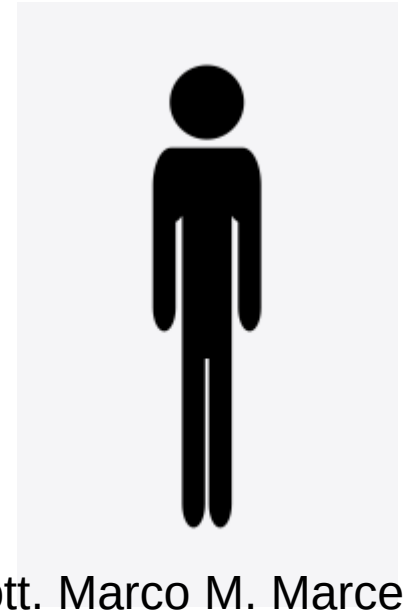
# LADA

## **L**atent **A**utoimmun **D**iabetes in **A**dult

…slowly progressive form of autoimmune diabetes
with serum immune markers of T1D…



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# Caratteristiche salienti

Table 1

Broad characteristics of LADA*

- Age >30 years**
- Family/personal history of autoimmunity
- Reduced frequency of metabolic syndrome compared with T2D—lower HOMA, lower BMI, lower blood pressure, and normal HDL compared with T2D
- No disease-specific difference in cardiovascular outcomes between these patients and those with T2D
- C-peptide levels decrease more slowly than in T1D
- Positivity for GADA as the most sensitive marker; other autoantibodies less frequent (ICA, IA-2A, ZnT8A, and tetraspanin 7 autoantibodies)
- Non–insulin requiring at onset of diabetes

Raffaella Buzzetti, Tiinamaija Tuomi et all. Management of Latent autoimmune Diabetes in Adults: A consensus statement from an international expert panel. Diabetes 2020 Oct; 69 (10): 2037-2047.

# Epidemiologia LADA

Epidemiological studies suggest that LADA may account for 2–12% of all cases of diabetes in adult population.

Naik RG, Palmer JP. Latent autoimmune diabetes in adults (LADA). *Rev Endocr Metab Disord* 2003; **4**: 233–41.

Higher disease rates are reported in Northern Europe and regions of China (7–14%) compared with African American and Hispanic individuals .

Mishra R, Hodge KM, et all. A global perspective of latent autoimmune diabetes in adults. Trends Endocrinol Metab 2018; 29:638–650.

# LADA Europe vs LADA Asia

**Table 1.** Features of LADA in Caucasian and Asian patients (ref. 28)

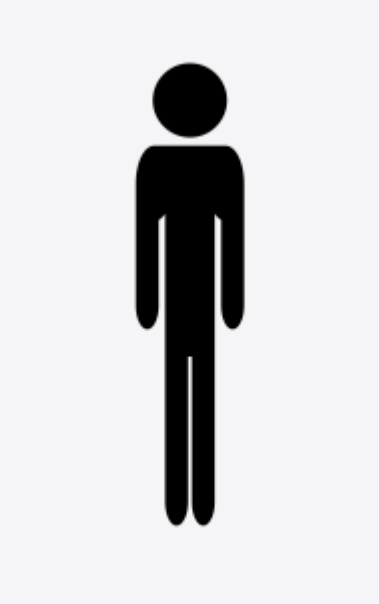
| | Caucasian LADA (*n* = 193) | Asian LADA (*n* = 39) | *P*-value |
|---|---|---|---|
| Age at diagnosis (years) | 50.3 ± 12 | 49.6 ± 8.3 | NS |
| BMI (kg/m2) | 27 ± 5.1 | 25.3 ± 3.3 | < 0.01 |
| HbA1c (%) | 7.5 ± 1.7 | 7.4 ± 1.5 | |
| Fasting blood glucose (mg/dl) | 168.1 ± 58 | 134 ± 34 | < 0.001 |
| HDL Cholesterol (mg/dl) | 50 ± 3 | 44.7 ± 11 | < 0.03 |
| Triglycerides (mg/dl) | 144 ± 104 | 201 ± 169 | < 0.01 |

Values are mean ± SD

Petrone A, Park Y, Genovese S, *et al*. for the NIRAD Study Group and the Korean National Diabetes Program Similarities and differences between Caucasian and Asian LADA. *Diabetologia* 2008; **51**: S155

# Clinica

- Lower BMI
- Lower HOMA insulin resistance
- Lower Blood pressure
- Lower dyslipidemia



Characteristics of LADA

i) Phenotypical Features Data obtained from all major studies including the UK Prospective Diabetes Study (UKPDS) (4) and the Botnia study (5) show that the autoantibody frequency (GADA) in patients diagnosed with T2D is higher in younger patients compared with older patients (e.g., in UKPDS from 34% when aged 25–34 years to 7% in older patients aged 55–65 years). On average, patients with LADA, compared with those with antibody-negative T2D, are younger at diabetes diagnosis with lower BMI and have a personal or family history of autoimmune diseases. Metabolic syndrome tends to have a similar or higher frequency in LADA compared with adult-onset T1D (5,22,26), but compared with autoantibody-negative T2D patients, LADA patients show a lower frequency, with lower HOMA of insulin resistance index (HOMA-IR) and blood pressure (BP) and less diabetic dyslipidemia (5,9). However, there is considerable heterogeneity, with some patients having a T1D phenotype (without metabolic syndrome) while others are indistinguishable from T2D (with metabolic syndrome) (22,27). Although patients with LADA have less major cardiovascular risk factors, i.e., they are leaner, with better lipid and BP profiles, there is no difference in cardiovascular outcomes in them compared with T2D patients after adjustment for traditional cardiovascular risk factors (28,29).

# Diagnosi

**Esami di laboratorio:**

- Glicemia
- Hb glicata

- Autoanticorpi:
–> Anti GAD autoantibody against glutamic acid decarboxylase
(Marker di patologia più frequente)
–> ICA, IA-2A, ZnT8A, and tetraspanin 7 autoantibodies
(Marker di patologia meno frequente)

- C-peptide
(Stadiazione della funzionalità beta pancreatica)

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# Flow-chart diagnostica

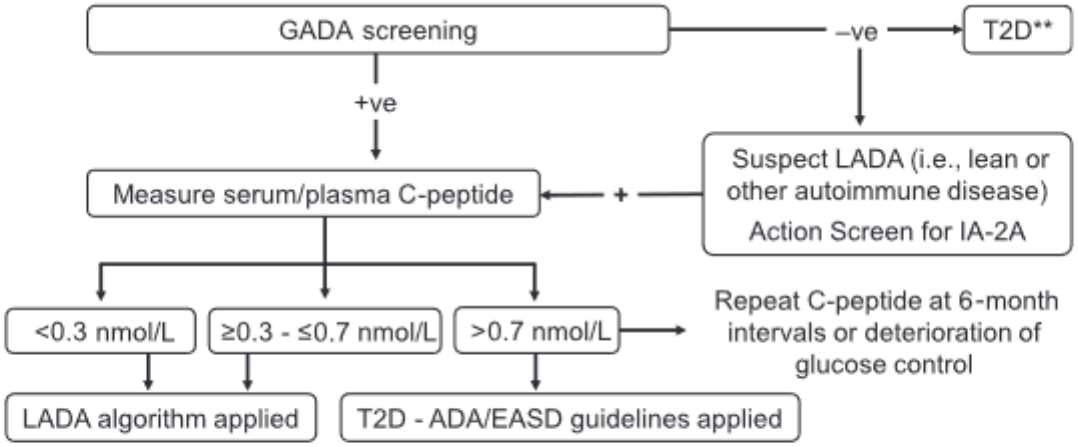


**Figure 1**—Algorithm for LADA diagnostic pathway based on autoantibody screening and C-peptide levels at diagnosis (to be used when financial restriction does not apply). **Consider also pancreatitis or monogenic diabetes.

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# Terapia LADA senza ASCVD/CKD

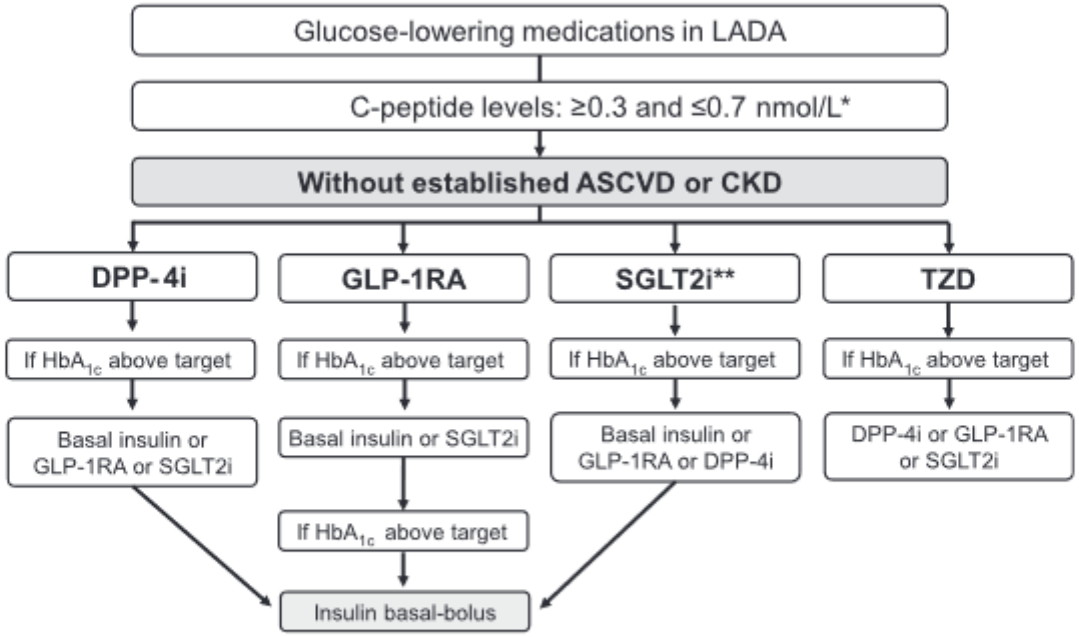


**Figure 3**—Algorithm for glucose-lowering medications in LADA patients with C-peptide levels ≥0.3 and ≤0.7 nmol/L without established ASCVD (atherosclerotic cardiovascular disease) or CKD (chronic kidney disease). *Deviation from ADA/EASD T2D algorithm. **Increased risk of diabetic ketoacidosis, especially in patients with BMI ≤27.

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# Terapia LADA con ASCVD/CKD

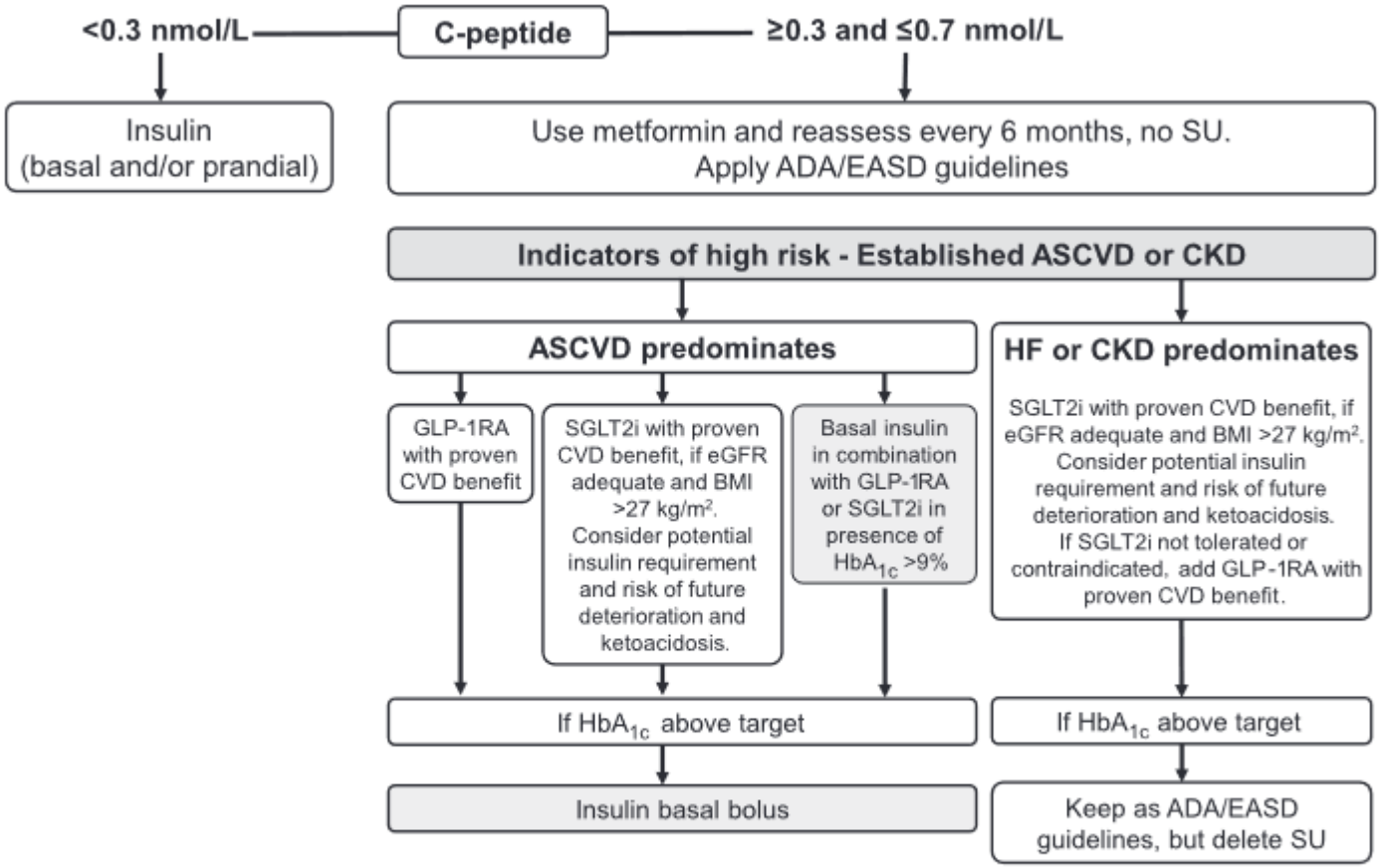


**Figure 2**—Algorithm for glucose-lowering medications in LADA patients with C-peptide <0.3 mmol/L or with C-peptide ≥0.3 and ≤0.7 nmol/L. ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HF, heart failure.

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# Terapia

## Metformina e pioglitazone

The panel concluded that there is limited evidence supporting the use of metformin and few studies using TZD, so the efficacy of both compounds appears inconclusive. For TZD, the potential risk of atypical bone fractures, macular edema, and weight gain could be a limitation to the use of these compounds.

## Insulina

The panel concluded that insulin intervention is effective and safe for LADA patients; however, it still remains to be established whether insulin should be administered in the early stages of LADA, especially when substantial residual β-cell function is present.

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# Terapia

## Sulfoniluree

The panel concluded that sulfonylureas are not recommended for the treatment of LADA, as deterioration of β-cell function as a consequence of this treatment cannot be ruled out.

## Gliptine

The panel concluded that DPP-4i may improve glycemic control in LADA patients with a good safety profile. Larger randomized studies are warranted to prove that DPP-4i might preserve C-peptide secretion.

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# Terapia

## Glifozine

The panel concluded that the approved use of SGLT2i in both T2D and selected T1D patients, in particular those overweight, suggests that they may be promising agents in LADA. However, no studies have been performed in LADA and attention should be paid to ketoacidosis in patients with medium to low C-peptide.

## GLP-1 agonisti

The panel concluded that GLP-1RA have shown beneficial results in terms of improving metabolic control in LADA patients unless C-peptide levels are very low. These drugs are approved in T2D and in insulin-treated patients, but more evidence is required in patients with LADA.