# Optimisation of quality indicators for lipid-lowering treatment of type 2 diabetes mellitus

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## ABSTRACT

**INTRODUCTION:** The Danish Adult Diabetes Database (DADD) annually reports a quality indicator for lipid-lowering treatment of type 2 diabetes mellitus (T2DM) patients. This retrospective cohort study aims to A) investigate the reasons for inadequate or lacking lipid-lowering treatment and to B) assess the validity of the DADD indicator as a measure of quality of care.

**METHODS:** A) A pop-up questionnaire enquiring about reasons for lack of treatment was added to the clinicians' data entry tool in the Central Denmark Region. B) The DADD indicator was compared on a per-clinic basis with the achieved median low-density lipoprotein (LDL) cholesterol level and with an internationally widely used indicator of lipid-lowering treatment quality.

**RESULTS:** A) A total of 3,491 patients were registered from 1 January 2013 to 28 February 2015. For 170 (62%) of 309 patients with an LDL level > 2.5 mmol/l who were not receiving lipid-lowering treatment, there was no "good" explanation for lacking treatment. Among 518 patients with an LDL level > 2.5 mmol/l despite lipid-lowering treatment, 259 (50%) did not receive high-intensity treatment. B) The DADD quality indicator was neither associated with the international quality indicator nor with the median per-clinic LDL level for T2DM patients.

**CONCLUSIONS:** A) We found substantial potential for improvement of lipid management among T2DM patients in Denmark by initiating and/or intensifying lipid-lowering treatment. B) The current DADD indicator is not a valid measure of lipid-lowering quality of care.


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Patients with type 2 diabetes (T2DM) are at a high risk of cardiovascular mortality and morbidity. A 2008 meta-analysis found a 9% reduction in all-cause mortality and a 13% reduction in vascular mortality for each mmol/l reduction in low-density lipoprotein cholesterol (LDL) [1]. Current guidelines recommend moderate-intensity statins in addition to lifestyle therapy for patients with T2DM aged 40-75 years and high-intensity statins for patients with an increased cardiovascular risk [2].

A central issue is insufficient adherence to lipid-lowering therapy [3, 4]. Studies have shown that one year after initiating statin therapy, only 40-60% of patients fill their prescriptions for statins [3], and overall adherence is 36-93% among T2DM patients. A substantial gap remains in our knowledge about the extent to which clinicians are aware of their patients' adherence.

Evidence is accumulating that better performance on treatment quality indicators leads to better outcomes [5, 6]. Studies have shown an association between treatment quality indicators and intermediate outcomes [7, 8] and an association between lipid-lowering and albuminuria treatment status and a composite of cardiovascular events and all-cause death [9].

Internationally, it is most common to measure performance of a well-validated intermediate outcome, such as: "The fraction of type 2 diabetic patients ≥ 40 years old with an LDL cholesterol > 2.5 mmol/l". Using this international indicator has been shown to improve care and cardiovascular outcomes for T2DM patients [9-11], and the indicator is now widely used in the US, Canada, The UK, the Netherlands, Sweden and Norway. However, The Danish Adult Diabetes Database (DADD) has used another indicator since 2010: "The fraction of type 2 diabetic patients ≥ 40 years old with an LDL cholesterol > 2.5 mmol/l who do not receive lipid-lowering treatment". In contrast to the international indicator, the DADD indicator has not been validated against intermediate or hard endpoints.

This retrospective study of the DADD cohort was undertaken in order to A) investigate the reasons for inadequate or lacking lipid-lowering treatment, and to B) assess the validity of the DADD indicator as a measure of quality of care.

## METHODS

This was a retrospective cohort study. The DADD cohort includes all patients with diabetes who have had contact with a hospital outpatient clinic for adult patients in Denmark. The clinician in charge of each patient's care submits data to the DADD annually. This study describes a subset of the DADD patients. Specifically, our inclusion criteria were type 2 diabetes mellitus, age above 40 years of age, followed at a hospital

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clinic for a minimum of 12 months, and a minimum of one fractionated lipid measurement including an LDL result within the previous 24 months.

We defined lack of lipid-lowering treatment as absence of at least one redeemed prescription of any lipid-lowering drug within the previous nine months before each patient's status date.

Data in part A of the study included all DADD-eligible patients with an LDL level > 2.5 mmol/l within the Central Denmark Region in the period from 1 January 2013 to 28 February 2015. For these patients, we employed data from a point-of-care pop-up questionnaire completed by clinicians while submitting DADD data during the same period. The pop-up questionnaire inquired about reasons for lack of treatment. In addition, we also employed direct electronic medical record data capture of biochemical data and data from the Danish National Prescription Registry on redeemed prescriptions for the included patients from the Central Denmark Region.

Data in part B of the study only included data from the national DADD 2014/2015 annual report. The DADD report provides only aggregated data on a per-clinic level. Thus, we used the reported median LDL levels for each clinic and treatment status percentages reported for each of the 40 Danish outpatient diabetes clinics that had reported at least 100 T2DM patients.

### Data analysis

Continuous variables are presented as mean ± standard deviation or median and interquartile ranges in case of a non-normal distribution as assessed by a Q-Q plot. Differences between groups were tested with unpaired t-test or the Mann Whitney test as appropriate. Categorical data were evaluated by the chi-squared

**TABLE 1**

Characteristics, the Central Denmark Region, January 1 2013-February 28 2015 cohort.

| | Group A vs. group B, LDL level ⟩ 2.5 mmol/l | | | Group C vs. group D, LDL level ≤ 2.5 mmol/l | | |
|---|---|---|---|---|---|---|
| | A: without treatment (N = 309) | B: with treatment (N = 518) | p-value | C: without treatment (N = 332) | D: with treatment (N = 2,332) | p-value |
| Males, n (%) | 168 (54.4) | 324 (62.5) | 0.02 | 220 (66.3) | 1,474 (63.2) | 0.28 |
| Age, mean ± SD, yrs | 60.2 ± 11.4 | 61.9 ± 10.7 | 0.025 | 61.6 ± 11.8 | 64.1 ± 10.0 | ⟨ 0.001 |
| Weight, mean ± SD, kg | 91.5 ± 18.8 (n = 293) | 93.8 ± 20.8 (n = 497) | 0.11 | 94.2 ± 23.3 (n = 312) | 94.7 ± 20.7 (n = 2,217) | NS |
| BMI, mean ± SD, kg/m$^2$ | 30.6 ± 5.6 (n = 288) | 31.4 ± 6.2 (n = 491) | 0.07 | 31.1 ± 7.0 (n = 305) | 31.7 ± 6.1 (n = 2,183) | NS |
| LDL concentration, median (25-75% IQR), mmol/l | 3.2 (2.8-3.7) | 3.0 (2.7-3.5) | ⟨ 0.001 | 2.1 (1.7-2.3) | 1.7 (1.4-2.1) | 0.005 |
| HDL concentration, median (25-75% IQR), mmol/l | 1.2 (1.1-1.4) | 1.2 (1.0-1.4) | 0.092 | 1.2 (0.9-1.5) | 1.1 (0.9-1.4) | 0.044 |
| Triglyceride concentration, median (25-75% IQR), mmol/l | 1.8 (1.3-2.7) | 2.1 (1.4-2.8) | 0.001 | 1.5 (1.1-2.5) | 1.7 (1.2-2.5) | 0.018 |
| Total cholesterol concentration, median (25-75% IQR), mmol/l | 5.3 (4.7-5.9) | 5.0 (4.6-5.6) | ⟨ 0.001 | 4.0 (3.5-4.4) | 3.7 3.2-4.1) | 0.001 |
| Smoking, % (n/N) | 20.7 (64/309) | 21.1 (108/513) | NS | 23.0 (76/330) | 20.2 (465/2,297) | 0.21 |
| DM duration, median (25-75% IQR), mo.s | 131 (55-205) (n = 307) | 151 (91-210) (n = 511) | ⟨ 0.001 | 140 (74-198) (n = 331) | 158 (98-222) (n = 2,317) | 0.006 |
| $HbA_{1c}$ concentration, mean ± SD, mmol/mol | 65.1 ± 18.4 | 65.6 ± 16.2 | NS | 60.2 ± 15.0 | 62.0 ± 14.3 | 0.028 |
| P-creatinine concentration, median (25-75% IQR), µmol/l | 75 (62-93) (n = 248) | 81 (65-107) (n = 398) | 0.002 | 75 (65-99) (n = 290) | 82 (67-110) (n = 1,911) | 0.018 |
| BP systolic, mean ± SD, mmHg | 139 ± 17 | 138 ±18 | NS | 136 ± 17 | 135 ± 16 | NS |
| BP diastolic, mean ± SD, mmHg | 81 ± 11 | 79 ± 12 | 0.059 | 79 ± 10 | 77 ± 10 | 0.001 |
| Albuminuria status, normo/micro/macro, n (%) | 199/71/30 (66/24/10) (N = 300) | 322/121/66 (63/24/13) (N = 509) | 0.43 | 218/75/27 (68/23/8) (N = 320) | 1,496/599/203 (65/26/9) (N = 2,298) | 0.55 |
| Anti-hypertensive treatment, % (n) | 70.6 (218) | 85.9 (445) | ⟨ 0.001 | 78.0 (259) | 92.3 (2,143) | ⟨ 0.001 |
| Insulin treatment, % (n) | 72.2 (223) | 71.4 (370) | 0.82 | 69.3 (230) | 75.9 (1,770) | 0.009 |
| Peroral treatment, % (n) | 61.5 (190) | 69.1 (358) | 0.025 | 67.8 (225) | 72.4 (1,689) | 0.078 |
| GLP1 analogue treatment, % (n) | 28.2 (87) | 29.9 (155) | 0.59 | 29.5 (98) | 36.8 (859) | 0.009 |

BP = blood pressure; DM = diabetes mellitus; GLP = glucagon-like peptide; $HbA_{1c}$ = glycated haemoglobin; HDL = high-density lipoprotein; IQR = interquartile range; LDL = low-density lipoprotein; NS = not significant; SD = standard deviation.

test. The correlation between the DADD indicator and the international indicator or LDL were tested by non-parametric correlation analysis and calculation of Spearman's rho. SPSS ver. 2.0 was used for statistical analysis.

*Trial registration*: not relevant.

## RESULTS

Within the Central Denmark Region, 3,491 patients who met the inclusion criteria were registered with DADD in the period from 1 January 2013 to 28 February 2015 and were thus included in part A of this study (**Table 1**). Among the patients with an LDL level > 2.5 mmol/l, those without (Group A) and those with treatment (Group B) were similar in terms of mean age, weight, BMI, smoking status, glycated haemoglobin ($HbA_{1c}$) levels and blood, pressure as well as insulin and glucagon-like peptide-1 analogue treatment status. The difference in median LDL levels was small between Groups A (3.2 mmol/l) and B (3.0 mmol/l). Similar minor differences were observed in triglyceride and total cholesterol levels. We also note that patients in Group B had a longer mean duration of disease (151 months) than patients in Group A (131 months).

The questionnaire was completed for 273 (88%) of the patients with an LDL level > 2.5 mmol/l without treatment. In **Figure 1**, we see that 104 patients (38%) did not receive treatment either because they declined (61 patients) or because the clinician decided that treatment was not indicated (43 patients). Thus, we found that among patients with an LDL level > 2.5 mmol/l who were not on lipid-lowering drugs, 62% lacked a "good" explanation for not receiving lipid-lowering treatment. For the majority of those without a good explanation for their lack of treatment, the physician had responded "other or unkown" to the question.

In Figure 1, we show results for patients with an LDL level > 2.5 mmol/l while on lipid-lowering treatment. 50% of these patients received statins not including atorvastatin or rosuvastatin, which are the high-intensity statins available in Denmark.

In part B of this study, we compared the DADD indicator with the international indicator of lipid-lowering treatment quality. In **Figure 2**, we see that there is no association between performance on the DADD indicator and performance on the international indicator (Spearman's rho –0.097, p = 0.55). Furthermore, in **Figure 3**, we show that the DADD indicator is not associated with achieved median LDL levels on a per-clinic population basis (Spearman's rho –0.240, p = 0.13).

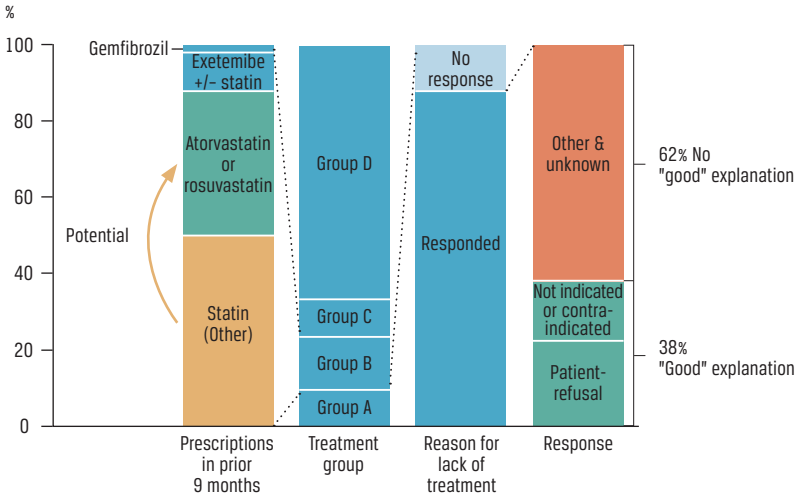
## DISCUSSION

In part A of this study, we found that there was no "good" explanation for the absence of lipid-lowering treatment in 62% of the patients with an LDL level > 2.5 mmol/l who were without lipid-lowering treatment. Among patients with an LDL level > 2.5 mmol/l despite lipid-lowering treatment, more than half did not receive high-intensity treatment. In part B of this study, we found that performance on the current DADD indicator was neither correlated with the gold standard intermediate outcome, i.e. median LDL level, nor with the widely used international indicator of treatment quality.

Overall, our findings are consistent with and extend those of previous studies. Several studies have found incomplete adherence among diabetes patients. A 2005 US study on statin therapy for T2DM patients found prescription redemption rates of 66% for women and 75% for men [12]. A 2008 study including 162,667 patients at Kaiser Permanente concluded that both non-adherence and lack of treatment intensification contributed to insufficient attainment of treatment goals [13]. In a Dutch cohort of T2DM patients, patterns of statin treatment were found to be suboptimal; thus, discontinuation, inadequate adherence levels and lack of treatment intensification were seen in those who had an inadequate LDL cholesterol reduction after two years of follow-up [14]. Currie and colleagues found that medication non-compliance among diabetes patients was associated with an increased risk of death [15]. These studies beg the question why lipid-lowering treatment is not started or intensified when appropriate in T2DM.

**FIGURE 1**

**Clinician responses to the pop-up questionnaire distributed in the Central Denmark Region, inquiring about reasons for lacking or insufficient lipid-lowering treatment.**




LDL = low-density lipoprotein.
Group A: LDL level ⟩ 2.5 mmol/l without treatment, Group B: LDL level ⟩ 2.5 mmol/l with treatment, Group C: LDL level ≤ 2.5 mmol/l without treatment, Group D: LDL level ≤ 2.5 mmol/l with treatment.

The quality of treatment is at least as important as the choice of drug. A range of quality indicators for cardiovascular risk management have been proposed and implemented. Most quality indicators in this area are either process measures or intermediate outcome measures. Process measures typically include treatment status, such as the percentage of patients who receive a certain category of treatment. Intermediate outcomes include serum LDL levels, systolic blood pressure and albumin/creatinine ratio. Clinical action indicators constitute an alternative set of quality indicators. These combine process and intermediate outcome indicators to measure, e.g., the percentage of patients in whom treatment is started or intensified when indicated.

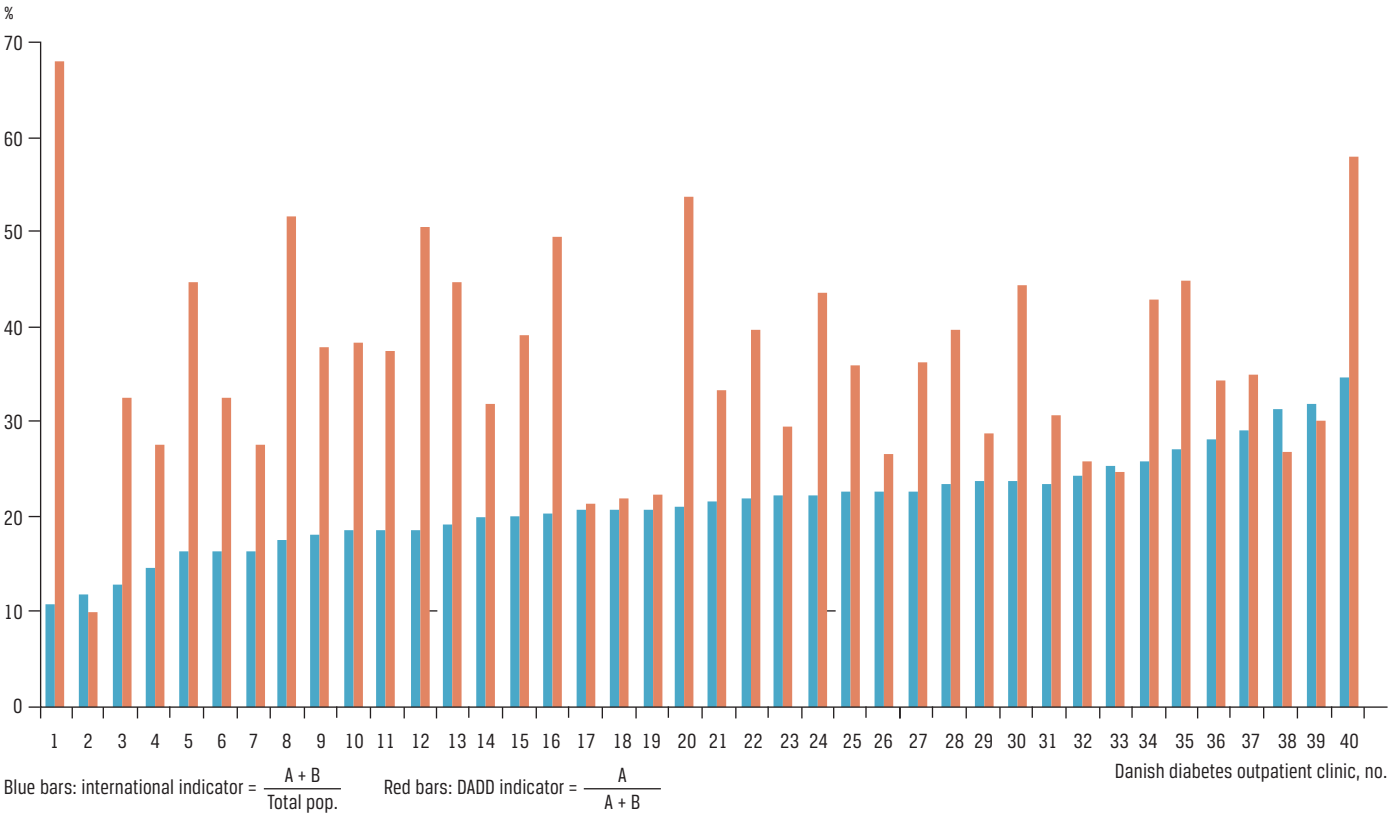
This study has several implications. First, our findings indicate that a substantial fraction of T2DM patients does not receive lipid-lowering treatment or receives only inadequate treatment. Furthermore, for many, there is no good reason why they receive inadequate treatment. This calls for targeted initiatives to improve the care for these patients, for example, timely patient-level feedback to care providers, which has been shown to change physician behaviour and improve quality [16]. However, the current DADD set-up provides monthly raw data and one aggregated report per clinic per year. We believe that the DADD should aim to provide timely and user-friendly patient-level data, available to the care provider at the point of care, in order to facilitate high-impact dialogues with the patients.

Second, and consistent with findings by de Vries and colleagues [14], we found a potential for treatment intensification among the 50% of patients with an LDL level > 2.5 mmol/l while they are on lipid-lowering therapy. This treatment intensification could potentially be accomplished simply by switching to a high-intensity statin.

Third, given the absence of any association between the DADD indicator and the international indicator and the lack of association between the DADD indicator and the achieved LDL level, we believe that the DADD indicator is inappropriate and should be replaced by another indicator, such as the fraction of T2DM patients with an LDL level > 2.5 mmol/l. A counterargument

**FIGURE 2**

**Per-clinic aggregate performance on the international indicator compared to the Danish Adult Diabetes Database (DADD) indicator[a].**




a) % of patients per clinic in Group A (low-density lipoprotein (LDL) level 〉 2.5 mmol/l without treatment), divided by the sum of the number of patients in Group A and Group B (LDL level 〉 2.5 mmol/l with treatment).

could be that as a clinical action indicator, the current DADD indicator is intended to maximise a minimum standard of care, namely the fraction of T2DM patients with an LDL level > 2.5 mmol/l who are on (any) statin therapy. However, one could plausibly perform well on the DADD indicator while providing sub-optimal treatment quality, e.g., by increasing the number of patients on minimal and insufficient lipid-lowering treatment (Group B). Indeed, the clinic with the most favourable performance with respect to the international indicator had the poorest performance according to the DADD indicator (Figure 2).

This study has several strengths. Notably, we employed reliable data based on Danish high-fidelity registries. We also used a validated measure for treatment status that is based on redeemed prescriptions for treatment status categorisation.

This study also has several limitations. First, we relied on retrospective data from hospital diabetes outpatient clinics, which only see approximately 20% of the T2DM population in Denmark, the majority of which is being followed in primary healthcare. This potentially limits the generalisability of our findings, although it is plausible that there is at least similar room for improvement in non-specialised diabetes healthcare. Second, we found a relatively high level of imprecision in the answers to the pop-up questions in part A of the study, which highlights the need for more accurate data on the reasons for sub-optimal treatment. Third, redeeming a prescription does not necessarily equal taking it as prescribed. However, pharmacy data are widely used to assess treatment adherence and have previously been shown to be a reliable proxy for true drug exposure status [17]. Fourth, the LDL cut-off of 2.5 mmol/l was widely recognised when the DADD indicator was established. However, in recent evidence-based clinical guidelines, indication for lipid-lowering treatment and the level of intensity are based on cardiovascular risk factors rather than on absolute LDL values. We had no data on the dose of the lipid-lowering drugs or on risk factors, which could indicate a lower LDL target as indicated by current clinical guidelines [2]. Knowledge of cardiovascular risk factors would most likely imply an increased potential for treatment optimisation, which further underlines our finding that there is substantial potential for treatment optimisation.

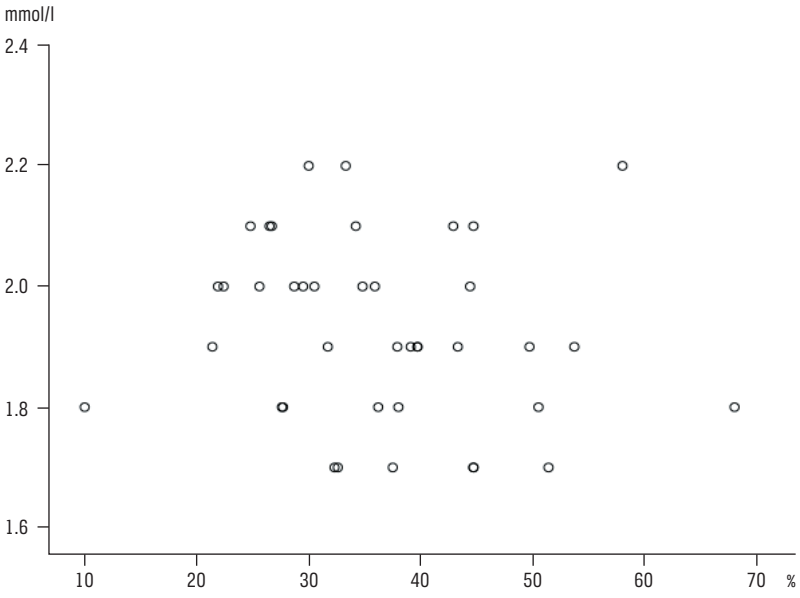
## CONCLUSIONS

In part A of this study, we identified two potential areas for treatment optimisation in Danish outpatient endocrinology clinics; initiation of statin treatment for relevant patients not receiving lipid-lowering therapy, and switching those patients who receive inadequate lipid-lowering therapy to a high-intensity statin. To facilitate this, we suggest that DADD data should be made available in a timely and user-friendly manner to the clinicians in order to facilitate high-impact dialogues with each patient.

Based on the findings in part B of this study, we conclude that the DADD indicator is not a valid measure of treatment quality, and we believe it should be retired in favour of a validated indicator of treatment quality.

**FIGURE 3**

**Per-clinic median low-density lipoprotein (LDL) levels achieved in 2014/2015 compared with per-clinic performance on the Danish Adult Diabetes Database indicator: the fraction of type 2 diabetic patients ≥ 40 years old with an LDL level ⟩ 2.5 mmol/l without lipid-lowering treatment.**

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**LITERATURE**

1. Kearney PM, Blackwell L, Collins R, et al. Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: a meta-analysis. Lancet 2008;371:117-25.
2. American Diabetes Association. 9. Cardiovascular disease and risk management. Diab Care 2017;40(suppl 1):S75-S87.
3. Krumme AA, Franklin JM, Isaman DL et al. Predicting 1-year statin adherence among prevalent users: a retrospective cohort study. J Manag Care Spec Pharm 2017;23:494-502.
4. Cramer JA. A systematic review of adherence with medications for diabetes. Diab Care 2004;27:1218-24.
5. Hemmingsen B, Lund SS, Gluud C et al. Intensive glycaemic control for patients with type 2 diabetes: systematic review with meta-analysis and trial sequential analysis of randomised clinical trials. BMJ 2011;343:d6898.
6. de Vries FM, Denig P, Pouwels KB et al. Primary prevention of major cardiovascular and cerebrovascular events with statins in diabetic patients: a meta-analysis. Drugs 2012;72:2365-73.
7. Sidorenkov G, Haaijer-Ruskamp FM, de Zeeuw D et al. Review: relation between quality-of-care indicators for diabetes and patient outcomes: a systematic literature review. Med Care Res Rev 2011;68:263-89.
8. Sidorenkov O, Nilssen O, Grjibovski AM. Determinants of cardiovascular and all-cause mortality in northwest Russia: a 10-year follow-up study. Ann Epidemiol 2012;22:57-65.

9. Sidorenkov G, Voorham J, de Zeeuw D et al. Do treatment quality indicators predict cardiovascular outcomes in patients with diabetes? PLoS One 2013;8:e78821.
10. Khunti K, Gadsby R, Millett C et al. Quality of diabetes care in the UK: comparison of published quality-of-care reports with results of the Quality and Outcomes Framework for Diabetes. Diabet Med 2007;24:1436-41.
11. Voorham J, Haaijer-Ruskamp FM, van der Meer K et al. Identifying targets to improve treatment in type 2 diabetes; the Groningen Initiative to aNalyse Type 2 diabetes Treatment (GIANTT) observational study. Pharmacoepidemiol Drug Saf 2010;19:1078-86.
12. Parris ES, Lawrence DB, Mohn LA et al. Adherence to statin therapy and LDL cholesterol goal attainment by patients with diabetes and dyslipidemia. Diab Care 2005;28:595-9.
13. Schmittdiel JA, Uratsu CS, Karter AJ et al. Why don't diabetes patients achieve recommended risk factor targets? Poor adherence versus lack of treatment intensification. J Gen Intern Med 2008;23:588-94.
14. de Vries FM, Voorham J, Hak E et al. 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;70:482-92.
15. Currie CJ, Peyrot M, Morgan CL et al. The impact of treatment noncompliance on mortality in people with type 2 diabetes. Diab Care 2012;35:1279-84.
16. Lu CY, Vinci LM, Quinn MT et al. Using feedback to change primary care physician behavior. J Ambul Care Manage 2015;38:118-24.
17. Lau HS, de Boer A, Beuning KS et al. Validation of pharmacy records in drug exposure assessment. J Clin Epidemiol 1997;50:619-25.