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PERSPECTIVE

Metformin in prediabetes: Opportunity or over-treatment?

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Even though the United States Food Drug Administration (US-FDA) did not approve any pharmacological agents for the prevention of type 2 diabetes (T2D) in people with prediabetes (PwPd), metformin has a therapeutic indication in people at risk for the prevention or delay of a new diagnosis of T2D, in nearly 66 countries [1]. In 2022, The Drug Controller General of India (DCGI) also extended metformin use to PwPd [2] at risk, failing despite intensive lifestyle modification (iLSM) for 3 to 6 months; however, no cut-off or threshold has been laid down for the age, body mass index (BMI), fasting plasma glucose (FPG) or glycated hemoglobin (HbA1c). The latest 2025 position statement of the American Diabetes Association (ADA) recommends metformin pharmacotherapy in PwPd, along with LSM, in specific situations. This includes adults aged 25–59 years with a BMI of ≥ 35 kg/m^2, higher FPG ≥ 110 mg/dL (≥ 6 mmol/L), and higher HbA1c of ≥ 6.0% (≥ 42 mol/mol), and in women with a prior history of gestational diabetes mellitus (GDM) [3]. The National Institute for Health and Care Excellence, United Kingdom (NICE-UK) suggests using metformin in PwPd when iLSM fails using clinical judgment or in BMI ≥ 35 kg/m^2 if doing iLSM is impossible. Contrarily, the 2019 European Society of Cardiology and European Association of Studies in Diabetes (ESC-EASD) did not recommend pharmacotherapy with metformin in PwPd [4]. This point-of-view article aims to analyze the ambiguity of metformin in PwPd and assess whether it is a good opportunity or an unnecessary over-treatment rather than a proper prevention of progression to overt T2D.

Although the term "prediabetes" remains widely used, including by the ADA-EASD, this term has attracted controversy, partly due to a perception that large numbers of people with prediabetes will never develop overt T2D but are nevertheless associated with it and thus become "medicalized." The World Health Organization (WHO) has abandoned the term prediabetes in favor of "intermediate hyperglycemia." Importantly, prediabetes is not associated with a substantial risk of microvascular disease, unlike overt T2D. However, it is associated with an increased risk of conversion to full-blown T2D (especially in people with impaired fasting glucose [IFG]) and an increased risk of cardiovascular disease (CVD, especially in people with impaired glucose tolerance [IGT]). Notwithstanding, prediabetes is significantly associated with increased coronary heart disease (CHD, relative risk [RR] 16%), CVD (RR 15%), stroke (RR 14%), and all-cause mortality (RR 13%), as evidenced by a recent meta-analysis of 129 prospective studies and post-hoc analysis of clinical trials, involving more than 10 million individuals with prediabetes with a mean follow-up of 9.8 years [5]. These data suggest that some intervention is needed in PwPd to prevent – a. conversion to overt T2D, b. long-term macrovascular complications, and c. mortality. To this end, metformin was the first pharmacological agent tested extensively in PwPd and has been compared with a placebo or LSM/iLSM.

Historically, in 1999, the first double-blind, randomized controlled trial (RCT) that tested metformin in Chinese PwPd was conducted by Li et al. [6], which showed a significant 66% relative risk reduction (RRR) in the conversion

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rate of frank T2D by metformin compared to placebo, over one year. The largest (n = 3,234) and the longest double-blind RCT was the US-based Diabetes Prevention Program (US-DPP), an RCT conducted in 2002 by Knowler et al. [7], and a subsequent 10, 15, and 22-year observational follow-up outcome study (DPPOS) [8–10]. US-DPP randomized PwPd in a 1:1:1 fashion to either iLSM (target weight loss of at least 7% and 150 min/week of moderate exercise such as brisk walking) or metformin or control. During the randomized phase of mean 2.8 years of US-DPP, both iLSM and metformin reduced T2D conversion by an RRR of 58% and 31%, respectively, compared to control. However, the incidence of T2D with iLSM was 39% lower than metformin [7]. The subsequent observational 10, 15, and 22-year follow-up of DPPOS [8–10] also showed a significant decrease in RRR concerning progression to frank T2D compared to control; however, the quantum of benefit reduced over time in both metformin and iLSM arms (Fig. 1). Meanwhile, several other RCTs (mainly open-label) have been conducted in PwPd [11–17] that assessed the effects of – a. metformin vs. control/standard of care (SOC)/placebo or b. LSM/iLSM vs. control/SOC/placebo or c. metformin vs. LSM/iLSM or d. metformin plus LSM/iLSM vs. control/SOC/placebo, showing positive or neutral effects on T2D conversion [11–17]. Interestingly, no RCT was used to compare the effectiveness of LSM/iLSM plus metformin vs. metformin alone. The results from all these RCTs conducted are summarized in Table 1 chronologically [6, 7, 11–17]. Briefly, amongst the open-label studies, two RCTs were also conducted in the Indians – a. Indian Diabetes Prevention Program-1 (IDPP-1) was the four-armed study (n = 531), randomized in 1:1:1:1 fashion (LSM [150 min/week of brisk walking/cycling] vs. metformin vs. LSM plus metformin vs. SOC [control arm]) with a mean follow-up of 3.0 years [12] and b. Diabetes Community Lifestyle Improvement Program (D-CLIP) was a two-armed study (n = 576) that compared iLSM (target weight loss of at least 7% and 150 min/week of brisk walking) plus metformin to control (SOC or placebo) with a mean follow-up of 3.0 years [15]. IDPP-1 showed that metformin and LSM significantly reduced the RR of T2D progression by 26% and 29%, respectively, compared to the control/SOC/placebo. The Indian studies, IDPP-1 and D-CLIP, showed metformin plus LSM having a significant 28% and 32% RRR in T2D conversion, respectively, compared to control/SOC/ placebo. The other large study was the Chinese Diabetes Prevention Program (CDPP), a two-armed, 2-year follow-up study (n = 1678) that compared LSM (150 min/week of brisk walking) plus metformin to LSM alone and showed a 17% RRR with the former compared to the latter [17]. Summarily, the only RCT that reported the outcome of T2D conversion between iLSM vs. metformin was US-DPP, which showed a 39% RRR with the former compared to the latter [6]. Surprisingly, no statistical calculation was made between LSM vs. metformin in IDDP-1 [12]. While the first RCT by Li et al. [6] showed 66% RRR with

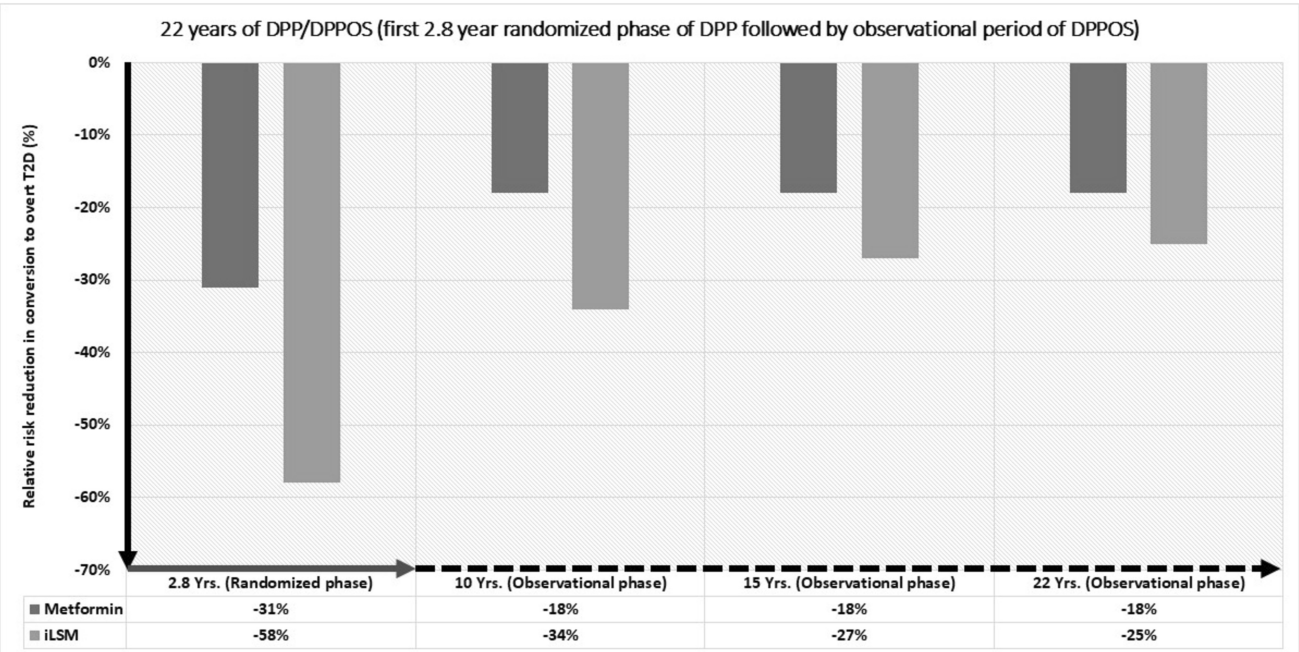

Fig. 1 Relative risk reduction in conversion to frank type 2 diabetes with metformin and intensive lifestyle modification (iLSM) in people with prediabetes at 2.8 years (randomized phase of US-DPP) and observational periods of 10, 15, and 22 years (DPPOS).[7–10] [(US-DPP: United States Diabetes Prevention Program; DPPOS: Diabetes Prevention Program Outcome Study)]

Table 1 Randomized controlled trials conducted with metformin in prediabetes that studied diabetes conversion rates (in chronological order)

Study/ First author (Country), Year	Type of study, Duration of study	Types of prediabetes; (Criteria used for diagnosis)	N	Max. MET dose used	Comparator arms, n (at final follow-up)				Outcomes for T2D progression: % RRR (95% CI) Note: No studies compared outcomes between MET + LSM/iLSM *vs.* MET alone			
					MET alone	LSM^/ iLSM[!] alone	MET + LSM^^/ iLSM[!!]	SC/ Control/ PBO	MET *vs.* SC/ Control/PBO	LSM^/ iLSM[!] *vs.* MET	MET + LSM^^/ iLSM[!!] *vs.* SC/ Control/PBO	LSM^/iLSM[!] *vs.* SC/Control/ PBO
Li et al[6] (China), 1999	DBRCT, 1 Yr	IGT; (WHO 1985)	70	250 mg TID	33	-	-	37	*66%, p = 0.01*	-	-	-
US-DPP[7] (USA), 2002	DBRCT, 2.8 Yr	IFG, IGT; (ADA 1997)	3234	850 mg BID	1073	1079[!]	-	1082	*31% (17 to 43)*	*39%[!] (24 to 51)*	-	*58%[!] (48 to 66)*
EDIT[11] (UK), 2003	DBRCT, 6.0 Yr	IFG, IGT; (ADA 1997, WHO 1985)	631	500 mg TID	NR	-	-	NR	IFG: RR = 0.99, IGT: RR = 1.09	-	-	-
IDPP-1[12] (India), 2006	OLRCT, 3.0 Yr	IGT; (WHO 1999)	531	250 mg BID	128	120^	121^^	133	*26.4% (19.1 to 35.1)*	NC	*28.2%^^ (20.3–37.0)*	*28.5%^^ (20.5 to 37.3)*
Lu et al[13] (China), 2011	OLRCT, 2.0 Yr	IFG, IFG + IGT; (ADA 2003)	210	250 mg TID	-	-	46^^	41	-	-	0% vs. 12.2%, (RRR: NC)	-
Hydrie et al[14] (Pakistan), 2012	OLRCT, 1.5 Yr	IGT; (WHO 1999)	317	500 mg BID	-	107[!]	85[!!]	82	-	-	*76.5%!! (19.7 to 93.1)*	*71%[!] (13.7 to 90.3)*
D-CLIP[15] (India), 2016	OLRCT, 3 Yr	IFG, IGT, IFG + IGT; (ADA 2003)	576	500 mg BID	-	-	293[!!]	283	-	-	*32%[!!] (7 to 50)*	-
PREVENT-DM[16] (USA), 2017	OLRCT, 1 Yr	IFG, HbA1c; (ADA 2010)	92	850 mg BID	29	30[!]	-	28	1 event in PBO arm, RRR: NC	0 event	-	1 event in the PBO arm
CDPP[17] (China), 2023	OLRCT, 2 Yr	IFG, IGT, IFG + IGT; (WHO 1999)	1678	850 mg BID	-	714^	635^^	-	MET + LSM^^ *vs.* LSM^: *17% (1 to 30)*			

Italicized values suggest significance

RRR: Relative risk reduction; RR: Risk ratio; Max: Maximum; NC: Not calculated; NR: Not reported/retrievable; T2D: Type 2 diabetes; MET: Metformin; LSM^/^^: Lifestyle modification (Brisk walking or cycling for 150 min per week); iLSM[!/!!]: Intensive lifestyle modification (Brisk walking or cycling for 150 min per week plus 7% weight loss); SOC: Standard of care; PBO: Placebo; IGT: Impaired glucose tolerance; IFG: Impaired fasting glucose; DBRCT: Double-blind randomized controlled trial; OLRCT: Open-label randomized controlled trial; CI: Confidence interval; US-DPP: United States diabetes prevention program; EDIT: Early Diabetes Interventional Trial; IDPP-1: Indian diabetes prevention program; D-CLIP: Diabetes community lifestyle improvement program; PREVENT-DM: Promotora effectiveness versus metformin trial; CDPP: Chinese diabetes prevention program; BID: Twice daily; TID: Thrice daily; Yr: Years; ADA: American Diabetes Association; WHO: World Health Organization; USA: United States of America; UK: United Kingdom

Table 2 Absolute benefit of metformin or lifestyle medication (LSM) compared to placebo, and metformin plus LSM compared to placebo or LSM

Study	Background patient's characteristics at baseline	Duration (Years)	Cumulative incidence (%) of T2D between -PBO/Control/SOC *vs* MET *vs.* iLSM[!] / LSM[^] *vs.* MET + iLSM[!!] / LSM[^^]	The number-needed-to-treat (NNT)				Final interpretation of the study
				MET *vs.* PBO	iLSM[!] / LSM[^] *vs.* PBO	MET + iLSM[!!] / LSM[^^] *vs.* PBO	MET + iLSM[!!] / LSM[^^] *vs.* iLSM[!] / LSM[^]	
Li et al[6]	Mean age: 50 years, mean BMI: 26.0 kg/m^2, 29% were female, HbA1c was 7.4% and 7.3% in PBO and MET arms, respectively	1	16.2 *vs.* 3.0	7.6	-	-	-	To prevent one overt T2D, 8 people need to be treated with metformin alone for 1 year
US-DPP[7]	Mean age: 51 years, mean weight: 94 kg, mean BMI: 34.0 kg/m^2, and mean HbA1c: 5.9%. 55% were Whites, 4% were Asians, 69% had family h/o T2D, 68% were female, and 16% had h/o GDM	3	28.9 *vs.* 21.7 *vs.* 14.4[!]	13.9	6.9[!]	-	-	To prevent one overt T2D, 14 people need to be treated with metformin, and 7 people need to do iLSM alone for 3 years
IDPP-1[12]	Mean age: 46 years, mean BMI: 26.0 kg/m^2, and mean HbA1c: 6.2%. 100% were Asian Indians, 50% had family h/o T2D, and 21% were female	3	55 *vs.* 40.5 *vs.* 39.3[^] *vs.* 39.5[^^]	6.9	6.4[^]	6.5[^^]	-	To prevent one overt T2D, 7 people need to be treated with metformin alone or metformin plus LSM, and 6 people need to do LSM alone for 3 years
Lu et al[13]	Mean age: 62 years, mean weight: 72 kg, mean BMI: 27.0 kg/m^2, and mean HbA1c: 5.9%	2	12.2 *vs.* 0[^^]	-	-	8.2[^^]	-	To prevent one overt T2D, 8 people need to be treated with metformin plus LSM for 2 years
Hydrie et al[14]	Mean age: 44 years, mean BMI: 27.0 kg/m^2, 100% Asian Pakistani, and 49% had family h/o T2D	1.5	NR	-	9[!]	8[!!]	-	To prevent one overt T2D, 9 people need to be treated with metformin alone, and 8 people need to be treated with metformin plus iLSM for 1.5 years
D-CLIP[15]	Mean age: 44 years, mean weight: 75 kg, mean BMI: 28.0 kg/m^2, and mean HbA1c: 6.0%. 100% were Asian Indians, 57% had family h/o T2D, and 37% were female	3	34.9 *vs.* 25.7[!!]	-	-	9.8[!!]	-	To prevent one overt T2D, 10 people need to be treated with iLSM plus metformin for 3 years

Table 2 (continued)

Study	Background patient's characteristics at baseline	Duration (Years)	Cumulative incidence (%) of T2D between -PBO/Control/SOC *vs* MET *vs.* iLSM$^{!}$ / LSM$^{\wedge}$ *vs.* MET + iLSM$^{!!}$ / LSM$^{\wedge\wedge}$	The number-needed-to-treat (NNT)				Final interpretation of the study
				MET *vs.* PBO	iLSM$^{!}$ / LSM$^{\wedge}$ *vs.* PBO	MET + iLSM$^{!!}$ / LSM$^{\wedge\wedge}$ *vs.* PBO	MET + iLSM$^{!!}$ / LSM$^{\wedge\wedge}$ *vs.* iLSM$^{!}$ / LSM$^{\wedge}$	
CDPP[17]	Median age: 53 years, mean weight: 73 kg, mean BMI: 26.0 kg/m^2, and mean HbA1c: 6.0%. 100% were Asian Chinese, and 53% were female	2	25.1$^{\wedge}$ *vs.* 21.5$^{\wedge\wedge}$	-	-	–	27.8$^{\wedge\wedge}$	To prevent one overt T2D, 28 people need to be treated with LSM plus metformin for 2 years

MET: Metformin; T2D: Type 2 diabetes; BMI: Body mass index; h/o: History of; LSM$^{\wedge/\wedge\wedge}$: Lifestyle modification (Brisk walking or cycling for 150 min per week); iLSM$^{!/!!}$: Intensive lifestyle modification (Brisk walking or cycling for 150 min per week plus 7% weight loss); SOC: Standard of care; PBO: Placebo; GDM: Gestational diabetes mellitus; US-DPP: United States diabetes prevention program; IDPP-1: Indian diabetes prevention program; D-CLIP: Diabetes community lifestyle improvement program; CDPP: Chinese diabetes prevention program

metformin compared to placebo in people with IGT (defined by WHO 1985 criteria), baseline HbA1c was 7.3% and 7.4% in the metformin and placebo arm, respectively. Indeed, the author reports that nearly 50% of people with IGT in this trial would have been diagnosed with frank T2D if the ADA 1997 criteria based on the FPG threshold had been used instead. Nonetheless, the number needed to treat (NNT) to develop frank T2D for metformin was impressive across RCTs, and iLSM had even better NNT than metformin in preventing frank/overt T2D conversion. Table 2 summarizes the absolute risk reduction and NNT with metformin alone, LSM/iLSM, and metformin plus LSM/iLSM, compared to control/SOC/placebo. It should be noted that while the reducing effect of metformin in T2D conversion could be explained by the anti-hyperglycemic impact suggestive of a "masking effect" rather than a preventive nature, an actual preventive effect of T2D conversion can only be assessed after a sufficient wash-out period. In this regard, only US-DPP studied the impact of the 1- to 2-week (mean 11 days) wash-out period of metformin on T2D conversion. This study showed a curtailed effect of metformin at washout (Odds ratio [OR]: 1.49) compared to before washout (OR 0.66), suggesting a 1.5-fold increase in development of T2D compared with control. Precisely, there was a small but significant + 4.5 mg/dL increase ($p < 0.001$) in fasting plasma glucose without any considerable increase in 2-h glucose (+ 2.9 mg/dL) assessed by oral glucose tolerance test during the washout period [18]. Nonetheless, the authors suggested that nearly one-quarter (25%) of the effect of metformin is attributable to a pharmacological effect that did not persist during the drug withdrawal or washout period. Similarly, a weight loss of −1.7 kg with metformin vs. weight gain of + 0.3 kg in the placebo arm also explained the 64% beneficial effect of the drug at the end of US-DPP. This could also explain the nearly twice larger iLSM (58% RRR) effect intended to cause 7% weight loss on T2D prevention than metformin (31% RRR) in US-DPP.

About systematic reviews and meta-analyses (SRM) of RCTs that were also expected to be conducted [19–23], the largest Cochrane meta-analysis (pooled data from 12 RCTs) showed a 50% RRR in T2D conversion with metformin compared to control/placebo [20]. However, no difference in T2D conversion was observed between LSM vs. metformin in Cochrane SMR (pooled data from 7 RCTs) [20]. Similarly, another SRM found no difference in T2D progression between LSM and metformin [22]. Contrarily, one SRM showed a 27% less T2D conversion with LSM compared with metformin [23]. Nevertheless, except the Cochrane meta-analysis, most SRMs have specific weaknesses, including- a. some used intention-to-treat, others used per-protocol analysis, b. some used fixed-model while others used random models' analysis, c. most of them clubbed the data of metformin plus LSM

Table 3 Systematic reviews and meta-analyses (MA) of randomized controlled trials (RCTs) conducted with- A. metformin vs. control/placebo (PBO) and B. metformin vs. lifestyle modification (LSM) in prediabetes

First author, Year	Comparator arms	Total RCTs (n) included in the MA, Participant (N)	Progression to T2D: % RRR (95% CI, P value, I^2)	Limitations
A. Metformin vs. control/PBO				
Lily et al[19], 2009	MET *vs.* Control/PBO	3, N = 2,486	35% decreased odds (22 to 45%, $p < 0.00001$, $I^2 = 5.8\%$) in PP analysis, and 31% decreased odds in ITT analysis (18 to 42%, $p < 0.0001$, $I^2 = 0\%$)	Fixed model analysis was used. The n/N does not match for some of the data for both PP and ITT analysis
Madsen et al[20], 2019	MET *vs.* Control/PBO	12, N = 3,632	50% decreased risk (35 to 62%, $p < 0.0001$) in ITT analysis, $I^2 = 48\%$	ITT analysis was used, but eight studies included in this MA were published in a non-English language. Needs an update in light of a few more RCTs published later
Patel et al[21], 2023	MET *vs.* Control/PBO	8, N = 6,320	42% decreased risk (23 to 56%, $p < 0.00001$, $I^2 = 82\%$)	Of the 8 RCTs included, 4 were subgroup/post-hoc analyses of the parent study. The n/N does not match for some of the data. PP analysis was done. One included study in the metformin-alone group was done with metformin plus rosiglitazone. Significant I^2
B. Metformin vs. LSM				
Madsen et al[20], 2019	MET *vs.* LSM	7, N = 2,960	No significant difference ($p = 0.42$, $I^2 = 85\%$)	Three studies included were published in a non-English language. Significant I^2
Vajje et al[22], 2023	MET *vs.* LSM	5, N = 4,334	No significant difference ($p = 0.52$, $I^2 = 83\%$)	PP analysis was used. Many studies included in this MA used LSM plus MET instead of MET alone. Significant I^2
Mousavi et al[23], 2023	LSM *vs.* MET	5, N = 3,120	25% reduced risk with LSM (8 to 40%, $p = 0.007$, $I^2 = 39\%$)	PP analysis was used. n/N not matching for some studies. Many studies included in this MA used LSM plus MET instead of MET alone

RCTs: Randomized controlled trials; PBO: Placebo; MA: Meta analysis; T2D: Type 2 diabetes; RRR: Relative risk reduction; LSM: Lifestyle modification; ITT: Intention-to-treat; PP: Per-protocol; I: Heterogeneity; MET: Metformin; n: Number of events; N: Number of patients; CI: Confidence interval

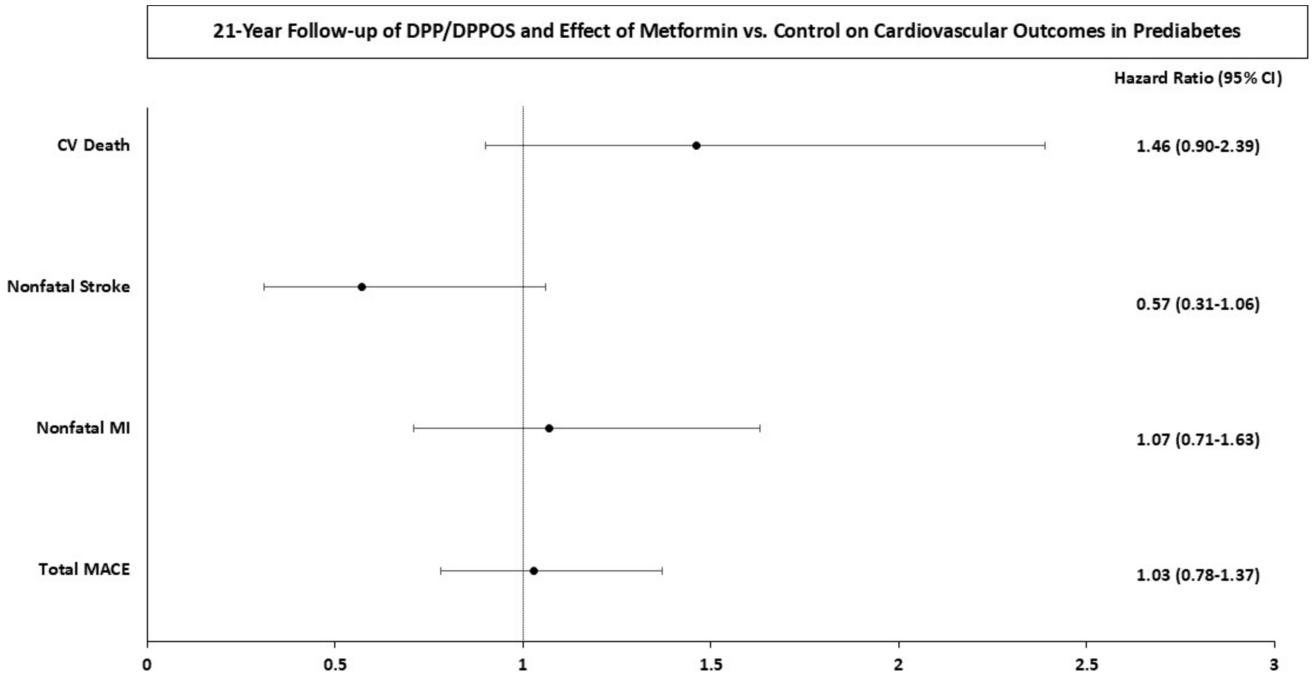

Fig. 2 Cardiovascular and mortality outcomes with metformin vs. control at 21 years of DPP/DPPOS.[26] [(US-DPP: United States Diabetes Prevention Program; DPPOS: Diabetes Prevention Program Outcome Study; MACE: Major Adverse Cardiovascular Events; CV: Cardiovascular; MI: Myocardial infarction; CI: Confidence interval)]

or iLSM arm with metformin alone arm, d. similarly, most of them clubbed the data of LSM with control/SOC/placebo together and compared it against metformin alone, and e. one SRM has pooled the multiple publications of DPPOS along with the original randomized phase of US-DPP. Table 3 summarizes these findings, including their shortcomings, which may limit any concrete conclusion. Nonetheless, all these data collectively suggest that metformin is superior to placebo/SOC/Control but not superior to LSM/iLSM in T2D conversion. However, specific nuances need to be considered – i. the definition of IFG and IGT varied amongst all RCTs. Older RCTs used WHO 1985, ADA 1997, and WHO 1999 criteria, while newer RCTs used ADA 2003 and 2010 criteria. Surprisingly, the CDPP conducted in 2017–2019 used WHO 1999 criteria (Table 1). It should also be noted that IGT criteria have not changed since the National Diabetes Data Group (NDDG) laid it down in 1979, while the FPG threshold kept changing until ADA 2003. Contrarily, no RCTs chose the IFG criteria laid down by the ADA in 2010 (HbA1c cut-off lowered to 5.7% for prediabetes) followed until today except the PREVENT-DM study that did not report T2D progression with metformin or LSM vs. control due to zero to one event [16], ii. Baseline glucose, HbA1c, BMI values, family history of T2D, and history of GDM differed amongst RCTs; thus, outcomes are not comparable (Table 3), iii. dosage of metformin used across RCTs varied from 500 to 1750 mg daily, and thus, it is not precisely known what dose of metformin should be the ideal one in PwPd. To this end, a recent meta-analysis suggested that 750 mg of metformin daily is the optimal dose in PwPd [24]. However, IDPP-1 showed that a daily dose of as low as 500 mg was effective in Indians, and indeed, a higher dose of 1000 mg daily caused hypoglycemic symptoms in 45% PwPd, iv. US-DPP indicated that to reduce a 31% risk of frank T2D, 100% of PwPd have to take metformin for 3 years, but it is not known whether 69% of them who develop frank T2D later, despite metformin treatment, should continue on either metformin or change to other anti-hyperglycemic medications. In other words, what would be the rationality of taking metformin in 100 PwPd to prevent frank T2D if 70 of them ultimately develop the disease and then need to take the same or other medicine, v. long-term data of DPPOS suggested that even though over half of PwPd were taking metformin at 10 years follow-up, metformin delayed the frank T2D conversion by around 2 years but did not prevent it [8], and finally, vi. In the 1- to 2-week washout period of US-DPP, metformin did show an attenuating effect on T2D progression in PwPd compared to the non-washout period, suggesting a pharmacological effect and not complete prevention [18]. Thus, despite ample positive RCTs, various brownie points are eligible to raise ambiguity regarding metformin's role in PwPd.

Table 4 Points in favor and against metformin pharmacotherapy in prediabetes

Patients' characteristics	Favor	Against
Labeling the patient with prediabetes as having a "disease" or "illness."	Patients with prediabetes have higher rates of macrovascular complications, and hence, identifying prediabetes as an entity would increase awareness of a condition associated with a higher risk for cardiovascular disease and mortality	There are no longitudinal follow-up data to show whether metformin use can benefit in reducing either macro or microvascular complications or mortality in prediabetes
Definition of "prediabetes"	The definition of IGT has remained the same since the NDDG criteria of 1979, although the cut-off for FPG has changed	The definition of IFG varied across the trials (WHO considers FPG to be between 110 and 125 mg/dL, while ADA considers IFG 100 to 125 mg/dL). Studies used various criteria of IFG, ranging from WHO 1985 to ADA 2010, and thus, very heterogeneous inclusion criteria were used across RCTs
Dose of metformin used	Even the dose of 250 mg BID was beneficial in IDPP-1 study	Differences in dose between trials from 250 mg BID to 850 mg BID. No comparative dose studies have been conducted to demonstrate the lowest effective dose except one meta-analysis[24] that suggested 750 mg daily is the optimal dose
Effect of metformin on prediabetes subtypes	Theoretically, metformin should reduce FPG by impacting endogenous hepatic glucose production. Indeed, in US-DPP, the IFG cohort in the higher quartile of FPG had the largest RRR (48% RRR in FPG ≥ 110 mg/dL and 15% RRR in < 110 mg/dL). No difference was noted concerning quartiles of IGT	The trials that looked at IFG and IGT separately revealed that patients with IFG had lower RRR regarding progression to diabetes than the IGT arm. Conversion to T2D with metformin was quantitatively less in IGT (31% RRR) compared with IFG (12% RRR) in D-CLIP. IDDP-1 did not include IFG patients
GI adverse effects	Overall, the majority of the patients tolerated metformin well	GI adverse effects were greater than those of the control/lifestyle group, and many trials did not separate the results into "intention to treat" and "per protocol" sets
Hypoglycemia	Metformin is usually not associated with hypoglycemia as an adverse effect	Only two trials provided data on hypoglycemia. In IDPP-1, up to 45% of patients reported hypoglycemic symptoms necessitating a reduction of metformin dose. None of the other trials have detailed any information regarding hypoglycemia
Patients who failed on metformin (that is, those who progressed to T2D)	-	No follow-up was provided for patients who progressed to T2D while on metformin for prediabetes. Given metformin's failure in the prediabetes stage, there is no recommendation as to whether it should be continued when diagnosed with T2D. What is the point of taking metformin for 3 years if 69% eventually develop the disease and have to take the same medicine?
Cardiovascular outcome	Coronary artery calcium (CAC) measurements after 14 years of follow-up of DPPOS revealed that CAC severity and presence were significantly lower in men in the metformin group than in the placebo group, with no CAC differences between the lifestyle and placebo groups	Metformin did not reduce major cardiovascular events in DPPOS over 21 years despite long-term prevention of diabetes

Table 4 (continued)

Patients' characteristics	Favor	Against
Absolute benefit on T2D progression	NNT for metformin to prevent T2D is pretty impressive compared to placebo or control	NNT for LSM and iLSM is even more impressive than metformin. Moreover, US-DPP indicated that to reduce a 31% risk of frank T2D, 100% of PwPd have to take metformin for 3 years, but it is unknown whether 69% of them who develop frank T2D later should continue on metformin. A 10-year follow-up of DPPOS suggested metformin delayed the frank T2D conversion by around 2 years but did not prevent it. Furthermore, in a 1- to 2-week washout period of US-DPP, metformin did show an attenuating effect of metformin in T2D progression

T2D: Type 2 diabetes; WHO: World Health Organization; ADA: American diabetes association; NDDG: National Diabetes Data Group; FPG: Fasting plasma glucose; IFG: Impaired fasting glucose; IGT: Impaired glucose tolerance; RRR: Relative risk reduction; IDPP-1: Indian diabetes prevention program; D-CLIP: Diabetes community lifestyle improvement program; GI: Gastrointestinal; BID: Twice daily; US-DPP: United States Diabetes Prevention Program; DPPOS: Diabetes prevention outcome study; BID: Twice daily; NNT: Number needed to treat; RCTs: Randomized controlled trials; LSM: Lifestyle modification; iLSM: Intensive lifestyle modification

Metformin's role in preventing CVD and mortality in PwPd is the second most significant point. To this end, there is minimal data concerning metformin's effectiveness in preventing CHD, CVD, stroke, and mortality in PwPd. US-DPP is the only study that evaluated the effect of metformin on these outcomes in PwPd. The 14-year follow-up of observational DPPOS assessed the impact of iLSM, control, or metformin on coronary artery calcium (CAC) scoring. This study found no age-adjusted CAC score severity difference between iLSM vs. control and metformin vs. iLSM. While metformin showed a significantly 41% lesser age-adjusted CAC severity than control (39.5 vs. 66.9 Agatston units, $p = 0.04$) in men, no such significant difference was observed in women [25]. The 21-year follow-up of observational DPPOS assessed the impact of iLSM, control, or metformin in PwPd on total major adverse cardiovascular events (nonfatal myocardial infarction [MI], nonfatal stroke, and fatal CVD), nonfatal MI, nonfatal stroke, and CV death. There was no difference in outcomes between metformin vs. control (Fig. 2) and iLSM vs. control [26]. These data suggest that neither metformin nor iLSM has a consistent beneficial effect on CV and mortality outcomes compared to control/placebo.

Finally, while a 10-year cost-effective analysis of metformin in DPPOS showed a significant beneficial effect of metformin in PwPd [27], a recent analysis challenged those findings. This new US-DPP re-analysis hinted at no metformin cost-effectiveness in PwPd [28]. Notwithstanding, all these findings led to an ongoing debate, and both the proponents [29, 30] and the opponents [31, 32] of metformin pharmacotherapy in PwPd have their own arguments. It should also be noted that a debate on "prediabetes" terminology already exists, and strong points and counterpoints have already been made earlier [33–35]. Table 4 summarizes points in favor or against pharmacotherapy with metformin in PwPd based on all those arguments. So, what is the way forward? The only solution is reconciling all the available evidence and striking a balance [36]. Figure 3 represents the balance sheet of how defining prediabetes as a disease entity and pharmacotherapy of prediabetes may or may not be beneficial. In conclusion, PwPd needs some interventions. Notwithstanding, iLSM targeting 5–7% weight loss should be the first and foremost advice, followed by LSM. However, for some unavoidable reasons, if iLSM or even LSM is not possible, we propose that metformin therapy be advised in selected high-risk cases. These high-risk cases include adults of age < 60 years having a family history of T2D and IFG with fasting plasma glucose ≥ 110 mg/dL or HbA1c ≥ 6.0% and BMI ≥ 35 kg/m^2 (this BMI cut-off can be lowered to at least ≥ 30 kg/m^2 in Asians including Indians and Chinese—as both IDDP-1 and CDPP had a mean BMI of 26 kg/m^2 while D-CLIP had a mean BMI of 28 kg/m^2—and the fact that Asians tend to progress faster in developing frank T2D) or a history of GDM.

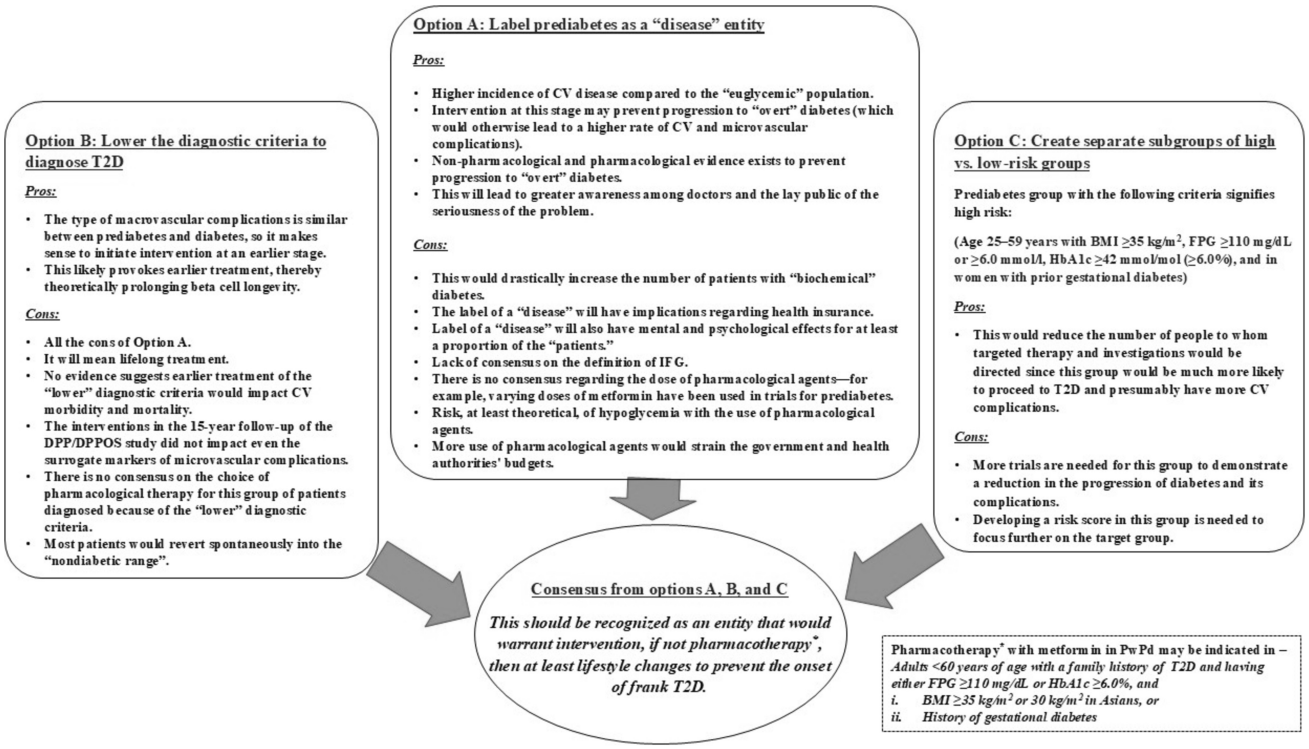

Fig. 3 Reconciling available evidence with the balance sheet.[29–36] [(T2D: Type 2 diabetes; BMI: Body mass index; CV: Cardiovascular; FPG: Fasting plasma glucose; IGF: Impaired fasting glucose; US-DPP: United States Diabetes Prevention Program; DPPOS: Diabetes Prevention Program Outcome Study)]

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