Longitudinal audit of assessment and pharmaceutical intervention for cardiovascular risk in the Australasian Diabetes Data Network (ADDN)

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Abbreviations: ACR, Albumin-creatinine ratio; ADA, American Diabetes Association; ADDN, Australasian Diabetes Data Network; BMI, body mass index; BP, blood pressure; CSII, continuous subcutaneous insulin infusion; HbA1c, glycated haemoglobin A1c; HDL, high-density lipoprotein; HREC, Hunter New England Human Research Ethics Committee; IQR, interquartile range; ISPAD, International Society of Paediatric and Adolescent Diabetes; LDL, low-density lipoprotein; MDI, multiple daily injection; SD, standard deviation; TID, Type 1 diabetes.

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Dr Jenny Couper and Dr Arul Earnest are the guarantors of this work and, as such, 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.

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WORDS = 2103

Background

Cardiovascular disease is the primary cause of increased morbidity and reduced longevity in type 1 diabetes (TID)\(^1\)\(^-\)\(^2\). Children who develop T1D before 10 years are particularly at risk of cardiovascular disease in adult life\(^3\). Monitoring of cardiovascular risk factors during childhood and adolescence is recognised as an essential part of care. The International Society of Paediatric and Adolescent Diabetes (ISPAD)\(^4\), American Diabetes Association (ADA)\(^5\) and National Institute for Health and Care Excellence (NICE)\(^6\) provide recent guidelines for screening and treatment of elevated blood pressure, dyslipidaemia and albuminuria. Achievement of targets early in the course of T1D may provide early cardio-renal protection, as suggested in a two-year follow-up of children with T1D who were screened according to international guidelines\(^7\). The achievement of target metabolic control is also crucial to improve cardiovascular risk and specific risk factors such as dyslipidaemia.

Recent cross-sectional review identifies the ongoing problems with under-treatment of cardiovascular risk factors and therapeutic inertia in young people with T1D in Europe and USA\(^8\). Factors contributing to under-treatment may include adherence issues\(^9\), lack of provider familiarity with prescribing antihypertensive and lipid lowering agents in adolescents\(^10\), the perspective of patients and their families\(^11\) and delays in pharmaceutical treatment after lifestyle intervention has proven ineffective\(^10\).

We recently reported the determinants of cardiovascular risk in young people aged 2 – 25 years with T1D who were enrolled in the Australasian Diabetes Data Network (ADDN)\(^12\). This audit aims to extend this work to measure first, the frequency of assessments of blood pressure (BP), lipid profile and urinary albumin-creatinine ratio (ACR) in young people aged 2 – 25 years with T1D who are enrolled in the Australasian Diabetes Data Network (ADDN) and second, the number of participants who received pharmaceutical treatment for raised BP, abnormal lipid profile or raised ACR, according to current ISPAD\(^4\) and ADA guidelines\(^5\).

Methods

Study Design and Participants
The ADDN model involves the transfer of de-identified, prospectively collected participant data from the databases or electronic medical record systems of participating ADDN centres to a web-based server hosted by the University of Melbourne\textsuperscript{13,14}. Participating centres collect data using a common data dictionary. Data are transferred every 6 months to the registry\textsuperscript{14}. Participant data were entered prospectively at each site since January 2012.

Participants attended T1D multidisciplinary clinics in ten (eight in Australia; two in New Zealand) paediatric and five adult public teaching hospitals providing metropolitan and regional clinics. T1D was diagnosed according to ADA criteria and the date of initiation of insulin as the date of onset. Inclusion criteria were participants with T1D, aged 2 – 25 years at the beginning of ADDN follow-up. Exclusion criteria were other forms of diabetes.

As guidelines differ as to their recommendations less than 10 – 11 years and above according to age, we analysed assessments in two groups: participants who were either under 11 years or ≥11 years at their last visit.

**Thresholds for raised cardiovascular outcomes**
Thresholds for the definition of raised outcomes were according to recently published ISPAD\textsuperscript{4} and ADA\textsuperscript{5} thresholds. Thresholds for raised systolic or diastolic BP were > 95\textsuperscript{th} centile for age and gender and height on at least two occasions. Thresholds for abnormal lipid profile were LDL cholesterol >3.4mmol/L, and/or total cholesterol >5.2 mmol/L, and/or HDL <0.9mmol/L on at least one occasion. Thresholds for raised ACR were >2.5 mg/mmol in males and >3.5 mg/mmol in females on at least two occasions.

**Clinical and laboratory methods**
Height was measured using a Harpenden stadiometer, weight using a floor scale, and BP was measured sitting at rest using a sphygmomanometer with the appropriate cuff size. Insulin delivery system [continuous subcutaneous insulin infusion (CSII), multiple daily injection (MDI) or twice daily insulin injections] was recorded at each visit, as described\textsuperscript{13}. BMI standard deviation scores were calculated using the Centre for Disease Control and Prevention 2000 reference scale (CDC-2000)\textsuperscript{15}. Urine was collected as a spot early morning sample.

Lipids were measured in the non-fasting state using commercial enzymatic assays on Roche Hitachi Cobas C systems. Urinary albumin was measured by immunoassay predominantly immunoturbidimetric, and urinary creatinine by an enzyme colorimetric method (Roche Cobas C501; Hitachi). HbA\textsubscript{1c} was measured using point-of care or laboratory testing methods, commonly Vantage analyzer (Siemens Diagnostics, Camberley, U.K.) or Variant analyzer (Bio-Rad Laboratories, Hercules, CA). All laboratory methods participated in the ongoing Royal Australasian College of Pathologists Quality Assurance Programs.

Ethics approval was obtained through the Human Research Ethics Committee for each of the participating centres. Informed written consent was obtained from parents and adults over 17.9 years\textsuperscript{13}. Deidentified data from young adults transitioning to adult care was collected as a waiver.

**Statistical analysis**
Pearson Chi-squared test was used to compare proportion between two groups. For continuous variables, we used the independent student t-test to compare means between groups and presented as mean (standard deviation). In the event of departure from normality, we used the non-parametric equivalent of Wilcoxon rank-sum test and presented as median (interquartile
range). Data analysis was undertaken in Stata V16 (Stata Corp, College Station, Tx, USA) and level of significance set at 5%.

Results

Baseline characteristics
The ADDN registry included 11,562 individuals with T1D aged 2 – 25 years at the beginning of their follow-up from diagnosis. All 11,562 were included in the study. Their characteristics are presented in Table 1. Frequency of assessment and treatment of cardiovascular risk factors are presented in Table 1 and Figure 1.

Assessment of cardiovascular risk factors in participants who were under 11 years at their last visit
Blood Pressure measurements: Of 2144 individuals, 889 (41.5%) had no recorded blood pressure measurement during follow-up, 281 (13.1%) had one measurement, and the remainder had two or more measurements.
Lipids measurements: Of 2,144 individuals, 1,755 (81.9%) had no recorded lipids measurement, 281 (13.1%) had one measurement, and the remainder had two or more measurements.
ACR measurements: Of 2,144 individuals, 2035 (94.9%) had no recorded ACR measurement, 90 (4.2%) had one measurement, and the remainder had two or more measurements.

Assessment of cardiovascular risk factors in participants who were ≥11 years at their last visit
Frequency of assessment increased with longer duration of type 1 diabetes and older age.

Blood Pressure measurements: Of 9418 individuals, 2954 (31%) had no recorded blood pressure measurement during follow-up, 853 (9.1%) had one measurement of blood pressure, and the remainder had two or more measurements.

Lipids measurements: Of 9418 individuals, 4690 (49.8%) had no recorded lipids measurement, 1813 (19.3%) had one measurement, and the remainder had two or more measurements.

ACR measurements: Of 9418 individuals, 5761 (61.2%) had no recorded ACR measurement, 1378 (14.6%) had one measurement and the remainder had two or more measurements.

Pharmaceutical Treatment of cardiovascular risk factors
Only 2/ 2144 participants under 11 years were treated for any cardiovascular risk factor; in both cases for an abnormal lipid profile with statins.

In participants ≥11 years at their last visit there was no difference in gender, HbA1c, or remoteness (metropolitan, regional or remote) as determined by post code at diagnosis between those that were and were not treated for an abnormal cardiovascular risk factor. Duration of T1D was longer in those treated for any risk factor (p=0.02). BMI z-score was higher in those treated for an abnormal lipid profile (p<0.001). Blood pressure measurements were more frequent in those treated for any risk factor and in those treated for raised ACR ((Table 1).

In participants ≥11 years at their last visit, who had any raised cardiovascular risk factor during follow-up, only 66/2441 (2.9%) received pharmaceutical treatment.
Treatment of raised blood pressure: 978/6464 (15.1%) participants who were ≥11 years at their last visit and who had blood pressure assessments during follow-up met criteria for raised blood pressure (Table 1). Of these, 34/978 (3.5%) were prescribed one or more anti-hypertensive medications over follow-up, namely ACE inhibitors n=27, angiotensin receptor blockers n=6, calcium channel blockers n=1, beta blockers n=4, alpha blockers n=3, diuretics n=1.

Treatment of an abnormal lipid profile: 1588/4728 (33.6%) participants who were ≥11 years at their last visit and who had lipid assessments during follow-up met criteria for an abnormal lipid profile (Table 1). Of these, 14/1588 (0.9%) were prescribed statins.

Treatment of raised ACR: 248/3657 (6.8%) participants who were ≥11 years at their last visit and who had ACR assessments during follow-up met criteria for raised ACR. Of these, 18/248 (7.2%) participants were prescribed ACE inhibitors n=12, or angiotensin receptor blockers n=6.
Table 1: Demographic and clinical characteristics of ADDN participants, according to testing for and treatment of cardiovascular risk factors

<table>
<thead>
<tr>
<th>Variable</th>
<th>Whole cohort</th>
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<th>Not Treated</th>
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<tbody>
<tr>
<td>N participants (≥11 years)</td>
<td>11562 (9418)</td>
<td>66</td>
<td>2375</td>
<td>34</td>
<td>944</td>
<td>14</td>
<td>1574</td>
<td>18</td>
<td>231</td>
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<td>Age at last visit in years, mean (SD)</td>
<td>15.9 (5.6)</td>
<td>19.5 (3.0)</td>
<td>18.9 (5.5)</td>
<td>19.0 (2.4)</td>
<td>17.2 (3.1)</td>
<td>20.2 (3.6)</td>
<td>19.6 (6.1)</td>
<td>18.3 (2.3)</td>
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<tr>
<td>Female</td>
<td>5590 (48.3%)</td>
<td>37 (56.1%)</td>
<td>1305 (54.9%)</td>
<td>20 (58.8%)</td>
<td>554 (58.7%)</td>
<td>10 (71.4%)</td>
<td>884 (56.2%)</td>
<td>9 (52.9%)</td>
<td>112 (48.5%)</td>
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<tr>
<td>Male</td>
<td>5972 (51.7%)</td>
<td>29 (43.9%)</td>
<td>1070 (45.1%)</td>
<td>14 (41.2%)</td>
<td>390 (41.3%)</td>
<td>4 (29.0%)</td>
<td>690 (43.8%)</td>
<td>8 (47.1%)</td>
<td>119 (51.5%)</td>
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<tr>
<td>Age at diagnosis in years, mean (SD)</td>
<td>8.6 (4.6)</td>
<td>8.2 (4.5)</td>
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<td>8.4 (4.2)</td>
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<td>6.8 (4.2)</td>
<td>8.7 (4.5)</td>
<td>7.7 (4.7)</td>
<td>8.9 (4.7)</td>
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<td>Duration of diabetes at last visit in years, median (IQR)</td>
<td>6.3 (2.9, 10.7)</td>
<td>10.8 (7.6, 14.50)</td>
<td>9.5 (6.1, 13.2) **</td>
<td>10.1 (7.4, 10.0)</td>
<td>8.1 (5.2, 11.2)</td>
<td>14.7 (9.4, 17) **</td>
<td>9.6 (5.9, 13.8) **</td>
<td>8.7 (7.4, 14.0)</td>
<td>12.0 (7.9, 18.7)</td>
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<td>Number of visits, mean (SD)</td>
<td>15.7 (13.4)</td>
<td>24.2 (15.0)</td>
<td>23.4 (15.3)</td>
<td>25.5 (12.3)</td>
<td>25.4 (13.0)</td>
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<td>HbA1c at last visit, median (IQR)</td>
<td>8.2 (7.3, 9.3)</td>
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<td>8.2 (7.8, 7.8)</td>
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<td>1.5 (0.4)**</td>
<td>0.8 (0.9)**</td>
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<td>0.4 (1.0)</td>
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<td>BMI z-score at last visit, mean (SD)</td>
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<td>23 (35.4%)</td>
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<td>MDI</td>
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<tr>
<td>Aboriginal/ Torres Strait Islanders</td>
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<tr>
<td>Non-Aboriginal/ Torres Strait Islanders</td>
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<td>58 (100%)</td>
<td>1701 (93.6%)</td>
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<td>New Zealand Maori</td>
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<td>0 (0%)</td>
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<td>Australian born</td>
<td>7826 (84.4%)</td>
<td>48 (87.3%)</td>
<td>1711 (86.5%)</td>
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<tr>
<td>Metro</td>
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<td>36 (73.5%)</td>
<td>1393 (83.8%)</td>
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<tr>
<td>Regional</td>
<td>1190 (15.1%)</td>
<td>11 (22.4%)</td>
<td>239 (14.4%)</td>
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<td>Remote</td>
<td>121 (1.5%)</td>
<td>2 (4.1%)</td>
<td>30 (1.8%)</td>
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<td>Remoteness according to post code at last visit †:</td>
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<tr>
<td>Metro</td>
<td>8416 (84%)</td>
<td>48 (78.7%)</td>
<td>1872 (84.4%)</td>
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<tr>
<td>Regional</td>
<td>1488 (14.9%)</td>
<td>12 (19.7%)</td>
<td>325 (14.6%)</td>
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<td>Remote</td>
<td>English as main language</td>
<td>Number of lipid profile measurements, mean (SD)</td>
<td>Number of blood pressure measurements, mean (SD)</td>
<td>Number of ACR measurements, mean (SD)</td>
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<td>113 (1.1%)</td>
<td>6498 (96.9%)</td>
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<td>English as main language</td>
<td>1 (1.6%)</td>
<td>21 (84.0%) **</td>
<td>3.2 (2.1)</td>
<td>10.5 ** (7.5)</td>
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<td>22 (1.0%)</td>
<td>1429 (97.3%) **</td>
<td>2.9 (3.6)</td>
<td>8 ** (8.0)</td>
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<td>12.9 (5.7) *</td>
<td>5.4 (2.1)</td>
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<td>4.4 (4.9)</td>
<td>5.9 (6.1) *</td>
<td>9.7 (15.5)</td>
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* p<0.001  **p<0.05

† Missing data for the whole cohort were as follows: Insulin Delivery at last visit n= 543 (remaining 507 were on BD regimen), Indigenous Status n=2298, Remoteness according to post code at diagnosis n=3664, Remoteness according to post code at last visit n=1545, Australian born n=2289, English as main language  n=4856.
Conclusions
We report low rates of assessment and particularly low rates of pharmaceutical treatment for abnormal cardiovascular risk factors, namely raised BP, abnormal lipid profiles and raised ACR, in this longitudinal Australasian cohort. Assessment rates were lower in children less than 11 years, as recommended. Approximately half had blood pressure measurements recorded, and the majority had neither lipids nor ACR measured; neither of which are recommended to be regularly assessed before 10 – 11 years of age, other than baseline lipids at diagnosis or in those with a family history of dyslipidaemia. While the majority of adolescents who were 11 years or older at their last visit had blood pressure measurements recorded, the frequency of any assessment for lipids and ACR remained at approximately 40-50%. Over all just under 3.0% of participants ≥11 years at their last visit, who had a raised cardiovascular risk factor during follow-up, had received pharmaceutical treatment. Rates of treatment were particularly low for the treatment of an abnormal lipid profile. As expected duration of T1D was longer in those who received treatment for any risk factor, and BMI was higher in those treated for an abnormal lipid profile. Otherwise there were no clear differences in gender, HbA1c or socioeconomic demographic of remoteness between participants who did and did not have assessments or receive treatment. These findings are noteworthy – the centres were in teaching hospital settings, and clearly the endocrinologists were circumspect about prescribing life-long statins, in particular, in young people.

Rates of pharmaceutical treatment in participants who were 11 years or older at their last visit were comparable to those of a recent cross-sectional audit of the Type 1 diabetes exchange clinic network (T1DX) and the Prospective Diabetes Follow-up (DPV) registries across US and Europe in which ≤5% adolescents and young adults aged 12 – 26 years with raised blood pressure or an abnormal lipid profile received anti-hypertensives or statins. Further, these rates of treatment of hypertension or dyslipidaemia were not higher than those reported in a large cross-sectional DPV cohort over 15 years ago. The frequency of detection of microalbuminuria in young people with T1D in T1DX and SEARCH has been reported at 4.4% and 9.2% respectively, comparable with our findings, but with higher treatment rates. Failure to detect raised ACR has implications for the development of both micro- and macrovascular complications.

Strengths of the audit are the prospectively collected longitudinal data for a relatively long average duration of 8 years in those over 11 years at their last visit, in comparison to other audits in this age group. There are also several limitations. It is difficult to separate failure to enter data in the ADDN database from a lack of assessment, or assessment by an external pathology provider. An audit of participant case notes across the 15 sites to resolve this was beyond the scope of this project. While blood pressure is measured and entered at the time of the clinic visit, pathology results are uploaded regularly prior to 6 monthly ADDN data reviews. In addition, we could not audit the uptake of lifestyle intervention as recommended as a first line measure for an abnormal lipid profile before beginning medication, nor the use of ambulatory blood pressure monitoring in the case of raised clinic blood pressure, as is also recommended. Finally, ADDN, while representative of the ethnicity, urban and regional demographic, and health care systems in Australia and New Zealand, represents at present approximately 60% of all young people in Australia and New Zealand with T1D.

In conclusion, our findings highlight the need to prioritise discussion around uptake of screening and pharmaceutical intervention guidelines for the prevention of premature cardiovascular disease in young people with T1D, in addition to interventions to improve metabolic control. Further investigation will explore solutions to increase the frequency of
assessments and to guide appropriate treatment for cardiovascular risk\textsuperscript{19}, both from the physicians’ and the patients’ perspectives.

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Figure 1 shows the frequency of assessment and frequency of treatment of cardiovascular risk factors in the ADDN participants. The Whole Cohort stacked bars refer to all participants. The stacked bars for blood pressure, lipids and ACR refer to those participants who were aged 11 years of more at their last visit and are categorised into those who were not tested, those who were tested and had normal measures, and those who were tested and had abnormal measures; the last are further divided into either treated or untreated. The numbers of treated participants are represented on the right hand scale.
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