Therapy escalation thresholds and the potential for biased cost effectiveness analysis when failing to sample baseline HbA1c in type 2 diabetes

Authors: Phil McEwan [1], Volker Foos [2], Adam Lloyd [3], James Palmer [2], Mark Lamotte [4] and David Grant [3]

1 Centre for Health Economics, Swansea University, United Kingdom; 2 IMS Health, Basel, Switzerland; 3 IMS Health, London, United Kingdom; 4 IMS Health, Brussels, Belgium.

Introduction

Due to the progressive nature of type 2 diabetes mellitus (T2DM), patients inevitably require therapy escalation or intensification.

Modeling analyses commonly assume escalation to rescue therapy once the projected HbA1c time path exceeds a defined threshold level. Hence, time to treatment escalation is a function of both initial treatment effect and the long term ability to maintain HbA1c control.

In deterministic (non-sampled) analysis, HbA1c trajectory is equal for all patients and hence time to treatment escalation occurs at a single point in time for all patients that are included in the modeling.

Consequently, deterministic analysis does not address the heterogeneity of patient profiles including baseline HbA1c level and related differences in time to treatment escalation. Heterogeneity, however, can be incorporated if baseline HbA1c and/or HbA1c treatment effect is subjected to random sampling.

In health economic analyses, sampling input parameters is routinely undertaken for probabilistic analysis but non-sampled analysis (mean values) is still commonplace if parameter uncertainty is not intended to be assessed.

Considering costs and efficacy of the selected rescue therapy, differences in time to treatment escalation reflecting heterogeneity in HbA1c baseline level and treatment effect may have remarkable impact on cost effectiveness.

Objectives

The objective of this study was to assess how sampling baseline HbA1c in combination with therapy escalation thresholds influences predicted costs and quality adjusted life expectancy (QALE) in T2DM economic evaluations.

Methods

This study used the IMS Core Diabetes Model (CDM) (1; 2), a validated and established diabetes model, to evaluate the cost effectiveness of metformin+ sulphonylurea (M+S) compared to metformin + DPP-4 (M+D).

Basal insulin rescue therapy (BI) was applied to both arms at three HbA1c threshold levels of 6.5%, 7.0% and 7.5%.

Baseline HbA1c was set to 7.39% (non-sampled scenario) with standard error of 1.79 (sampled scenario).

Efficacy data for dual therapy was sourced from a published systematic review (3); HbA1c and BMI change of -0.8% and 0.199kg/m2 (M+D); -0.79% and 0.707kg/m2 (M+S) and -0.82 and 0.545 kg/m2 (BI), respectively, were applied (Table 1).

Hypoglycemia rates were estimated from odds ratios obtained from a systematic review (3); 8.22, 1.05 and 5.2 for SU, DPP4 and basal insulin add on therapy to metformin vs. metformin monotherapy, respectively.

The background risk of hypoglycemia with metformin monotherapy was sourced from the UKPDS 73 (4); 0.3 and 1.7 events per 100 patient years for symptomatic and severe episodes, respectively (Table 1).

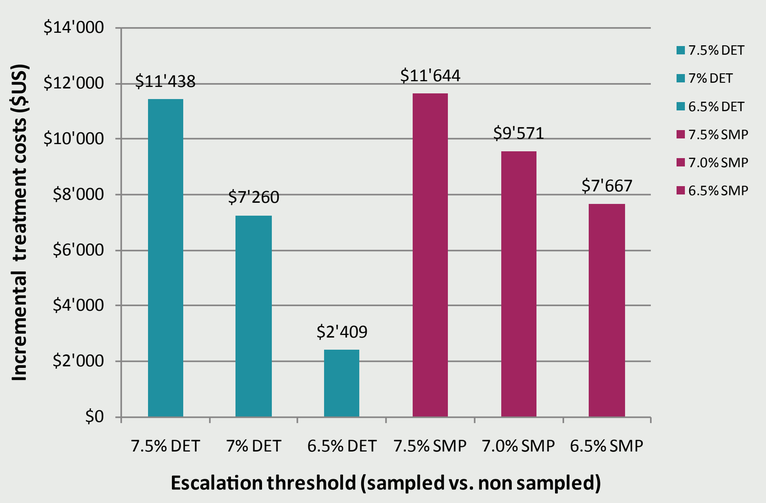
Annual treatment costs were expected at $67.6, $2520.0 and $1869.7 for (M+S), (M+D) and (BI), respectively and based on wholesale acquisition cost (WAC) obtained from standard US list prices (2012) (Table 1) .

Disutilities of -0.0052 (5) and -0.0038 (6) were applied to each symptomatic hypoglycemia event and 1 unit increase in BMI above 25 Kg/m2, respectively.

The model was run over a lifetime using NHANES (7) cohort to populate the patient characteristics.

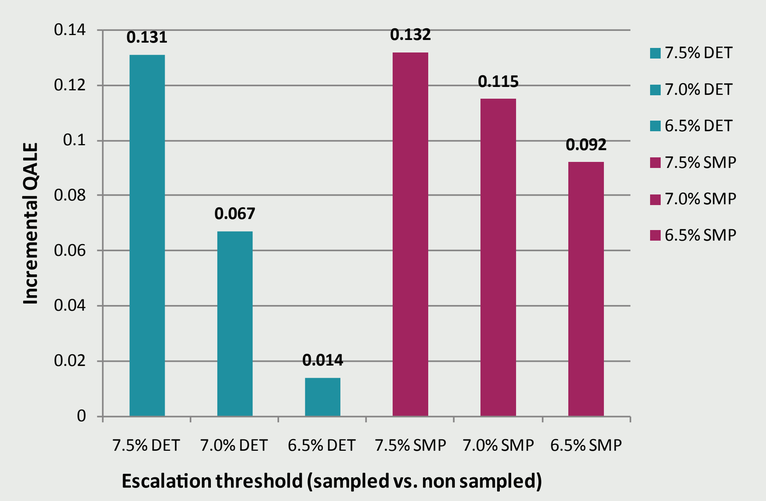
Costs (US$) and benefits were discounted at 3.0%.

Figure 1) Incremental treatment costs of M+D vs. M+S followed by BI for 3 HbA1c thresholds



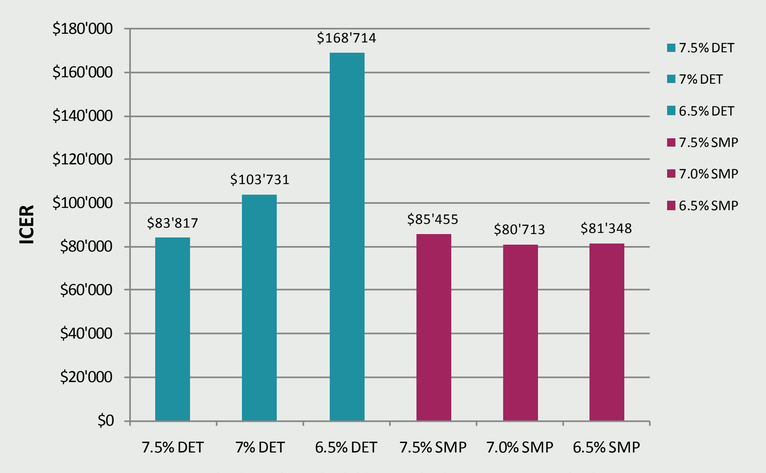
DET = deterministic (non-sampled); SMP = sampled

Figure 2) Incremental QALE of M+D vs. M+S followed by BI for 3 HbA1c thresholds



DET = deterministic (non-sampled); SMP = sampled

Figure 3) Incremental costs per QALE gained for M+D vs. M+S followed by BI for 3 HbA1c thresholds



DET = deterministic (non-sampled); SMP = sampled

Table 1 – Efficacy and safety assumptions and treatment costs for (M+S), (M+D) and (BI)

	(M+S)	(M+D)	(BI)
HbA1c (%)	-0.0079	-0.008	-0.0082
BMI (kg/m2)	+0.707	+0.199	+0.545
Symptomatic hypoglycemia	13.974*	1.785*	8.84*
Severe hypoglycemia	2.466*	0.315*	1.56*
Tx costs ($ USD)	$67	$2,520	$1,869

*= Events per 100 patient years

Results

Lifetime cost differences for the compared treatment strategies were found to be predominantly driven by differences in treatment costs.

Incremental treatment costs were $2,409, $7,260 and $11,438 for M+D versus M+S using non-sampled baseline HbA1c for therapy escalation thresholds of 6.5%, 7.0% and 7.5% respectively; and were increased to $7,667, $9,571 and $11,644 in sampled analyses. This corresponds to a 218%, 31.3% and 1.8% increase of incremental treatment costs in sampled vs. non sampled analyses, respectively (Figure 1).

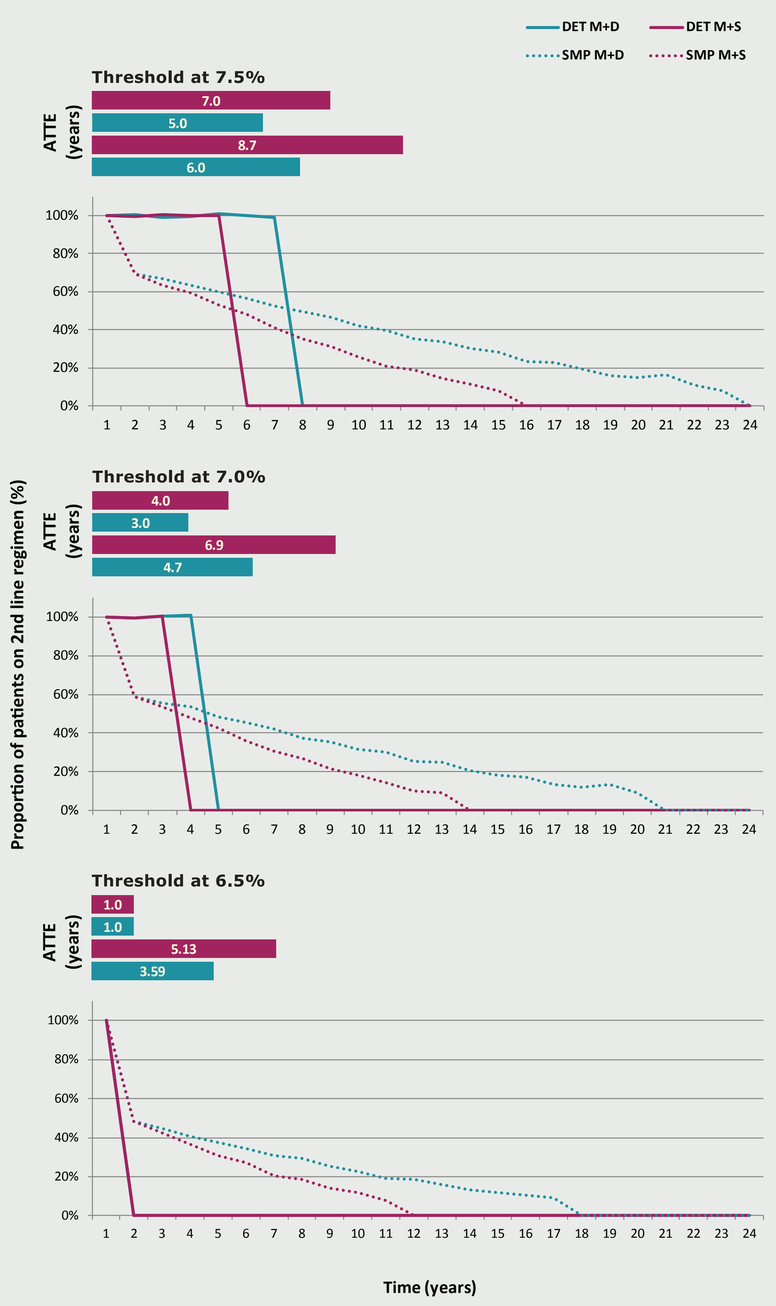
A similar pattern was observed for incremental QALE: Incremental scores of 0.013, 0.067 and 0.014 were observed in non-sampled analyses vs. 0.132, 0.115 and 0.092 in sampled analyses for escalation thresholds of 6.5%, 7.0% 7.5%, respectively; corresponding to a percentage increase of 557.14%, 71.64% and 0.76% in sampled vs. non sampled analyses (Figure 2).

Incremental costs per quality adjusted life year gained (ICER) decreased in sampled vs. non sampled analysis by 51.78% and 22.19% for escalation thresholds of 6.5% and 7.0%, respectively and increased by 1.95% for the 7.5% escalation threshold (Figure 3).

Average time to therapy escalation increased for M+S from 1, 4 and 7 years (non sampled) to 5.13, 6.93 and 8.70 years (sampled). For M+D, time to therapy escalation increased from 1, 3 and 5 years (non sampled) to 3.59, 4.69 and 6.0 years (sampled) using escalation thresholds of 6.5%, 7.0% and 7.5%.

Figure 4 presents the proportion of patients on 2nd line regimen over time (prior to BI escalation) in non-sampled versus sampled analyses.

Figure 4) Proportion of patients on dual therapy over time in deterministic vs. sampled analyses



ATTE = Average time to treatment escalation
DET = deterministic (non-sampled)
SMP = sampled

Conclusion

Probabilistic analyses predicted a considerably longer time to treatment escalation for both, M+D and M+S.

Overall, this resulted in notable increases in incremental treatment costs and incremental QALE which overall lead to a reduction of incremental costs per quality adjusted life year gained (ICER) for escalation thresholds of 7.0% and 6.5% and a marginal ICER increase at 7.5% escalation threshold.

The decline in ICER was especially noticeable for smaller escalation thresholds where time to therapy escalation was considerably higher in sampled vs. non sampled analysis.

The importance of probabilistic analysis within cost effectiveness models extends beyond quantifying the effects of parameter uncertainty.

When treatment decision rules are dependent on patient attributes that are subject to variability (such as HbA1c) then failing to accommodate this within the model can significantly bias predicted costs and QALE.

References

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FOR FURTHER INFORMATION: Please contact Phil McEwan (phil.mcewan@heor.co.uk) or Volker Foos (vfoos@ch.imshealth.com)
IMS HEALTH | 210 PENTONVILLE ROAD, LONDON N1 9JY, UNITED KINGDOM