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Kelsey K. Abraham
University of North Dakota

Jeanie McHugo
University of North Dakota

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The Effects of Initiating Metformin, to Prevent or Delay Type II Diabetes, in Patients with Prediabetes

Kelsey K. Abraham, PA-S, Contributing Author: Dr. Jeanie McHugo, PhD, PA-C
 Department of Physician Assistant Studies, University of North Dakota School of Medicine & Health Sciences
 Grand Forks, ND 58202-9037



Abstract

The purpose of this literature review is to explore metformin's role in the treatment of patients with prediabetes within the primary care setting. The efficacy of metformin versus lifestyle modifications will be compared as well as metformin, as adjunctive therapy, to lifestyle modifications. Along with efficacy, a systematic analysis will examine the three above-mentioned therapies regarding diabetes risk reduction. Lastly, this review will examine the safety and tolerability of metformin, specifically in patients with prediabetes. The data presented shows evidence that lifestyle modifications are first-line treatment for prediabetes while metformin use should be reserved for those who fail lifestyle modifications or are considered to be high risk and/or patients that have shown more effective results with metformin therapy: BMI ≥ 35 kg/m², patients less than 60 years old, and women who have a prior history of gestational diabetes mellitus. Decades of research show that metformin is an effective and safe treatment option for patients with prediabetes. However, the combined efficacy of lifestyle modifications and metformin use in prediabetic patients needs to be further studied to find out why additive benefits are not demonstrated.

Keywords: prediabetes, metformin in prediabetes, lifestyle modifications and prediabetes, and prevention of diabetes

Introduction

Prediabetes affects approximately one in three adults, 84 million people, in the United States (CDC, 2019). Lifestyle modifications, consisting of diet and exercise, have been the longstanding initial treatment in patients diagnosed with prediabetes. Lifestyle interventions alone often prove difficult for patients to sustain, and weight shed can be regained. Metformin is a well-established drug that has demonstrated its effectiveness in decreasing A1C levels in patients with diabetes for decades. The purpose of this study is to reveal the most effective treatment plan for patients who are diagnosed with prediabetes, to avoid disease progression to type II diabetes mellitus.

Statement of the Problem

- The American Diabetes Association (ADA) has given an "A" recommendation for the use of metformin to be considered in prediabetic patients (Standards of Medical Care in Diabetes, 2018).
- Less than 1% of prediabetic patients are prescribed metformin (Tseng et al. 2017).



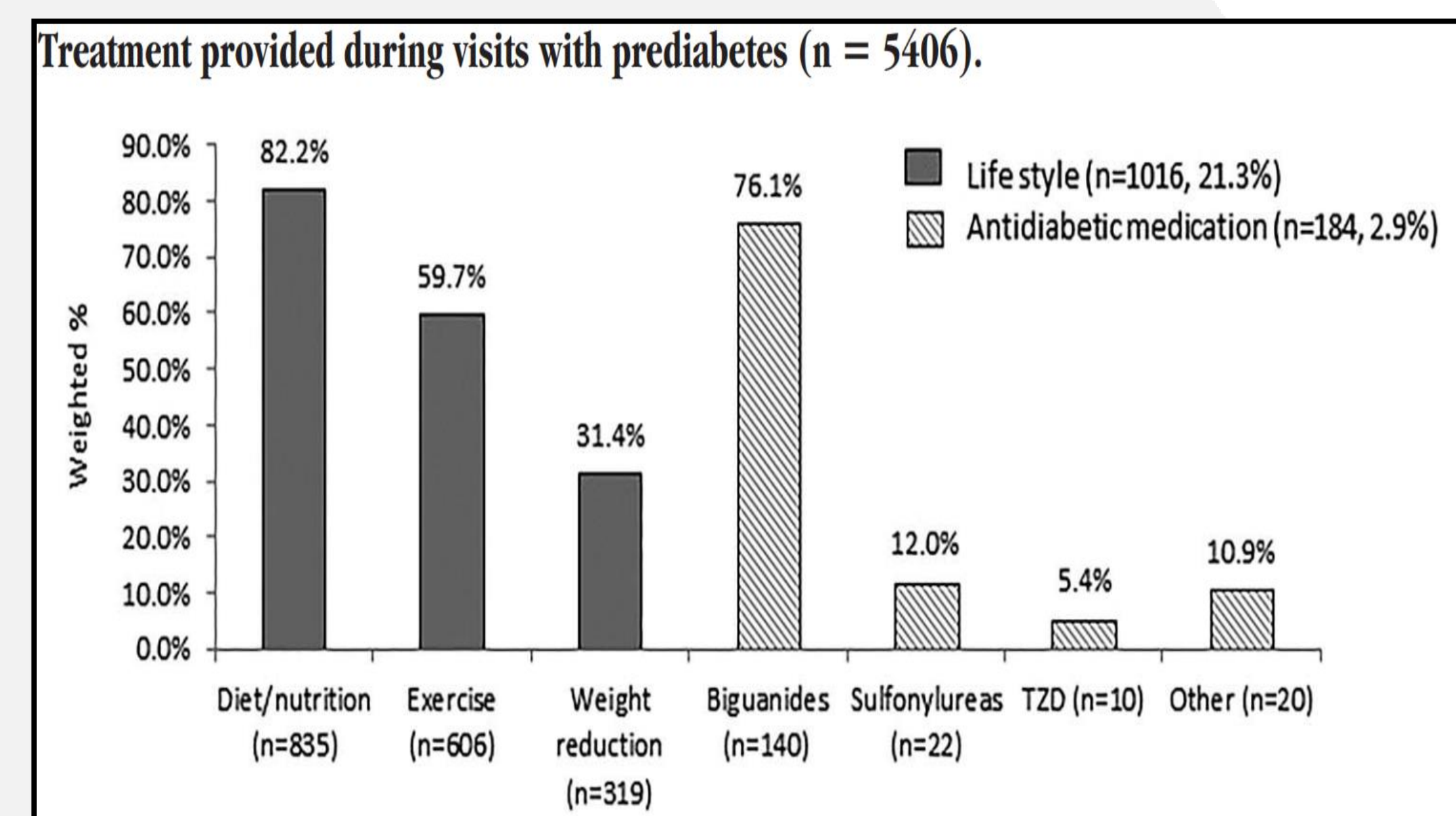
Research Questions

- What is the efficacy of metformin versus lifestyle modifications and how do they compare in reducing the incidence of diabetes?
- What is the efficacy of metformin, as an adjunctive therapy, to lifestyle modifications?
- What is the safety and tolerability of metformin in prediabetic patients?

Literature Review

Prevalence of Metformin Use in Prediabetes

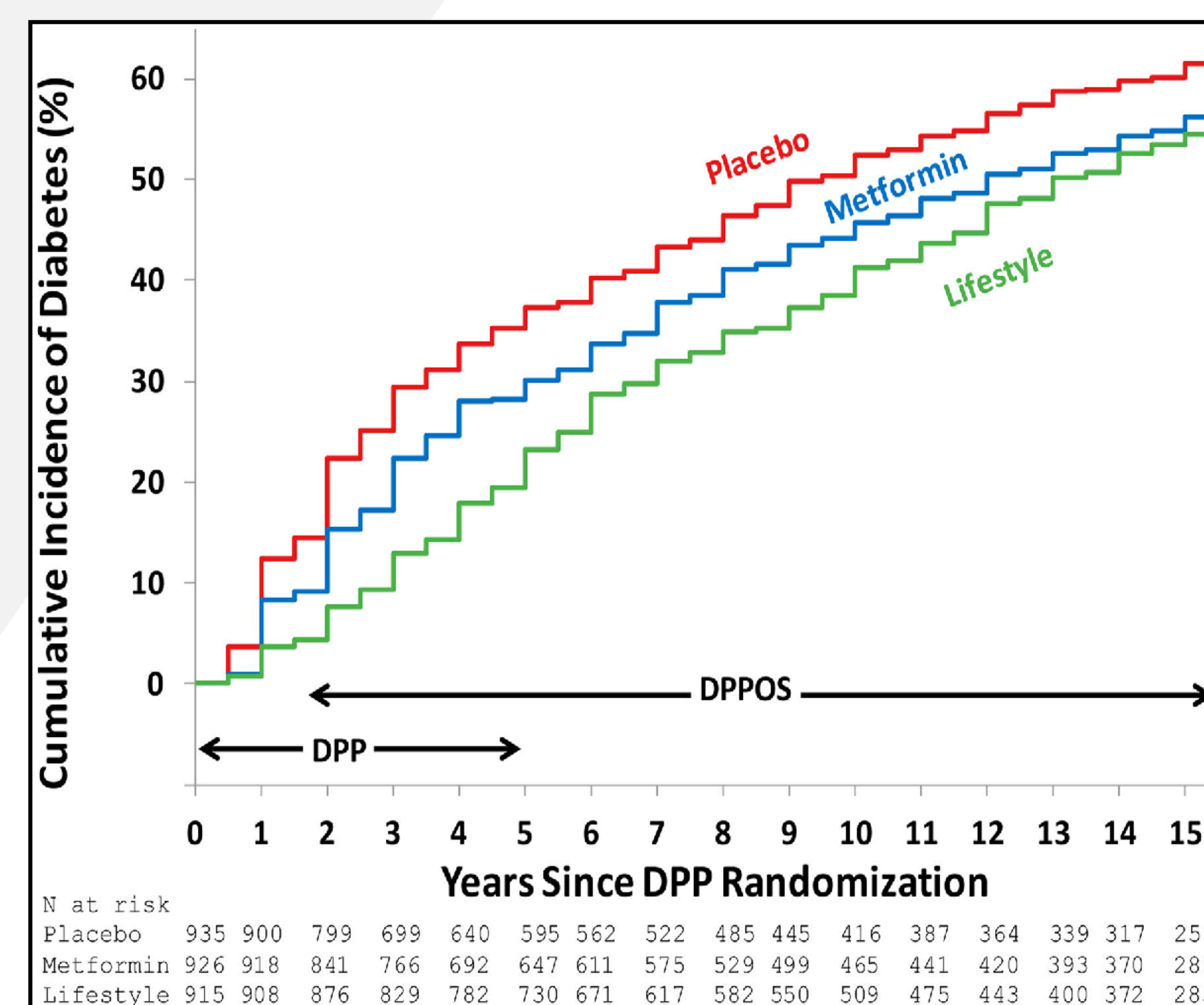
- Patients with prediabetes (n=5,406) were mainly suggested lifestyle management (21.3%, n=1,016) (Shealy et al., 2019).
- Shealy et al. (2019) found that 2.6% of patients with prediabetes were prescribed metformin.
- Greater than 75% of patients found to have prediabetes were not prescribed either lifestyle modifications or pharmacologic interventions to combat progression of prediabetes to overt diabetes (Shealy et al., 2019).



Note. Adapted from "Patterns of Diabetes Screening and Prediabetes Treatment During Office Visits in the US" by Shealy et al, 2019, *The American Board of Family Medicine*, 32(2), 209-217.

Efficacy of Lifestyle Modifications vs. Metformin in Prediabetic Patients

- The Diabetes Prevention Program (DPP) represents the largest and longest duration of a randomized controlled clinical trial comparing intensive lifestyle intervention versus masked metformin with placebo group (DPP, 2002)
 - After 2.8 years of follow-up, diabetes incidence was significantly reduced by 31% (95% CI=17%, 43%) in the metformin group and by 58% (95% CI=48%, 66%) in the intensive lifestyle group in comparison to placebo.
- Diabetes Prevention Outcomes Study (DPPOS)
 - After 15 years of follow-up, researchers found that metformin reduced diabetes incidence by 18% (p=0.001) while the intensive lifestyle group reduced the incidence of diabetes by 27% (p<0.0001) (DPPOS, 2015).



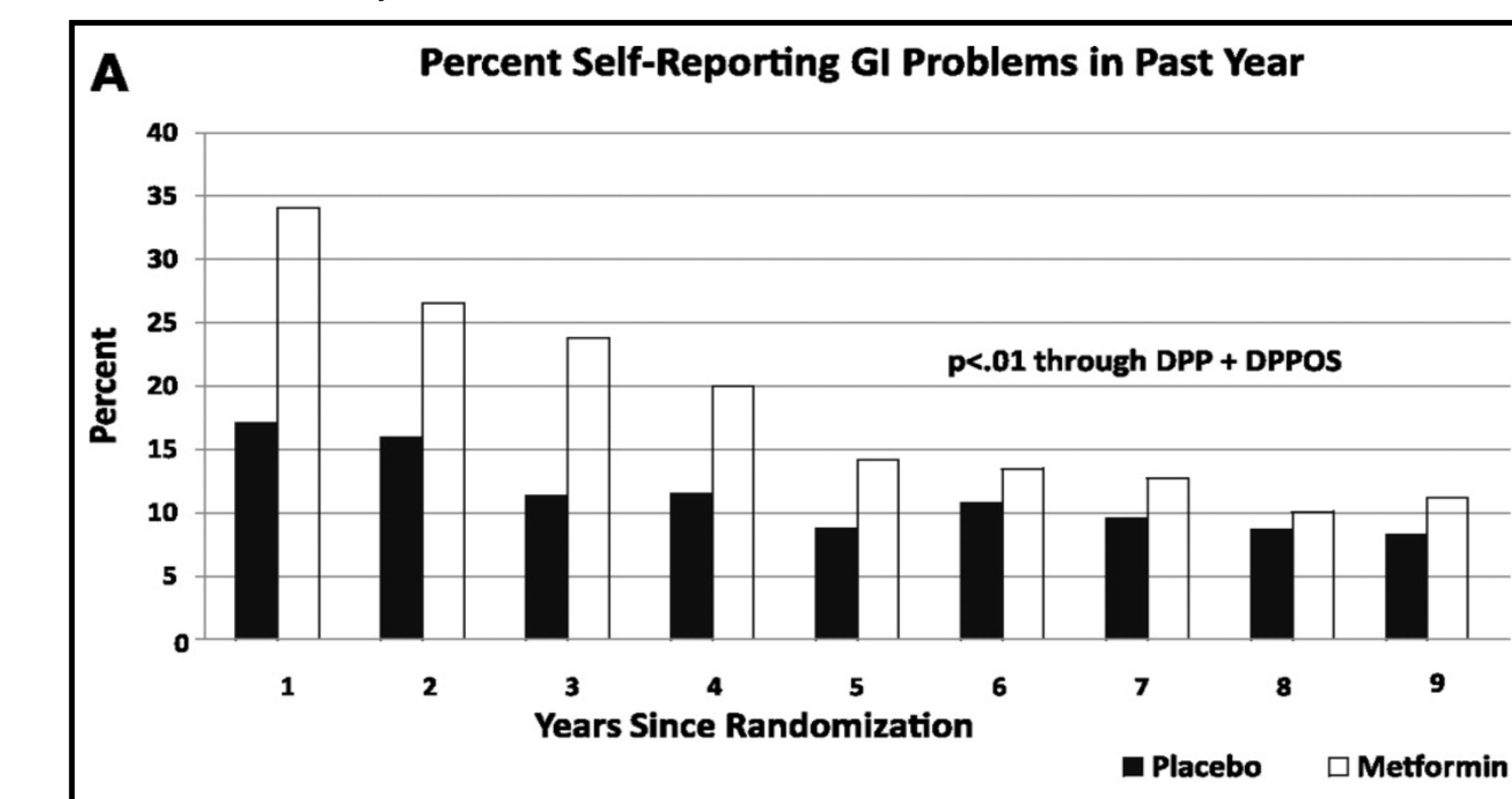
Note. Adapted from "Long-term Effects of Lifestyle Intervention or Metformin on Diabetes Development and Microvascular Complications: the DPP Outcomes Study" by The Diabetes Prevention Program Research Group, 2015, *The Lancet Diabetes & Endocrinology* 3(11), 866-875.

Efficacy of Lifestyle Modifications Plus Metformin in Patients with Prediabetes

- Ramachandran et al. (2006) conducted a randomized controlled clinical trial of 531 participants with prediabetes. After two years of follow-up, the progression of prediabetes to overt diabetes was reduced by:
 - 28.5% (CI 95% CI=20.5, 37.3, p=0.018) in lifestyle modification-only group.
 - 28.2% (CI 95% CI=20.3, 37.0, p=0.022) in lifestyle modification plus metformin group.
 - 26.4% (CI 95% CI=19.1, 35.1, p=0.029) in metformin-only group.
- Malin et al. (2012) found similar results to the study above and speculated that metformin could be blunting the effects of exercise training.

Safety & Tolerability of Metformin in Prediabetic Patients

- The Diabetes Prevention Research Group (2012) extrapolated data from the DPP Outcomes Study
 - Did not uncover any detrimental side effects or reports of lactic acidosis.
 - Gastrointestinal (GI) symptoms were among the most common adverse effects reported.
 - 9.5% of patients taking metformin versus 1.1% of patients receiving placebo experienced GI symptoms (p<0.01)
 - Reported GI symptoms showed a downward trend throughout the study.



Note. Adapted from "Long-Term Safety, Tolerability, and Weight Loss Associated With Metformin in the Diabetes Prevention Program Outcomes Study" by The Diabetes Prevention Program Research Group, 2012, *Diabetes Care* 35(4), 731-737.

Discussion

Efficacy of Lifestyle Modifications vs. Metformin in Prediabetic Patients

- Metformin was overall less effective than lifestyle modifications in the DPP and DPPOS, though group differences declined over time.
- Metformin was as effective as lifestyle modifications in specific patient populations:
 - BMI ≥ 35 kg/m²
 - Age 60 years or younger
 - Women with a history of gestational diabetes

Efficacy of Lifestyle Modifications Plus Metformin in Patients with Prediabetes

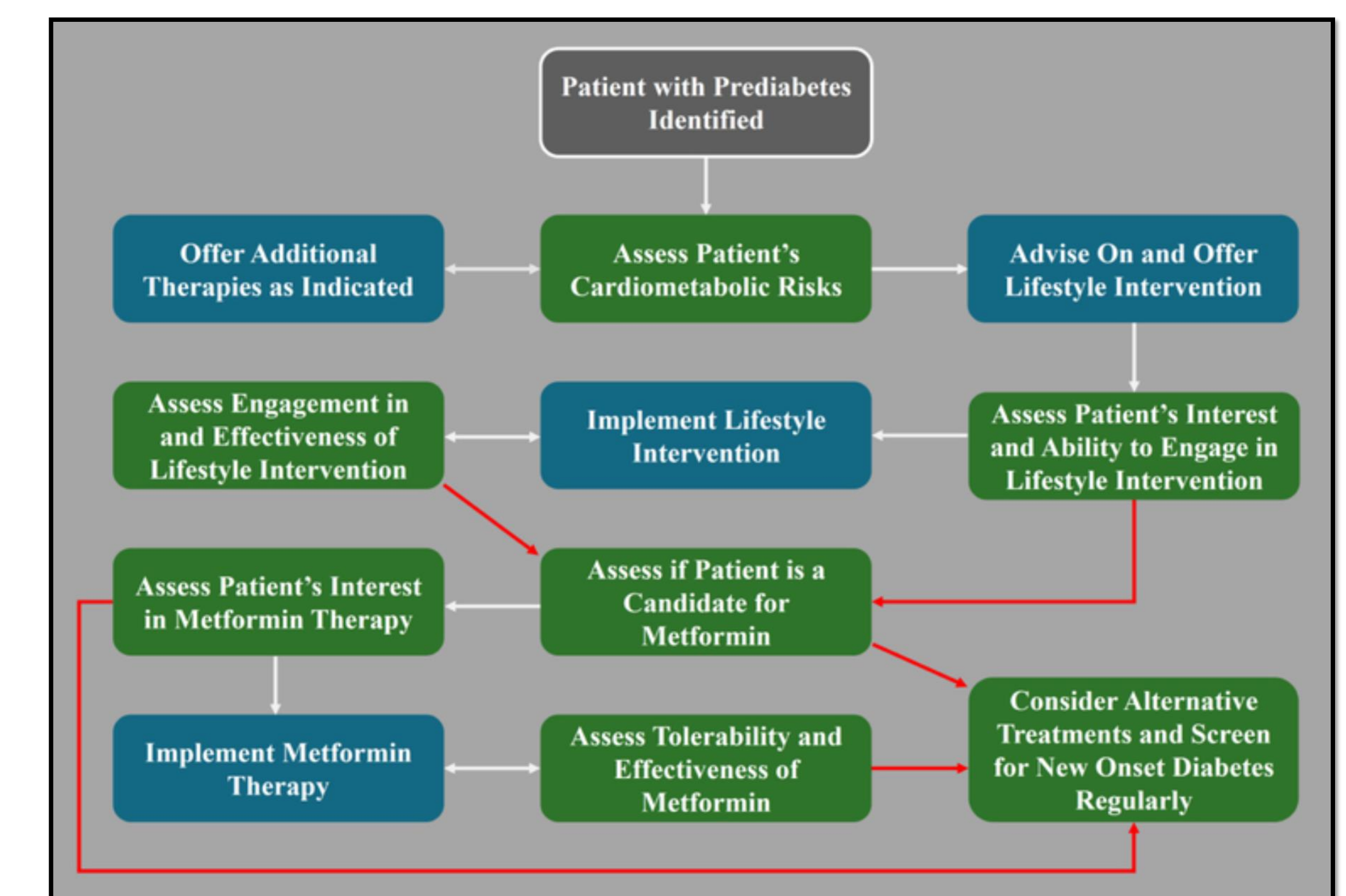
- There was not a statistically significant difference when adding metformin to intensive lifestyle modifications in several studies. This indicates a need for further research in this area.

Safety & Tolerability of Metformin in Prediabetic Patients

- GI symptoms are the most common adverse effect with metformin use and are statistically significant when compared with placebo.

Applicability to Clinical Practice

- The patient's primary care provider plays a vital role in both detecting and treating prediabetes. However, guidelines for prediabetes treatment are often unclear to the primary care provider, and patients may go untreated.
- This literature review aims to further educate the primary care provider in making the proper treatment decisions for patients with prediabetes, based on decades of evidence-based research.
- Provide patient-centered care for all patients by weighing relative risks and benefits and making choices that are aligned with the patient's values and preferences.
- Help patients understand management options for prediabetes.
- Initiating lifestyle interventions has been proven to be the first-line treatment for prediabetes, but metformin should be considered as a safe and effective treatment option for patients who fail lifestyle interventions, have a history of gestational diabetes, are 60 years of age or younger, or those with a BMI ≥ 35 kg/m².



Note. Adapted from "Prevention of Diabetes Mellitus in Patients With Prediabetes" by Carris et al., 2018, *The American Journal of Cardiology*, 123(9), 507-512.

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