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PA Portfolio III – Fall 2023

Clinical Scenario:

27 y/o obese male patient presents to the clinic for wellness visit patient most recent A1c has increased from 6.0 to 6.2. The patient is curious about pharmacological treatment such as metformin to help prevent the progression of Type 2 Diabetes.

Search Question:

Patients who are obese and prediabetic, does early pharmacological treatment such as Metformin help prevent diabetes when compared to no pharmacological intervention?

PICO Table:

Population	**Intervention**	**Comparison**	**Outcome(s)**
Pre-diabetic	Metformin	No pharmacological intervention	Prevent progression to type 2 diabetes
Obese patient		Placebo	Low glycemic
BMI over 30		Exercise	
Pre-diabetic	Metformin	No pharmacological intervention	Prevent progression to type 2 diabetes
Obese patient		Placebo	Low glycemic

Search Strategy and Databases Used:

Please indicate what data bases/tools you used, provide a list of the terms you searched together in each tool, and how many articles were returned using those terms and filters. Explain how you narrow your choices to the few selected articles.

Results found:

All filters included meta-analysis, systematic review, Retrospective Cohort study and RCT, published in the last 10 years.

PubMed:

Metformin for patents with prediabetes→ 336 results → Filter by RCT, Systemic Review, Clinical Trial, and Meta-analysis -→ 59 Results → Filter by last 10 years -→ 45 results

Prediabetes and metformin and prevention→ 374 results → Filter by RCT, Systemic Review, Clinical Trial, and Meta-analysis → 205 results → filter by 10 years → 131 results

Google Scholar.

Obese patients and prediabetes and metformin -→42, 200 Results → Since 2019 →16,900 -→ Review Articles -→ 17,000 results.

metformin for prediabetes -→17, 200 Results → Since 2019 →16,900 -→ Review Articles -→ 17,000 results.

Metformin and Type 2 Diabetes and Prevention-→294, 200 Results → Since 2019 →17,400 -→ Review Articles -→ 18,100 results.

Cochrane Search-database:

Prediabetes → Cochrane Review → 5 results

Explanation: When it came to choosing articles to research my topic on, I looked for studies done in the United States, and I used PubMed, Google scholar, and Cochrane. PubMed, and Google Scholar yielded me the most results for my PICO questions, and from there I narrowed down my search to articles completed within the last 10 years. I looked for mainly systemic-review, and meta-

analysis articles that looked at patients who were obese and prediabetic and were treated with Metformin. I wasn't able to find many articles that looked specifically at patients with BMI over 30, thus I focused mainly on patients with prediabetes.

Title: Metformin use in prediabetes: is earlier intervention better?
Type of study: RCT
Citation: Warrilow, A., Somerset, S., Pumpa, K. et al. Metformin use in prediabetes: is earlier intervention better?. Acta Diabetol 57, 1359–1366 (2020). https://doi-org.york.ezproxy.cuny.edu/10.1007/s00592-020-01559-9
Hyperlink: https://link-springer-com.york.ezproxy.cuny.edu/article/10.1007/s00592-020-01559-9#citeas

Abstract: Purpose of this study is to investigate effectiveness of metformin in diabetes prevention in a prediabetic population across a range of fasting plasma glucose (FPG) levels at baseline. A secondary aim was to assess the effectiveness of metformin in preventing diabetes in those participants where impaired fasting glucose (IFG) was relatively more pronounced as opposed to impaired glucose tolerance (IGT).
Materials and Methods: Participants randomized to metformin and placebo arms in the Diabetes Prevention Program study were stratified into cohorts according to level of FPG at baseline. Eligibility criteria for the original DPP study included an age of at least 25 years, a body mass index of 24 or higher (22 or higher in Asians), and a plasma glucose concentration of 95–125 mg per decilitre (5.3–6.9 mmol per litre) in the fasting state
Results. The largest reductions in incidence of diabetes and FPG occurred within prediabetic persons with a higher level of FPG at baseline. Metformin was able to stabilize insulin sensitivity in every stratified sub-cohort except one. Sub-cohorts which had higher levels of insulin sensitivity at baseline experienced the largest increases in insulin sensitivity. Metformin reduced the incidence of diabetes by 43% (RR 0.57, CI 0.4–0.9) in those prediabetic persons whose IFG was more pronounced compared to a 26% (RR 0.74 CI 0.7–0.8) when all participants in the study were included.
Conclusion: The largest reductions in both incidence of diabetes and FPG occurred in prediabetic persons with a higher level of FPG at baseline. Metformin was able to stabilize insulin sensitivity and was more effective in persons with more pronounced IFG.

Key points:

- At four years, FPG levels were lower in every metformin sub-cohort compared to its placebo counterpart
- When only prediabetic persons with more pronounced IFG were included, the reduction in incidence of diabetes increased to 43% (RR 57%, CI 0.4–0.9) over the period of the DPP study
- This analysis of the DPP study found that metformin reduced the incidence of diabetes by 26% (RR 74%, CI 0.65–0.83).

Why I chose it: I chose this article because it's an RCT that followed patients over several years and included patients with a baseline of 24 or higher, and minimum age of 25 years or older. The authors also had a strict plasma glucose concentration at fasting state to be included in the study. Also, this RCT supports that Metformin can help stabilize insulin sensitivity especially with patients with more pronounced impaired fasting glucose.

Title: Review of Metformin Use for Type 2 Diabetes Prevention
Type of study: Systemic Review
Citation: Moin T, Schmittdiel JA, Flory JH, Yeh J, Karter AJ, Kruge LE, Schillinger D, Mangione CM, Herman WH, Walker EA. Review of Metformin Use for Type 2 Diabetes Prevention. Am J Prev Med. 2018 Oct;55(4):565-574. doi: 10.1016/j.amepre.2018.04.038. Epub 2018 Aug 17. PMID: 30126667; PMCID: PMC6613947
Hyperlink: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6613947/

Abstract: This review summarizes the evidence surrounding metformin use for type 2 diabetes prevention.
Materials and Methods: Authors searched articles between 1998 and 2017 examining metformin use for the primary indication of diabetes prevention available on MEDLINE. Forty articles met inclusion criteria and were summarized into four general categories: (1) RCTs of metformin use for diabetes prevention (*n*=7 and *n*=2 follow-up analyses), (2) observational analyses examining metformin use in heterogeneous subgroups of patients with prediabetes (*n*=9 from the Diabetes Prevention Program, *n*=1 from the biguanides and the prevention of the risk of obesity [BIGPRO] trial), (3) observational analyses examining cost effectiveness of metformin use for diabetes prevention (*n*=11 from the Diabetes Prevention Program, *n*=1 from the Indian Diabetes Prevention Program), and (4) real-world assessments of metformin eligibility or use for diabetes prevention (*n*=9).
Results: Studies to date demonstrate that metformin use may be beneficial in subsets of the patients who are at higher risk of progression to diabetes. For example, when HbA1c was used to define the outcome of incident diabetes in a DPP post-hoc analysis, metformin and lifestyle interventions were equally effective, contrasting the OGTT-based outcome showing lifestyle interventions as the most effective therapy.23 Therefore, there may be some evidence to suggest that patients with abnormal HbA1c, particularly those with HbA1c values in the upper end of the prediabetes range (i.e., 6.0%–6.4%), may benefit from metformin therapy. Examination of treatment effects within the DPP and DPPOS demonstrate significant heterogeneity, such that obese participants (BMI 35 or more kg/m2), those with higher fasting glucose levels, and women with a history of gestational diabetes had greater risk reduction with metformin
Conclusion: The current evidence suggests that metformin is an effective, safe, tolerable, cost effective, and possibly even cost-saving intervention to prevent or delay incident diabetes. Evidence for metformin use is strongest in those with IGT and IFG at higher risk; age 60 or less years, BMI 35 or more kg/m2, and in women with histories of gestational diabetes.

Key points:

- strongest evidence for use in those at highest risk (i.e., aged <60 years, BMI ≥35 kg/m2, and women with histories of gestational diabetes).
- There may be some evidence to suggest that patients with abnormal HbA1c, particularly those with HbA1c values in the upper end of the prediabetes range (i.e., 6.0%–6.4%), may benefit from metformin therapy.

Why I chose it: I chose this article because it is a systemic review that looked at studies from 1998 to 2017 so there is two decades worth of studies in this systemic review. The systemic review included real-world assessment of metformin, observational analyze as well as cost, and RCT studies.

Title: Impact of Lifestyle and Metformin Interventions on the Risk of Progression to Diabetes and Regression to Normal Glucose Regulation in Overweight or Obese People With Impaired Glucose Regulation
Type of study: RCT and Review
Citation: Herman WH, Pan Q, Edelstein SL, Mather KJ, Perreault L, Barrett-Connor E, Dabelea DM, Horton E, Kahn SE, Knowler WC, Lorenzo C, Pi-Sunyer X, Venditti E, Ye W; Diabetes Prevention Program Research Group. Impact of Lifestyle and Metformin Interventions on the Risk of Progression to Diabetes and Regression to Normal Glucose Regulation in Overweight or Obese People With Impaired Glucose Regulation. Diabetes Care. 2017 Dec;40(12):1668-1677. doi: 10.2337/dc17-1116. Epub 2017 Oct 11. Erratum in: Diabetes Care. 2018 Feb 23;: Erratum in: Diabetes Care. 2019 Apr;42(4):701. PMID: 29021207; PMCID: PMC5711336.
Hyperlink: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5711336/

Abstract: Both lifestyle and metformin interventions can delay or prevent progression to type 2 diabetes mellitus (DM) in people with impaired glucose regulation
Materials and Methods: The study population included overweight and obese adults with IGT and fasting hyperglycemia enrolled in the DPP, a randomized, controlled clinical trial comparing the impact of intensive lifestyle intervention, metformin, and placebo on the development of DM over an average 3.2 years. Inclusion criteria included age ≥25 years, BMI ≥24 kg/m2 (≥22 kg/m2 in Asian Americans), plasma glucose 2-h after a 75-g oral glucose load (2-h PG) of 140–199 mg/dL, and fasting PG (FPG) of 95–125 mg/dL
Results: Participants at highest risk of developing DM who adhered to a lifestyle intervention had a 39% ARR of developing diabetes and a 24% greater absolute likelihood of reverting to NGR, whereas those who adhered to the metformin intervention had a 25% ARR of developing diabetes and an 11% greater absolute likelihood of reverting to NGR.

Conclusion: The DPP demonstrated the efficacy of lifestyle and metformin interventions for delaying progression to DM in diverse participants at high-risk for DM

Key points:

- Lifestyle intervention was also more effective than metformin intervention in promoting regression to NGR (absolute increase in predicted probability of regression to NGR 30% for lifestyle and 14% for metformin)
- Absolute reduction in the predicted 3-year probability of progression to DM is 20% for participants who adhered to the lifestyle intervention and 9% for participants who adhered to the metformin intervention
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Why I chose it: I chose this article because it looked at the impact of lifestyle, and Metformin intervention for patients are diabetic. It found that a combo of both lifestyle, and Metformin can have the greatest impact on patient who are pre-diabetic.

Title: Treating Prediabetes with Metformin
Type of study: Meta-analysis, and Systemic Review
Citation: Lily M, Godwin M. Treating prediabetes with metformin: systematic review and meta-analysis. Can Fam Physician. 2009 Apr;55(4):363-9. Erratum in: Can Fam Physician. 2010 Jan;56(1):18. Lilly, Muriel [corrected to Lily, Muriel]. PMID: 19366942; PMCID: PMC2669003.
Hyperlink: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2669003/

Abstract: To determine if the use of metformin in people with prediabetes would prevent or delay the onset of frank type 2 diabetes mellitus.

Materials and Methods: Randomized controlled trials that involved administration of metformin to delay or prevent type 2 diabetes in individuals with impaired glucose tolerance or impaired fasting glucose were included. Development of diabetes was a required outcome measure; follow-up time of at least 6 months was required. Three studies met these criteria.

Results The study conducted in China had an overall rate of conversion to diabetes of 10%; the study in India a rate of 48%; the DPP study,24 in which ethnicity was mixed (55% white, 20% African American, and only 5% Asian), a rate of conversion to diabetes midway between the other 2 studies at 24%. This fits with the recognized higher prevalence of diabetes and metabolic syndrome in people of South Asian descent. It is difficult to know from this review whether the relative effectiveness of the lower dosage of metformin (250 mg twice or 3 times daily) compared with the higher dosage (850 mg twice daily) used in the DPP study would hold true for all people. The 2 studies that used lower dosages were conducted in China and India, where conversion rates to diabetes are different from that in the study using the higher metformin dosage. In the 2 studies that used lower dosages, only the Indian study (in which the overall conversion rate was much higher) showed a statistically significant difference in rates of conversion between treatment and control. It is possible that the effectiveness of the lower dosage is somehow related to genetics or ethnicity

Conclusion: Metformin decreases the rate of conversion from prediabetes to diabetes. This was true at higher dosage (850 mg twice daily) and lower dosage (250 mg twice or 3 times daily);

Key points:

- Studies show that patients with prediabetes who take metformin are less likely to have blood glucose levels in the diabetic range after 3 years.
- It is probably best to use a metformin dosage of 850 mg twice daily except in people of South Asian descent, for whom this dosage might be higher than needed

Why I chose it: I chose this article because it's a systemic review that looked at research going back to 1960, and looked at RCT from other countries as well. Currently I'm on my family medicine rotation, and a large percentage of the population I see are south Asian who are diabetic or prediabetes.. This article included a study patient of South Asian descent, so it is another reason why I chose it.

Title: Therapeutic Use of Metformin In Prediabetes and Diabetes Prevention
Type of study: Meta-analysis, and Systemic Review
Citation: Hostalek, U., Gwilt, M. & Hildemann, S. Therapeutic Use of Metformin in Prediabetes and Diabetes Prevention. Drugs 75, 1071–1094 (2015). https://doi.org/10.1007/s40265-015-0416-8
Hyperlink: https://link.springer.com/article/10.1007/s40265-015-0416-8#citeas

Abstract: Metformin enhances the action of insulin in liver and skeletal muscle, and its efficacy for delaying or preventing the onset of diabetes has been proven in large, well-designed, randomized trials, such as the Diabetes Prevention Program and other studies

Materials and Methods: The authors searched PubMed for articles that were published in English they used terms such as "Prediabetes", "Impaired glucose", "Prevention of diabetes".

Results: Diabetes incidence rates (per 100 person-years) during the DPPOS, according to treatment assignment in the DPP, were 4.9 (95 % CI 4.2–5.7) for metformin, 5.9 (95 % CI 5.1–6.8) for the intensive lifestyle intervention, and 5.6 (95 % CI 4.8–6.5) for placebo. The apparent benefit for metformin relative to lifestyle intervention during the DPPOS phase was due to reduced diabetes incidence rates in the metformin (and placebo) group compared with an increasing rate in the intensive lifestyle group.

Conclusion: The authors concluded that patients who are prediabetic are likely to benefit from a combination of lifestyle intervention and pharmacologic changes to prevent or delay the onset of Type 2 Diabetes. The authors conclude there is evidence to support the role of Metformin in diabetes prevention.

Key points:

- Significant reductions in the risk of progressing from prediabetes (principally IGT) to type 2 diabetes in subjects treated with metformin were observed.
- Current evidence supports a role for metformin in diabetes prevention, given in addition to lifestyle intervention, in people with prediabetes

Why I chose it: I chose this article because it's a systemic review of multiple studies not only from the U.S, but several other countries as well. The article didn't only just look at how Metformin helps prevent diabetes, but also the cardiovascular impact from Metformin, and cholesterol as well.

Title: Metformin for prevention or delay of type 2 diabetes mellitus and its associated complications in persons at increased risk for the development of type 2 diabetes mellitus
Type of study: Meta-analysis, and Systemic Review
Citation: Madsen KS, Chi Y, Metzendorf MI, Richter B, Hemmingsen B. Metformin for prevention or delay of type 2 diabetes mellitus and its associated complications in persons at increased risk for the development of type 2 diabetes mellitus. Cochrane Database Syst Rev. 2019 Dec 3;12(12):CD008558. doi: 10.1002/14651858.CD008558.pub2. PMID: 31794067; PMCID: PMC6889926.
Hyperlink: https://pubmed.ncbi.nlm.nih.gov/31794067/

Abstract: To assess the effects of metformin for the prevention or delay of T2DM and its associated complications in persons at increased risk for the T2DM.
Materials and Methods: The authors searched Cochrane Central Register of Controlled Trials, MEDLINE, Scopus, WHO Trials. The authors included RCT with a duration of one-year or more comparing Metformin with any pharmacological glucose-lowering intervention, behavior-changing intervention, placebo or standard care in people with impaired glucose tolerance, impaired fasting glucose, moderately elevated glycosylated hemoglobin A1c (HbA1c) or combinations of these.
Results: A total of nine out of 161 participants developed T2DM in the metformin group versus nine out of 159 participants in the comparator group (RR 0.99, 95% CI 0.41 to 2.40; P = 0.98; 320 participants. Eight RCTs compared metformin with intensive diet and exercise: all-cause mortality was 7/1278 versus 4/1272 (RR 1.61, 95% CI 0.50 to 5.23; P = 0.43; 2550 participants, 4 trials); incidence of T2DM was 304/1455 versus 251/1505 (RR 0.80, 95% CI 0.47 to 1.37; P = 0.42; 2960

Conclusion: Metformin compared with placebo or diet and exercise reduced or delayed the risk of T2DM in people at increased risk for the development of T2DM.

Key points:

• Metformin compared to intensive diet and exercise did not reduce or delay the risk of T2DM (moderate-quality evidence) • Reports of serious side effects was sparse
Why I chose it: I chose this article because it's a review of several RCT, and the authors ranked the RCT from low-level of certainty to high-level certainty.

Summary of Evidence:

Author (Date)	Level of Evidence	Sample/Setting (# of subjects/ studies, cohort definition etc.)	Outcomes Studied	Key Findings	Limitations and Biases
6/30/2020	Level 2: RCT	Participants randomized to metformin and placebo arms in the Diabetes Prevention Program study were stratified into cohorts according to level of FPG at baseline. Eligibility criteria for the original DPP study included an age of at least 25 years, a body mass index of 24 or higher (22 or higher in Asians), and a plasma glucose concentration of 95–125 mg per decilitre (5.3–6.9 mmol per litre) in the fasting state	Is to investigate effectiveness of metformin in diabetes prevention in a prediabetic population across a range of fasting plasma glucose (FPG) levels at baseline	Metformin was able to stabilize insulin sensitivity and was more effective in persons with more pronounced IFG.	One of the major limitations of this study is that it doesn't look into how long the subjects were on Metformin for, and what the optimal dosage is to prevent Type 2 DM.

10/01/2019	Level 1: Systemic Review	(1) RCTs of metformin use for diabetes prevention (*n*=7 and *n*=2 follow-up analyses), (2) observational analyses examining metformin use in heterogeneous subgroups of patients with prediabetes (*n*=9 from the Diabetes Prevention Program, *n*=1 from the biguanides and the prevention of the risk of obesity [BIGPRO] trial), (3) observational analyses examining cost effectiveness of metformin use for diabetes prevention (*n*=11 from the Diabetes Prevention Program, *n*=1 from the Indian Diabetes Prevention Program), and (4) real-world assessments of metformin eligibility or use for diabetes prevention (*n*=9).	FDA has not approved the off-label use of Metformin for pre-diabetic patients. However, numerous studies have shown Metformin is beneficial in reducing the possibility of pre-diabetes turning into diabetes. This study is to review the literature to better understand the current state of evidence surrounding metformin use for diabetes prevention.	Evidence for metformin use is strongest in those with IGT and IFG at higher risk; age 60 or less years, BMI 35 or more kg/m2, and in women with histories of gestational diabetes. There may be some evidence to suggest that patients with abnormal HbA1c, particularly those with HbA1c values in the upper end of the prediabetes range (i.e., 6.0%–6.4%), may benefit from metformin therapy	There are several limitations to this article one that the authors were searching articles from 1998, and two they also researched studies outside of the U.S, which may not have the standards of publication as the U.S does. Also, the methodologies of conducting studies have changed and articles from 1998 can be outdated.

12/2017	Level 1: Review	The study population included overweight and obese adults with IGT and fasting hyperglycemia enrolled in the DPP, a randomized, controlled clinical trial comparing the impact of intensive lifestyle intervention, metformin, and placebo on the development of DM over an average 3.2 years. Inclusion criteria included age ≥25 years, BMI ≥24 kg	Both lifestyle and metformin interventions can delay or prevent progression to type 2 diabetes mellitus (DM) in people with impaired glucose regulation	Absolute reduction in the predicted 3-year probability of progression to DM is 20% for participants who adhered to the lifestyle intervention and 9% for participants who adhered to the metformin intervention	The authors mention several limitations from this study. Individuals who participated in this study were more likely motivated to prevent their prediabetes from becoming diabetes and were more likely adhere to the program.
04/2009	Level 1: Meta-analysis, and Systemic Review	Administration of metformin to delay or prevent type 2 diabetes in individuals with impaired glucose tolerance or impaired fasting glucose were included. Development of diabetes was a required outcome measure; follow-up time of at least 6 months was required	To determine if the use of metformin in people with prediabetes would prevent or delay the onset of frank type 2 diabetes mellitus	Patients with prediabetes who take metformin are less likely to have blood glucose levels in the diabetic range after 3 years.	The authors note limitation of this paper is how to apply the results to clinical practice. This could be because most physicians are not prescribing metformin to their patients who are prediabetic, instead using lifestyle treatment.
6/10/2015	Level 1: Meta-analysis, and Systemic Review	The authors searched for article Published in English. They used several DDP studies across several different nations. The U.S, India, China, Canada, and Pakistan.	Analyze the benefits of Metformin on patients who are pre-diabetic. Numerous studies have shown Metformin for	Diabetes incidence rates (per 100 person-years) during the DPPOS, according to treatment assignment in the DPP, were 4.9 (95 % CI 4.2–5.7) for metformin, 5.9 (95 % CI 5.1–6.8) for the intensive lifestyle intervention, and 5.6	A limitation of this study is that authors used studies from other countries which may not have the same standards as U.S studies do, and methodologies can vary from country to country

			delaying or preventing the onset of diabetes	(95 % CI 4.8–6.5) for placebo. The apparent benefit for metformin relative to lifestyle intervention during the DPPOS phase was due to reduced diabetes incidence rates in the metformin (and placebo) group compared with an increasing rate in the intensive lifestyle group.	
12/3/2019	Level 1: Systemic Review	The authors searched Cochrane Central Register of Controlled Trials, MEDLINE, Scopus, WHO Trials. The authors included RCT with a duration of one-year or more comparing Metformin with any pharmacological glucose-lowering intervention, behavior-changing intervention, placebo or standard care in people with impaired glucose tolerance, impaired fasting glucose, moderately elevated glycosylated hemoglobin A1c (HbA1c) or combinations of these	To assess the effects of metformin for the prevention or delay of T2DM and its associated complications in persons at increased risk for the T2DM.	Metformin compared with placebo or diet and exercise reduced or delayed the risk of T2DM in people at increased risk for the development. However, metformin compared to intensive diet and exercise did not reduce or delay the risk ofT2DM (moderate-quality evidence). Likewise, the combination of metformin and intensive diet and exercise compared to intensive dietand exercise only neither showed an advantage or disadvantage regarding the development of T2DM	The authors note that many of the trials they researched were not designed or powered to detect a predefined outcome. Additionally, not all ethnicities were represented in the trials, and could show a bias to specific race. Also, detailed information about patients were lacking from some trials.

Conclusion: Briefly summarize the conclusions of each article then provide overarching conclusion

Article 1: Metformin is a safe and effective medication that is cost-effective in preventing Type 2DM in patients who are pre-diabetic.

Article 2: Patients who are high-risk for Type 2 DM, due to BMI can benefit from Metformin as well as lifestyle intervention in the prevention of Type 2 DM.

Article 3: Authors concluded that lifestyle intervention was more effective than Metformin in promoting regression to Normal glucose levels. But still support that Metformin is a safe, and effective medication in helping reduce the conversion of Pre-diabetes to Type 2 DM.

Article 4: The Authors found that high dosage of Metformin , and lower dosage of Metformin taken 3x was effective in reducing the likelihood of patient developing Type 2 DM.

Article 5: A combination of lifestyle changes and Metformin can be an effective way of treating patients with Pre-diabetes, and preventing Type 2 DM.

Article 6: Metformin compared with placebo or diet and exercise reduced or delayed the risk of T2DM in people at increased risk for the development of T2DM.

Overarching Conclusion: Current research does support that Metformin for high risk patients can delay the progression of type 2 DM. Combining Metformin with lifestyle intervention can be the best way to treat patients with Type 2 DM.

Magnitude of effects/statistical significance:

Article 1: When only prediabetic persons with more pronounced IFG were included, the reduction in incidence of diabetes increased to 43% (RR 57%, CI 0.4–0.9) over the period of the DPP study. The lifestyle intervention reduced the incidence by 58% (95% CI 48–66%) and metformin by 31% (95% CI 17–43%), as compared with placebo;

Article 2: 9 Eligible participants from 27 U.S. medical centers were randomized to metformin (850 mg twice per day [bid], n=1,073), or an intensive lifestyle intervention (16 weekly, one-on-one lifestyle intervention sessions with a health coach and monthly follow-up thereafter, n=1,079), or placebo (n=1,082). Over 2.8 years of follow-up, diabetes incidence was significantly reduced by 31% (95% CI=17%, 43%) in the metformin arm and by 58% (95% CI=48%, 66%) in the intensive lifestyle intervention arm as compared with placebo. The intensive lifestyle intervention arm provided 39% (95% CI=24%, 51%) relative risk reduction of incident diabetes compared with metformin across the pooled sample and was also effective for individuals aged >60 years

Article 3: Metformin intervention in increasing the probability of regression to NGR was greatest in the quartile at highest risk of progressing to DM (35 vs. 17% and difference of 18%). In those at lowest risk of progressing to DM, the corresponding rates were 24 and 11% (difference of 13%)

Article 4: The study conducted in China had an overall rate of conversion to diabetes of 10%; the study in India a rate of 48%; the DPP study,24 in which ethnicity was mixed (55% white, 20% African American, and only 5% Asian), a rate of conversion to diabetes midway between the other 2 studies at 24%

Article 5: Significant improvements in the metformin group were observed for BMI (the primary endpoint) at 6 months, with a mean change of -0.1 SD (95 % CI -0.18 to -0.02; p = 0.02), and at 3 months for FPG (-0.16 mmol/L; 95 % CI -0.31 to -0.00; p = 0.047); alanine aminotransferase levels (-19 %; 95 % CI -5 to -36 %; p = 0.008) and adiponectin: leptin ratio (32 %; 95 % CI 4–67; p = 0.02). Another randomized, placebo-controlled study in 52 glucose-intolerant pediatric subjects showed that 12 weeks of treatment with metformin 850 mg twice daily significantly reduced levels of resistance.

Article 6: A total of nine out of 161 participants developed T2DM in the metformin group versus nine out of 159 participants in the comparator group (RR 0.99, 95% CI 0.41 to 2.40; P = 0.98; 320 participants. Eight RCTs compared metformin with intensive diet and exercise: all-cause mortality was 7/1278 versus 4/1272 (RR 1.61, 95% CI 0.50 to 5.23; P = 0.43; 2550 participants, 4 trials); incidence of T2DM was 304/1455 versus 251/1505 (RR 0.80, 95% CI 0.47 to 1.37; P = 0.42; 2960

Clinical Bottom line/significance: Type 2 Diabetes is a disease that can be well controlled, but the cost is high, and many patients can be non-compliant with their medication. Type 2 Diabetes is not curable and patients who become pre-diabetic are at an increased risk of becoming diabetic can benefit from taking Metformin especially those who are at higher risk because they are unable to make lifestyle changes. Metformin has been approved by the FDA for off-label use, but the evidence does show that patients who are at high risk for Type 2 Diabetes can benefit from Metformin intervention.

Considerations: Even though Metformin has shown to help prevent the transition of pre-diabetes to Type 2 diabetes there are some concerns with prescribing patients Metformin if they are not diabetic. Firstly, it should be noted that two-thirds of people with prediabetes will not develop diabetes, one-third will return to normal glucose levels, and patients who are prediabetic are not at any risk of diabetic complications. Metformin works by lessening the amount of sugar the body produces, and absorbs, this can lead to patients becoming hypoglycemic from Metformin. Additionally, prescribing patients Metformin who are prediabetic can create a "moral hazard", patients will look to medication to solve their health problems instead of taking initiatives with exercising and eating healthier. Finally, cost needs to be considered as well will insurance companies pay for patients Metformin if they are not diabetic? Patients who are diabetic and have insurance pay an avg of $3-11 for a 30 day supply, and without insurance can cost $20 dollars for a 30 day supply and cost can become a burden for patients who are low-income.

Mayer B. Davidson; Metformin Should Not Be Used to Treat Prediabetes. *Diabetes Care* 1 September 2020; 43 (9): 1983–1987. https://doi.org/10.2337/dc19-2221