MICROSIMULATION IN OBESITY: A FEASIBILITY STUDY

Volker Foos[1], Phil McEwan[1], Alik Vodyanov[1], Ben Modley[2], Jason Flavin[3]

[1] Health Economics & Outcomes Research Ltd, Rhymney House, Unit A Copse Walk, Cardiff Gate Business Park, Cardiff, CF23 8RB, UK;
[2] leads.healthcare, Eschwaldweg 1, 79219 Staufen, Germany;
[3] Boehringer Ingelheim Pharma GmbH & Co. KG, Binger Straße 173, 55216 Ingelheim am Rhein, Germany

What was known

- **Obesity is a highly prevalent health condition** [1] with severe sequalae and complications [2,3] that result in impaired health-related quality of life [4] and considerable cost burden [2]
- Several pharmaceuticals for treatment of obesity have been assessed by NICE; while **patient population in routine care is heterogenous with complex interactions between risk-factor**s, cost-effectiveness analyses have relied on markov cohort models [5-7]
- **Patient-level health economic models** have been utilized in other chronic disease areas [8] and just recently in obesity [9,10] to **model heterogenous patient populations and complex interactions of risk-factors** that determine long-term outcomes

What's new

- **A patient-level microsimulation was developed in the obesity indication to address heterogeneity in the patient population** and to allow modelling sub-groups through distinct risk-factor profiles
- **This research demonstrates general feasibility of a microsimulation approach in obesity** for cost-effectiveness assessment with sub-group and sensitivity analyses for NICE technology appraisal

Background

In the UK, most adults, 67% of men and 60% of women, are overweight or suffer from obesity, and 26% of men and 29% of women suffer from obesity [1]. Obesity is associated with multiple complications and increased mortality [2,3]. Spending on overweight and obesity-related ill-health is expected to reach £9.7 billion by 2050 in the UK National Health Service (NHS) [2].

Health economic models to assess cost-effectiveness have utilised Markov cohort approaches that classify obesity mainly by body mass index (BMI) and type-2 diabetes mellitus (T2DM) status to model complication rates, costs, and utilities [6-7]. To account for heterogeneity in the patient population and complex interdependencies between risk-factors new patient-level health economic models have been implemented in obesity and in other chronic diseases [8-10]. Such models are valuable in assessing cost-effectiveness and impact on long-term outcomes, especially for stratified and/or sub-group specific analyses with distinct risk profiles.

Objective

The objective of this study was to assess the feasibility of developing a microsimulation in obesity for technology appraisal (TA) by the National Institute for Health and Care Excellence (NICE) and to validate the model results against results from past NICE TAs and published models.

Methods

A systematic literature review of published cost-effectiveness modelling was performed to inform model concept. To supplement cost-effectiveness studies from pre-2015 identified in a published systematic review [11], a systematic search of electronic databases (MEDLINE, Embase, the Cochrane Library and EconLit) was conducted from 1 May 2015 to 24 August 2020. A total of 15 cost-effectiveness models were identified to extract relevant disease states and model events. The model diagram is outlined in Figure 1.

A patient-level simulation model was implemented in C++ programming language [12] using an object-oriented approach and Monte Carlo techniques for event prediction. Discounting of 3.5% for costs and utilities and a lifetime horizon were implemented as per the NICE guidance for reference case [13]. The microsimulation approach was chosen to account for heterogeneity in the modelled patient population mapping continuous variables to outcomes on the patient level through risk equations.

Natural history of BMI trajectories was estimated based on equations from a UK study that analyzed 100,000 patients from the UK general practice research database [14]. Two predictive equations were defined, relating BMI to age and sex for diabetic and non-diabetic cohorts.

Risk-equations

For patients entering the model without type-2 diabetes mellitus (T2DM) the Qdiabetes-2018 risk model was used to estimate time to onset of T2DM [15]. T2DM-related complications (e.g., amputation, blindness, ESRD, ulcer) were modelled using the UKPDS 82 risk equations [16].

The Qrisk3 risk model was used to estimate the risk of primary CV events [17] in patients without T2DM. For secondary CV events, the risk was estimated using the Framingham Recurring Coronary Heart Disease Risk Model [18]. CVD events were simulated as composite events due to lack of granularity in the risk equations for predicting these events individually (MI, angina, stroke, TIA). CVD events were then disaggregated into their individual components based on a predefined distribution [18,19].

Other clinical events modelled included e.g., onset of hypertension, osteoarthritis and obstructive sleep apnea. A full list of clinical events and risk equations used to model time to event is outlined in Table 1.

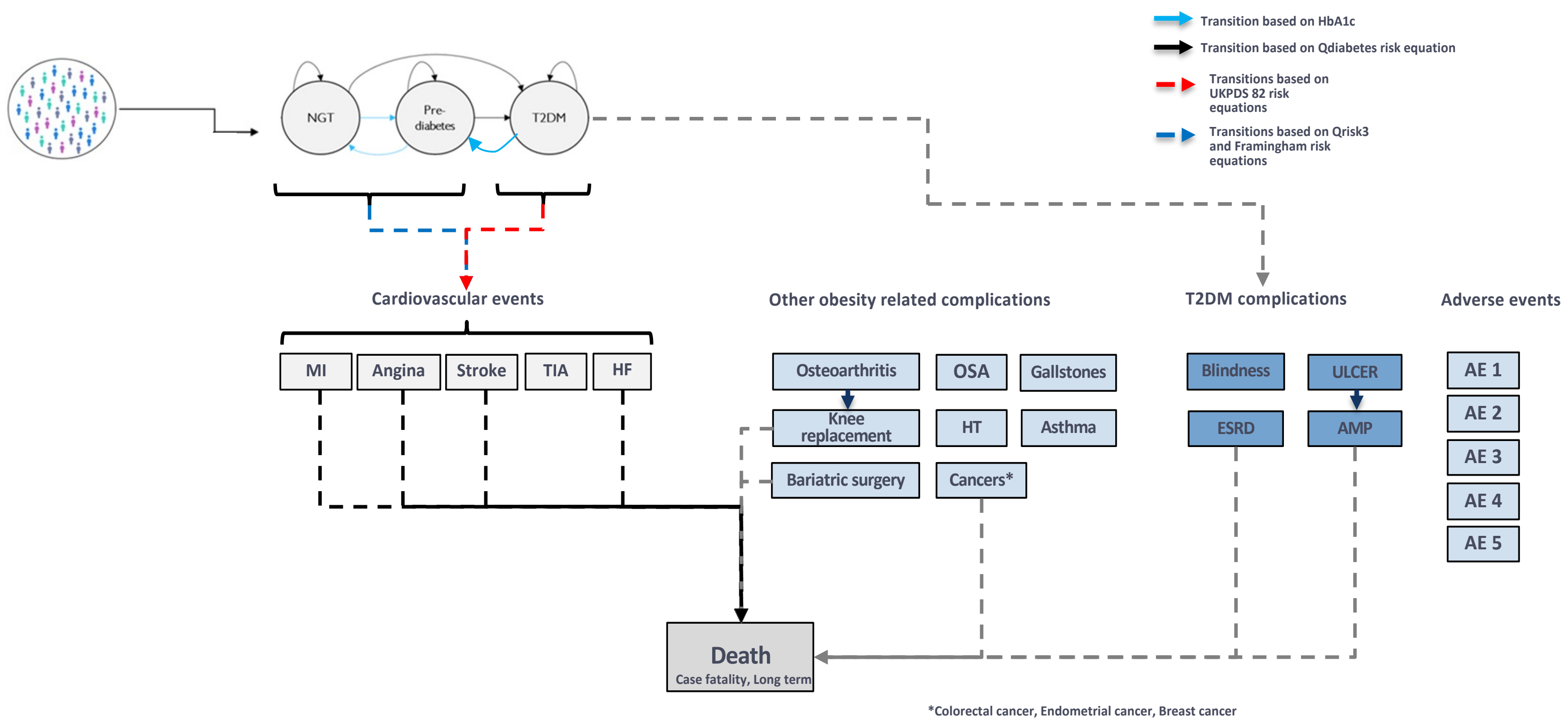
Mortality

All-cause mortality for patients with and without T2DM was accounted for in the model based on comorbidity adjusted UK life-tables. To account for the increased mortality risk in T2DM, a hazard ratio of 2.19 was applied [20]. Further, event-specific mortality was modelled using equations and published hazard ratios that estimate the excess risk of mortality associated with an event i.e., case fatality rates (acute mortality) and HRs of excess mortality (post-acute mortality).

Cost

Obesity management cost related to the patient's BMI was derived from a study by Wang et al. [21]. Costs associated with events that are accounted for by the model were removed from the obesity management costs to avoid double-counting. Accordingly, the BMI-specific management cost represents direct medical costs that are not accounted for in acute and long-term event costs, such as general prescription and obesity related visit costs. Event costs were derived from published literature identified during systematic literature review.

Figure 1. Model diagram for micro-simulation in obesity



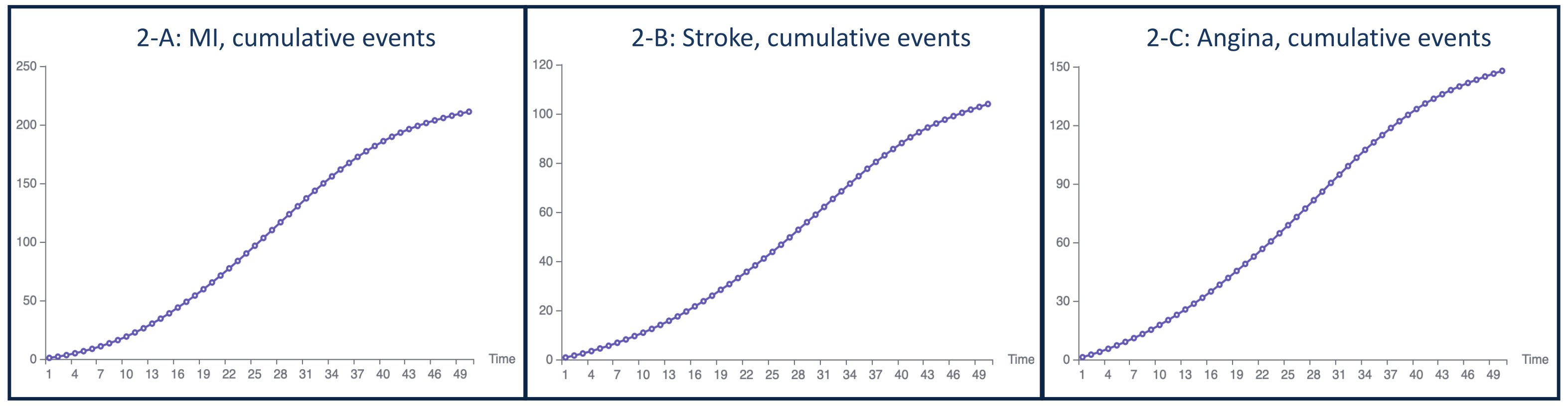
Abbreviations: AE = adverse event, AMP = amputation, CVD = cardiovascular disease, ESRD = end stage renal disease, HF = heart failure, HT = hypertension, MI = myocardial infarction, NGT = normal glucose tolerance, OSA = obstructive sleep apnea, T2DM = type-2 diabetes mellitus, TIA = transient ischemic attack.

Table 1. Summary of model events and risk equations

Obesity-related event	Description of risk/hazard model	Source
Onset of T2DM	Qdiabetes-2018 risk model	[15]
Onset of first CV event in non-T2DM patients	Qrisk3 risk model	[17]
Onset of second CV event in non-T2DM patients	Framingham Recurrent Coronary Heart Disease risk model	[18]
T2DM complications including microvascular and cardiovascular equations	UKPDS82 risk model	[16]
T2DM remission	HbA1C <6.5% threshold	[22]
Hypertension	Risk model derived from the Third National Health and Nutrition Examination Survey, the Framingham Heart Study and other sources	[23]
Osteoarthritis	Hazard ratios for knee and hip replacement relating to osteoarthritis and BMI	[24]
Gallstones	Risk model derived from US Health Professionals Follow-up Study and the Nurses' Health Study	[25]
Knee replacement	Risk model based on odds rations reported by Wendelboe et al.	[26]
Onset of OSA	Prevalence by BMI level derived from the Sleep Heart Study	[27]

Abbreviations: BMI = body mass index, CKD = chronic kidney disease, CV = cardiovascular, ESRD = end-stage renal disease, HbA1C = glycated haemoglobin, OSA = obstructive sleep apnoea, T2DM = type-2 diabetes mellitus.

Figure 2 A-C. Plotted lifetime incidence of main model events

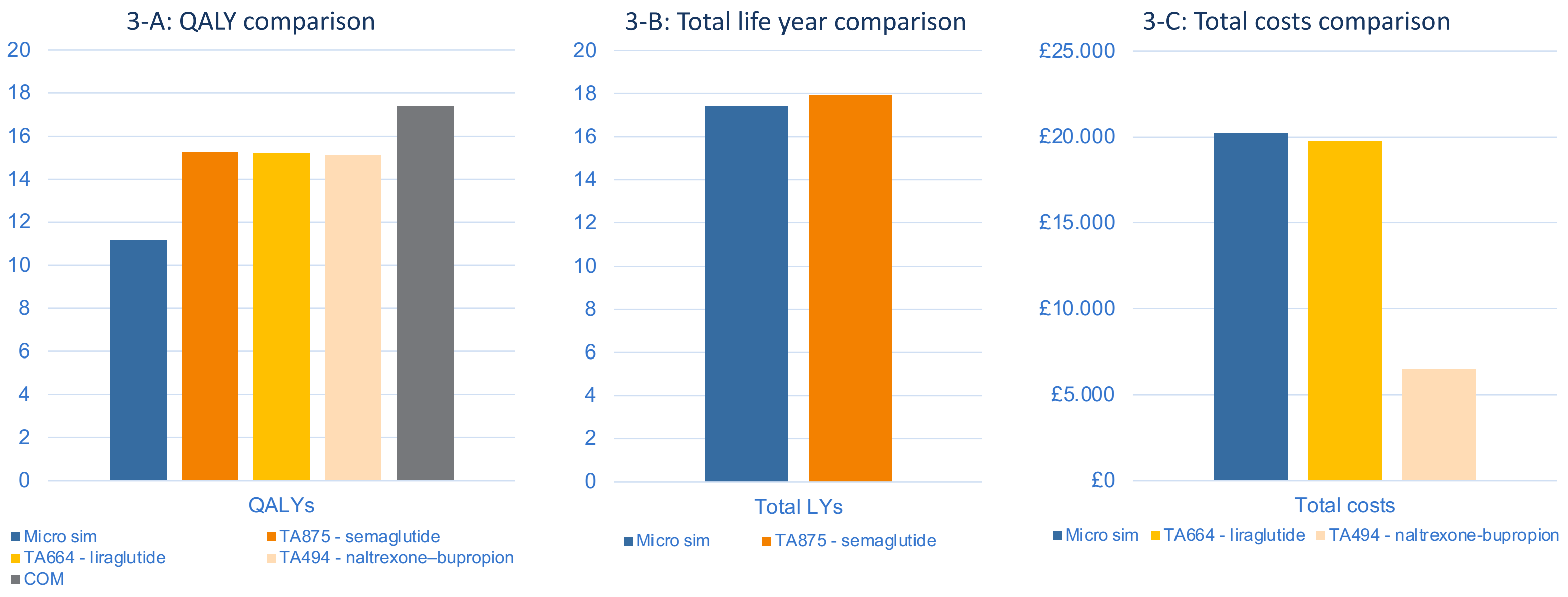

2-A: MI, cumulative events

2-B: Stroke, cumulative events

2-C: Angina, cumulative events

Abbreviations: MI = myocardial infarction.

Figure 3 A-C. Comparison of QALYs, life years and costs


3-A: QALY comparison

3-B: Total life year comparison

3-C: Total costs comparison

Abbreviations: COM = Core Obesity Model, Lys = total life years, QALY = quality adjusted life-year, TA = technology appraisal

Sources: NICE 2017 [5], NICE 2020 [6], NICE 2022 [7] and data on file.

Methods continued

Health-related quality of life

Patients were assigned a baseline utility based on age at entry to the model. Baseline utilities were obtained from the Department of Health's Health Survey for England [28]. Utility gain or loss related to weight loss or gain, respectively, was derived from a regression analysis of the relationship between BMI and health utility [4] and implemented in the model accordingly.

Incidence of clinical events predicted within the model is associated with reductions in health-related quality of life (HRQL). Disutility was defined by two model inputs. The first disutility value is applied during the year of the event and represents acute impairment of HRQL. The second disutility value is applied in subsequent years and represents chronic impairment of HRQL. Data for the first and second disutility were derived from systematic literature review.

Results

1,000 patients were simulated in a total of 1,000 probabilistic model runs for base case feasibility analysis of routine care management with diet and exercise in obesity. Model events included e.g., onset of T2D, sleep apnea, cardiovascular disease, knee replacement and all-cause mortality. Lifetime incidence and costs per patient of main clinical events are outlined in Table 2. Plotted lifetime incidence of the three most common clinical events (MI, stroke and angina) is depicted in Figure 2 A-C.

Modelled QALYs amounted to 11.198 and were lower than published results from TA 875 (QALYs: 15.269), TA 664 (QALYs: 15.216) and TA 494 (QALYs: 15.134). Modelled life years amounted to 17.400 and were comparable to published results from TA 875 (QALYs: 17.924) and TA 664 (QALYs: 18.496). Modelled total costs per patient amounted to £20,236 per patient and were comparable to TA664 (£19,780) [6] but higher than estimates from TA494 (£6,502) [5]. Total costs for TA875 were censored in the NICE report and therefore not available for comparison [7]. A comparison of model outcomes is depicted in Figure 3 A-C.

An exploratory comparison of the incidence of CV events over patient lifetime with those of the Core Obesity Model (COM) [29] is outlined in Table 2. Lifetime incidence per patient of CV event of this microsimulation and the COM were comparable. CV event incidence was not available for TA 875, TA 664 and TA 494 [5-7].

Table 2. Lifetime incidence and cost of modelled clinical events vs. COM, per patient

Event	Incidence	
	Microsimulation	COM
MI	0.25	0.22
Stroke	0.10	0.16
Angina	0.15	0.28

Abbreviations: COM = Core Obesity Model, MI = myocardial infarction

Conclusions

Probabilistic microsimulation in obesity is feasible in the C++ programming language. Model runtime for 1,000 patients in a total of 1,000 probabilistic model runs was less than 5 minutes and the described modelling approach will allow running large cohorts with sensitivity analysis and acceptable runtime for NICE TA.

A key difference between this model and previously published obesity models is the use of updated, recent risk equations and cost data as well as consideration of additional clinical events. The additional clinical events were turned off for this feasibility analysis and comparison against published NICE TA results.

For this model as well as the NICE TA models [5-7] BMI and age dependent utility was derived from the Health Survey for England [28] and linear functions were fitted to the BMI dependent utility for BMI > 25 kg/m². Though total life years were similar with the modelling approach described herein and models from recent NICE TAs [6,7], total QALYs were substantially lower with this microsimulation approach. The difference is assumed to be due to different baseline utility assumptions and how linear functions were fitted to the BMI dependent utility curve [4,7,28,30]. The difference in calculated total QALYs needs further investigation and benchmarking against other models and studies.

Considering the results from this feasibility analysis, fully validating results according to ISPOR standards [31] and benchmarking economic outcomes against data from other published models, clinical trials and real-world evidence databases is warranted.

Disclosures

VF, PM and AV are employees of Health Economics & Outcomes Research Ltd. that developed the model. BM has received consulting honoraria from Boehringer Ingelheim. JF is an employee of Boehringer Ingelheim.

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Presenter: Ben Modley; Email: ben.modley@leads.healthcare