Lower mortality and cardiovascular event rates in patients with latent autoimmune diabetes in adults (LADA) as compared with type 2 diabetes and insulin deficient diabetes: A Cohort Study of 4,368 Patients.

Wod, Mette; Thomsen, Reimar Wernich; Yderstræde, Knud Bonnet; Beck-Nielsen, Henning; Højlund, Kurt; Pedersen, L.

Published in: Diabetes Research and Clinical Practice

DOI: 10.1016/j.diabres.2018.02.042

Publication date: 2018

Document version Peer reviewed version

Document license CC BY-NC-ND

Citation for published version (APA):

Terms of use
This work is brought to you by the University of Southern Denmark through the SDU Research Portal. Unless otherwise specified it has been shared according to the terms for self-archiving. If no other license is stated, these terms apply:

- You may download this work for personal use only.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying this open access version

If you believe that this document breaches copyright please contact us providing details and we will investigate your claim. Please direct all enquiries to puresupport@bib.sdu.dk
Lower mortality and cardiovascular event rates in patients with latent autoimmune diabetes in adults (LADA) as compared with type 2 diabetes and insulin deficient diabetes: A Cohort Study of 4,368 Patients

Mette Wod, Reimar W. Thomsen, Lars Pedersen, Knud B. Yderstraede, Henning Beck-Nielsen, Kurt Højlund

PII: S0168-8227(17)32005-3
DOI: https://doi.org/10.1016/j.diabres.2018.02.042
Reference: DIAB 7255

To appear in: Diabetes Research and Clinical Practice

Received Date: 18 December 2017
Revised Date: 2 February 2018
Accepted Date: 27 February 2018

Please cite this article as: M. Wod, R.W. Thomsen, L. Pedersen, K.B. Yderstraede, H. Beck-Nielsen, K. Højlund, Lower mortality and cardiovascular event rates in patients with latent autoimmune diabetes in adults (LADA) as compared with type 2 diabetes and insulin deficient diabetes: A Cohort Study of 4,368 Patients, Diabetes Research and Clinical Practice (2018), doi: https://doi.org/10.1016/j.diabres.2018.02.042

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.
Lower mortality and cardiovascular event rates in patients with latent autoimmune diabetes in adults (LADA) as compared with type 2 diabetes and insulin deficient diabetes

A Cohort Study of 4,368 Patients

Mette Wod¹,²*, MSc, PhD; Reimar W. Thomsen³, MD, PhD; Lars Pedersen³, MSc, PhD; Knud B. Yderstraede¹, MD, PhD; Henning Beck-Nielsen¹, MD, DMSc; Kurt Højlund¹,⁴, MD, DMSc

¹Diabetes Research Centre, Department of Endocrinology, Odense University Hospital, Odense, Denmark; ²Epidemiology, Biostatistics & Biodemography, University of Southern Denmark, Odense, Denmark; ³Department of Clinical Epidemiology, Institute of Clinical Medicine, Aarhus University Hospital, Aarhus, Denmark; ⁴Section of Molecular Diabetes & Metabolism, Institute of Clinical Research and Institute of Molecular Medicine, University of Southern Denmark.

Corresponding author:
*Mette Wod, MSc PhD
Diabetes Research Centre, Department of Endocrinology, Odense University Hospital, Odense, Denmark
Kloverveenget 6, 5000 Odense C, Denmark
Telephone: (+45) 6550 9588
Email: mwod@health.sdu.dk

Word count: Abstract 250 (250 allowed), main text =2,693 + Legends = 147 (4,000 allowed)

Running title: Clinical outcomes in patients with LADA

Key Words: LADA, outcomes, mortality
Abstract

Background: Latent Autoimmune Diabetes in Adults (LADA) is the second most common form of diabetes, but data on its clinical course and prognosis are scarce. We compared long-term risk of mortality and cardiovascular outcomes in patients with LADA, type 2 diabetes mellitus (T2D), and insulin deficient diabetes (IDD).

Methods: We conducted a cohort study of 4,368 adults with diabetes referred to the Department of Endocrinology, Odense University Hospital, Denmark, between 1997 and 2012. Data on comorbidity, cardiovascular outcomes and death were obtained from prospective medical databases. We compared adjusted hazard ratios (HRs) of mortality and cardiovascular outcomes for patients with LADA, T2D and IDD, respectively.

Results: We included 327 patients with LADA, 3,539 with T2D and 502 with IDD. At diagnosis, patients with LADA were older (50 years (IQR 37-59)) than IDD patients (40 years (IQR 28-52)), but younger than patients with T2D (55 years (IQR 45-64)). During a median follow-up period of 6.6 years (IQR 3.4-9.4), patients with IDD had higher mortality than patients with LADA, age- and gender-adjusted HR 2.2 (95% CI, 1.5-3.2). T2D also conferred higher mortality than LADA, HR 1.4 (95% CI, 1.0-1.9). Compared with LADA patients, cardiovascular outcome rates were increased both with IDD, HR 1.2 (95% CI, 0.7-2.0) and T2D, HR 1.2 (95% CI, 0.8-1.8), with the strongest association observed for T2D vs. LADA and acute myocardial infarction HR 1.7 (95% CI, 0.8-3.5).

Conclusion: LADA seems to be associated with lower mortality and lower risk of cardiovascular events, compared with both T2D and IDD.
Introduction

Between 5% and 10% of patients who present with phenotypic characteristics similar to type 2 diabetes mellitus (T2D) have circulating islet autoantibodies as seen in type 1 diabetes mellitus (T1D) [1-3]. This subgroup, which represents the second most common form of diabetes, has been defined as Latent Autoimmune Diabetes in Adults (LADA) [4, 5]. In LADA, unlike T1D there is no absolute insulin requirement at the time of diagnosis [6] and the disease can frequently be controlled initially with diet or oral antihyperglycemic drugs although progression towards insulin deficiency is faster than in T2D [7-9]. Even though LADA may account for up to 10% of all diabetes and thus be more common than T1D [1], studies investigating long-term outcomes including macrovascular complications [10-13] and mortality [10-12] in patients with LADA compared with T1D and T2D patients are scarce. A few previous studies suggest that patients with LADA have similar risk of coronary heart disease [10, 11, 13], cardiac-related mortality [10-12] and all-cause [10-12] mortality compared to patients with T2D, but previous studies have been hampered by small sample size, inclusion of selected patients with LADA [11, 13-17], short follow-up [13, 15] and missing comparisons with T1D [11-14, 16, 18]. Thus, firm conclusions regarding long-term clinical outcomes of LADA patients compared with T1D and T2D patients from the same source population have not yet been made. In the present study, we used prospectively collected data and linkage with Danish health registries [19] to conduct a cohort study of patients with different forms of diabetes referred to the Department of Endocrinology, Odense University Hospital from 1997 to 2012. The aim of our project was to determine to what extent the prognosis of LADA patients regarding long-term risk of mortality and cardiovascular outcomes is different from that of T2D and a previously defined group of insulin deficient diabetes (IDD) comparable to T1D [20].
Methods
Setting and study population

We conducted this study in the Region of Southern Denmark, with a mixed rural/urban population of approximately 1.15 million. We included all adult patients (aged ≥ 18 years) referred to the Department of Endocrinology, Odense University Hospital between January 1, 1997 and June 30, 2012. Odense University Hospital is a 1000-bed hospital serving as a tertiary referral center for the Region of Southern Denmark, but also as a local hospital for a catchment area of 300,000 residents. The Danish National Health Service provides free universal tax-supported health care, including reimbursement of most prescription medication costs [21]. Since 1968, all Danish residents have been assigned a unique civil registration number (CPR number), which is used in all health databases and permits unambiguous record linkage among different Danish medical and administrative registries [19]. Population-based registries in Denmark offer unique possibilities for studies on long-term occurrence of cardiovascular outcomes and mortality. We had access to data from 1977-2013.

Patients with diabetes referred to the Department of Endocrinology, OUH

We identified all patients with diabetes referred to the Department of Endocrinology at Odense University Hospital, Denmark from 1997 to 2012 [20]. The patient cohort, comprising 4,374 patients, and its baseline phenotypic characteristics at admission to the Department of Endocrinology at Odense University Hospital have been described in detail elsewhere [20]. Presence of autoimmunity was assessed through linkage to a laboratory database, which prospectively stores records on all specimens send by the Department of Endocrinology, at the time of patient enrollment. The date of diabetes diagnosis was obtained from a local diabetes database or from the patients’ medical records. The cohort comprised a total of 4,368 patients with diabetes.
Categorization of diabetes

Type of diabetes was categorized according to each patient’s fasting C-peptide and anti-GAD antibody (GADab) status at their first admission to the Department of Endocrinology at Odense University Hospital. LADA was defined as GADab positive patients with a fasting C-peptide > 300 pmol/l. IDD was defined as patients with fasting C-peptide < 300 pmol/l independent of GAD status. T2D was defined as anti-GADab negative patients with fasting C-peptide > 300 pmol/l [20].

Comorbidities

Based on each patient’s complete hospital discharge history before the diagnosis of diabetes, we collected data on 19 different major disease categories as included in the Charlson comorbidity index (except for diabetes, as this was our index disease) [19, 22]. Disease categories include major risk factors for CVD and death, such as previous cardiovascular and cerebrovascular diseases, chronic pulmonary disease, liver disease, renal disease, and cancer. We defined three comorbidity levels as low (Charlson score of 0), medium (1–2), and high (3+).

Outcomes

Main outcomes in our study were 1) any major cardiovascular disease (CVD) event, defined as first hospital contact after diabetes diagnosis with either acute myocardial infarction (AMI), heart failure (HF) or stroke (apoplexy, APO), and these events individually; and 2) death from any cause. Complete data on incident hospital contacts with CVD events were ascertained by linkage with the Danish National Patient Register (DNPR) [23]. The DNPR covers discharge records from all hospitalizations in Danish non-psychiatric hospitals since 1977, and all hospital outpatient and emergency department visits since 1995 [24]. Diagnoses in the DNRP are coded according to the International Classification of Diseases (ICD), 8th revision (ICD-8) codes until 1994 and 10th
revision (ICD-10) thereafter. [25]. Exact dates of death from any cause were ascertained from the Danish Civil Registration System.

**Statistical analysis**

Follow-up extended from the date of first Odense University Hospital contact with a diagnosis of diabetes until the end of 2013, death, or emigration out of Denmark, whichever came first. We constructed Kaplan-Meier survival curves for the three cohorts with LADA, T2D and IDD. We calculated incidence rates of any first event of CVD, AMI, HF, APO, and mortality per 1000 person years. We then used Cox proportional hazards regression analysis to compare the hazard rates of CVD events and death in the three cohorts, computing adjusted hazard ratios (HRs) for CVD events and death among patients with T2D and IDD respectively, as compared with LADA patients as the reference group while controlling for covariates. Successive adjustments were performed for 1) age and gender; 2) age, gender and modified Charlson Comorbidity Index (CCI) score level excluding disease categories likely to constitute classical chronic diabetes complications (i.e., previous MI, peripheral vascular disease, cerebrovascular disease, and renal disease); and 3) age, gender and full CCI score level. We used duration of diabetes (in years) as the underlying scale in the Cox model, which provides adjustment for confounding from duration of diabetes disease. Descriptive data were compared using unpaired t-test and chi² test were appropriate. Data were analyzed using SAS software (Version 9.2; SAS Institute, Cary, NC) and STATA version 12.1. The Danish Data Protection Agency and Aarhus University Hospital Registry Board approved the study.
Results

Descriptive data

Of 4,374 eligible patients referred to the Department of Endocrinology OUH during the study period 4,368 patients residing in Denmark at referral were included in the study. 327 (7.5%) patients with diabetes had LADA, 3,539 (81.0%) had T2D and 502 (11.5%) had IDD. Patients with LADA were older at debut (49.9 (interquartile range (IQR), 36.6-59.2) years) than patients with IDD (39.9 (IQR, 28.0-51.7) years, p<0.001) but younger than those with T2D (54.6 (IQR, 45.3-63.5) years, p<0.001). Table 1 shows characteristics of patients with IDD, LADA and T2D. Median follow-up time was 6.6 years (IQR 3.4-9.4). The prevalence of having a comorbidity index level of >1 was higher in patients with T2D (34%) compared with patients with IDD (21%) or LADA (25%) (p<0.001 and p=0.001, respectively) (Table 1).

Cardiovascular outcomes

Among LADA patients, 8.9% experienced any CVD outcome event during a median follow-up of 6.8 years. The respective summary measures were 7.9% and 5.9 years in the IDD cohort and 11.6% and 6.2 years in the T2D cohort. The incidence rate of any CVD outcome event was 13.0 (95% CI, 8.9-19.0) per 1000 person years at risk (pyrs) for LADA, 13.0 (95% CI, 9.5-17.8) for IDD and 18.2 (95% CI, 16.4-20.2) for T2D (Table 2). Compared with the LADA patients, the crude CVD HR for IDD patients was 1.0 (95% CI, 0.6-1.6). Adjusting for gender differences and in particular for the lower age among IDD patients increased their CVD HR: adjusted HR vs. LADA, to 1.2 (95% CI, 0.7-2.0). The crude CVD HR for T2D patients vs. LADA was increased at 1.4 (95% CI, 0.9-2.1). Adjusting for higher age as well as gender decreased the HR for T2D vs. LADA patients to 1.2 (95% CI, 0.8-1.8). Further adjustment for comorbidities with or without diabetic complications left the CVD risk estimates virtually unchanged (HRs are shown in Table 2).
Generally, the direction of the risk estimates for IDD and T2D versus LADA were similar when AMI, HF and APO were analyzed separately, as for CVD events overall, see Table 2. The AMI rate per 1000 pyrs was 3.1 (95% CI, 1.5-6.5) for LADA, 2.6 (95% CI, 1.3-5.2) for IDD and 5.7 (95% CI, 4.8-6.8) for T2D, corresponding to age- and gender adjusted HRs of 1.0 (95% CI, 0.3-2.7) for IDD vs. LADA and 1.7 (95% CI, 0.8-3.5) for T2D vs LADA. The HF rate was 4.8 (95% CI, 2.7-8.7) per 1000 pyrs for LADA, 3.2 (95% CI, 1.7-6.0) for IDD and 8.3 (95% CI, 7.1-9.6) for T2D, corresponding to age- and gender adjusted HRs of 0.9 (95% CI, 0.4-2.2) for IDD vs. LADA and 1.4 (95% CI, 0.7-2.5) for T2D vs. LADA. In contrast to cardiac event rates, the APO rates were similarly high for all three diabetes types, i.e.; 6.8 (95% CI, 4.1-11.3) per 1000 pyrs for LADA, 6.5 (95% CI, 4.2-10.1) for IDD and 7.2 (95% CI, 6.2-8.5) for T2D, corresponding to age- and gender adjusted HRs of 1.2 (95% CI, 0.6-2.3) for IDD vs. LADA and 0.9 (95% CI, 0.5-1.5) for T2D vs. LADA.

Mortality
Mortality rate was 16.9 (95% CI, 12.4-23.0) per 1000 pyrs for LADA, 23.9 (95% CI, 19.1-30.0) for IDD and 28.6 (95% CI, 26.5-30.8) for T2D. Thus, in contrast with findings for CVD event rates, LADA showed lower crude mortality rates, not only vs. T2D but also vs. IDD. Figure 1 shows mortality curves for LADA, IDD and T2D. Mortality appeared to rise earlier after first contact in both IDD and T2D patients, compared with LADA patients. The mortality HR for IDD vs. LADA was 1.4 (95% CI, 1.0-2.1). When adjusting for lower age and gender, a substantially increased mortality HR was observed for IDD vs. LADA: 2.2 (95% CI, 1.5-3.2). Additional adjustment for comorbidities did not have much impact on the estimate; age-, gender- and comorbidity- (except diabetic complications) adjusted mortality HR 2.3 (95% CI, 1.5-3.3), age- gender- and full Charlson index-adjusted mortality HR 2.3 (95% CI, 1.5-3.4). Crude mortality HR for T2D vs. LADA was 1.7
(95% CI, 1.2-2.4). The age- and gender-adjusted HR for T2D vs. LADA was lower than the crude HR, but still increased at 1.4 (95% CI, 1.0-1.9). Additional adjustment for comorbidities (without and with diabetic complications) did not have much impact (Table 2).
Comment

In this large cohort study, LADA was associated with decreased mortality and modestly lower rates of CVD events as compared to T2D and IDD.

To our knowledge this study is one of the largest to date on the prognosis of patients with LADA, and may be the first to compare adjusted mortality rates in LADA and IDD patients. We used prospectively recorded data from independent medical databases with complete follow-up to ascertain data on comorbidity, CVD outcome events and death, thus limiting opportunities for recall, selection or surveillance bias. Finally, severe confounding by socioeconomic differences is less likely given Denmark’s universal health care [26].

Our study also has limitations. Use of routine hospital discharge data could be associated with coding errors, yet the positive predictive value of the discharge diagnoses that we used has been reported to be high [24]. By study design, patients were immortal from the time of their diabetes diagnosis until their first hospital contact at OUH. Patients with different types of diabetes may have been channeled to the OUH at different point of times in their disease course. However, we took diabetes duration into account by study design, using duration of diabetes as the underlying scale in our Cox model, and we were furthermore able to adjust for differences in a range of important comorbidities at the time of first OUH contact. As in all observational studies, there may have been residual confounding by imperfectly measured confounding factors, as well as confounding by unmeasured factors including lifestyle and socioeconomic characteristics in our study. Finally, even in our rather large study, results for many events showed limited statistical precision.

Earlier studies of LADA prognosis found no difference between patients with LADA and patients with T2D concerning cardiac-cause mortality [10-12] and all-cause mortality [11, 12]. This is striking as patients with LADA generally have a healthier metabolic profile than patients with T2D.
[20, 27-29]. We have previously found that patients with LADA had higher HbA1c but otherwise lower cardiometabolic risk (lower BMI, systolic blood pressure, triglycerides, alanine aminotransferase and higher HDL) than patients with type 2 diabetes, and that patients with IDD had higher HbA1c but otherwise lower cardiometabolic risk (lower BMI, BP, LDL, triacylglycerol, and ALT, and higher HDL) than both patients with LADA and T2D [20]. Thus, LADA defined an intermediate group regarding cardiometabolic risk factors. In a recent large multicenter study, Olsson et al., compared mortality in patients with LADA and patients with T2D followed for 9-11 years to that of individuals with no diabetes [12]. They found similarly increased age- and gender adjusted mortality (1.4-1.5 fold) for patients with LADA and patients with T2D. When adjusting for not only age and gender, but also BMI, waist-hip-ratio, physical activity, smoking, alcohol consumption, educational level, family history of diabetes, LDL and the metabolic syndrome they still found similar higher mortality HRs versus persons without diabetes for LADA patients (60% higher mortality rate) and T2D patients (40% higher mortality rate). The authors concluded that mortality in LADA was as high as in T2D despite a more favorable baseline metabolic profile, and that the increased risk was associated with poor glycemic control. In addition, they found similar increased HRs for CVD mortality in both diabetic groups compared with individuals with no diabetes [12]. These results conflict with our findings that the prognosis of LADA overall seems to be better than for both IDD and T2D. It should be mentioned that comparing LADA and IDD may not be directly comparable to comparing LADA and T1D, as IDD may include a few patients with secondary causes of diabetes with loss of residual beta cell function due to e.g. pancreatitis, pancreatic cancer and other pancreatic diseases. A study performed by Isomaa et al. found that during a follow-up period of 5.7 years, 16/90 patients with LADA died compared with 186/929 patients with T2D and that cardiovascular mortality was numerically but not statistically lower in LADA (7.4 vs. 12.4%, p=0.2) [10], to some extent corroborating our findings.
Few studies have investigated CVD outcomes in patients with LADA [10, 11, 13]. Myhill et al., besides mortality, also compared AMI and HF in patients with LADA (n=45) and T2D (n=1,210) during a follow-up period of ~4 years. [11]. They found similar HRs of AMI rates in LADA and T2D patients, whereas HF rates tended to be increased; HR 1.51 (95% CI, 0.60-3.21) in patients with LADA [11]. Similar results were reported in the study by Isomaa et al., looking at AMI in patients with LADA within the first year of diagnosis compared patients with T2D [10]. A small study of consecutive patients compared CVD risk in patients with LADA (n=26) with patients with T2D (n=198). The sample size was most likely too little to demonstrate a numerical less incidence of coronary damage (11.5% vs. 19.7%) to be numerical less prevalent in patients with LADA, whereas the incidence of peripheral vascular disease (30.8% vs. 27.1%) appeared rather similar in the two groups. However, cerebrovascular incidents were fewer in LADA than in T2D (19.2% vs. 34.9%, p<0.01) [13], corroborating our findings. A reason for the observed differences in outcomes between LADA, IDD and T2D could be due to an interaction of genetically predisposed beta cell function including factors such as insulin resistance, environmental factors and immune dysregulation [30]. Schwartz et al. propose a new classification system for diabetes in a recent study [30]. Our findings corroborate this. Due to the results of this paper demonstrating that LADA, T2D and IDD have different mortality risk, it would be interesting to examine possible markers (genomic, metabolic and proteomic) that may lead to hyperglycemia and complications derived hereof. This could be a step toward precision medicine.

In conclusion, our study suggests that patients with LADA have a lower mortality and possibly also lower CVD risk, compared with both patients with T2D and patients with IDD.
Acknowledgements: None

Funding: The study was supported by grants from Odense University Hospital. KH was funded by the Danish Council for Independent Research (including Sapere Aude, DFF Starting Grant) and the Novo Nordisk Foundation.

Duality of interest: None

Contribution statement: Dr. Wod 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, and is the guarantor.

Study concept and design: Wod, Thomsen, Yderstræde, Pedersen, Beck-Nielsen, Højlund.

Acquisition of data: Thomsen, Pedersen.

Analysis and interpretation of data: Wod, Thomsen, Pedersen, Højlund.

Drafting of the manuscript: Wod, Thomsen, Højlund.

Critical revision of the manuscript for important intellectual content: Wod, Thomsen, Pedersen Yderstræde, Beck-Nielsen, Højlund.

Statistical analysis: Wod, Pedersen.

Study supervision: Thomsen, Pedersen.
References


Figure 1. Unadjusted Kaplan-Meier survival curves with time (years) to death for patients with LADA (n=327, solid line), IDD (n=502, dashed line) and T2D (n=3,539, punctuated line).

LADA: Latent Autoimmune Diabetes in Adults

IDD: Insulin Deficient Diabetes

T2D: Type 2 Diabetes
Table 1. Characteristics among patients with insulin deficient diabetes (IDD), Latent Autoimmune Diabetes in Adults (LADA), and type 2 diabetes (T2D)

<table>
<thead>
<tr>
<th></th>
<th>IDD n=502</th>
<th></th>
<th>LADA n=327</th>
<th></th>
<th>T2D n=3,539</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age at diabetes debut in years, median(IQR)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>39.9 (28.0-51.7)</td>
<td>49.9 (36.6-59.2)</td>
<td>54.6 (45.2-63.5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>313</td>
<td>62.4%</td>
<td>175</td>
<td>53.5%</td>
<td>2,030</td>
<td>57.4%</td>
</tr>
<tr>
<td>Female</td>
<td>189</td>
<td>37.6%</td>
<td>152</td>
<td>46.5%</td>
<td>1,509</td>
<td>42.6%</td>
</tr>
<tr>
<td><strong>Pre-existing comorbidity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical conditions included in the CCI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>9</td>
<td>1.8%</td>
<td>11</td>
<td>3.4%</td>
<td>199</td>
<td>5.6%</td>
</tr>
<tr>
<td>Congestive cardiac insufficiency</td>
<td>10</td>
<td>2.0%</td>
<td>9</td>
<td>2.8%</td>
<td>216</td>
<td>6.1%</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>18</td>
<td>3.6%</td>
<td>10</td>
<td>3.1%</td>
<td>163</td>
<td>4.6%</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>21</td>
<td>4.2%</td>
<td>17</td>
<td>5.2%</td>
<td>261</td>
<td>7.4%</td>
</tr>
<tr>
<td>Dementia</td>
<td>1</td>
<td>0.2%</td>
<td>1</td>
<td>0.3%</td>
<td>19</td>
<td>0.5%</td>
</tr>
<tr>
<td>Hemiplegia</td>
<td>2</td>
<td>0.4%</td>
<td>0</td>
<td>0%</td>
<td>8</td>
<td>0.2%</td>
</tr>
<tr>
<td>Chronic pulmonary disease</td>
<td>19</td>
<td>3.8%</td>
<td>15</td>
<td>4.6%</td>
<td>279</td>
<td>7.9%</td>
</tr>
<tr>
<td>Connective tissue disease</td>
<td>10</td>
<td>2.0%</td>
<td>6</td>
<td>1.8%</td>
<td>85</td>
<td>2.4%</td>
</tr>
<tr>
<td>Peptic ulcer disease</td>
<td>21</td>
<td>4.2%</td>
<td>3</td>
<td>0.9%</td>
<td>140</td>
<td>4.0%</td>
</tr>
<tr>
<td>Mild liver disease</td>
<td>7</td>
<td>1.4%</td>
<td>5</td>
<td>1.5%</td>
<td>92</td>
<td>2.6%</td>
</tr>
<tr>
<td>Moderate or severe liver disease</td>
<td>2</td>
<td>0.4%</td>
<td>2</td>
<td>0.6%</td>
<td>25</td>
<td>0.7%</td>
</tr>
<tr>
<td>Moderate or severe renal disease</td>
<td>7</td>
<td>1.4%</td>
<td>6</td>
<td>1.8%</td>
<td>72</td>
<td>2.0%</td>
</tr>
<tr>
<td>Solid cancer</td>
<td>20</td>
<td>4.0%</td>
<td>19</td>
<td>5.8%</td>
<td>226</td>
<td>6.4%</td>
</tr>
<tr>
<td>Metastatic solid cancer</td>
<td>4</td>
<td>0.8%</td>
<td>1</td>
<td>0.3%</td>
<td>29</td>
<td>0.8%</td>
</tr>
<tr>
<td>Leukemia</td>
<td>1</td>
<td>0.2%</td>
<td>0</td>
<td>0%</td>
<td>7</td>
<td>0.2%</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>1</td>
<td>0.2%</td>
<td>0</td>
<td>0%</td>
<td>16</td>
<td>0.45%</td>
</tr>
<tr>
<td>HIV/AIDS</td>
<td>0</td>
<td>0%</td>
<td>1</td>
<td>0.3%</td>
<td>3</td>
<td>0.1%</td>
</tr>
<tr>
<td><strong>Charlson comorbidity index score</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>395</td>
<td>78.7%</td>
<td>245</td>
<td>74.9%</td>
<td>2,320</td>
<td>65.6%</td>
</tr>
<tr>
<td>1</td>
<td>63</td>
<td>12.5%</td>
<td>49</td>
<td>15.0%</td>
<td>645</td>
<td>18.2%</td>
</tr>
<tr>
<td>2</td>
<td>24</td>
<td>4.8%</td>
<td>21</td>
<td>6.4%</td>
<td>324</td>
<td>9.2%</td>
</tr>
<tr>
<td>≥3</td>
<td>20</td>
<td>4.0%</td>
<td>12</td>
<td>3.7%</td>
<td>250</td>
<td>7.1%</td>
</tr>
</tbody>
</table>

IQR = inter-quartile range
CCI = Charlson comorbidity index
Table 2. Hazard Ratios of mortality and cardiovascular events in patients with LADA, IDD and T2D.

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>N</th>
<th>Pyrs</th>
<th>Events</th>
<th>Rate</th>
<th>Crude HR* (95% CI)</th>
<th>Adj. HR† (95% CI)</th>
<th>Adj. HR‡‡ (95% CI)</th>
<th>Adj. HR‡‡‡ (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mortality</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LADA</td>
<td>327</td>
<td>2,366</td>
<td>40</td>
<td>16.9</td>
<td>1 (ref.)</td>
<td>1 (ref.)</td>
<td>1 (ref.)</td>
<td>1 (ref.)</td>
</tr>
<tr>
<td>IDD</td>
<td>502</td>
<td>3,176</td>
<td>76</td>
<td>23.9</td>
<td>1.4 (1.0-2.1)</td>
<td>2.2 (1.5-3.2)</td>
<td>2.3 (1.5-3.3)</td>
<td>2.3 (1.5-3.4)</td>
</tr>
<tr>
<td>T2D</td>
<td>3,539</td>
<td>23,221</td>
<td>663</td>
<td>28.6</td>
<td>1.7 (1.2-2.4)</td>
<td>1.4 (1.0-1.9)</td>
<td>1.3 (1.0-1.8)</td>
<td>1.4 (1.0-1.9)</td>
</tr>
<tr>
<td><strong>Any cardiovascular event</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LADA</td>
<td>302</td>
<td>2,077</td>
<td>27</td>
<td>13.0</td>
<td>1 (ref.)</td>
<td>1 (ref.)</td>
<td>1 (ref.)</td>
<td>1 (ref.)</td>
</tr>
<tr>
<td>IDD</td>
<td>479</td>
<td>2,926</td>
<td>38</td>
<td>13.0</td>
<td>1.0 (0.6-1.6)</td>
<td>1.2 (0.7-2.0)</td>
<td>1.2 (0.8-2.1)</td>
<td>1.2 (0.7-2.0)</td>
</tr>
<tr>
<td>T2D</td>
<td>3,038</td>
<td>19,274</td>
<td>351</td>
<td>18.2</td>
<td>1.4 (0.9-2.1)</td>
<td>1.2 (0.8-1.8)</td>
<td>1.2 (0.8-1.7)</td>
<td>1.2 (0.8-1.8)</td>
</tr>
<tr>
<td><strong>Acute Myocardial Infarction</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LADA</td>
<td>316</td>
<td>2,273</td>
<td>7</td>
<td>3.1</td>
<td>1 (ref.)</td>
<td>1 (ref.)</td>
<td>1 (ref.)</td>
<td>1 (ref.)</td>
</tr>
<tr>
<td>IDD</td>
<td>493</td>
<td>3,090</td>
<td>8</td>
<td>2.6</td>
<td>0.8 (0.3-2.3)</td>
<td>1.0 (0.3-2.7)</td>
<td>0.9 (0.3-2.6)</td>
<td>1.0 (0.3-2.6)</td>
</tr>
<tr>
<td>T2D</td>
<td>3,307</td>
<td>21,450</td>
<td>122</td>
<td>5.7</td>
<td>1.8 (0.9-4.0)</td>
<td>1.7 (0.8-3.5)</td>
<td>1.6 (0.8-3.5)</td>
<td>1.7 (0.8-3.6)</td>
</tr>
<tr>
<td><strong>Heart Failure</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LADA</td>
<td>322</td>
<td>2,294</td>
<td>11</td>
<td>4.8</td>
<td>1 (ref.)</td>
<td>1 (ref.)</td>
<td>1 (ref.)</td>
<td>1 (ref.)</td>
</tr>
<tr>
<td>IDD</td>
<td>495</td>
<td>3,107</td>
<td>10</td>
<td>3.2</td>
<td>0.7 (0.3-1.6)</td>
<td>0.9 (0.4-2.2)</td>
<td>1.0 (0.4-2.3)</td>
<td>0.9 (0.4-2.0)</td>
</tr>
<tr>
<td>T2D</td>
<td>3,363</td>
<td>21,772</td>
<td>180</td>
<td>8.3</td>
<td>1.7 (0.9-3.1)</td>
<td>1.4 (0.7-2.5)</td>
<td>1.4 (0.7-2.5)</td>
<td>1.3 (0.7-2.4)</td>
</tr>
<tr>
<td><strong>Stroke</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LADA</td>
<td>314</td>
<td>2,203</td>
<td>15</td>
<td>6.8</td>
<td>1 (ref.)</td>
<td>1 (ref.)</td>
<td>1 (ref.)</td>
<td>1 (ref.)</td>
</tr>
<tr>
<td>IDD</td>
<td>492</td>
<td>3,060</td>
<td>20</td>
<td>6.5</td>
<td>1.0 (0.5-1.9)</td>
<td>1.2 (0.6-2.3)</td>
<td>1.2 (0.6-2.3)</td>
<td>1.1 (0.6-2.2)</td>
</tr>
<tr>
<td>T2D</td>
<td>3,359</td>
<td>21,662</td>
<td>157</td>
<td>7.2</td>
<td>1.1 (0.6-1.8)</td>
<td>0.9 (0.5-1.5)</td>
<td>0.9 (0.5-1.5)</td>
<td>0.9 (0.5-1.5)</td>
</tr>
</tbody>
</table>

LADA: Latent Autoimmune Diabetes in Adults
IDD: Insulin Deficient Diabetes
T2D: Type 2 Diabetes
Pyrs = person years at risk
*HR = hazard ratio
† Adjusted for gender and age
‡‡ Adjusted for gender, age, and CCI except classical chronic diabetes complications (previous MI, peripheral vascular disease, cerebrovascular disease, and renal disease)
‡‡‡ Adjusted for gender, age and full CCI