EE71

Baseline Risk Heterogeneity in Cost-Effectiveness Analysis of the Diabetes Prevention Program

Rittenhouse B[1], Alolayan S[2], Eguale T[1,3], Segal A[1,3]

[1]Massachusetts College of Pharmacy & Health Sciences, Boston, MA, USA, [2]College of Pharmacy, Taibah University , Saudi Arabia

[3]Brigham and Women's Hospital, Boston, MA, USA

Introduction & Objectives

The Diabetes Prevention Program (DPP) and follow-on Outcomes Study (DPPOS) compared Placebo, Metformin (both including basic lifestyle modification advice) and intensive Individual Lifestyle counseling interventions (hereafter, PBO, MET and LS). A fourth, group-based LS (GLS), was ***modelled*** in DPP Cost-Effectiveness Analyses (CEAs) done with trial data. GLS was assumed to be less costly and equally effective to LS.

A number of CEAs based on the trial sample of patients at high risk for diabetes claimed to have shown that both MET and LS (or GLS) were cost-effective[1-3] Those results were subsequently shown to be in error due to inappropriate calculations of the Incremental Cost-effectiveness Ratios (ICER).[4-6] Only LS (or GLS) was cost-effective in the overall sample, but there has been speculation that the highest-risk patients may have different results.

Sussman[7] reported the DPP cumulative Incidence (CI) results at three years by baseline risk quartile, derived from a multivariate predictive model. We developed a CEA based on those reported data.

Methods

All data are from an earlier DPP CEA that used generic MET costs[3]. The Supplementary Data (SD) from that publication provided yearly sample sizes, numbers of diabetes (D) and non-diabetes (ND) patients, inside program costs (C^I), outside program costs (C^O) and utilities (U) – all differing by treatment, though we do not add treatment to the notation. Inside costs were those of the intervention; outside costs were those related to the intervention's performance (e.g. hospitalization). Yearly treatment-specific C_I were the same for D and ND for each treatment. Yearly C^O and U were available, conditioned on D status (C_D, C_{ND}, U_D and U_{ND}).

With P_t as the cumulative yearly (t) probability of D, U_t and Ct were weighted averages:[3]

$$U_t = P_t * U_D + (1- P_t) * U_{ND} \qquad \text{Eqn 1}$$

$$C_t^O = P_t * C_t^O{}_D + (1- P_t) * C_t^O{}_{ND} \qquad \text{Eqn 2}$$

QALYs were calculated in the conventional manner by averaging between yearly measures. Thus, in year t:

$$QALYs_t = (1/2) [U_{t-1} + U_t] \qquad \text{Eqn 3}$$

Total QALYs were the sum over three years. Total Costs were the sum of 3 years of C^I and C^O.

For the subgroup analysis we had only values for P_3. To implement the above, we needed estimates for P_1 and P_2. We estimated those with equations below as in Briggs[8]. Assuming a constant rate (r) of D development, we calculate that rate from P_3:

$$r = - \ln (1- P_3)/3 \qquad \text{Eqn 4}$$

Then we can calculate the P_1 and P_2 values from that r:

$$P_t = 1 - \exp (-r*t) \qquad \text{Eqn 5}$$

Results

We focus on generic MET results and only results from the highest risk quartile (Q4) where conclusions may be altered from those in the overall sample (the other three quartile results were consistent with overall sample results – lifestyle was cost-effective).

Table 1 shows the Q4 yearly results for r, P_t, Costs and QALYs. Table 2 shows Q4 Cost and QALY results by treatment, ordered by QALYs with ICERs appropriately calculated between contiguous treatments.[8]

In Q4 the ICER between LS and MET ($487,067) exceeds conventional WTP values. The ICER between GLS and MET was $155,449. WTP values this high are sometimes, though not always, considered acceptable, so it may be that GLS is not the cost-effective alternative (MET may be). If the GLS result lacks credibility due to it being only a modeled outcome, MET is clearly cost-effective for the Q4 group.

Table 1: High-Risk Subgroup P_t, Costs QALYs (constant rate assumption)

Treatment	Year	P_t (r)	Cost	QALYs
PLACEBO	1	0.261	$2254	0.699
	2	0.454	$2890	0.684
	3	0.596 (0.302)	$3197	0.674
	Sum	NA	$8341	2.057
METFORMIN	1	0.148	$3025	0.701
	2	0.274	$2679	0.689
	3	0.382 (0.160)	$2941	0.683
	Sum	NA	$8645	2.073
INDIVIDUAL	1	0.118	$4092	0.704
	2	0.221	$3396	0.690
	3	0.313 (0.125)	$3494	0.683
	Sum	NA	$10,982	2.078
GROUP	1	0.118	$3164	0.704
	2	0.221	$3071	0.690
	3	0.313 (0.125)	$3170	0.683
	Sum	NA	$9405	2.078

NA is not applicable; P_t is the cumulative probability of developing diabetes up to year t; r is the constant rate of developing diabetes that is consistent with the year-3 cumulative probability (P_3); QALYs are Quality-adjusted Life Years

Table 2: High-Risk Subgroup QALYs, Costs and ICERS

Tx	QALYs	Costs	ICERs*
PBO	2.057	$8341	NA
MET	2.073	$8645	$19,254
LS	2.078	$10,982	$478,067
GLS	2.078	$9405	$155,449

* Treatments are ranked by effectiveness (QALYs) and ICERs are calculated versus the next most effective alternative, using LS or GLS

Discussion

This result is in marked contrast to overall DPP sample results where MET was clearly not cost-effective.[4-6] In the highest risk subgroup here, MET may be cost-effective.

Interestingly, the original DPP CEA authors[1-3] used an unconventional QALY calculation that set yearly QALYs equal to (end of year) U_t values instead of the more conventional averaging calculation we used in Eqn 3. Using those original CEA QALYs, there is no role for MET as a cost-effective treatment in the DPP. The LS/GLS ICERs for Q4 were $98,109/$24,171, indicating, again, MET as not cost-effective. Ironically, the various original DPP original CEA claims for MET's cost-effectiveness overall are only supported, even in the high-risk subgroup, if the original QALY calculation used by those authors is rejected in favor of our more conventional one. The QALY calculation method is important.

There are limitations to our analyses. If conventional WTP thresholds are set too low for severe illness such as diabetes, as suggested in recent methods-oriented innovations (Generalized Risk-Adjusted Cost-Effectiveness: GRACE),[9] GLS becomes a clear cost-effective choice, not MET, even in the high-risk group

We note that Q4 included a very wide range of baseline risks (27-99.8%). Splitting this diverse risk group further could increase the likelihood of MET being cost-effective in the highest risk of Q4 patients, and reduce its likelihood in the remainder.

Any limitations in the data generation in the original DPP CEAs could influence our conclusions as we used those data in all analyses. A PSA would likely indicate substantial decision uncertainty in the Q4 group and Value of Information analysis could indicate where efforts could be made to reduce that uncertainty.

Lastly, we assumed a constant rate of developing diabetes in calculating subgroup P_t values. In a separate analysis (not shown here) we implemented the constant rate assumption for the entire DPP sample where we also had reported yearly P_t data as a gold standard for comparison to results calculated using the constant rate. The ICERs in analyses using the reported P_t were always within 6% of those calculated assuming a constant rate - and conclusions did not change, lending some credence to the constant rate assumption.

Conclusion

Early entire DPP sample CEAs claimed to have shown both MET and LS (or GLS) to be cost-effective. Revisions of those CEAs showed that MET was not cost-effective, only LS (or GLS) was. Speculation that there may be higher risk patients for whom MET was cost-effective has been shown here to be a possibility, depending on WTP values. However, traditional WTP values may be too low for the severe disease of diabetes. Further research using GRACE as well as estimating decision uncertainty would appear to be of value.

References

1. Diabetes Prevention Program Research G. Within-trial cost-effectiveness of lifestyle intervention or metformin for the primary prevention of type 2 diabetes. *Diabetes care.* 2003;26(9):2518-2523.
2. Herman WH, Hoerger TJ, Brandle M, et al. The cost-effectiveness of lifestyle modification or metformin in preventing type 2 diabetes in adults with impaired glucose tolerance. *Ann Intern Med.* 2005;142(5):323-332.
3. Diabetes Prevention Program Research G. The 10-year cost-effectiveness of lifestyle intervention or metformin for diabetes prevention: an intent-to-treat analysis of the DPP/DPPOS. *Diabetes Care.* 2012;35(4):723-730.
4. Rittenhouse BE, Alolayan S, Eguale T, Segal AR, Doucette J. The cost-effectiveness of metformin in the US diabetes prevention program trial: Simple interpretations need not apply. *Prev Med.* 2023;178:107819.
5. Rittenhouse BE, Alolayan S, Eguale T, Segal AR, Doucette J. Metformin in the Diabetes Prevention Program 3-year trial: The cost-effectiveness that never was. *Diabetes Obes Metab.* 2024;26(11):5097-5106.
6. Alolayan S, Eguale T, Segal AR, Doucette J, Rittenhouse BE. Incremental Cost- Effectiveness Ratios (ICERs) and Revised Metformin Cost-Effectiveness Conclusions in the Diabetes Prevention Program/ Diabetes Prevention Program Outcomes Study. *Am J Lifestyle Med.* 2025:15598276251315415.
7. Sussman JB, Kent DM, Nelson JP, Hayward RA. Improving diabetes prevention with benefit based tailored treatment: risk based reanalysis of Diabetes Prevention Program. *BMJ.* 2015;350:h454.
8. Briggs AH, Claxton K, Sculpher MJ. *Decision modelling for health economic evaluation.* Oxford: Oxford University Press; 2006.
9 Lakdawalla DN, Phelps CE. A guide to extending and implementing generalized risk-adjusted cost-effectiveness (GRACE). *Eur J Health Econ.* 2022;23(3):433-451