an urgent need for population-level evaluation of cardiometabolic risk and the pharmacological therapeutic management in incident T2DM across all age groups, particularly in the primary prevention setting.

Using nationally representative UK primary care electronic medical records (EMRs), in patients diagnosed with incident T2DM between 2005 and 2017, the aims were to evaluate (1) the temporal trends in the prevalence of hypertension and dyslipidaemia by year of diagnosis of diabetes, (2) determine delay in initiating anti-hypertensive therapy (AHT) and lipid-lowering therapy (LLT) when needed, and (3) the population level probability of achieving clinically acceptable systolic blood pressure (SBP) and lipid control by time to AHT and LLT initiation and by baseline cardiovascular risk status, with focus in people without history of atherosclerotic cardiovascular disease (ASCVD) at diagnosis of T2DM.

RESEARCH DESIGN AND METHODS

Data

The Health Improvement Network (THIN) database provides longitudinal patient-level UK primary care data, is representative of UK population with respect to demographics, major disease prevalence and death rates, and has been extensively used for observational studies [26-28]. The Read disease coding, BMI, blood pressure measures and dyslipidaemia in UK primary care data have been validated [29-32].

For more than 17 million individuals, longitudinal EMRs were available from 2000 – 2017 with comprehensive patient-level information on demographics, anthropometrics, clinical and laboratory measures, medication usages and disease events [28]. Medication data include generic ingredients of individual medications prescribed, along with prescription dates and dosage. Laboratory and clinical data are automatically downloaded into the EMR from nearly all practices.

Study population

People with T2DM were identified using a clinically guided machine learning algorithm [28,33]. The learning process included relevant diabetes-related Read codes and other associated codes, at least one prescription for an anti-diabetic drug or two elevated glucose measures within a year (Supplementary Text 1 and Figure 1). Those with type 1 diabetes, gestational diabetes, diabetes due to other causes such as maturity-onset diabetes of the young, prediabetes, or metformin prescribed for polycystic ovary syndrome were excluded. The earliest date of recorded diabetes from the learning process was considered as the index date (baseline). Those with unknown sex, age <18 or ≥80 years at index, or with index date prior to 2005 (start of UK Quality Outcomes

Framework with better recording of data) were excluded. To reduce the bias in identifying incident T2DM patients, those with first activity in the EMRs <6 months prior to the index date were excluded.

Two sub-cohorts were identified as having hypertension or dyslipidaemia prior to or within 6 months of diagnosis of T2DM. Hypertension cohort: i) a hypertension Read code or ii) high longitudinal systolic blood pressure (SBP ≥130 /140 mmHg for those with /without prior ASCVD); dyslipidaemia cohort: i) a dyslipidaemia Read code, ii) high longitudinal LDL cholesterol (LDL ≥1.8 /2.6 mmol/L for those with /without prior ASCVD) or iii) high longitudinal non-HDL cholesterol (non-HDL ≥2.6 /3.4 mmol/L for those with /without prior ASCVD) [Supplementary Figure 2].

Variable Definitions

ASCVD was defined by presence of a clinical diagnosis for myocardial infarction, ischemic heart disease, unstable angina, ischemic stroke, haemorrhagic stroke, transient ischemic attack, peripheral vascular disease, or cerebrovascular disease. Chronic kidney disease (CKD) definition included diagnostic codes (CKD stages 1-5, end stage renal disease, dialysis, transplant, nephropathy, proteinuria, albuminuria, nephrotic syndrome, and nephritis; excluding non-acute events and pyelonephritis), estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m^2 or urine albumin-creatinine ratio (UACR) >30 mg/mmol. Microvascular disease was defined by a clinical diagnosis of neuropathy, retinopathy or CKD. Cancer was defined as any malignant neoplasm excluding melanoma. Patients were identified to have depression (i) with a diagnosis code for depression or (ii) a record of at least two prescriptions for antidepressants in the absence of clinical codes for other mental illnesses [34].

AHT was identified using the Anatomical Therapeutic Classification and British National Formulary coding systems including diuretics, peripheral vasodilators (excluding nicotinic acid), beta blockers, calcium channel blockers, and agents acting on renin-angiotensin system. LLT included statins, bile acid sequestrants, fibrates, nicotinic acid, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, and potent (≥1g) forms of omega-3/fish/krill oil. A machine learning method based extraction of longitudinal prescription data from relational EMR databases has been validated [33].

Baseline HbA1c was obtained as the nearest measure within 3 months either side of index date. Baseline body weight, BMI, SBP, and lipids were calculated as the average of available measures within 3 months either side of index date. With the condition of at least two non-missing follow-up data over 24 months and complete data at baseline, the missing risk factor data were imputed using Bayesian Markov Chain Monte Carlo method based multiple imputation [35].

Cardiovascular Risk Identification

BMI measurement categories: normal weight (18.5–24.99 kg/m^2), overweight (25–29.99 kg/m^2), grade 1 obese (30–34.99 kg/m^2), and grade 2+ obese (≥35 kg/m^2). High ASCVD risk: ≥2 risk factors of current smoking, grade 2+ obesity, hypertension or dyslipidaemia (as appropriate for cohort), or microvascular disease, in people without ASCVD history at index date [28]. Those with missing BMI measurement / unknown smoking status were classified as not having grade 2+ obesity / non-smokers. In people without /with prior ASCVD, SBP control failure over 2 years post index was defined as having an SBP ≥130 /140 mmHg and lipid control failure as having either LDL-C ≥2.6 /1.8 mmol/L or non-HDL-C ≥3.4 /2.6 mmol/L.

Statistical analyses

The characteristics of study cohort and the sub-cohorts of people with hypertension and dyslipidaemia were summarised as number (%), mean (SD), or median (first quartile, third quartile), as appropriate by age groups 18-39, 40-49, 50-59, 60-69, 70-79 years at baseline. Joint point regression (JPR) analysis was used to estimate growth rates (95% CI) of the temporal trend in prevalence estimates over years of T2DM diagnosis [36].

In the hypertension /dyslipidemia cohorts, among those without ASCVD history and not on AHT /LLT at baseline, the median months (95% CI) to initiating an AHT /LLT by high and low ASCVD risk status were evaluated using parametric survival regression models adjusting for age, sex, cancer and any mental illness. People were censored at the end of follow-up (transfer out of practice, death or 30-Sep-2017) if no AHT /LLT was ever prescribed. Among those without ASCVD at baseline, the probabilities of having high SBP or lipids over 2-years post index by initiator status (early /late: initiating therapy within /after 1 year of index) was evaluated using logistic regression adjusting for age, sex, baseline SBP /lipids, cancer and any mental illness, separately for those with high and low ASCVD risk status.

Observational Routinely-collected Data (RECORD) guideline was followed to conduct the study and the study protocol was approved by the review board (Protocol number: SRC_Protocol_19THIN081_v1-11-10-2019). Aggregated data and study protocols are available upon request.

RESULTS

Patient characteristics

A total of 254,925 people with incident T2DM were identified with a mean follow-up of 5.3 years (Supplementary Figure 2). Proportions of people with dyslipidaemia, hypertension and both dyslipidaemia and hypertension at diagnosis were 66%, 66% and 46% respectively, while these proportions in people aged <50 years at diagnosis were 60%, 42% and 29% respectively (Table 1).

Prevalence of dyslipidaemia and hypertension at T2DM diagnosis

The prevalence of dyslipidaemia has been consistently increasing over the last decade in people aged <60 years at diagnosis (~10% increase between 2005-2016; Figure 1, Supplementary Table 1). The average percentage increase between consecutive years in dyslipidaemia prevalence was higher in people aged 18-60 years (2.3 – 3.9%), compared to 0.8% in people aged 60+ years. The proportions of people with hypertension at T2DM diagnosis remained stable during 2005-2016 across all age groups, while a marginal increasing trend (about 2-4% increase) in the proportion of people with both hypertension and dyslipidaemia was observed in people aged <50 years (Figure 1, Supplementary Table 1).

In the dyslipidaemia cohort (n=168,365), the proportion of people with HbA1c ≥7.5% [58 mmol/mol] and grade 2+ obesity were 56% and 43% respectively in people aged below 50 years, significantly higher than the proportions (38% and 27% respectively) observed in people aged ≥50 years (Table 2, all $p<0.01$), while proportions of current smokers were similar across age groups (35%). At baseline and within 6 months of T2DM diagnosis, overall 37% and 63% of the dyslipidaemia cohort were on LLT respectively, while these proportions in people aged <50 years were 13% and 43% respectively. In the 40-49 /50-59 years groups, only 49 /60% were on LLT within 6 months of diagnosis although 79 /84% of them were at high ASCVD risk.

In the hypertension cohort (n=167,896), the proportion of people with HbA1c ≥7.5% [58 mmol/mol] and grade 2+ obesity were 53% and 52% respectively in people aged below 50 years, significantly higher than the proportions (36% and 29% respectively) observed in people aged ≥50 years (Table 3, all p<0.01), while proportions of current smokers were similar across age groups (32%). At baseline and within 6 months of T2DM diagnosis, 68% and 78% of the hypertension cohort were on AHT respectively, while these proportions in people aged <50 years were 48% and 64% respectively. In the 40-49 /50-59 years groups, 67 /75% were on AHT within 6 months of diagnosis while 85 /86% of them were with high ASCVD risk.

The proportions with hypertension / dyslipidaemia in the dyslipidaemia / hypertension cohort were 70 /70%. Overall 85% people had high ASCVD risk at baseline in both hypertension and dyslipidaemia cohorts.

Time to initiating first LLT /AHT

Among those not on LLT at baseline in the dyslipidaemia cohort (n=106,488), the overall adjusted median months to initiating LLT in people with high/low ASCVD risk were 10.8/13.1 months and varied between age groups. The median months (95% CI) to initiate LLT in the high ASCVD risk group in the 18-39, 40-49 and 50-59 years groups were 20.4 (20.3, 20.5), 10.9 (10.8, 11.0) and 9.5 (9.4, 9.6) months respectively (Figure 2A, Supplementary Table 2). Older people aged ≥70 years had marginally delayed therapy initiation compared to that observed in the 50-70 years age groups. Across all age groups between 40-70 years, the average time to receiving the first LLT in people with high ASCVD risk (9.7 months) was only about one month sooner compared to the average time to first LLT in people with low ASCVD risk (10.9).

Among those not on AHT at baseline in the hypertension cohort (n=53,400), the overall adjusted median months to initiating AHT in people with high/low ASCVD risk were 20.2/22.2 months. The adjusted median months to initiating AHT in people with high ASCVD risk across all age groups 40-79 years were numerically similar (range of 95% CI of median month: 19.1-19.7), while the median time to initiating the first AHT in people aged below 40 years was 28 months. Across all age groups between 40-79 years, the average time to receiving the first AHT in people with high ASCVD risk (19.6 months) was only about 2 months earlier compared to the average time to first AHT in people with low ASCVD risk (21.9 months) (Figure 2B, Supplementary Table 2).

Probability of failing lipid and systolic blood pressure control over 2 years

In the dyslipidaemia cohort, regardless of having high or low ASCVD risk at baseline, those who initiated LLT late had significantly higher probability of lipid control failure than those who initiated LLT early (Figure 2C). The probability of lipid control failure among the late LLT initiators in high and low ASCVD risk groups ranged between 65.3–85.3% and 65.0–85.3% across all age groups. In the 18-39 /40-49 /50-59 /60-69 /70-79 years age-groups from the dyslipidaemia cohort, among people with high and low ASCVD risk status respectively, compared to early LLT initiators, those who initiated LLT after 1 year had 16 /20 /21 /24 /22% and 23 /22 /24/ 25/ 23% significantly higher probability of failing lipid control over 2 years of follow-up (Figure 2C, Supplementary Table 2).

In the hypertension cohort, regardless of having high or low ASCVD risk at baseline, those who initiated AHT late had significantly higher probability of SBP control failure than those who initiated AHT early (Figure 2D). The probability of systolic blood pressure control failure among the late AHT initiators in high and low ASCVD risk groups ranged between 46.5–57.9% and

40.0–58.7% across all age groups. In the 18-39 /40-49 /50-59 /60-69 /70-79 years age groups from hypertension cohort, among people with high and low ASCVD risk status respectively, compared to early AHT initiators, those who initiated AHT after 1 year had 9 /11 /14 /12 /10% and 12 /20 /11 15/ 10% significantly higher probability of failing SBP control over 2 years of follow-up (Figure 2D, Supplementary Table 2).

Those at low ASCVD risk and prescribed LLT /AHT after 12 months had 16-24% /2-14% higher risk of failing lipid / blood pressure control as compared to those with high ASCVD and prescribed LLT /AHT within 12 months.

CONCLUSIONS

Our study has a number of key novel findings. We are not aware of any study assessing therapeutic inertia for lipid and blood pressure control in people with incident T2DM under one study design. Firstly, in this large nationally representative primary care EMR based pharmaco-epidemiological study, the overall prevalence of dyslipidaemia and hypertension were similar at diagnosis of T2DM (66%), however, we observed significant increase in the prevalence of dyslipidaemia, particularly in people aged <60 years.

Secondly, in a holistic evaluation of AHT and LLT initiation timeline in people with hypertension and/or dyslipidaemia, with identification of high cardiometabolic risk at the time of diagnosis of T2DM, we observed median time to AHT /LLT initiation in those aged above 40 years with low ASCVD risk (21.9 /10.9 months) was numerically similar to that observed for people with high ASCVD risk (19.6 /9.7 months). We also observed that in the dyslipidaemia cohort only 16% and

30% people in the 40-49 years and 50-59 years age groups respectively were on LLT at baseline, despite more than 80% of them having high ASCVD risk. Thirdly, delay in initiating lipid and blood pressure control therapies was associated with significant cardiometabolic risk factor burden in people with T2DM over 2 years [3].

Although we are not aware of any published data evaluating time to antihypertensive and lipid control therapies in incident T2DM people with hypertension or dyslipidaemia, a recent UK database study reported that unlike usual-onset, young-onset T2DM have similar cardiovascular and mortality risk irrespective of their cardiometabolic risk level at diagnosis [28]. While NICE and NHS guidelines suggests initiation of AHT /LLT in people aged <80 years with high risk [8,9], our findings clearly indicate significant non-adherence to the national guidelines. Another recent US EMR based study in people with incident T2DM reported that 41 /29% among those on LLTs /AHTs continued to have high LDL-C /SBP over 2 years post therapy initiation. Among people with T2DM receiving cardioprotective therapies, 55% consistently failed to achieve LDL+SBP control over 2 years after therapy intensification [3]. In terms of lipid control in people with dyslipidaemia at diagnosis of T2DM, among those who initiated LLT after 1 year, we have observed very high and similar probability of risk factor control failure over 2 years in people with high and low ASCVD risk (probability range: 65-85%).

For blood pressure control over 2 years post diagnosis, those who initiated AHT after 1 year, the probability of SBP control failure ranged between 47-58% in people with high ASCVD risk, while this probability range in people with low ASCVD risk was 40-59%. Clearly, the late initiators of LLT and AHT had significantly higher probability to fail in controlling the risk factors across all

age groups, irrespective of the ASCVD risk status at baseline, compared with those who initiated the therapies within one year of diagnosis. It is particularly important to note here that those who are deemed to have low ASCVD risk at diagnosis and initiating therapy after one year in fact had higher probability of risk factor control failure compared with those who were deemed to have high ASCVD risk at baseline and initiating the therapy within one year of diagnosis. This unique finding is reflected across all age groups, suggesting the need for revising the current guideline(s) on better assessment and stratification of primary prevention of people with high and low ASCVD risk at diagnosis, and redefine the proactive pharmacological therapeutic intervention for blood pressure and lipid control. While our study presents population level findings, more research focusing on specific reasons around therapeutic inertia in the holistic management of glycaemic and cardiovascular risk factors in the primary care setting is much needed [37,38].

This study has several strengths, including the use of a nationally representative population based data with mean 5 years of follow-up, Quality and Outcomes Framework (QOF) influenced recording of disease events with dates of events, identification of people with T2DM using a robust clinically guided machine learning approach – reducing the bias due to under-identification and misclassification [33]. While the condition of being registered in the database for at least 6 months prior to diabetes diagnosis introduces some selection bias, such restriction reduces prevalent case inclusion in our study cohort [28]. Clinical diagnosis of diabetes is unlikely to reflect true disease onset time, reflecting common challenges in the conduct of studies in incident diabetes population. For identifying patients with hypertension /dyslipidaemia we have adopted validated approach combining disease identification codes and elevated SBP /lipid measures to reduce false negative cases [31]. The definitions of hypertension/dyslipidaemia subcohorts were based on the clinical diagnosis or elevated SBP/ lipids prior to or within 6 months of diagnosis of T2DM. While the

choice of such threshold was based on clinical and data considerations, we have conducted sensitivity analyses changing this threshold to 0-3 months, producing consistent results with the main analyses. Overall data capture in UK primary care EMR for risk factor control is good in view of pay for performance for assessment (QOF) of these risk factors. All prescriptions in UK primary care are also recorded on the EMR. While some missing clinical and laboratory data in EMRs could be due to both random as well as non-random reasons, use of validated multiple imputation of missing risk factors data in EMRs have strengthen our ability to evaluate the longitudinal risk factor dynamics in the study population enabling us to generate population level evidence with greater statistical robustness [35]. To define baseline high ASCVD risk, those with missing obesity categorisation were assumed not to have grade 2+ obesity, intentionally underestimating the number of people with high risk. One of the weakness of this study is the non-availability of reliable data on life-style advices for risk factor control. The approach to cardiovascular risk stratification based on EMRs is different than how the primary care clinicians are generally advised to estimate the risk at patient level. Our assertion on people at high risk depends on the risk assessment being valid, whilst we have considered combinations of reasonable risk factors to identify people by high/low risk in primary prevention setting.

The UK EMR did not contain any medication adherence data. Although the lack of information on medication adherence is a common problem in all clinical studies, detailed validation studies of EMRs suggest a high level of agreement between EMR prescription data and the pharmacy claims data, especially in medications for chronic diseases [39]. Other limitations include unavoidable indication bias that remains as a common problem in any EMR based study, and lack of detailed data on socioeconomic characteristics, diet, and physical activity. Finally, the other

pharmacologic effects and potential benefits of early initiation of treatment with novel anti-diabetic and cardioprotective therapies that benefit cardiovascular health are beyond the scope of this study. Despite these limitations, we believe that nationally representative EMRs, large cohort size, robust study design and advanced data mining methods applied, ensure reliable epidemiological inferences and reflect real-world experience of treatment patterns for general population over time.

To conclude, significant delay in initiating cardioprotective medications when needed, was observed in people with newly diagnosed T2DM. This resulted in very high probability of clinically unacceptable blood pressure and lipid burden during disease progression at population level. We have demonstrated that irrespective of baseline ASCVD risk status, earlier cardioprotective treatment initiation when needed, may reduce at least 20% of uncontrolled lipid and blood pressure burden at population level. Findings presented in this study suggest revisiting the guidelines for proactive management of hypertension and dyslipidaemia, particularly in people with young-onset T2DM.

ACKNOWLEDGEMENTS

SKP and JL conceptualized and designed the study. JL and OM conducted the data extraction. JL and SKP jointly conducted the statistical analyses. The first draft of the manuscript was developed by JL, OM and SKP, while KK, CX and AZ contributed in the interpretation of results and finalisation of the manuscript. SKP and JL had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Melbourne EpiCentre gratefully acknowledges the support from the National Health and Medical Research Council and the Australian Government's National Collaborative Research Infrastructure Strategy (NCRIS) initiative through Therapeutic Innovation Australia. JL has been supported by a RMIT University PhD Scholarship.

Source of funding

No separate funding was obtained for this project.

Declaration of interests

SKP has acted as a consultant and/or speaker for Novartis, GI Dynamics, Roche, AstraZeneca, Guangzhou Zhongyi Pharmaceutical and Amylin Pharmaceuticals LLC. He has received grants in support of investigator and investigator initiated clinical studies from Merck, Novo Nordisk, AstraZeneca, Hospira, Amylin Pharmaceuticals, Sanofi-Aventis and Pfizer. KK has served as a consultant for and received speaker fees from Amgen, AstraZeneca, Bayer, Berlin-Chemie AG/Menarini Group, Boehringer Ingelheim, Eli Lilly, Merck Sharp & Dohme, NAPP, Novartis, Novo Nordisk, Roche, Sanofi-Aventis, Servier, has served on an advisory board for AstraZeneca, Eli Lilly, Merck Sharp & Dohme, Novo Nordisk, Sanofi-Aventis, and has received grant in support of investigator and investigator initiated trials from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Merck Sharp & Dohme, Novartis, Novo Nordisk, Pfizer, Sanofi-Aventis, Servier. KK is supported by the National Institute for Health Research (NIHR) Applied Research Collaboration East Midlands (ARC EM) and the NIHR Leicester Biomedical Research Centre (BRC). JL, OM, CX and AZ have no conflict of interest to declare.

Data availability

IQVIA Medical Research Data UK incorporating THIN, THIN is a registered trademark of Cegedim SA in the United Kingdom and other countries. Reference made to the THIN database is intended to be descriptive of the data asset licensed by IQVIA. This work uses de-identified data provided by patients as a part of their routine primary care. Complete data is not available due to license agreement. Aggregated data may be provided upon request.

REFERENCES

1. World Health Organization. Raised cholesterol. 2020; Global Health Observatory (GHO) data,. Available at: https://www.who.int/gho/ncd/risk_factors/cholesterol_text/en/. Accessed 10Sep2020, 2020.
2. Patel KK, Gomes MB, Charbonnel B, et al. Global patterns of comprehensive cardiovascular risk factor control in patients with type 2 diabetes mellitus: Insights from the DISCOVER study. *Diabetes, Obesity and Metabolism.* 2020;23(1):39-48.
3. Montvida O, Cai X, Paul SK. Cardiovascular Risk Factor Burden in People With Incident Type 2 Diabetes in the U.S. Receiving Antidiabetic and Cardioprotective Therapies. *Diabetes Care.* 2019;42(4):644-650.
4. Chiang JI, Hanlon P, Li T-C, et al. Multimorbidity, mortality, and HbA1c in type 2 diabetes: A cohort study with UK and Taiwanese cohorts. *PLoS Med.* 2020;17(5):e1003094.
5. Zghebi SS, Steinke DT, Rutter MK, Ashcroft DM. Eleven-year multimorbidity burden among 637 255 people with and without type 2 diabetes: a population-based study using primary care and linked hospitalisation data. *BMJ Open.* 2020;10(7):e033866.
6. Haug N, Deischinger C, Gyimesi M, Kautzky-Willer A, Thurner S, Klimek P. High-risk multimorbidity patterns on the road to cardiovascular mortality. *BMC Medicine.* 2020;18(1):44.
7. Association AD. Standards of Medical Care in Diabetes—2020. *Diabetes Care.* 2020;43(Supplement 1).
8. NICE. Cardiovascular disease: risk assessment and reduction, including lipid modification. 2019.
9. NICE. Hypertension in adults: diagnosis and management. 2019.
10. Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J.* 2020;41(1):111-188.
11. Khunti K, Ceriello A, Cos X, De Block C. Achievement of guideline targets for blood pressure, lipid, and glycaemic control in type 2 diabetes: A meta-analysis. *Diabetes Research and Clinical Practice.* 2018;137:137-148.
12. Khunti K, Nikolajsen A, Thorsted BL, Andersen M, Davies MJ, Paul SK. Clinical inertia with regard to intensifying therapy in people with type 2 diabetes treated with basal insulin. *Diabetes Obes Metab.* 2016;18(4):401-409.
13. Paul SK, Klein K, Thorsted BL, Wolden ML, Khunti K. Delay in treatment intensification increases the risks of cardiovascular events in patients with type 2 diabetes. *Cardiovascular Diabetology.* 2015;14(1):100.
14. Gabbay RA, Kendall D, Beebe C, et al. Addressing Therapeutic Inertia in 2020 and Beyond: A 3-Year Initiative of the American Diabetes Association. *Clin Diabetes.* 2020:cd200053.
15. Okemah J, Peng J, Quiñones M. Addressing Clinical Inertia in Type 2 Diabetes Mellitus: A Review. *Adv Ther.* 2018;35(11):1735-1745.
16. Khunti S, Khunti K, Seidu S. Therapeutic inertia in type 2 diabetes: prevalence, causes, consequences and methods to overcome inertia. *Ther Adv Endocrinol Metab.* 2019;10.
17. Rea F, Corrao G, Merlino L, Mancia G. Initial Antihypertensive Treatment Strategies and Therapeutic Inertia. *Hypertension.* 2018;72(4):846-853.

18. Xu W, Goldberg SI, Shubina M, Turchin A. Optimal systolic blood pressure target, time to intensification, and time to follow-up in treatment of hypertension: population based retrospective cohort study. *BMJ.* 2015;350.
19. Muntner P, Hardy ST, Fine LJ, et al. Trends in Blood Pressure Control Among US Adults With Hypertension, 1999-2000 to 2017-2018. *JAMA.* 2020;324(12):1190.
20. Bruckert E, Parhofer KG, Gonzalez-Juanatey JR, et al. Proportion of High-Risk/Very High-Risk Patients in Europe with Low-Density Lipoprotein Cholesterol at Target According to European Guidelines: A Systematic Review. *Adv Ther.* 2020;37(5):1724-1736.
21. Leeson P. Hypertension and cardiovascular risk in young adult life: insights from CAVI. *Eur Heart J Suppl.* 2017;19(suppl_B):B24-B29.
22. Pollock BD, Harville EW, Mills KT, Tang W, Chen W, Bazzano LA. Cardiovascular Risk and the American Dream: Life Course Observations From the BHS (Bogalusa Heart Study). *J Am Heart Assoc.* 2018;7(3).
23. Kempegowda P, Chandan JS, Abdulrahman S, Chauhan A, Saeed MA. Managing hypertension in people of African origin with diabetes: Evaluation of adherence to NICE Guidelines. *Primary Care Diabetes.* 2019;13(3):266-271.
24. Karlsson SA, Franzen S, Svensson A-M, Miftaraj M, Eliasson B, Andersson Sundell K. Prescription of lipid-lowering medications for patients with type 2 diabetes mellitus and risk-associated LDL cholesterol: a nationwide study of guideline adherence from the Swedish National Diabetes Register. *BMC Health Serv Res.* 2018;18(1):900.
25. de Vries FM, Voorham J, Hak E, Denig P. Prescribing patterns, adherence and LDL-cholesterol response of type 2 diabetes patients initiating statin on low-dose versus standard-dose treatment: a descriptive study. *Int J Clin Pract.* 2016;70(6):482-492.
26. Blak B, Thompson M, Dattani H, Bourke A. Generalisability of The Health Improvement Network (THIN) database: demographics, chronic disease prevalence and mortality rates. *Journal of Innovation in Health Informatics.* 2011;19(4):251-255.
27. Vezyridis P, Timmons S. Evolution of primary care databases in UK: a scientometric analysis of research output. *BMJ Open.* 2016;6(10):e012785.
28. Koye DN, Ling J, Dibato J, Khunti K, Montvida O, Paul SK. Temporal Trend in Young-Onset Type 2 Diabetes—the Macrovascular and Mortality Risk: Study of U.K. Primary Care Electronic Medical Records. *Diabetes Care.* 2020.
29. Nicholson BD, Aveyard P, Hamilton W, et al. The internal validation of weight and weight change coding using weight measurement data within the UK primary care Electronic Health Record. *Clinical Epidemiology.* 2019;11:145-155.
30. Khan NF, Harrison SE, Rose PW. Validity of diagnostic coding within the General Practice Research Database: a systematic review. *Br J Gen Pract.* 2010;60(572):e128-e136.
31. Peng M, Chen G, Kaplan GG, et al. Methods of defining hypertension in electronic medical records: validation against national survey data. *J Public Health (Oxf).* 2016;38(3):e392-e399.
32. Weng S, Kai J, Akyea R, Qureshi N. Detection of familial hypercholesterolaemia: external validation of the FAMCAT clinical case-finding algorithm to identify patients in primary care. *The Lancet Public Health.* 2019;4(5):e256-e264.

33. Owusu Adjah ES, Montvida O, Agbeve J, Paul SK. Data Mining Approach to Identify Disease Cohorts from Primary Care Electronic Medical Records: A Case of Diabetes Mellitus. *The Open Bioinformatics Journal.* 2017;10(1).
34. Ingram WM, Baker AM, Bauer CR, et al. Defining major depressive disorder cohorts using the EHR: Multiple phenotypes based on ICD-9 codes and medication orders. *Neurology, Psychiatry and Brain Research.* 2020;36:18-26.
35. Thomas G, Klein K, Paul SK. Statistical challenges in analysing large longitudinal patient-level data: The danger of misleading, clinical inferences with imputed data. *Journal of the Indian Society of Agricultural Statistics.* 2014;68(2):39-54.
36. Kim HJ, Fay MP, Feuer EJ, Midthune DN. Permutation tests for joinpoint regression with applications to cancer rates. *Stat Med.* 2000;19(3):335-351.
37. Karam SL, Dendy J, Polu S, Blonde L. Overview of Therapeutic Inertia in Diabetes: Prevalence, Causes, and Consequences. *Diabetes Spectrum.* 2020;33(1):8-15.
38. Zhu NA, Harris SB. Therapeutic Inertia in People With Type 2 Diabetes in Primary Care: A Challenge That Just Won't Go Away. *Diabetes Spectrum.* 2020;33(1):44-49.
39. Rowan CG, Flory J, Gerhard T, et al. Agreement and validity of electronic health record prescribing data relative to pharmacy claims data: A validation study from a US electronic health record database. *Pharmacoepidemiology and Drug Safety.* 2017;26(8):963-972.

Table 1: Baseline characteristics of study cohort by age groups at the time of type 2 diabetes diagnosis.

	Age group	18-39 (N= 20,675)	40-49 (N= 40,692)	50-59 (N= 65,115)	60-69 (N= 73,396)	70-79 (N= 55,047)	Total (N= 254,925)
Follow-up from Dx (years)	Mean (SD)	5.3 (3.3)	5.4 (3.3)	5.4 (3.4)	5.4 (3.3)	5.0 (3.3)	5.3 (3.3)
Age (years)	Mean (SD)	33 (5.2)	45 (2.8)	55 (2.9)	64 (2.9)	74 (2.8)	58 (12.6)
Male	N (%)	10,345 (50)	25,021 (61)	38,983 (60)	42,543 (58)	27,861 (51)	144,753 (57)
Smoking status	Current, N (%)	6,492 (31)	13,914 (34)	22,214 (34)	23,585 (32)	15,130 (27)	81,335 (32)
	Unknown, N (%)	3,357 (16)	4,884 (12)	6,414 (10)	6,145 (8)	5,029 (9)	25,829 (10)
Townsend score category	Middle Class, N (%)	3,857 (19)	7,665 (19)	12,332 (19)	13,631 (19)	10,342 (19)	47,827 (19)
	Least Affluent, N (%)	6,538 (32)	12,832 (32)	20,145 (31)	22,903 (31)	16,868 (31)	79,286 (31)
	Unknown, N (%)	2,853 (14)	5,492 (13)	9,016 (14)	10,394 (14)	7,726 (14)	35,481 (14)
HbA1c (%)	N (% non-missing)	11,333 (55)	27,292 (67)	45,435 (70)	51,869 (71)	38,426 (70)	174,355 (68)
	Mean (SD)	8.6 (2.4)	8.4 (2.3)	8.1 (2.2)	7.8 (2.1)	7.5 (1.9)	7.9 (2.1)
HbA1c ≥7.5% [58 mmol/mol]	N (%)	6,533 (58)	14,693 (54)	20,795 (46)	19,016 (37)	11,603 (30)	72,640 (42)
Body weight (kg)	N (% non-missing)	13,704 (66)	29,754 (73)	48,378 (74)	54,836 (75)	39,669 (72)	186,341 (73)
	Mean (SD)	102.4 (26.8)	101.0 (23.4)	96.5 (21.1)	90.8 (18.9)	83.4 (16.7)	93.2 (21.5)
BMI (kg/m^2)	N (% non-missing)	13,569 (66)	29,556 (73)	48,118 (74)	54,577 (74)	39,414 (72)	185,234 (73)
	Mean (SD)	35.2 (8.4)	34.6 (7.6)	33.5 (6.8)	31.9 (6.1)	30.1 (5.4)	32.6 (6.8)
Obesity Grade 1	N (%)	3,301 (24)	8,490 (29)	15,349 (32)	17,869 (33)	11,796 (30)	56,805 (31)
Obesity Grade 2+	N (%)	6,357 (47)	12,551 (42)	16,993 (35)	14,355 (26)	6,523 (17)	56,779 (31)
SBP (mmHg)	N (% non-missing)	14,328 (69)	32,455 (80)	54,585 (84)	63,867 (87)	48,215 (88)	213,450 (84)
	Mean (SD)	130 (15.1)	135 (15.6)	138 (15.8)	140 (15.6)	140 (15.8)	138 (15.9)
High SBP	N (%)	3,601 (25)	12,654 (39)	26,739 (49)	35,877 (56)	28,615 (59)	107,486 (50)
LDL-C (mmol/L)	N (% non-missing)	7,631 (37)	21,112 (52)	37,582 (58)	44,122 (60)	32,166 (58)	142,613 (56)
	Mean (SD)	3.1 (1.0)	3.2 (1.0)	3.1 (1.0)	2.9 (1.0)	2.7 (1.0)	3.0 (1.0)
High LDL-C	N (%)	5,374 (70)	15,656 (74)	27,312 (73)	29,299 (66)	19,645 (61)	97,286 (68)
LDL-C ≥3.4 mmol/L	N (%)	2,955 (39)	8,921 (42)	14,935 (40)	13,637 (31)	7,322 (23)	47,770 (33)
LDL-C or non-HDL-C	N (% non-missing)	9,973 (48)	27,012 (66)	46,485 (71)	53,748 (73)	39,012 (71)	176,230 (69)
High LDL-C or non-HDL-C	N (%)	8,062 (81)	22,684 (84)	37,899 (82)	39,809 (74)	25,949 (67)	134,403 (76)
Triglyceride (mmol/L)	N (% non-missing)	9,637 (47)	25,800 (63)	44,213 (68)	50,577 (69)	36,365 (66)	166,592 (65)
	Median (Q1, Q3)	2.1 (1.5, 3.3)	2.1 (1.5, 3.2)	2.0 (1.4, 2.9)	1.9 (1.4, 2.6)	1.7 (1.2, 2.3)	1.9 (1.4, 2.7)
Triglyceride ≥2.26 mmol/L	N (%)	4,473 (46)	11,912 (46)	18,199 (41)	17,009 (34)	9,269 (25)	60,862 (37)
ASCVD	N (%)	315 (2)	2,221 (5)	7,884 (12)	16,200 (22)	17,939 (33)	44,559 (17)

Chronic kidney disease	N (%)	657 (3)	2,709 (7)	8,208 (13)	18,146 (25)	23,905 (43)	53,625 (21)
Microvascular disease	N (%)	957 (5)	3,486 (9)	9,728 (15)	20,013 (27)	25,092 (46)	59,276 (23)
Hypertension	N (%)	5,686 (28)	19,908 (49)	42,113 (65)	55,547 (76)	44,642 (81)	167,896 (66)
Dyslipidaemia	N (%)	10,028 (49)	26,862 (66)	45,558 (70)	50,521 (69)	35,396 (64)	168,365 (66)
Hypertension and dyslipidaemia	N (%)	3,521 (17)	14,274 (35)	30,952 (48)	39,673 (54)	29,900 (54)	118,320 (46)
High ASCVD risk*	N (%)	8,988 (44)	23,354 (61)	39,073 (68)	41,244 (72)	27,109 (73)	139,768 (66)
Depression	N (%)	5,028 (24)	11,226 (28)	16,912 (26)	16,801 (23)	10,391 (19)	60,358 (24)
Any mental illness	N (%)	7,287 (35)	15,988 (39)	25,474 (39)	27,749 (38)	18,618 (34)	95,116 (37)
Cancer excluding melanoma	N (%)	285 (1)	955 (2)	2,912 (4)	6,321 (9)	7,371 (13)	17,844 (7)
Antihypertensive therapy (AHT)	N (%)	3,362 (16)	13,391 (33)	31,732 (49)	45,845 (62)	39,322 (71)	133,652 (52)
AHT including 6m post index	N (%)	4,878 (24)	17,606 (43)	38,168 (59)	52,042 (71)	43,062 (78)	155,756 (61)
Lipid-lowering therapy (LLT)	N (%)	740 (4)	5,195 (13)	17,219 (26)	31,156 (42)	28,398 (52)	82,708 (32)
LLT including 6m post index	N (%)	3,704 (18)	15,924 (39)	34,211 (53)	47,039 (64)	37,067 (67)	137,945 (54)

*High ASCVD risk: ≥2 risk factors of current smoking, grade 2+ obesity, hypertension, dyslipidaemia, or microvascular disease (including kidney diseases), in people without ASCVD.

Table 2: Baseline characteristics of dyslipidaemia sub-cohort by age groups at the time of type 2 diabetes diagnosis.

	Age group	18-39 (N= 10,028)	40-49 (N= 26,862)	50-59 (N= 45,558)	60-69 (N= 50,521)	70-79 (N= 35,396)	Total (N= 168,365)
Follow-up from Dx (years)	Mean (SD)	5.0 (3.3)	5.3 (3.3)	5.3 (3.3)	5.3 (3.3)	5.0 (3.2)	5.2 (3.3)
Age (years)	Mean (SD)	34 (4.7)	45 (2.8)	55 (2.9)	64 (2.8)	74 (2.8)	59 (11.7)
Male	N (%)	6,051 (60)	17,011 (63)	27,238 (60)	28,941 (57)	17,320 (49)	96,561 (57)
Smoking status	Current, N (%)	3,741 (37)	10,188 (38)	16,776 (37)	17,359 (34)	10,505 (30)	58,569 (35)
	Unknown, N (%)	416 (4)	794 (3)	1,288 (3)	1,307 (3)	1,013 (3)	4,818 (3)
Townsend score category	Middle Class, N (%)	1,870 (19)	5,108 (19)	8,641 (19)	9,344 (18)	6,671 (19)	31,634 (19)
	Least Affluent, N (%)	3,194 (32)	8,364 (31)	14,108 (31)	15,799 (31)	10,788 (30)	52,253 (31)
	Unknown, N (%)	1,365 (14)	3,665 (14)	6,271 (14)	7,152 (14)	4,947 (14)	23,400 (14)
HbA1c (%)	N (% non-missing)	7,630 (76)	20,789 (77)	35,100 (77)	38,505 (76)	26,695 (75)	128,719 (76)
	Mean (SD)	8.7 (2.3)	8.5 (2.2)	8.1 (2.2)	7.8 (2.1)	7.5 (1.9)	8.0 (2.1)
HbA1c ≥7.5% [58 mmol/mol]	N (%)	4,616 (60)	11,324 (54)	16,072 (46)	14,157 (37)	7,980 (30)	54,149 (42)
Body weight (kg)	N (% non-missing)	8,293 (83)	22,414 (83)	37,259 (82)	40,861 (81)	27,879 (79)	136,706 (81)
	Mean (SD)	104.0 (25.4)	101.1 (22.7)	96.5 (20.7)	90.6 (18.5)	83.3 (16.3)	93.2 (21.0)
BMI (kg/m^2)	N (% non-missing)	8,229 (82)	22,280 (83)	37,079 (81)	40,712 (81)	27,749 (78)	136,049 (81)
	Mean (SD)	35.4 (8.0)	34.5 (7.3)	33.5 (6.6)	31.9 (6.0)	30.1 (5.3)	32.6 (6.6)
Obesity Grade 1	N (%)	2,085 (25)	6,636 (30)	12,055 (33)	13,616 (33)	8,458 (30)	42,850 (31)
Obesity Grade 2+	N (%)	3,917 (48)	9,334 (42)	13,023 (35)	10,533 (26)	4,538 (16)	41,345 (30)
SBP (mmHg)	N (% non-missing)	8,556 (85)	24,316 (91)	41,855 (92)	47,249 (94)	33,458 (95)	155,434 (92)
	Mean (SD)	132 (14.8)	136 (15.4)	139 (15.7)	140 (15.6)	140 (15.8)	139 (15.7)
High SBP	N (%)	2,473 (29)	9,779 (40)	21,017 (50)	27,274 (58)	20,497 (61)	81,040 (52)
LDL-C (mmol/L)	N (% non-missing)	6,150 (61)	18,015 (67)	32,049 (70)	36,077 (71)	25,040 (71)	117,331 (70)
	Mean (SD)	3.4 (0.8)	3.4 (0.9)	3.3 (0.9)	3.1 (1.0)	2.9 (0.9)	3.2 (1.0)
High LDL-C	N (%)	5,374 (87)	15,656 (87)	27,312 (85)	29,299 (81)	19,645 (78)	97,286 (83)
LDL-C ≥3.4 mmol/L	N (%)	2,955 (48)	8,921 (50)	14,935 (47)	13,637 (38)	7,322 (29)	47,770 (41)
LDL-C or non-HDL-C	N (% non-missing)	8,162 (81)	23,240 (87)	39,776 (87)	43,897 (87)	30,147 (85)	145,222 (86)
High LDL-C or non-HDL-C	N (%)	8,062 (99)	22,684 (98)	37,899 (95)	39,809 (91)	25,949 (86)	134,403 (93)
Triglyceride (mmol/L)	N (% non-missing)	7,581 (76)	21,466 (80)	36,824 (81)	40,422 (80)	27,552 (78)	133,845 (79)
	Median (Q1, Q3)	2.3 (1.6, 3.5)	2.3 (1.6, 3.4)	2.1 (1.5, 3.0)	1.9 (1.4, 2.7)	1.8 (1.3, 2.4)	2.0 (1.4, 2.8)
Triglyceride ≥2.26 mmol/L	N (%)	3,933 (52)	10,784 (50)	16,512 (45)	15,085 (37)	8,034 (29)	54,348 (41)
ASCVD	N (%)	167 (2)	1,590 (6)	5,928 (13)	12,266 (24)	12,796 (36)	32,747 (19)

Chronic kidney disease	N (%)	355 (4)	1,952 (7)	6,276 (14)	13,475 (27)	16,666 (47)	38,724 (23)
Microvascular disease	N (%)	464 (5)	2,443 (9)	7,304 (16)	14,666 (29)	17,382 (49)	42,259 (25)
Hypertension	N (%)	3,521 (35)	14,274 (53)	30,952 (68)	39,673 (79)	29,900 (84)	118,320 (70)
High ASCVD risk*	N (%)	7,137 (72)	19,891 (79)	33,296 (84)	33,679 (88)	20,619 (91)	114,622 (85)
Depression	N (%)	2,466 (25)	7,555 (28)	12,206 (27)	12,084 (24)	7,058 (20)	41,369 (25)
Any mental illness	N (%)	3,642 (36)	10,806 (40)	18,310 (40)	19,862 (39)	12,462 (35)	65,082 (39)
Cancer excluding melanoma	N (%)	119 (1)	611 (2)	1,933 (4)	4,239 (8)	4,695 (13)	11,597 (7)
Antihypertensive therapy (AHT)	N (%)	2,027 (20)	9,959 (37)	24,157 (53)	33,790 (67)	27,358 (77)	97,291 (58)
AHT including 6m post index	N (%)	3,032 (30)	13,117 (49)	28,810 (63)	37,976 (75)	29,514 (83)	112,449 (67)
Lipid-lowering therapy (LLT)	N (%)	571 (6)	4,196 (16)	13,580 (30)	23,383 (46)	20,147 (57)	61,877 (37)
LLT including 6m post index	N (%)	2,988 (30)	13,042 (49)	27,389 (60)	35,697 (71)	26,356 (74)	105,472 (63)

*High ASCVD risk: ≥2 risk factors of current smoking, grade 2+ obesity, hypertension, dyslipidaemia or microvascular disease (including kidney diseases), in people without ASCVD.

Table 3: Baseline characteristics of hypertension sub-cohort by age groups at the time of type 2 diabetes diagnosis.

	Age group	18-39 (N= 5,686)	40-49 (N= 19,908)	50-59 (N= 42,113)	60-69 (N= 55,547)	70-79 (N= 44,642)	Total (N= 167,896)
Follow-up from Dx (years)	Mean (SD)	5.4 (3.4)	5.6 (3.3)	5.5 (3.4)	5.4 (3.3)	5.1 (3.3)	5.4 (3.3)
Age (years)	Mean (SD)	34 (4.5)	45 (2.8)	55 (2.8)	65 (2.8)	74 (2.8)	61 (11.0)
Male	N (%)	3,538 (62)	12,493 (63)	25,437 (60)	32,077 (58)	22,063 (49)	95,608 (57)
Smoking status	Current, N (%)	1,912 (34)	6,912 (35)	14,587 (35)	18,095 (33)	12,519 (28)	54,025 (32)
	Unknown, N (%)	608 (11)	1,590 (8)	2,932 (7)	3,306 (6)	2,976 (7)	11,412 (7)
Townsend score category	Middle Class, N (%)	1,052 (19)	3,733 (19)	8,040 (19)	10,217 (18)	8,368 (19)	31,410 (19)
	Least Affluent, N (%)	1,809 (32)	6,254 (31)	12,986 (31)	17,346 (31)	13,676 (31)	52,071 (31)
	Unknown, N (%)	786 (14)	2,719 (14)	5,736 (14)	7,818 (14)	6,278 (14)	23,337 (14)
HbA1c (%)	N (% non-missing)	3,641 (64)	13,854 (70)	29,978 (71)	40,063 (72)	31,836 (71)	119,372 (71)
	Mean (SD)	8.5 (2.2)	8.2 (2.1)	8.0 (2.1)	7.7 (2.0)	7.4 (1.8)	7.8 (2.0)
HbA1c ≥7.5% [58 mmol/mol]	N (%)	2,129 (58)	7,106 (51)	12,961 (43)	14,005 (35)	9,203 (29)	45,404 (38)
Body weight (kg)	N (% non-missing)	4,271 (75)	15,512 (78)	32,694 (78)	43,113 (78)	33,370 (75)	128,960 (77)
	Mean (SD)	112.4 (27.2)	105.7 (23.6)	98.8 (21.2)	91.9 (19.0)	83.9 (16.7)	93.9 (21.5)
BMI (kg/m^2)	N (% non-missing)	4,230 (74)	15,424 (77)	32,546 (77)	42,943 (77)	33,193 (74)	128,336 (76)
	Mean (SD)	37.6 (8.4)	36.0 (7.5)	34.2 (6.8)	32.4 (6.1)	30.3 (5.4)	32.9 (6.7)
Obesity Grade 1	N (%)	982 (23)	4,420 (29)	10,573 (32)	14,444 (34)	10,223 (31)	40,642 (32)
Obesity Grade 2+	N (%)	2,499 (59)	7,730 (50)	12,821 (39)	12,287 (29)	5,892 (18)	41,229 (32)
SBP (mmHg)	N (% non-missing)	4,786 (84)	17,628 (89)	37,934 (90)	50,980 (92)	40,921 (92)	152,249 (91)
	Mean (SD)	144 (13.0)	144 (14.1)	144 (14.7)	143 (14.8)	142 (15.2)	143 (14.8)
High SBP	N (%)	3,601 (75)	12,654 (72)	26,739 (70)	35,877 (70)	28,615 (70)	107,486 (71)
LDL-C (mmol/L)	N (% non-missing)	2,575 (45)	11,205 (56)	25,761 (61)	34,913 (63)	27,182 (61)	101,636 (61)
	Mean (SD)	3.2 (1.0)	3.2 (1.0)	3.1 (1.0)	2.9 (1.0)	2.7 (1.0)	2.9 (1.0)
High LDL-C	N (%)	1,862 (72)	8,272 (74)	18,461 (72)	22,851 (65)	16,491 (61)	67,937 (67)
LDL-C ≥3.4 mmol/L	N (%)	1,054 (41)	4,659 (42)	9,827 (38)	10,231 (29)	5,966 (22)	31,737 (31)
LDL-C or non-HDL-C	N (% non-missing)	3,443 (61)	14,365 (72)	31,808 (76)	42,467 (76)	33,015 (74)	125,098 (75)
High LDL-C or non-HDL-C	N (%)	2,884 (84)	12,114 (84)	25,782 (81)	31,140 (73)	21,880 (66)	93,800 (75)
Triglyceride (mmol/L)	N (% non-missing)	3,356 (59)	13,737 (69)	30,367 (72)	40,069 (72)	30,766 (69)	118,295 (70)
	Median (Q1, Q3)	2.3 (1.6, 3.5)	2.2 (1.5, 3.3)	2.0 (1.5, 2.9)	1.9 (1.4, 2.6)	1.7 (1.3, 2.3)	1.9 (1.4, 2.7)
Triglyceride ≥2.26 mmol/L	N (%)	1,748 (52)	6,562 (48)	12,588 (41)	13,559 (34)	7,894 (26)	42,351 (36)
ASCVD	N (%)	198 (3)	1,512 (8)	5,963 (14)	13,391 (24)	15,367 (34)	36,431 (22)

Chronic kidney disease	N (%)	300 (5)	1,673 (8)	6,147 (15)	15,140 (27)	20,768 (47)	44,028 (26)
Microvascular disease	N (%)	382 (7)	2,034 (10)	7,082 (17)	16,494 (30)	21,686 (49)	47,678 (28)
Dyslipidaemia	N (%)	3,521 (62)	14,274 (72)	30,952 (73)	39,673 (71)	29,900 (67)	118,320 (70)
High ASCVD risk*	N (%)	4,435 (81)	15,710 (85)	31,112 (86)	35,970 (85)	24,625 (84)	111,852 (85)
Depression	N (%)	1,465 (26)	5,452 (27)	10,747 (26)	12,641 (23)	8,439 (19)	38,744 (23)
Any mental illness	N (%)	2,082 (37)	7,786 (39)	16,339 (39)	20,960 (38)	15,026 (34)	62,193 (37)
Cancer excluding melanoma	N (%)	101 (2)	453 (2)	1,824 (4)	4,684 (8)	5,916 (13)	12,978 (8)
Antihypertensive therapy (AHT)	N (%)	1,967 (35)	10,214 (51)	26,508 (63)	40,462 (73)	35,345 (79)	114,496 (68)
AHT including 6m post index	N (%)	2,925 (51)	13,382 (67)	31,632 (75)	45,545 (82)	38,306 (86)	131,790 (78)
Lipid-lowering therapy (LLT)	N (%)	437 (8)	3,518 (18)	13,445 (32)	26,430 (48)	24,986 (56)	68,816 (41)
LLT including 6m post index	N (%)	1,594 (28)	9,075 (46)	24,318 (58)	38,154 (69)	31,761 (71)	104,902 (62)

*High ASCVD risk: ≥2 risk factors of current smoking, grade 2+ obesity, hypertension, dyslipidaemia, or microvascular disease (including kidney diseases), in people without ASCVD.

Figure 1: By age groups at the time of incident type 2 diabetes diagnosis (type 2 diabetes), proportions of those with hypertension and dyslipidaemia by year of type 2 diabetes diagnosis.

Figure 2: In Dyslipidaemia and Hypertension sub-cohorts, by high and low cardiovascular risk status and age groups at the time of type 2 diabetes diagnosis, (i) adjusted median (95% CI) months to first lipid lowering therapy (LLT) /antihypertensive (AHT) prescription, and (ii) adjusted probability (95% CI) of Lipid /SBP control failure over 24 months of follow-up in people who initiated LLT /AHT therapies within or after 12 months of diabetes diagnosis (early or late initiator).