2019

Early Aggressive Insulin Therapy in Type 2 Diabetes

Bryan Johnson
University of North Dakota

[How does access to this work benefit you? Let us know!](#)

Follow this and additional works at: https://commons.und.edu/pas-grad-posters

Part of the Cardiovascular Diseases Commons, Endocrinology, Diabetes, and Metabolism Commons, and the Nutritional and Metabolic Diseases Commons

Early Aggressive Insulin Therapy in Type 2 Diabetes

Bryan Johnson PA-S
Department of Physician Assistant Studies, University of North Dakota School of Medicine & Health Sciences
Grand Forks, ND 58202-9037

UND SCHOOL OF MEDICINE & HEALTH SCIENCES
UNIVERSITY OF NORTH DAKOTA

Abstract

Metformin has been proven beneficial for the first-line treatment of type 2 diabetic mellitus (T2DM) due to its efficacy and low adverse effect profile. Current US guidelines do not address the use of early intensive insulin use in T2DM. Treatment plans are slowly adjusted over the months until the A1C goal is met. Insulin is initiated several years after the time of T2DM diagnosis and utilized as second-line therapy. Dual therapy of insulin and metformin have shown regression of T2DM in certain patient populations. However, the linear relationship between diabetes and cardiovascular disease does not show greater improvement with dual aggressive therapy. The ACCORD study found intensive insulin use has led to an increase in mortality in diabetic patients. The purpose of this literature review is to gather data using clinical studies and peer-reviewed articles that can determine if metformin and insulin should be used intensively to lower A1C aggressively compared to using standard therapy of metformin to decrease the long-term effects of abnormal A1C levels.

Keywords: *insulin, metformin, dual therapy, regression, mortality, A1C, intensive insulin therapy, guidelines*
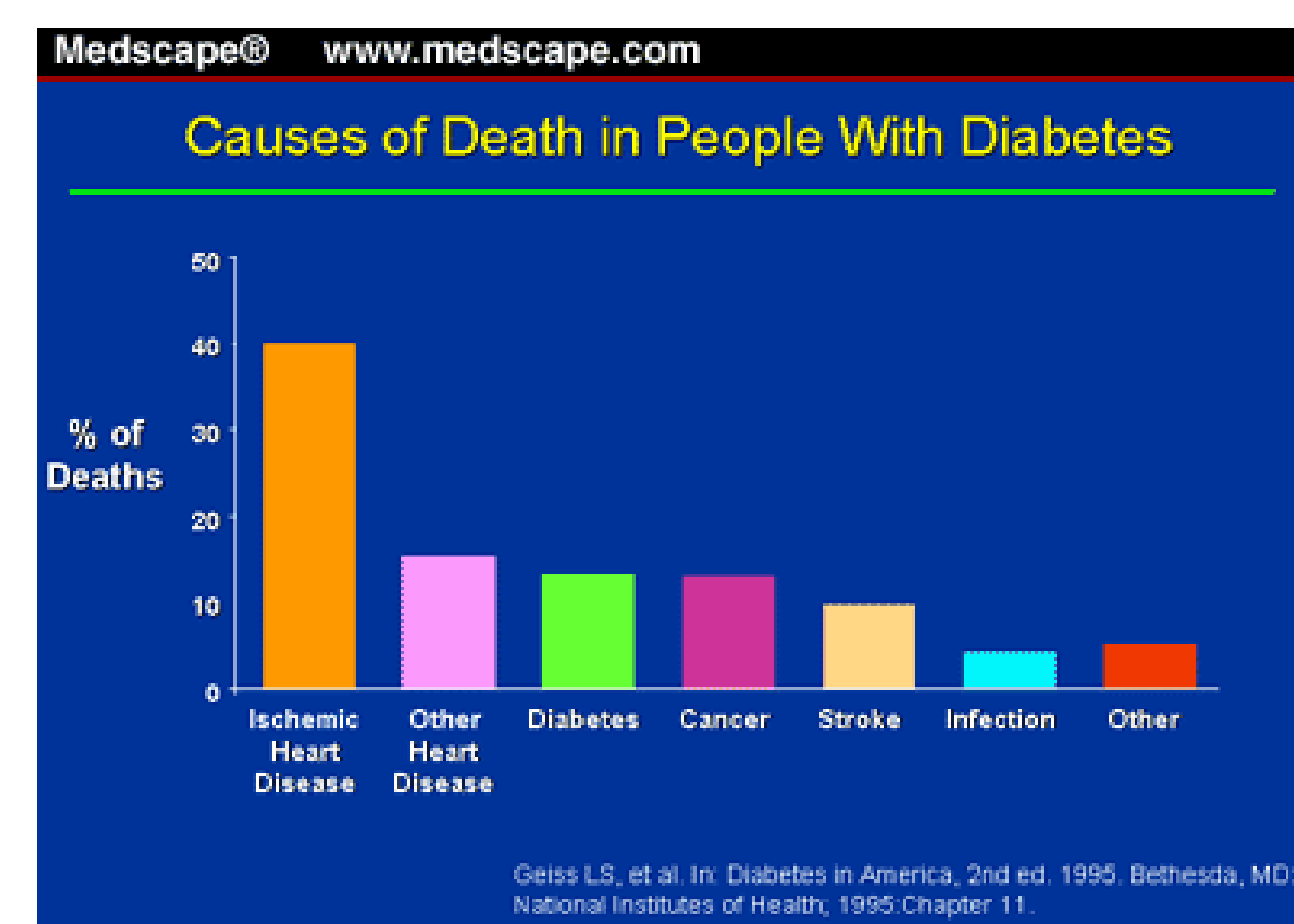
Introduction

- The Center for Disease Control and Prevention (CDC) estimates 9.4% of the U.S. population has T2DM, another 33% of adults have prediabetes.
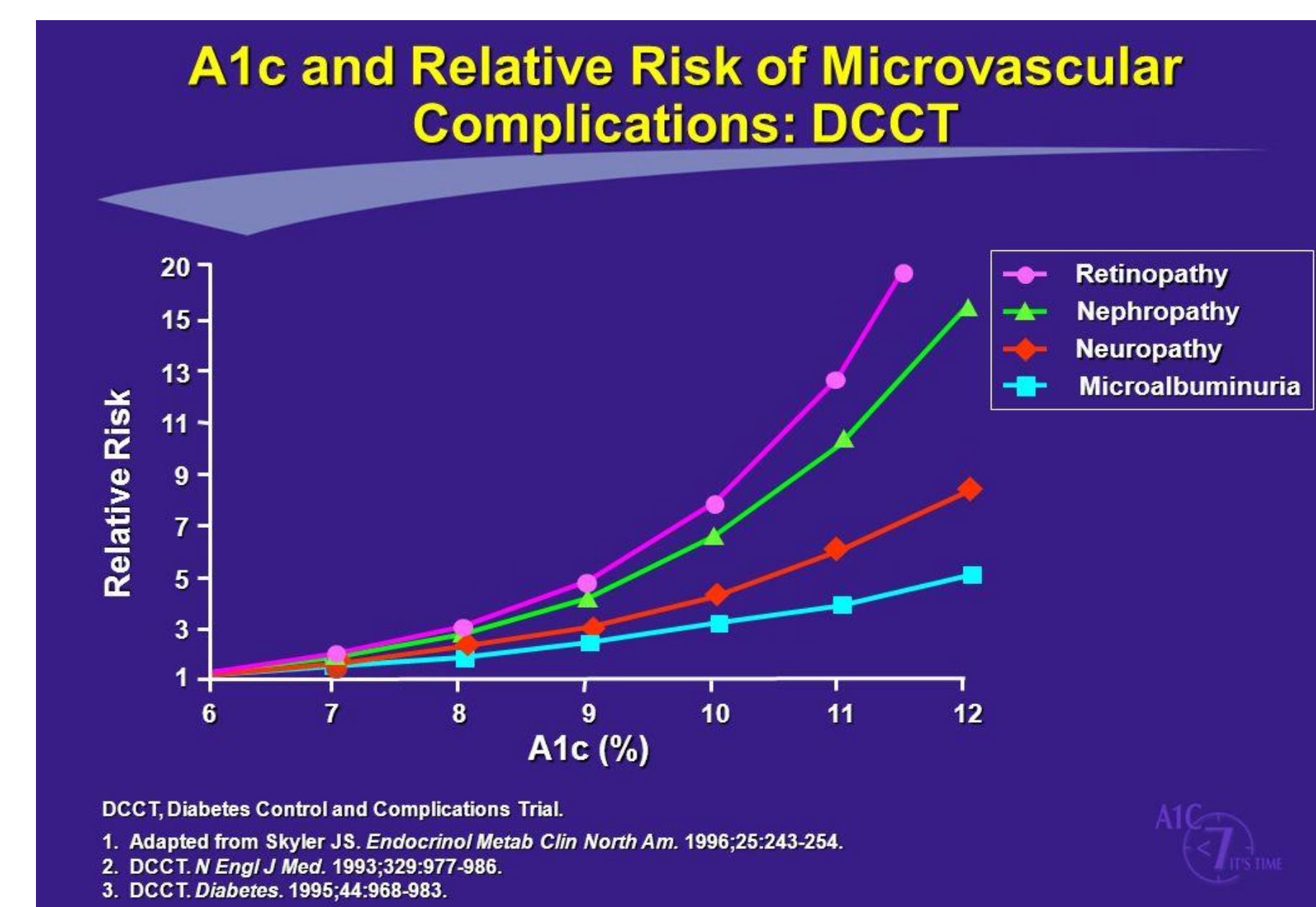
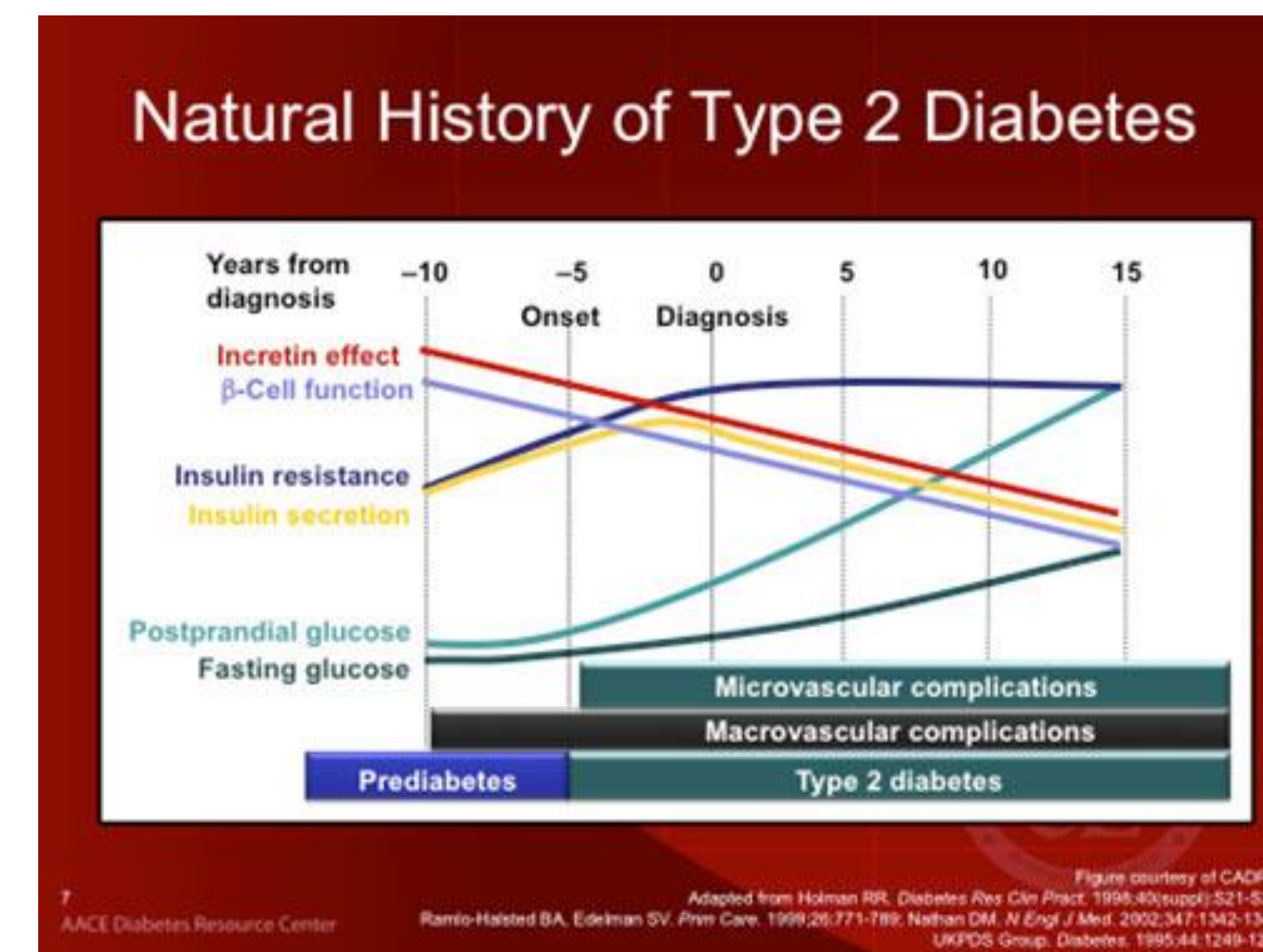- For every one percent increase in A1C, a patients risk of CVD event increases by 16%.

A1c and Relative Risk of Microvascular Complications: DCCT

DCCT, Diabetes Control and Complications Trial.
1. Adapted from Skyler JS. *Endocrinol Metab Clin North Am.* 1996;25:243-254.
2. DCCT *N Engl J Med.* 1993;329:977-986.
3. DCCT *Diabetes.* 1995;44:968-983.

Alam, I. (2019). Management of Diabetes Treat to Target Approach. *Lady Reading Hospital.* Retrieved from http://slideplayer.com/slide/242222/

- 7 in 10 people with diabetes over the age of 65 will die of some type of heart disease (CDC, 2017).

Medscape® www.medscape.com
Causes of Death in People With Diabetes

Geiss LS, et al. In: Diabetes in America, 2nd ed. 1995 Bethesda, MD. National Institutes of Health, 1995 Chapter 11.

- Reversing β-cell dysfunction can lead to remission after one year in 44% of type 2 diabetic patients that have been treated with intensive insulin therapy (Ferrannini et al., 2018).

Statement of the Problem

- The average time for insulin initiation is 11.5 years (Cohen et al., 2016). The importance of maintaining or achieving A1C goal is delaying the progression of microvascular, macrovascular, and other complications associated with T2DM.

- Despite evidence from landmark clinical trials and recommendations in published guidance, glycemic control is often poor for patients in clinical practice and insulin therapy can be delayed or not optimized (Cohen et al., 2016).

- CVD is a major reason for death among diabetics due to the extended period of abnormally high A1C.

- Current treatment guidelines do not have an option to treat patients with intensive insulin therapy.

Natural History of Type 2 Diabetes

Adapted from Holman RR. *Diabetes Res Clin Pract.* 1998;40(suppl):S21-S25.
Ramlo-Halsted BA, Edelman SV. *Prim Care.* 1999;26:771-789; Nathan DM. *N Engl J Med.* 2002;347:1342-1349.
UKPDS Group. *Diabetes.* 1995;44:1249-1258

Research Questions

- Does metformin at time of therapeutic treatment have more benefit then insulin in type 2 diabetics to control A1C?

- Is there a benefit of early intensive insulin therapy when added to metformin in type 2 diabetic patients to control their A1C?

- What is the safety profile of metformin and insulin as monotherapy and dual-therapy for type 2 diabetics?

- What are the long-term benefits of starting intensive insulin early in the treatment of type 2 diabetes?

Literature Review

- Remission rates after one year post therapy are found to be higher in the insulin group compared to the oral antihyperglycemic agents ($p = 0.0012$) (Cheng et al., 2008).

- The ACCORD study showed increase mortality rate due to intensive insulin therapy. Intensive insulin therapy was shown to have some benefit by reducing the risk of retinopathy and microalbuminuria (Genuth and Ismail- Beigi, 2012).

- Three months after stopping intensive insulin therapy 66.2% of patients were in drug-free remission. The remission rate after six months 58.9%, twelve months 46.3%, and 42.1% after 24 months. (Kramer, Retnakaran, and Zinman, 2013)

- Short-term intensive insulin with metformin suggests remission rates of 51.1% for the continuous subcutaneous insulin infusion and 44.9% for the multiple daily injections (Weng et al., 2017).

- Insulin has less risk of hypoglycemia and weight gain when used with metformin. Insulin dosage is also decreased using combination therapy (Halapy et al., 2012).

Discussion

- In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, intensive glycemic control significantly reduced the risk and/or progression of retinopathy, nephropathy, and neuropathy (ADA, 2009)

- The Action to Control Cardiovascular Risk in Diabetes (ACCORD) study had a premature stop due to the 22% increase in the mortality rate of intensively treated T2DM patients

- The United Kingdom Prospective Diabetes Study (UKPDS) data found no increase in mortality from intensive insulin therapy

- One of the downfalls of metformin is the progressive loss of efficacy as expressed in Ferrannini et al. (2018)

- Providers are more apprehensive of starting insulin than the patients are (Halapy et al. 2012).

- Insulin is often withheld from treatment regimens because of its perceived negative impact on the patient's quality of life (QOL) (Weng et al. 2017).

- Initiation of drug therapy should consider the clinical characteristics of the patient profile, efficacy of the drug, side effects, and cost.

- The ideal patient for receiving intensive therapy are lower fasting plasma glucose and a higher BMI at baseline (Kramer, 2013)

- Insulin has been used in short course studies such as Opsteen et al. (2010) and Ferrannini et al. (2018) to induce diabetic remission

Applicability to Clinical Practice

- Metformin used in dual therapy with insulin should be applied to a patient profile that meets current ADA guidelines.
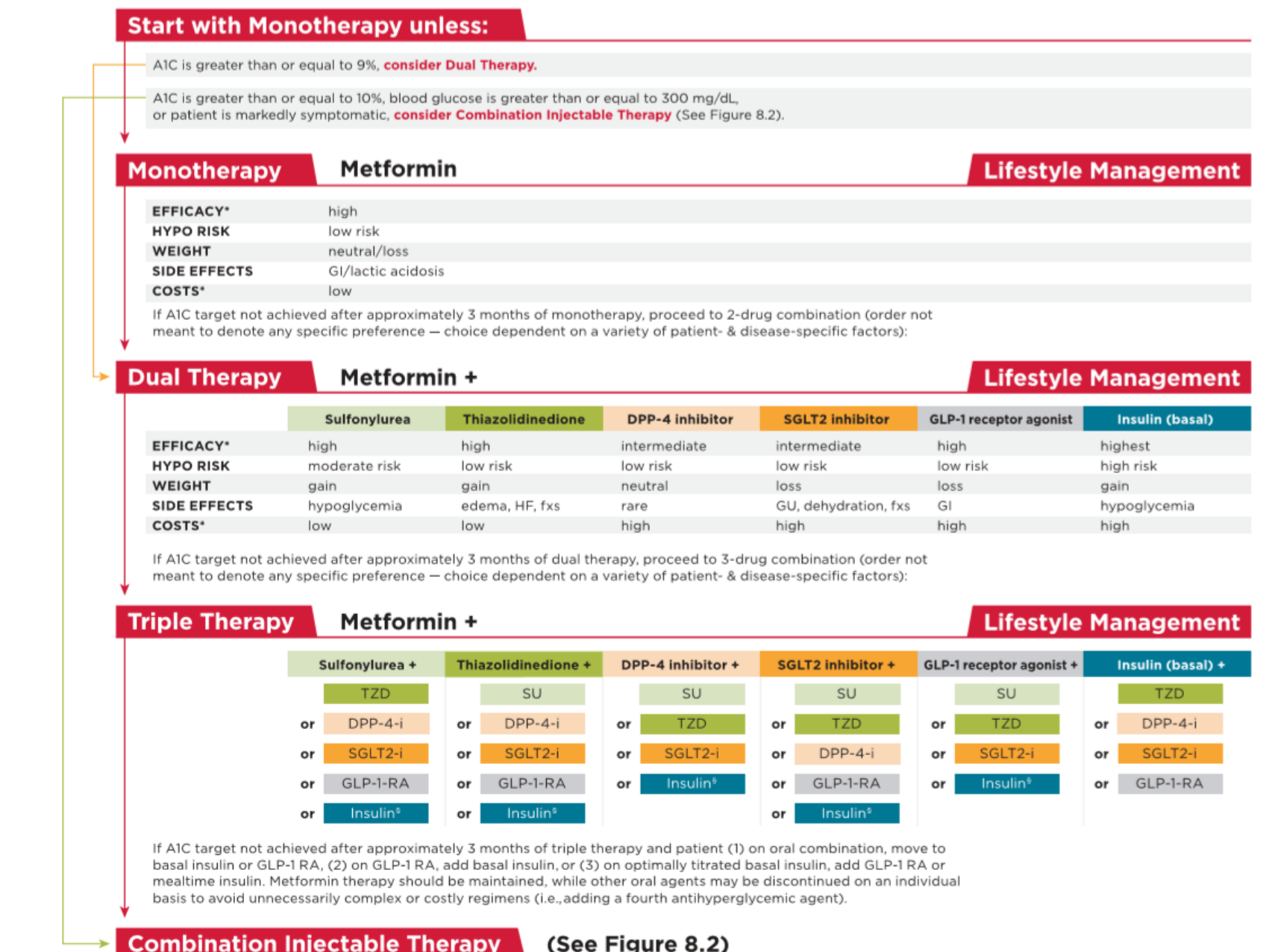

- Patients that could benefit from dual metformin and intensive insulin therapy are younger adults that have new onset of T2DM and lower baseline A1C

- The patients that should avoid or follow closely when intensive insulin therapy are older adults (> 55 years old), have had CVD or other risk factors for CVD, and have had T2DM for several years

- Start insulin therapy shortly after the diagnosis of T2DM when starting dual therapy with metformin.

References

- Alam, I. (2019). Management of Diabetes Treat to Target Approach. *Lady Reading Hospital.* Retrieved from http://slideplayer.com/slide/242222/
- Chamberlain, J., Herman, W., Leal, S., Rhinehart, A., Shubrook, J., Skolnik, N., Rastogi, R., (2017). Pharmacologic therapy for type 2 diabetes: Synopsis of the 2017 American Diabetes Association standards of medical care in diabetes. *Annals of Internal Medicine.* 166(8)572-578. http://doi.org/10.7326/M16-2937
- Cheng, H., Li, Y., Shi, L., Weng, J., Xu, W., Zhang, Q., …Zhu, D. (2008). Effect of intensive insulin therapy on beta-cell function and glycemic control in patients with newly diagnosed type 2 diabetes: a multicenter randomized parallel-group trial. *The Lancet,* 371(9626),1753-1760. http://doi.org/10.1016/s0140-6736(08)60762-x
- Cohen, O., Valentine, W. (2016). Do we need updated guidelines on the use of insulin pump therapy in type 2 diabetes? A review of national and international practice guidelines. *Journal of diabetes science and technology,* 10(6) 1388-1398. http://doi.org/10.1177/1932296816667747
- Ferrannini, E., Giorda, C., Mari, A., Rebelos, E., Sghieri, M., Sciangula, L., (2018). Short course of insulin treatment versus metformin in newly diagnosed patients with type 2 diabetes. *Journal of Clinical Medicine,* 7(9), 235. https://doi.org/10.3390/jcm7090235
- Genuth, S., Ismail-Beigi, F. (2012). Clinical implications of the ACCORD trial. *The Journal of Clinical Endocrinology & Metabolism,* 97(1,1) 41-48. http://doi.org/10.1210/jc.2011-1679
- Halapy, H., Lau, A., Tang, T., Thorpe, K., Yu, C. (2012). Initiating insulin in patient with type 2 diabetes. *Canadian Medical Association Journal,* 184(7), 767-776. http://doi.org/10.1503/cmaj.110779
- Kramer, C., Retnakaran, R., Zinman, B. (2013). Short-term intensive insulin therapy in type 2 systematic review and meta-analysis. *The Lancet Diabetes & Endocrinology,* 1(1) 28-34. http://doi.org/10.1016/s2213-8587(13)70006-8
- Opsteen, C., Qi, Y., Retnakaran, R., Zinman, B. (2010). Effect of Short-term Intensive Insulin Therapy on Quality of Life in Type 2 Diabetes. *Journal of Evaluation in Clinical Practice.* 18 (2) 256-261. http://doi.org/10.1111/j.1365-2753.2010.01552.x
- Weng, J. (2017). Short-term intensive insulin therapy could be the preferred option for new onset type 2 diabetes mellitus patient with HbA1C > 9%. *Journal of Diabetes,* 9(10), 890-893. http://doi.org/10.1111/1753-0407.12581

Acknowledgements