TREAT-TO-TARGET HbA1c AND LIPID PROFILE TO PROLONG β-CELL MASS/FUNCTION AND OPTIMIZE TREATMENT-GOAL ATTAINMENT

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Abstract

Aim: To evaluate the relation between different serum lipid fractions and other known barriers to attain the HbA1c ≤ 7.0% (53 mmol/mol) target.

Methods: Data on 2719 patients with type 2 diabetes were collected from the five waves of the International Diabetes Mellitus Practice Study implemented in Argentina (2006 to 2012) including: demographic/socioeconomic profile, clinical, metabolic (HbA1c and serum lipids) data, and treatment type; also, percentage of treatment goal attainment. Descriptive statistical analyses included ANOVA, Chi2 test, and Fisher’s exact test; univariate and multivariate logistic regression analyses, that identified predictive factors for HbA1c ≤7% (53 mmol/mol).

Results: The average age was 63 years, primary/secondary education, health insurance, 10-year type 2 diabetes duration, most associated with cardiovascular risk factors and some microvascular/macrovascular complications; 94.5% received antihyperglycemic drugs. Percentage of people on target: HbA1c 51.2%, blood pressure 23.5%, total cholesterol 62.6%, LDL-cholesterol 38.9% and triglycerides 61.1%. HbA1c on target depended markedly on treatment type: more of those treated with lifestyle changes and significantly fewer of those receiving insulin. Only 4.1% had all parameters simultaneously on target. Multivariate logistic regression analyses showed that achieving HbA1c≤7.0% (53 mmol/mol) was associated with higher educational level, shorter diabetes duration, and having reached goals for LDL-cholesterol and triglycerides, whereas opposite results were obtained with insulin treatment and longer diabetes duration.

Conclusions: High LDL-cholesterol and triglycerides levels simultaneously potentiate development/progression of chronic complications, exerting this effect in the long term by decreasing β-cell mass/function, thereby making it more difficult to reach HbA1c values able to prevent complications.
1. Introduction

Type 2 diabetes is a chronic disease frequently associated with other cardiovascular risk factors (CVRF) that facilitate development/progression of chronic complications and increase treatment costs (1), thereby becoming a heavy burden on patients and the health budget (2,3).

This disease is characterized by sustained hyperglycemia caused by progressive failure of β-cell secretion failing to cope with increased demand for hormone by peripheral tissues (insulin deficiency + insulin resistance) (4-7). This deficient response results from progressive impairment of β-cell mass and function (8-10); consequently, at some stage of the disease, insulin administration may be necessary to attain recommended HbA1c target values, which requires overcoming physicians’ and patients’ barriers (7,11,12). Time-course changes in treatment type leads to a different percentage of people with HbA1c on target: in a previous International Diabetes Mellitus Practice Study report (IDMPS), we showed that for people with type 2 diabetes, short disease duration and use of few oral glucose-lowering drugs (OGLDs) were predictive factors of attaining target HbA1c values in all regions studied (13).

Available evidence also shows that diabetes is an independent risk factor for developing cardiovascular risk; with such events being the most common cause of death in type 2 diabetes (14,15). However, multifactorial care of people with type 2 diabetes (simultaneous treatment of hyperglycemia, hypertension, and dyslipidemia) effectively reduced rates of death and cardiovascular disorders (16). Also, this multifactorial approach could have additional advantages: since dyslipidemia exerts a direct deleterious effect on β-cell mass/function (17), its control might not only prevent occlusive atherosclerosis, but could also prolong β-cell half-life and consequently, improve chances of reaching HbA1c goal values.

We now provide additional evidence to support the latter assumption by evaluating the relation between attainment of HbA1c ≤ 7.0% (53mmol/mol) values and of different serum lipid
fractions, as well as other known barriers to attain this goal by analyzing data from the five waves of the IDMPS implemented in Argentina between 2006 and 2012.

2. Methods

2.1. Study design

IDMPS is an international, multicenter, prospective, observational study on patients with type 1 and type 2 diabetes. This survey is designed following STROBE guidelines as described elsewhere (13,18). Briefly, IDMPS is composed of 5 cross-sectional registries (operationally called “waves”) over a 5-year period to assess changing practices in the management of people with diabetes. Each wave consists of two phases: a 2-week cross-sectional registry and a 9-month longitudinal survey. A 3-month interval separates the end of the longitudinal survey and the start of the next wave. Only cross-sectional registry data from Argentina are analyzed in the present report.

2.2. Data collection and outcome measures

Data were collected on case report forms recording demographic and socioeconomic profile, medical history, medications, glycemic control, blood pressure and lipid status, self-care, access to patient education, follow-up mode, work absenteeism, and hospitalization. Outcome measurement included attainment of treatment goals defined as HbA1c ≤7% (53 mmol/mol), blood pressure ≤130/80 mmHg, and LDL cholesterol ≤100 mg/dl (19).

2.3. Sample size estimation and selection of physicians

The number of subjects to be recruited in each participating country was determined on a country basis. Based on the assumption that insulin is the least prescribed therapy, the sample was determined in order to establish the frequency of insulin-treated patients (13,18). Therefore, physicians with experience on the initiation and titration of insulin therapy were
invited to participate. A total of 210 Argentinian physicians participated in the 5 waves (2719 patients with type 2 diabetes).

2.4. Study implementation
A steering committee advised the project team on the study design and registry structure, monitored study progress, reviewed and validated all study-related documents, and proposed and approved decisions on protocol amendments, analyses, and publications. The study was coordinated by Sanofi-Aventis Intercontinental. In each country, the study was advocated by a leading diabetologist who compiled and endorsed the list of investigators. The latter were assisted by local Sanofi-Aventis staff in collecting relevant information including clinical and laboratory parameters. Ethics approval was obtained from institutional boards from each country. All participants provided their written informed consent.

2.5. Statistical analysis
Statistical analyses were conducted with the Statistical Package for Social Sciences version 15 (SPSS Inc., Chicago, IL, USA). Descriptive Analysis, ANOVA, Chi2 Test, and Fisher’s Exact Test were used as appropriate. Univariate and multivariate logistic regression analyses were run to identify predictive factors for HbA1c ≤7% (53 mmol/mol). Potential predictive factors included gender, age, diabetes duration, education level, health insurance, Body Mass Index (BMI), blood pressure, lipid profile (Total Cholesterol, LDL Cholesterol, and TG), and diabetes treatment. A backward selection procedure identified predictive factors significant at 5%.

3. Results
Most of our study population was urban (93.9%), had a primary/secondary education, declared combined social security/prepaid health insurance, had some degree of
microvascular/macrovascular complications and were treated with different antihyperglycemic drugs (94.4%). Regarding treatments, most patients were treated with OGLDs (60.8%), while insulin treatment (alone [12.5%] or combined with OGLD [21.1%]) represented 33.6% (Table 1).

Their clinical-metabolic characteristics showed an average of 63 years of age, of 10-year duration of type 2 diabetes; most having associated CVRFs, specifically, overweight/obesity (87.5%), hypertension (73%) and dyslipidemia (70.3%) (Table 1). Average values for the parameters recorded showed blood pressure within target values recommended by ADA/EASD guidelines (23), moderate increase in fasting blood sugar, HbA1c levels close to those recommended by guidelines, and uneven control of their serum lipid profile (Table 1). In fact, whereas total cholesterol, HDL-c and TG levels were within control levels, those of LDL-c were above treatment goals (Table 1).

Despite this acceptable average value profile, a different picture emerged when it was considered the percentage of people on target for each parameter, i.e. values able to prevent development/progression of chronic complications (Table 1): for HbA1c it was 51.2%, for blood pressure 23.5%, for total cholesterol 62.6%, for LDL-cholesterol 38.9%, and for TG 61.1%. It has to be stressed that the percentage of people with HbA1c on target varied markedly depending on treatment type: higher in the group of people treated with lifestyle changes and significantly lower in those receiving insulin (Figure 1). However, when we measured the percentage of people having their HbA1c, blood pressure and complete lipid profile simultaneously on target, we found that only 4.1% attained that goal.

Regarding our main objective –to verify the negative influence of dyslipidemia on attainment of the HbA1c goal- when we tracked the population according to their Hba1c levels ≤ 7.0% (53 mmol/mol), we found that those who attained HbA1c target values exhibited significantly lower levels of lipid fractions (Table 2).
The results of multivariate logistic regression analyses presented in Figure 2, show that for people with type 2 diabetes, achieving HbA1c ≤7.0% (53 mmol/mol) was a positively association with a higher educational level (OR: 1.399, 95% CI: 1.107 - 1.767), and with having reached the goal for LDL-cholesterol (OR: 1.344, 95% CI: 1.091 - 1.656) and TG (OR: 1.854, 95% CI: 1.501 - 2.290), whereas it was negatively associated with insulin treatment (OR: 0.296, 95% CI: 0.186 - 0.470) and diabetes duration (either OR: 0.762, 95% CI 0.588 - 0.987 or OR: 0.541, 95% CI 0.420 – 0.696).

4. Discussion

Chronic type 2 diabetes complications result in high morbidity, mortality, and socio-economic costs, which can be significantly reduced by control of hyperglycemia and associated CVRF - unfortunately achieved infrequently (2, 20-22). In our study, approximately 50% of the population was on the target values recommended by ADA standards for HbA1c and other CVRFs (23). On the other hand, the intensive multifactorial approach to treat these people has been shown to be an efficient and cost-effective way to prevent development and progression of these complications (16, 24, 25). However, in our country, only about 4% of the population attain this multifactorial goal.

For HbA1c the target is ≤ 7.0%; the attainment of this value depends on many factors: in our study, treatment type was significantly associated with different percentages of people on target: a higher percentage was attributable to healthy lifestyle and a lower percentage to insulin treatment. Similar polarizations were also found by other authors (26). In a previous IDMPS report performed worldwide, we found that people with short duration type 2 diabetes and use of few OGLDs were predictive factors of attaining HbA1c at target values in all regions studied (13). Similarly, the United Kingdom Prospective Diabetes Study (14),
which examined the time-course of islet dysfunction in patients with type 2 diabetes, showed that β-cell function - estimated by HOMA index - underwent progressive deterioration during the first 6 years of observation in patients without insulin therapy (27). Comparable data were reported by De Pablo et al: using a logistic model, they found that disease duration was predictive of glycemic control (longer was associated with higher frequency of poor glycemic control (OR = 1.033) and stable insulin treatment (OR = 4.054)) (28). These data suggest that early diagnosis may increase the likelihood of attaining glycemic targets, probably because people with type 2 diabetes show progressive deterioration of both β-cell mass and function (7,8,10). Accordingly, we may reasonably assume that remnant functional β-cell mass efficiently controls glucose homeostasis at an earlier stage of the disease, whereas later on this control depends on the physician-patient couple’s abilities/commitment. However, other factors may also participate in triggering the impaired mechanism: the multiple variable analysis performed in our study demonstrated that educational level, disease duration, blood pressure, total cholesterol, LDL-cholesterol and TG levels as well as treatment type (except OGLDs), also significantly affect attainment of HbA1c ≤ 7.0% (53 mmmol/mol) (Figure 2). Reciprocally, HbA1c is not only a reliable biomarker of glycemic control but also may be a good predictor of serum lipid profile in people with type 2 diabetes: those with HbA1c ≤ 6%–9% (42-75 mmol/mol) and >9% (75 mmol/mol) tend to have moderate and severe dyslipidemia, respectively (29), even though further studies need to be driven to assess this. The principal aim of our study is to gain deep insight into the analysis of dyslipidemia’s role in attainment of target HbA1c values.

People with normal glucose tolerance (NGT) and dyslipidemia characterized by abnormal high TG and low HDL-c have also been shown to have impaired insulin sensitivity and β-cell function: levels of these lipid fractions correlated with insulin resistance (IR), while they were negatively correlated with pancreatic β-cell response to IR (30). The HOMA-IR score is
a useful but costly indicator of IR and therefore frequently inaccessible for general purposes; for this reason, the TG/HDL-cholesterol ratio has been proposed for use as a simple IR marker (31, 32); with some ethnic restrictions, it might be inversely related to β-cell function (33). The cut-off value for this TG/HDL-cholesterol ratio was validated in our country as >3.5 and >2.5 for men and women, respectively (34). Following this reasoning, in a longitudinal assessment of the temporal relations between serum lipids and IR using cross-lagged path analysis models, Han et al found that abnormally high levels of TG and low HDL-cholesterol probably precede those of peripheral IR (35). They also showed a significant causal mediating effect of 2-h insulin on the unidirectional relation running from blood lipids to IR. These findings provide more evidence for effective IR prevention by improving dyslipidemia.

Further, LDL-cholesterol can decrease maximal glucose-stimulated insulin secretion (GSIS) already in the normal range (3.1 mmol/L) in isolated human and murine islets (17). These results were confirmed and extended by in vivo conditions: mice with hypercholesterolemia induced by feeding a cholesterol-rich Western type diet showed increased cholesterol content in their β-cells associated with reduced GSIS and hyperglycemia; while LDL-cholesterol decreased the proliferation of primary β-cells in mouse or human islets (17). Identification of plasma lipoprotein receptor in pancreatic β cells involved in their binding/processing, as well as the report that LDL-cholesterol particles reduce insulin mRNA levels and β-cell proliferation and also induce a dose-dependent increase in their apoptotic rate, support this assumption. Conversely, HDL-cholesterol particles antagonize the proapoptotic effect of LDL-cholesterol. The antagonistic effect of LDL-, HDL- and cholesterol on regulation of β-cell function and survival as well as on target tissue insulin sensitivity and consequently on type 2 diabetes development were reviewed by von Eckardstein and Siblera (36). These and other reports suggest that the deleterious effect of increased LDL-cholesterol on β-cell
function/mass could be potentiated by the simultaneous decrease in HDL-cholesterol concentration (17,37,38).

Related to the relation between HbA1c and LDL-cholesterol levels and their impact on cardiovascular complications, a retrospective study among US veterans with type 2 diabetes concluded that simultaneous target achievement of these two metabolic indicators rather than each one separately was associated with lower risk of microvascular and macrovascular events, fewer hospitalization days and outpatient visits; thus resulting in better outcomes and lower resource consumption (39).

Based on this evidence, we could conclude that dyslipidemia, particularly high LDL-cholesterol and TG levels, not only may potentiate development/progression of chronic complications, but also could exert this effect in the long term by decreasing β-cell mass and function which making more difficult to reach HbA1c target values able to prevent this effect. Our data also show that these dual negative effects of dyslipidemia are not seriously considered by our physicians since an important percentage of people with high LDL-cholesterol and TG levels were not treated or not treated specifically to bring them down to target values.

We assume that, although consistent, our data have some weaknesses and must therefore be considered with caution: a) it is a retrospective data analysis; b) it is not a strict population study, since providers were mainly specialists, consequently not representative of large population health care quality. However, the latter factor is particularly alarming, since if serious failures were detected at this level, patient care at the primary care level must presumably be worse.

Data obtained from our ongoing primary care level, showing the beneficial effects of education of physicians, nurses, and type 2 diabetes patients for attaining target values of HbA1c and serum lipids, as well as its cost-effective ratio (40), support the concept that
education is a reliable tool to modify the current impaired prescription/adherence and to optimize the quality of care and prevention of complications.

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Conflict of interest: The authors Juan J. Gagliardino and Jorge Elgart do not present a conflict of interest. Lujan Forti, María Silvina Guaita and Jean Marc Chantelot are members of Sanofi's medical department.

JJG is part of the IDMPS global study steering committee, representative in Argentina and intellectual author of the publication. JE, SG, LF and JMC contributed to the analysis of the data and drafting of the manuscript. All authors have read and approved the final manuscript.
References
1. Elgart JF, Asteazarán S, De La Fuente JL, Camillucci C, Brown JB, Gagliardino JJ. Direct and indirect costs associated to type 2 diabetes and its complications measured in a social security institution of Argentina. International Journal of Public Health. 2014 Oct;59(5):851-7
2. Williams R, Van Gaal L, Lucioni C, CODE-2 Advisory Board. Assessing the impact of complications on the costs of Type II diabetes. Diabetologia 2002; 5: S13–7.
3. Morsanutto A, Berto P, Lopatriello S et al. Major complications have an impact on total annual medical costs of diabetes: results of a database analysis. J Diabetes Complications 2006; 20: 163–9.
4. Groop L. Pathogenesis of type 2 diabetes: the relative contribution of insulin resistance and impaired insulin secretion. Int J Clin Pract Suppl. 2000;113:3-13
5. DeFronzo RA. Pathogenesis of type 2 diabetes mellitus. Medical Clinics of North America. America. 2004;88:787-835
6. Del Prato S. Role of glucotoxicity and lipotoxicity in the pathophysiology of Type 2 diabetes mellitus and emerging treatment strategies. Diabet Med. 2009; 26:1185-1192
7. Kahn SE, Cooper ME, Del Prato S. Pathophysiology and treatment of type 2 diabetes: perspectives on the past, present, and future. Lancet. 2014;383:1068-1083
8. Butler AE, Janson J, Bonner-Weir S, Ritzel R, Rizza RA, Butler PC. Beta-cell deficit and increased beta-cell apoptosis in humans with type 2 diabetes. Diabetes 2003;52:102-110
9. Ahren B. Type 2 diabetes, insulin secretion and beta-cell mass. Curr Mol Med. 2005;5:275-286
10. Kahn SE, Zraika S, Utzschneider KM, et al. The beta cell lesion in type 2 diabetes: there has to be a primary functional abnormality. Diabetologia 2009; 52: 1003-1012
11. Polinski JM, Connolly JG, Curtis BH, Seeger JD, Gaskins K, Perez M, Smith BF, Shrank WH. Patterns and trends in insulin intensification among patients with type 2 diabetes: a systematic review. Prim Care Diabetes. 2014 Jul;8(2):101-109
12. Polinski JM, Smith BF, Curtis BH, Seeger JD, Choudhry NK, Connolly JG, Shrank WH. Barriers to insulin progression among patients with type 2 diabetes: a systematic review. The Diabetes Educator. 2013 Jan-Feb;39(1):53-65
13. Chan JC, Gagliardino JJ, Baik SH, Chantelot JM, Ferreira SR, Hancu N, Ilkova H, Ramachandran A, Aschner P; IDMPS Investigators. Multifaceted determinants for achieving glycemic control: the International Diabetes Management Practice Study (IDMPS). Diabetes Care. 2009 Feb;32(2):227-33
14. Valensi P, Avignon A, Sultan A, et al.: Atherogenic dyslipidemia and risk of silent coronary artery disease in asymptomatic patients with type 2 diabetes: a cross-sectional study. Cardiovasc Diabetol. 2016, 15:104
15. Schofield JD, Liu Y, Rao-Balakrishna P, et al.: Diabetes dyslipidemia. Diabetes Therapy. 2016, 7:203–219
16. Gaede P, Lund-Andersen H, Parving HH, Pedersen O. Effect of a multifactorial intervention on mortality in type 2 diabetes. N Engl J Med. 2008;358(6):580-91
17. Rutti S, Ehres JA, Sibler RA, et al. Low- and high-density lipoproteins modulate function, apoptosis, and proliferation of primary human and murine pancreatic beta-cells. Endocrinology 2009; 150:4521-4530
18. Ringborg A, Cropet C, Jönsson B, Gagliardino JJ, Ramachandran A, Lindgren P. Resource use associated with type 2 diabetes in Asia Latin America, the Middle East and Africa: results from the International Diabetes Management Practices Study (IDMPS). International Journal of Clinical Practice. 2009;63:997-1007.
19. American Diabetes Association: Summary of revisions for the 2007 clinical practice recommendations. Diabetes Care 30 (Suppl. 1):S3–S4, 2007
20. Gray A, Clarke P, Farmer A, Holman R; UK Prospective Diabetes Study (UKPDS) Group. Implementing intensive control of blood glucose concentration and blood pressure in type 2 diabetes in England: cost analysis (UKPDS 63). Br Med J 2002; 325: 860
21. The ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med 2008; 358: 2560–2572
22. Duckworth W, Abraira C, Moritz T, Reda D, Emanuele N, Reaven PD, et al.; VADT Investigators. Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med 2009; 360: 129–139
23. Standards of Medical Care in Diabetes-2017 Abridged for Primary Care Providers. Diabetes Care 2017;40(Suppl. 1):S1–S135
24. Gaede P, Valentine WJ, Palmer AJ, Tucker DM, Lammert M, Parving HH et al. Cost-effectiveness of intensified versus conventional multifactorial intervention in type 2 diabetes: results and projections from the Steno-2 study. Diabetes Care 2008; 31: 1510–1515
25. Simmons RK, Borch-Johnsen K, Lauritzen T, Rutten GEHM, Sandbæk A, van den Donk M, Black JA, Tao L, Wilson ECF, Davies MJ, Khunti K, Sharp SJ, Wareham NJ and Griffin SJ. A randomised trial of the effect and cost-effectiveness of early intensive
multifactorial therapy on 5-year cardiovascular outcomes in individuals with screen-detected type 2 diabetes: the Anglo–Danish–Dutch Study of Intensive Treatment in People with Screen-Detected Diabetes in Primary Care (ADDITION-Europe) study. Health Technology Assessment 20:2016

26. Porcellati F, Lin J, Lucidi P, Bolli GB, Fanelli CG. Impact of patient and treatment characteristics on glycemic control and hypoglycemia in patients with type 2 diabetes initiated to insulin glargine or NPH: A post hoc, pooled, patient-level analysis of 6 randomized controlled trials. Medicine 96(5):e6022, 2017

27. United Kingdom Prospective Diabetes Study Group. U.K. prospective diabetes study 16. Overview of 6 years’ therapy of type II diabetes: a progressive disease. Diabetes 1995;44:1249-1258

28. de Pablos Velasco P, Franch J, Banegas Banegas JR, Fernández Anaya S, Sicras Mainar A, Díaz Cerezo S. Cross-sectional epidemiological study of clinical profiles and glycemic control in diabetic patients in primary care in Spain (the EPIDIAP study). Endocrinología y Nutrición. 2009 May;56(5):233-40

29. Khan HA, Sobki SH and Khan SA. Association between glycaemic control and serum lipids profile in type 2 diabetic patients: HbA1c predicts dyslipidaemia. Clininical and Experimental Medicine. 2007;7:24-29

30. Zheng S, Xu H, Zhou H, Ren X, Han T, Chen Y, Qiu H, Wu P, Zheng J, Wang L, Liu W, Hu Y. Associations of lipid profiles with insulin resistance and β cell function in adults with normal glucose tolerance and different categories of impaired glucose regulation. PLoS One. 2017;12(2):e0172221

31. McLaughlin T, Abbasi F, Cheal K, Chu J, Lamendola C, Reaven G. Use of metabolic markers to identify overweight individuals who are insulin resistant. Annals of internal medicine. 2003; 139:802–9

32. McLaughlin T, Reaven G, Abbasi F, et al. Is there a simple way to identify insulin-resistant individuals at increased risk of cardiovascular disease? American Journal of Cardiology. 2005; 96:399–404

33. Zhou M, Li Z, Min R, et al. Log (TG)/HDL-C ratio as a predictor of decreased islet beta cell function in patients with type 2 diabetes: 6-year cohort study. Journal of Diabetes. 2014. doi:10.1111/1753-0407.12229

34. Salazar MR, Carbajal HA, Espeche WG, et al. Comparison of the abilities of the plasma triglyceride/high-density lipoprotein cholesterol ratio and the metabolic syndrome to identify insulin resistance. Diab Vasc Dis Res. 2013; 10:346-352
35. Han T, Cheng Y, Tian S, Wang L, Liang X, Duan W, Na L, Sun C. Changes in triglycerides and high-density lipoprotein cholesterol may precede peripheral insulin resistance, with 2-h insulin partially mediating this unidirectional relationship: a prospective cohort study. Cardiovasc Diabetol 2016;15:154

36. von Eckardstein A and Siblera R A. Possible contributions of lipoproteins and cholesterol to the pathogenesis of diabetes mellitus type 2. Current Opinion in Lipidology 2011, 22:26-32

37. Hao M, Head WS, Gunawardana SC, Hasty AH, Piston DW. Direct effect of cholesterol on insulin secretion: a novel mechanism for pancreatic beta-cell dysfunction. Diabetes 2007; 56:2328-38

38. Abderrahmani A, Niederhauser G, Favre D, et al. Human high-density lipoprotein particles prevent activation of the JNK pathway induced by human oxidised low-density lipoprotein particles in pancreatic beta cells. Diabetologia 2007; 50:1304-1314

39. Shi L, Ye X, Lu M, Wu EQ, Sharma H, Thomason D, Fonseca VA. Clinical and economic benefits associated with the achievement of both HbA1c and LDL cholesterol goals in veterans with type 2 diabetes. Diabetes Care 36:3297–3304, 2013

40. Gagliardino JJ, Lapertosa S, Pfrirter G, Villagra M, Caporale JE, Gonzalez CD, Elgart J, Gonzalez L, Cernadas C, Rucci E, Clark C Jr; PRODIACOR. Clinical, metabolic and psychological outcomes and treatment costs of a prospective randomized trial based on different educational strategies to improve diabetes care (PRODIACOR). Diabet Med. 2013 Sep;30(9):1102-11.
Figure 1. People with type 2 diabetes on Target (HbA1c ≤7% /<53 mmol/mol) by Treatment

D&F: Diet and Physical Activity, OGLDs: Oral glucose lowering drugs
Figure 2. Multivariate Logistic Regression

*Reference modality in underlined and italic text*
Table 1. Characteristics of the study population

| Parameter                        | Mean ± SD | %   | N   |
|----------------------------------|-----------|-----|-----|
| Male (%)                         | -         | 51.8| 1,376|
| Age (years)                      | 63.4 ± 11.1| -   | 2,716|
| Diabetes duration (years)        | 10.2 ± 8.6| -   | 2,620|
| Educational Level                |           |     |     |
| - Illiterate (%)                 | 1.0       | 27  |     |
| - Primary / Secondary (%)        | 73.7      | 1,924|    |
| - University or higher (%)       | 25.3      | 662 |    |
| Type of Coverage                 |           |     |     |
| - Public (%)                     | 40.7      | 943 |    |
| - Private / Mixed (%)            | 59.3      | 1,374|   |
| BMI (kg/m2)                      | 30.8 ± 5.6| -   | 2,709|
| - Normal weight (18.5 ≤ BMI <25) (%) | -  | 12.6| 340 |
| - Overweight (25 ≤ BMI < 30) (%) | -         | 38.0| 1,029|
| - Obesity (30 ≤ BMI < 35) (%)    | -         | 29.3| 793 |
| - Morbid obesity (BMI ≥ 35) (%)  | -         | 20.2| 546 |
| SBP (mmHg)                       | 130.2 ± 15.0| - | 2,701|
| DBP (mmHg)                       | 78.6 ± 9.7 | - | 2,702|
| SBP<130 and DBP<80 (%)           | -         | 23.5| 636 |
| FBG (mg/dl)                      | 137.5 ± 49.0| - | 2,621|
| HbA1c (%)                        | 7.3 ± 1.6 | - | 2,552|
| HbA1c ≤ 7% (53 mmol/mol)         | -         | 51.2| 1,306|
| Total Cholesterol (mg/dl)        | 189.5 ± 38.7| - | 2,516|
| Total Cholesterol < 200mg/dl (%) | -         | 62.6| 1,576|
| HDL-c (mg/dl)                    | 49.5 ± 16.6| - | 2,401|
| LDL-c (mg/dl)                    | 111.2 ± 33.6| - | 2,323|
| LDL-c < 100 mg/dl (%)            | -         | 38.9| 911 |
| Triglycerides (mg/dl)            | 151.2 ± 83.4| - | 2,493|
| Triglycerides < 150 mg/dl (%)    | -         | 61.1| 1,523|
| Hypertension (%)                 | -         | 73.0| 1,976|
| Dyslipemia (%)                   | -         | 70.3| 1,892|
| Treatment type                     | Micro- or macrovascular Complications (%) | 43.9 | 1,119 |
|-----------------------------------|------------------------------------------|------|-------|
| D&F (%)                           |                                          | 5.6  | 144   |
| OGLDs Only (%)                    |                                          | 60.8 | 1,551 |
| OGLDs and Insulin (%)             |                                          | 21.1 | 538   |
| Insulin alone (%)                 |                                          | 12.5 | 319   |

SD: standard deviation. SBP: Systolic blood pressure; DBP: Diastolic blood pressure; FBG: Fasting blood glucose; HDL-c: High density lipoprotein cholesterol; LDL-c: Low-density lipoprotein cholesterol; BMI: Body mass index. D&F: Diet and Physical Activity, OGLDs: Oral Glucose Lowering Drugs.
Table 2. Dyslipidemia according to HbA1c level.

| Parameter                  | HbA1c > 7% (53 mmol/mol) | HbA1c ≤ 7% (53 mol/mol) | P-value |
|----------------------------|--------------------------|--------------------------|---------|
| Total Cholesterol (mg/dl)  | 193.3 ± 40.1 (1,167)     | 184.2 ± 36.3 (1,243)     | 0.000   |
| Total Cholesterol < 200 mg/dl (%) | 59.2 (691)               | 68.1 (846)               | 0.000   |
| HDL-c (mg/dl)              | 49.2 ± 18.4 (1,110)      | 49.9 ± 14.6 (1,207)      | 0.341   |
| LDL-c (mg/dl)              | 114.5 ± 34.7 (1,071)     | 107.2 ± 31.7 (1,171)     | 0.000   |
| LDL-c < 100 mg/dl (%)      | 35.6 (384)               | 42.9 (507)               | 0.000   |
| Triglycerides (mg/dl)      | 162.6 ± 94.8 (1,154)     | 138.9 ± 67.7 (1,239)     | 0.000   |
| Triglycerides < 150 mg/dl (%) | 55.5 (640)              | 67.2 (833)               | 0.005   |

Values are mean ± standard deviation (SD). Number of cases in parentheses.

HDL-c: High density lipoprotein cholesterol; LDL-c: Low-density lipoprotein cholesterol.