The impact of statins and RAS inhibitors on the association between delayed antidiabetic treatment and the risk of cardiovascular event in patients with a first HbA1c between 48–57 mmol/mol

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Background: In addition to lifestyle intervention, guidelines recommend initiation of antidiabetic (AD) treatment within 3 months of diagnosing type 2 diabetes (T2D). Yet, patients with an initial HbA1c level between 48 and 57 mmol/mol may await effects of lifestyle intervention up to 6 months. Omitting initial AD treatment and any lifestyle-induced remission, may affect initiation of statins and renin-angiotensin system inhibitors (RASi) and, thus, cardiovascular risk.

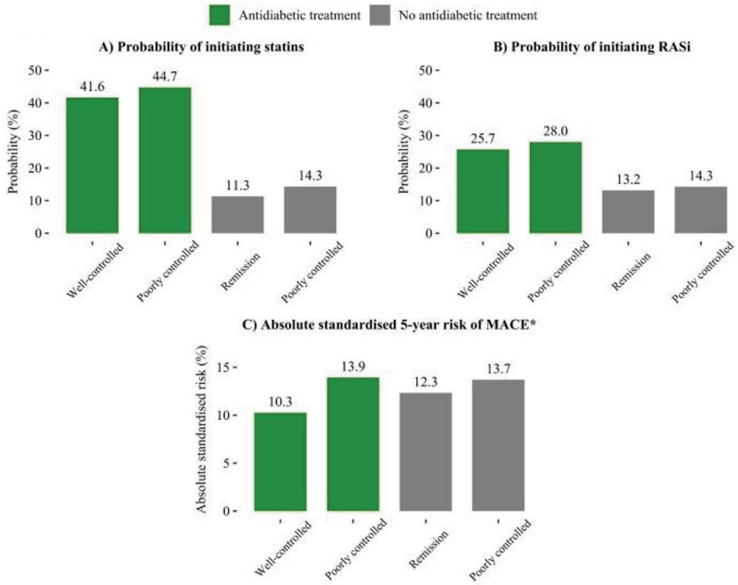
Purpose: To examine whether omission of initial AD treatment is associated with an increased 5-year risk of first-time major cardiovascular event (MACE: myocardial infarction/stroke/all-cause death) compared with well-controlled patients on AD. Further, whether lower initial use of statins and RASi could explain this excess risk of MACE.

Methods: We used Danish registers to identify patients with a first-measured HbA1c of 48–57 mmol/mol between 2014 and 2020. We included patients aged 40–80 years without prior atherosclerotic disease that were alive the following 180 days (the index date). At date of index, we divided patients into four groups according to AD treatment and achieved HbA1c (mmol/mol): well-controlled (HbA1c ≤47) on AD; poorly controlled (HbA1c ≥48) on AD; remission (HbA1c ≤47) not on AD; poorly controlled (HbA1c ≥48) not on AD. Based on a Cox-regression model and imputations of treatment values of statins and RASi from two logistic regression models, we examined to what extent the observed standardised 5-year risk of MACE within each group could be reduced if each group had the same probability of treatment initiation with statin and RASi as well-controlled patients on AD.

Results: We included 14,206 patients (median age 59 [IQR 51–68] years; 52.0% men) with the following distribution according to AD group: well-controlled on AD: 22.3%; poorly controlled on AD: 14.7%; remission not on AD: 38.3%; poorly controlled not on AD: 24.6%. Patients not on AD had lower probabilities of initiation of statins and RASi compared with patients on AD (Figure 1). Compared with well-controlled on AD, the absolute 5-year risk of MACE was increased with 3.7% (95% CI 1.6–6.1) in poorly controlled on AD; 2.1% (95% CI 0.3–3.8) in remission not on AD; 3.4% (95% CI 1.6–5.3) in poorly controlled not on AD (Figure 1 and 2). If initiation of statins and RASi were the same as in the well-controlled group on AD, patients not on AD could reduce their risk of MACE with 1.0% (95% CI 0.2–1.8) in the remission group and with 2.2% (95% CI 1.2–3.2) in the poorly controlled group (Figure 2).

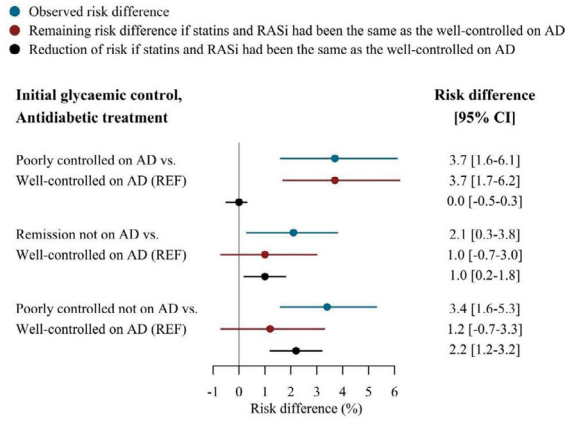
Conclusions: Patients not on initial AD treatment had an increased 5-year risk of MACE, even among those who experienced remission of T2D. Lower initial use of statin and RASi seem to explain some of the excess risk of MACE in patients not on initial AD treatment. This study emphasizes the need for greater focus on primary prevention with statins and RASi in T2D, especially among patients not on AD treatment.

Figure 1. Probability of iniating statins and RASi and absolute standardised 5-year risk of MACE, according to antidiabetic treatment and initial glycaemic control, 180 days after first-measured HbA1c ≥ 48 mmol/mol.



*Standardised to the distribution of age, sex, cohabitation status, ethnicity, income, type of requester (general practitioner or other), first-measured HbA1c level, estimated glomerular filtration rate, and comorbidities according to antidiabetic treatment and initial glycaemic control. MACE: major adverse cardiovascular event consisting of stroke, myocardial infarction, or all-cause death. RASi: renin-angiotensin system inhibitor.

Figure 2. Changes in 5-year risk of MACE if each group had the same probability of initiation with statins and RASi as the well-controlled group on antidiabetics (reference group).



AD: antidiabetic; CI: confidence interval; MACE: major adverse cardiovascular event consisting of storke, myocardial infarction or all-cause death; RASi: renin-angiotensin system inhibitor; REF: reference.