Cost-Effectiveness of DPP-4 Inhibitor and SGLT2 Inhibitor Combination Therapy for Type 2 Diabetes

Manjiri Pawaskar, PhD; S. Pinar Bilir, MS; Stacey Kowal, MS; Claudio Gonzalez, MD; Swapnil Rajpathak, MD; and Glenn Davies, DrPH

ABSTRACT

OBJECTIVES: Maintaining glycemic control limits costly health risks in patients with type 2 diabetes (T2D), but accomplishing this may require individualized strategies. Generic medications (eg, sulfonylureas [SU], insulin) are common in T2D management due to their efficacy and costs; however, relatively new drug classes (eg, dipeptidyl peptidase 4 [DPP-4] inhibitors, sodium-glucose cotransporter 2 [SGLT2] inhibitors) have demonstrated clinical benefits in combination therapy. The objective of this study was to evaluate the long-term cost-effectiveness of a strategy involving branded combination therapy with DPP-4 inhibitors and SGLT2 inhibitors (pathway 1) compared with a generic alternative with SU and insulin (pathway 2) on a background of metformin.

STUDY DESIGN: Cost-effectiveness analysis using the validated IQVIA CORE Diabetes Model from the US payer perspective.

METHODS: Cost-effectiveness analysis. Lifetime clinical and economic outcomes (discounted 3%/year) were modeled for a T2D cohort failing to achieve glycemic goal on metformin monotherapy. Patient baseline data and treatment effects reflect results of clinical trials. Direct medical cost inputs are from multiple published sources. Scenario analyses on key intervention effects and assumptions tested robustness of results.

RESULTS: Pathway 1 had higher direct medical costs compared with pathway 2, yet also increased total quality-adjusted life-years (QALYs) by 0.24. Increased costs were partially offset by a reduction in diabetes-related complications and delayed insulin initiation. The incremental cost-effectiveness ratio (ICER) for pathway 1 is favorable at $64,784/QALY. Scenario analyses showed limited impact; nearly all ICERs were less than $100,000/QALY.

CONCLUSIONS: In the United States, sequential addition of SGLT2 inhibitors to DPP-4 inhibitors may be considered cost-effective compared with traditional treatment with generic medications for patients who fail to achieve glycemic goal on metformin.

Am J Manag Care. 2019;25(5):231-238

Of 23 million diabetes diagnoses in the United States, approximately 21.9 million are type 2 diabetes (T2D).[1] T2D is known to increase the risk of various complications and comorbidities throughout a patient's lifetime; in addition to generally raised mortality, patients with diabetes face higher risks of specific chronic conditions, such as cardiovascular disease (CVD), kidney disease, and blindness, as well as costly events, such as amputation, myocardial infarction, and stroke.[1,2] Maintaining glycemic control has a direct relationship with mitigating risk,[3] and patients with glycated hemoglobin (A1C) of 7.0% or less have been shown to have lower rates of comorbidities.[4]

Appropriately managing glycemic levels will help minimize economic burden as well. A study by the American Diabetes Association (ADA) estimated total direct diabetes-related expenditures at $237 billion for 2017,[5] and other evidence has shown that higher A1C levels were linked with higher healthcare costs (for A1C levels >7.5%).[6,7] Past data have also shown that patients with diabetes without comorbidities may have annual healthcare costs that are only one-fourth as large as those of patients with cardiovascular complications.[8] Considering healthcare costs from the opposite perspective, more than 25% of total national costs to manage ophthalmological, renal, and cardiovascular conditions are incurred by patients with diabetes.[5]

Although initial medical treatment includes metformin monotherapy when tolerated, ADA guidelines recommend intensification with a sodium-glucose cotransporter 2 (SGLT2) inhibitor or liraglutide (a glucagon-like peptide 1 [GLP-1] receptor agonist) in patients with established CVD due to evidence of cardiovascular benefit.[9] In patients without established CVD or heart failure, the first intensification may combine metformin with therapies such as a dipeptidyl peptidase 4 (DPP-4) inhibitor, an SGLT2 inhibitor, a thiazolidinedione, a sulfonylurea (SU), a GLP-1 receptor agonist, or basal insulin. Subsequent intensification includes triple therapies composed of these options.[9]

Commonly used therapies for intensification after metformin failure may include generic medications like SU or, later, insulin, due to a combination of established efficacy and relative costs compared with branded medications.[10-12] However, the American

TAKEAWAY POINTS

- Generic medications (eg, sulfonylureas followed by insulin) are commonly used as therapy intensifies after metformin, but a pathway of newer medications (eg, dipeptidyl peptidase 4 [DPP-4] inhibitors and sodium-glucose cotransporter 2 [SGLT2] inhibitors prior to insulin) may be cost-effective over a lifetime.
- Evaluation of this sequence revealed that it increased costs compared with a generic pathway, yet also improved quality-adjusted life-years (QALYs) by 0.24 for an incremental cost-effectiveness ratio of $64,784/QALY.
- Costs were partially offset by a reduction in diabetes-related complications and delayed insulin initiation.
- In the United States, sequential addition of SGLT2 inhibitors to DPP-4 inhibitors may be cost-effective compared with traditional treatment using generic medications for patients not at glycemic goal on metformin.

College of Physicians has noted that evidence indicates potential safety differences with these therapy choices, including a higher risk of hypoglycemia and weight gain for metformin + SU compared with metformin combinations with DPP-4 inhibitors or SGLT2 inhibitors.[10] Insulin likewise conveys increased risks of hypoglycemia and weight gain,[13-15] whereas both SU and insulin may be associated with increased CVD risk.[16-18] In addition to the negative impact to patient health, the additional costs associated with managing downstream complications can be substantial; both clinical and financial factors may be relevant to consider when making therapeutic choices.

At the same time, findings of recent clinical trials of triple-therapy combinations with newer (and thus branded) medications, such as DPP-4 inhibitors and SGLT2 inhibitors, have demonstrated significant clinical benefit over the use of each individual component when on a background of metformin.[19,20] Multiple SGLT2 inhibitors have also been shown to convey CVD protective effects in this population, including reduced risk of heart failure, myocardial infarction, and stroke.[16,21,22] Additionally, recent evidence suggests that remaining on DPP-4 inhibitor therapy provides significant improvement in A1C without increasing the risk of hypoglycemia compared with stopping it when initiating insulin.[23] Clinicians may therefore find it valuable to consider these newer therapies in combination prior to further intensification.

Given available clinical evidence, this study sought to model the overall impact on a lifetime of patient health outcomes, costs, and cost-effectiveness of a specific intensification pathway utilizing branded medications alone and in combination, sequentially. In this pathway, US patients with T2D that is poorly controlled on metformin alone transition from DPP-4 inhibitor to DPP-4 inhibitor + SGLT2 inhibitor on a background of metformin prior to insulin initiation. This pathway is compared against a more generic pathway in which patients intensify to metformin + SU, followed by initiation of insulin.

METHODS

IQVIA CORE Diabetes Model Summary Description

This study utilized the IQVIA CORE Diabetes Model (CDM) v9.0, a well-validated model that has been published previously in detail.[24-26] This simulation model, which is programmed in C++, cycles a cohort of patients annually through a series of diabetes complication–related Markov modules over a lifetime. Treatment efficacy and safety data are used to project the impact of different therapeutic choices on major micro- and macrovascular diabetes complications, survival, quality of life, and medical costs. Efficacy benefits (eg, A1C decline) occur in the initial year of treatment, whereas safety effects (eg, hypoglycemic event rates) are applied throughout the years of therapy in the model. In addition to intervention-specific inputs, the model tracks patient profiles (eg, current blood glucose, blood pressure, weight) and comorbidity status (eg, history of CVD, renal disease) to adjust risk of diabetes-related events. Key risk equations are derived from large cohort studies. A1C progression and A1C-dependent adjustments in T2D analyses reflect the United Kingdom Prospective Diabetes Study risk engine.[3,27-29] Early A1C levels indirectly affect downstream events, as the initial value affects downstream A1C. Other physiological parameters projections reflect findings from the Framingham Heart Study.[30]

Model outputs include differences in life expectancy, quality-adjusted life-years (QALYs), costs, cumulative incidences of complication events due to intervention effects on diabetes-related adverse events, and A1C levels and other physiological parameters that affect risks of major diabetes complications. Incremental costs and QALYs are then used to estimate an incremental cost-effectiveness ratio (ICER) in terms of dollar amount per QALY.

Although there is no official threshold that specifies what makes an intervention a good value in the United States, a 2008 study summarizing the cost-effectiveness of interventions that have been approved and reimbursed found that the implicit US threshold ranges from $109,000 to $294,000 per QALY.[31] Historical cited values, such as $50,000 and $100,000 per QALY, are currently thought to be low given available evidence about true reimbursement and societal preferences.[32]

Analyses were run with 1000 patients for 1000 iterations each over a lifetime time horizon of 40 years from a US payer perspective, using a discount rate of 3% for costs and outcomes as recommended for cost-effectiveness analyses in the United States.[33]

Model Inputs

The model cohort was designed to represent patients not at A1C goal on metformin and who have intensified to dual therapy; thus, they are the appropriate target population for this type of therapy intensification in the United States. Patient characteristics were derived from the GE Centricity electronic medical record database, with supplemental data provided to align with clinical trial data (key inputs shown in **Table 1**[34-39]; the **eAppendix** [available at **ajmc.com**] shows the full set of cohort inputs). The mean

baseline age for this group is 57.9 years, with 3 years duration of diabetes and a baseline A1C level of 8.37%.

Intervention effects. Full pathways under consideration are depicted in **Figure 1**. In pathway 1, intensification following failure with metformin monotherapy includes DPP-4 inhibitors followed by the addition of SGLT2 inhibitors prior to insulin; whereas pathway 2, which is more generic, follows intensification with SU followed by the addition of insulin(s). Clinical inputs for each therapeutic step in each pathway were obtained from randomized clinical trials or large meta-analyses (**Table 2**[40-43]). Treatments were assumed to have no impact on any clinical parameters not specified in Table 2,[40-43] reflecting an interpretation that values not reported are not significantly different. Patients moved from one therapeutic line to the next when their A1C level exceeded 7.5%, as an indication of failing to meet their A1C goal. However, as this threshold is considered aggressive for some patients (eg, older patients, for whom consequences of hypoglycemic events may be more severe), this value was tested in scenario analysis (described in the Analyses section).

Regimen details. With the exception of insulin, treatment dosing reflects official prescribing information. For basal insulin, the dose reflects consumption as quantified in the metformin + sitagliptin + insulin glargine arm of the recently completed PN845 study (Merck, unpublished data [PN845 trial], 2018),[23] although costs are assumed to reflect a weighted average of available forms including glargine, detemir, and degludec (Merck, unpublished data, 2018). Bolus insulin (insulin aspart) dosing reflects published daily average consumption of 0.2 units per kg weight (average weight, 84.9 kg).[34]

Estimates of additional resource use, such as test strips for self-monitoring of blood glucose, lancets, and needles for insulin, were based on literature or assumptions about typical usage (2.7 test strips daily,[44] daily replacement of lancets, and 2 needles per day with bolus insulin; note that basal insulin is provided in an injection pen or other prefilled syringe format).

Unit costs. Key cost inputs for the analyses are shown in Table 1.[34-39] Costs are reported in 2017 US$ and reflect published values from MediSpan PriceRx for drugs[35] or a combination of literature and Medicare fee schedules[45] for complications and events. The full list of cost inputs and references is housed in the eAppendix.

Quality of life. Quality of life is captured via adjusting total life-years with utilities and disutilities associated with health status and health events. Utility and disutility input values reflect IQVIA CDM defaults for a T2D population (Table 1[34-39]).[36-39]

TABLE 1. Key Model Inputs[34-39]

	Default Value	Source
Baseline characteristics		
Start age in years, mean (SD)	57.9 (11.9)	[a]
Duration of diabetes in years, mean (SD)	3.0 (3.6)	34,[a]
Male, %	51.8	34,[a]
A1C, mean (SD)	8.37% (1.84%)	34,[a]
Systolic blood pressure in mm Hg, mean (SD)	130.94 (16.90)	34,[a]
BMI, mean (SD)	34.40 (7.87)	34,[a]
Key intervention annual costs		
Metformin + DPP-4 inhibitor class	$4853.39	35
Metformin + DPP-4 inhibitor class + SGLT2 inhibitor class[b]	$6416.46	35
Metformin + DPP-4 inhibitor class + basal insulin	$9928.09	34,[c]
Metformin + basal insulin + bolus insulin	$5240.17	34,35
Metformin + SU	$1844.29	35
Metformin + SU + basal insulin	$4814.32	35,[c]
Metformin + DPP-4 inhibitor class + NPH insulin (scenario)	$7049.59	34,35
Metformin + SU + NPH insulin (scenario)	$4040.49	34,35
Metformin + NPH insulin + bolus insulin (scenario)	$4466.34	34,35
Quality of life inputs		
Baseline utility	0.785	36
Disutility for myocardial infarction	−0.055	36
Disutility for angina	−0.090	36
Disutility for stroke event	−0.164	36
Disutility for neuropathy	−0.084	36
Disutility for active ulcer	−0.170	36
Disutility for amputation event	−0.280	36
Disutility for NSHE (diminishing approach)	Automatically calculated per line of therapy	39
Disutility for SHE 1 (during daytime or nighttime)	−0.0183	38
Disutility for SHE 2 (during daytime)	−0.055	37
Disutility for SHE 2 (nocturnal)	−0.057	37
Disutility for hemodialysis	−0.164	36
Disutility for peritoneal dialysis	−0.204	36
Disutility for background diabetic retinopathy	−0.040	36
Disutility for proliferative diabetic retinopathy	−0.070	36
Disutility for macular edema	−0.040	36
Disutility for severe vision loss	−0.074	36

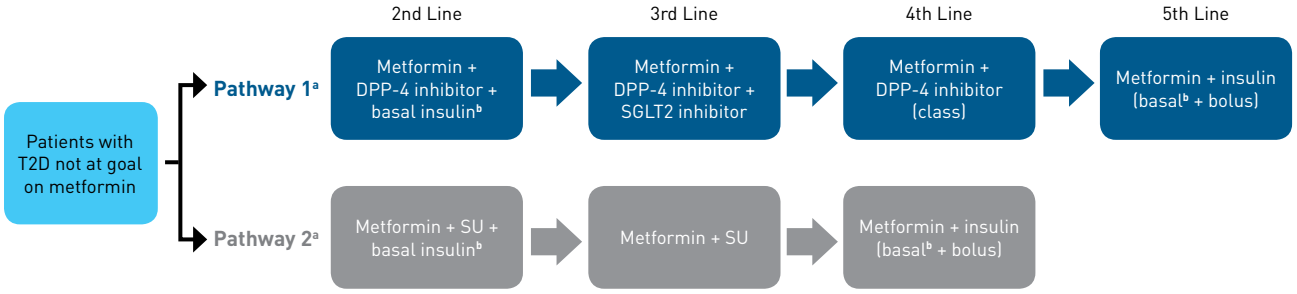
A1C indicates glycated hemoglobin; BMI, body mass index; DPP-4, dipeptidyl peptidase 4; NPH, neutral protamine Hagedorn; NSHE, nonsevere hypoglycemic event; SGLT2, sodium-glucose cotransporter 2; SHE, severe hypoglycemic event; SU, sulfonylurea.

[a]GE Healthcare Centricity electronic medical record, 2015.

[b]SGLT2 inhibitor class represented by least costly option, canagliflozin.

[c]Merck, unpublished data (PN845 trial), 2018.

FIGURE 1. Intervention Pathways



A1C indicates glycated hemoglobin; DPP-4, dipeptidyl peptidase 4; SGLT2, sodium-glucose cotransporter 2; SU, sulfonylurea; T2D, type 2 diabetes.

[a]This analysis assumes that patients switch lines of therapy when A1C exceeds 7.5%.

[b]Basal insulin reflects the effects of insulin glargine.

TABLE 2. Key Intervention Effects[40-43]

Line	Therapy	A1C Change, % (SE)	BMI Change, kg/m² (SE)[a]	Hypoglycemic Event Rate per 100 Patient-Years[b]	SBP Change, mm Hg (SE)[a]
	Pathway 1				
2nd	Metformin + DPP-4 inhibitor class[40]	−0.65 (0.026)	0.04 (0.03)	7.28	−3.04 (0.68)
3rd	Metformin + DPP-4 inhibitor class + SGLT2 inhibitor class[c]	−0.86 (0.069)	−1.07 (0.079)	3.88	−4.82 (0.88)
4th	Metformin + DPP-4 inhibitor class + basal insulin[d]	−1.88 (0.051)	0.56 (0.068)	145.43	−0.303 (0.4)
5th	Metformin + basal insulin + bolus insulin[41,42]	−1.5 (0.10)	1.27	784.43	0
	Pathway 2				
2nd	Metformin + SU[40]	−0.94 (0.13)	0.42 (0.09)	19.44	0
3rd	Metformin + SU + basal insulin[43]	−1.70 (.029)	0.70	137.36	0
4th	Metformin + basal insulin + bolus insulin[41,42]	−1.5 (0.10)	1.27	784.43	0

A1C indicates glycated hemoglobin; BMI, body mass index; DPP-4, dipeptidyl peptidase 4; SBP, systolic blood pressure; SE, standard error; SGLT2, sodium-glucose cotransporter 2; SU, sulfonylurea.

[a]Treatment effect assumed to be 0 when not otherwise specified in data source; unreported variability information was not incorporated into probabilistic sensitivity analysis.

[b]Rates were assumed to reflect nonsevere hypoglycemic events when otherwise unspecified severity in publication. For metformin + DPP-4 inhibitor class + basal insulin, details were available and 9.11 nonsevere (no medical assistance) and 0.46 severe (medical assistance) hypoglycemic events were also included.

[c]Merck, unpublished data (VERTIS 006 trial), 2017.

[d]Merck, unpublished data (PN845 trial), 2018.

Analyses

The base-case analysis compares a pathway with patients on a background of metformin remaining on DPP-4 inhibitors when adding SGLT2 inhibitors as a second intensification therapy prior to insulin initiation versus a pathway in which patients intensify to insulin initiation from metformin + SU. These pathways reflect intervention effects as summarized in Table 2.[40-43] The deterministic base-case analysis was supplemented with probabilistic sensitivity analysis to capture potential variation in results due to known parameter variation as captured in distributions around parameters.

Additionally, a series of scenario analyses were defined to assess the impact of key model inputs and assumptions. Among these, potential variation in treatment effects across all lines of therapy within a pathway (eg, for A1C, hypoglycemic event rates, body mass index [BMI]) were tested using 95% CIs for each line from their respective primary data source. An alternate intensification regimen utilizing neutral protamine Hagedorn (NPH) insulin in place of other basal insulin was also explored, due to its generic nature and thus potential preferred use by some payers.

Generalizability across somewhat different diabetes populations was also tested via alternate cohort definitions. These include older patients (≥65 years) with a higher A1C target threshold of 8% to affect treatment intensification and patients with lower and higher baseline A1C levels (7% and 9%, based on the range found in published trial populations).[40]

Evidence from the CANVAS, CVD-REAL, and EMPA-REG trials suggests that SGLT2 inhibitor therapies convey additional CVD protective effects,[16,21,22] lowering risk of heart failure and/or myocardial infarction and stroke. Therefore, a set of analyses tested these potential benefits, as well as the impact of insulin glargine[17] and a weighted average DPP-4 inhibitor effect on heart failure.[46] However, no additional effect on CVD-related mortality was implemented

with these individual components, to avoid any potential double counting of effects given the mortality risk offset through these other cardiovascular events.

Scenarios with discounting (25%, 50%) across branded product pricing, including DPP-4 inhibitors, SGLT2 inhibitors, and basal insulin, were also performed. Given negotiations between payers and manufacturers, the wholesale acquisition costs that define treatment costs in the base-case analyses do not reflect the true reimbursement rates and therefore are likely to overestimate the incremental costs and cost-effectiveness ratio associated with pathway 1.

RESULTS

Base-case analysis results indicate that pathway 1—in which patients intensify to triple therapy with DPP-4 inhibitors and SGLT2 inhibitors before transitioning to triple therapy with DPP-4 inhibitors and basal insulin—improves life-years and QALYs by 0.133 and 0.240, respectively, compared with a generic pathway (transitioning from metformin + SU to triple therapy including metformin + SU + basal insulin). This is simultaneously associated with a relatively limited increase in overall medical costs over a patient's lifetime ($15,548), as shown in **Table 3**, along with total costs, life-years, and QALYs per pathway. Overall, higher total treatment costs in pathway 1 are partially offset by lower costs associated with managing complications in comparison with a more generic medication pathway. These results translate to an ICER for pathway 1 of $64,784/QALY.

Probabilistic sensitivity analysis confirms the robustness of results, showing an acceptable mean ICER of $75,943/QALY. Given sampling to account for variation in parameters values, results remain cost-effective at $100,000/QALY approximately 60% of the time (see **eAppendix Figure**).

The majority of scenarios tested continued to provide QALY improvement with limited cost increases; ICERs remained under thresholds approved in real-world settings (**Figure 2**[16,17,21,22]),[31] with only 1 scenario (older baseline age) resulting in an ICER higher than $100,000/QALY. Simultaneously varying input values across all lines of therapy in each pathway to reflect 95% CI values in A1C led to an 8% increase or a 51% decrease in the ICER, for a total range of $31,945 to $70,126/QALY. However, similar explorations of 95% CI variation in hypoglycemic event rates and BMI had negligible impact on ICERs, with only 1% to 2% change from baseline. Use of a fully generic sequence, assuming NPH insulin rather than more often branded basal insulins (eg, glargine), had limited impact on the ICER, leading to a $60,031/QALY ICER (a decline of ~7%).

Despite sensitivity of the ICER value to changes in population characteristics, such as A1C level, interpretation would not necessarily change. Patients with different baseline A1C levels (7%, 9%) continue to benefit from pathway 1, with consistent incremental QALY benefits ranging from 2.5 to 3 quality-adjusted months. Coupled with therapy switching rules (eg, that therapy should be changed upon reaching A1C >7.5%), different baseline levels mean that patients may stay on initial lines of therapy for more or fewer years than in the base case; associated changes to treatment-related cost differences mean that ICERs range from less than $40,000/QALY to just over $90,000/QALY.

TABLE 3. Base-Case Results[a]

	Pathway 1	Pathway 2	Incremental Value
Projected direct medical costs per patient (cost of drugs, complications, AEs)	$145,029	$129,481	$15,548
Treatment	$121,343	$104,616	$16,727
CVD	$13,801	$14,571	–$770
Renal	$1142	$1359	–$217
Ulcer/amputation/ neuropathy	$5479	$5594	–$115
Eye	$954	$993	–$39
Hypoglycemia (all levels)	$710	$764	–$54
Life-years	14.334	14.201	0.133
QALYs	9.722	9.482	0.240
ICER: ΔCosts/ΔQALY	Pathway 1 is cost-effective compared with pathway 2 (ICER <$100,000)		$64,784

AE indicates adverse event; CVD, cardiovascular disease; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

[a]All results are discounted at 3% per year.

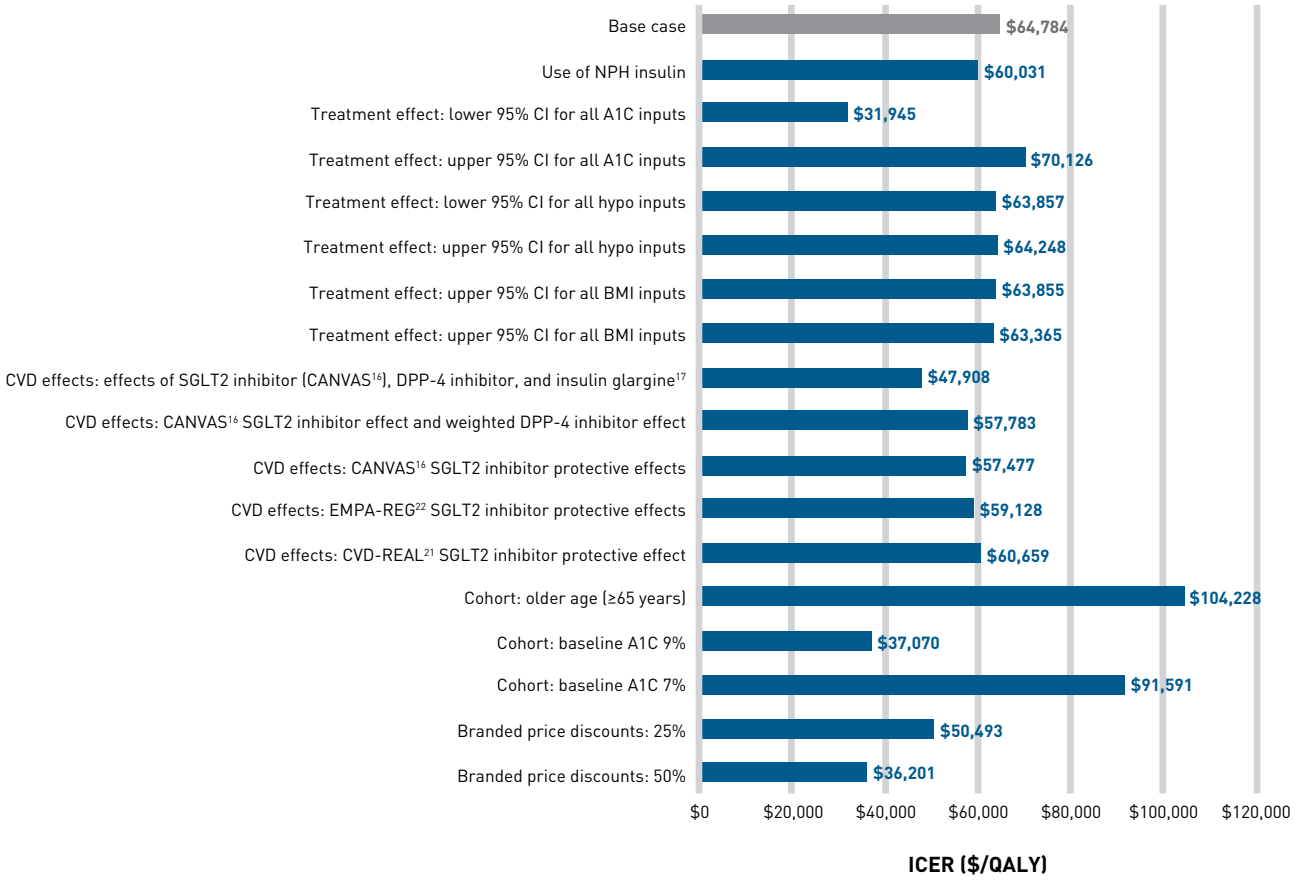
In addition to consistently favorable results given potential alternate key treatment effects and assumptions about the patient population, the ICER fell below even the most stringent of traditional willingness-to-pay thresholds ($50,000/QALY) when considering the impact on potential CVD event risks across all lines of therapy, including both protective effects (SGLT2 inhibitors) and potential harms associated with other medications. Individual consideration of SGLT2 inhibitor benefits led to ICER reductions of 6% to 11%, whereas simultaneously considering potential harms associated with early transition to insulin decreased the ICER by 26%.

Finally, price discounting to more accurately reflect costs associated with the pathways under consideration showed an ICER of $50,493/QALY with 25% discounts. Larger discounting of branded products at a 50% level led to an ICER of $36,201/QALY.

DISCUSSION

Results of base-case and scenario analyses demonstrate that for patients who are not at their A1C goal on metformin, intensification with DPP-4 inhibitors (second line) followed by addition of SGLT2 inhibitors (third line) on a background of metformin may be considered cost-effective compared with a more generic treatment strategy with metformin + SU prior to insulin initiation, with an ICER well under $100,000/QALY. Although the addition of costlier branded oral medications after metformin failure increased direct

FIGURE 2. Scenario Results[16,17,21,22]



A1C indicates glycated hemoglobin; BMI, body mass index; CVD, cardiovascular disease; DPP-4, dipeptidyl peptidase 4; hypo, hypoglycemic event; NPH, neutral protamine Hagedorn; SGLT2, sodium-glucose cotransporter 2; SU, sulfonylurea; T2D, type 2 diabetes.

medical costs in pathway 1, the health benefits associated with pathway 1 medications partially offset treatment costs, improving life expectancy and quality of life over a patient's lifetime.

With all scenarios demonstrating cost-effectiveness relative to willingness-to-pay thresholds, results are robust to alternate assumptions. Notably, the base-case analysis did not incorporate the potential cardiovascular protective effects of adding an SGLT2 inhibitor as documented in multiple clinical trials,[16,21,22] yet scenarios incorporating cardioprotective effects further improved QALYs and lowered total costs to the point of reducing ICER results to below $50,000/QALY. Most other scenarios remained similar to the base case; the exceptions were those that led to limited duration of therapy, such as starting at a higher baseline A1C level, such that the benefits outweighed the costs accrued. This and other scenarios reinforce the conclusion that use of relatively new branded medications that rely on novel mechanisms of action may provide long-term benefits compared with traditional generic therapies. When additionally accounting for the range of price discounts that are commonly negotiated between payers and manufacturers on branded medications, ICERs fell close to $50,000/QALY with 25% discounts and as far as $36,201/QALY with 50% discounts, thereby indicating that pathway 1 is highly cost-effective compared with pathway 2 according to any willingness-to-pay threshold typically considered in the United States.[32]

To the authors' knowledge, no economic evaluation has been performed to assess the cost-effectiveness of specific sequential treatment pathways, and the multiple intensification steps included in this analysis limit comparability with other publications. As noted in a review of diabetes-related cost-effectiveness publications, nearly all studies have evaluated the cost-effectiveness of a single intervention, whereas in the real world, patients will receive multiple interventions over a lifetime, both sequentially and simultaneously as suggested in guidelines.[9,47] However, it is possible to consider the results of this analysis given the general literature on cost-effectiveness thresholds. ICERs are often evaluated relative to willingness-to-pay thresholds, and although $50,000/QALY or $100,000/QALY is often used as a point of comparison, the rationale is outdated.[32] The World Health Organization's

WHO-CHOICE program suggests that 2 to 3 times the national gross domestic product would be appropriate in developed countries (approximately $115,000-$172,000),[32] and alternate suggested values have ranged between approximately $110,000/QALY and close to $300,000/QALY.[31,48,49] The present analysis results can be interpreted as falling under those suggested values and thus indicate that it represents good value for money.

Limitations

Although the results of this analysis are robust, it does have some limitations to consider. When initiating insulin, it is assumed that patients drop SGLT2 inhibitors and thus do not continue to receive the benefits of potential weight loss and CVD protection associated with those medications. This was done due to lack of clinical data regarding the effects of combination therapy including metformin + DPP-4 inhibitor + SGLT2 inhibitor + basal insulin. Omitting the potential long-term benefits may also be offset by eliminating the associated long-term medication costs. The analysis was also simplified by assuming that insulin dosage within each line of therapy remained constant. This simplification was also used due to lack of additional data to inform changes over time. However, because any insulin change would apply to both strategies equally, the incremental results are anticipated to remain similar and thus have limited impact on study conclusions. Additionally, a less costly option among several rapid-acting forms of bolus insulin was selected as a proxy for this last line of therapy in both pathways. This assumption was considered conservative, as it limits cost offsets due to delaying the basal-bolus line of therapy and thus removes any potential bias associated with adding a step into the treatment pathway.

Another point of consideration is that this analysis did not incorporate certain potential adverse event differences. For instance, this analysis did not include costs related to infrequent adverse events that may be associated with some of the drugs in the SGLT2 inhibitor class, such as diabetic ketoacidosis or amputations,[16] as these would have limited impact on analytic results. No association was incorporated between hypoglycemic events and other downstream complications, such as cardiovascular events, although recent study results have indicated a potential link between these events.[50,51] Adding this relationship would only improve an already cost-effective result. Finally, no association between A1C treatment switching threshold and potential mortality (eg, if it is aggressive for some subgroups) was implemented; however, this was not required in the deterministic base-case analysis, as the threshold was appropriate for the cohort average.

CONCLUSIONS

Despite its limitations, by estimating lifetime direct medical costs and clinical outcomes of potential therapeutic pathways, this study improves on available information regarding the potential economic value of different treatment strategies that could be used for management of T2D. Specifically, this analysis shows that additional anticipated long-term health benefits of a sequential pathway with branded oral medication including DPP-4 inhibitors and subsequent addition of SGLT2 inhibitors prior to insulin initiation provides acceptable value relative to costs compared with a generic treatment pathway of metformin with SU and insulin in the United States. ■

Author Affiliations: Merck & Co, Inc (MP, CG, SR, GD), Kenilworth, NJ; IQVIA, Inc (SPB, SK), San Francisco, CA.

Source of Funding: Merck & Co.

Author Disclosures: Drs Pawaskar, Rajpathak, and Davies are employed by and own stock in Merck. Ms Bilir is employed by IQVIA, which was paid for this research. Ms Kowal is employed by IQVIA and was paid by Merck to conduct the full modeling study, which included manuscript development. Dr Gonzalez is an employee of Merck, which developed and commercializes a dipeptidyl peptidase 4 inhibitor.

Authorship Information: Concept and design (MP, SPB, SK, SR, GD); acquisition of data (SPB, CG); analysis and interpretation of data (MP, SPB, SK, CG, SR, GD); drafting of the manuscript (MP, SPB, SR, GD); critical revision of the manuscript for important intellectual content (MP, SPB, SK, CG, GD); statistical analysis (MP); obtaining funding (SR); administrative, technical, or logistic support (SK, GD); and supervision (MP, GD).

Address Correspondence to: S. Pinar Bilir, MS, IQVIA, 135 Main St, Floors 21 and 22, San Francisco, CA 94015. Email: Pinar.bilir@iqvia.com.

REFERENCES

1. National diabetes statistics report, 2017: estimates of diabetes and its burden in the United States. CDC website. cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.pdf. Published 2017. Accessed May 2018.
2. Forbes JM, Cooper ME. Mechanisms of diabetic complications. *Physiol Rev*. 2013;93(1):137-188. doi: 10.1152/physrev.00045.2011.
3. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33) [erratum in *Lancet*. 1999;354(9178):602]. *Lancet*. 1998;352(9131):837-853. doi: 10.1016/S0140-6736(98)07019-6.
4. Stark Casagrande S, Fradkin JE, Saydah SH, Rust KF, Cowie CC. The prevalence of meeting A1C, blood pressure, and LDL goals among people with diabetes, 1988-2010. *Diabetes Care*. 2013;36(8):2271-2279. doi: 10.2337/dc12-2258.
5. American Diabetes Association. Economic costs of diabetes in the U.S. in 2017. *Diabetes Care*. 2018;41(5):917-928. doi: 10.2337/dci18-0007.
6. Gilmer TP, O'Connor PJ, Rush WA, et al. Predictors of health care costs in adults with diabetes. *Diabetes Care*. 2005;28(1):59-64. doi: 10.2337/diacare.28.1.59.
7. Menzin J, Korn JR, Cohen J, et al. Relationship between glycemic control and diabetes-related hospital costs in patients with type 1 or type 2 diabetes mellitus. *J Manag Care Pharm*. 2010;16(4):264-275. doi: 10.18553/jmcp.2010.16.4.264.
8. Gilmer TP, O'Connor PJ, Manning WG, Rush WA. The cost to health plans of poor glycemic control. *Diabetes Care*. 1997;20(12):1847-1853.
9. American Diabetes Association. 8. Pharmacologic approaches to glycemic treatment: *Standards of Medical Care in Diabetes–2018*. *Diabetes Care*. 2018;41(suppl 1):S73-S85. doi: 10.2337/dc18-S008.
10. Hauk L. Type 2 diabetes mellitus: ACP releases updated recommendations for oral pharmacologic treatment. *Am Fam Physician*. 2017;96(7):472-473.
11. Swinnen SG, Hoekstra JB, DeVries JH. Insulin therapy for type 2 diabetes. *Diabetes Care*. 2009;32(suppl 2):S253-S259. doi: 10.2337/dc09-S318.
12. Vashisht R, Jung K, Shah N. Learning effective treatment pathways for type-2 diabetes from a clinical data warehouse. *AMIA Annu Symp Proc*. 2017;2016:2036-2042.
13. Vilsboll T, Rosenstock J, Yki-Järvinen H, et al. Efficacy and safety of sitagliptin when added to insulin therapy in patients with type 2 diabetes. *Diabetes Obes Metab*. 2010;12(2):167-177. doi: 10.1111/j.1463-1326.2009.01173.x.
14. Canagliflozin, dapagliflozin and empagliflozin as monotherapies for treating type 2 diabetes. National Institute for Health and Care Excellence website. nice.org.uk/guidance/ta390. Published May 25, 2016. Accessed May 15, 2018.
15. Jansen HJ, Vervoort GM, de Haan AF, Netten PM, de Grauw WJ, Tack CJ. Diabetes-related distress, insulin dose, and age contribute to insulin-associated weight gain in patients with type 2 diabetes: results of a prospective study. *Diabetes Care*. 2014;37(10):2710-2717. doi: 10.2337/dc13-1205.
16. Neal B, Perkovic V, Mahaffey KW, et al; CANVAS Program Collaborative Group. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med*. 2017;377(7):644-657. doi: 10.1056/NEJMoa1611925.
17. Marso SP, McGuire DK, Zinman B, et al; DEVOTE Study Group. Efficacy and safety of degludec versus glargine in type 2 diabetes. *N Engl J Med*. 2017;377(8):723-732. doi: 10.1056/NEJMoa1615692.
18. Azoulay L, Suissa S. Sulfonylureas and the risks of cardiovascular events and death: a methodological meta-regression analysis of the observational studies. *Diabetes Care*. 2017;40(5):706-714. doi: 10.2337/dc16-1943.
19. DeFronzo RA, Lewin A, Patel S, et al. Combination of empagliflozin and linagliptin as second-line therapy in subjects with type 2 diabetes inadequately controlled on metformin. *Diabetes Care*. 2015;38(3):384-393. doi: 10.2337/dc14-2364.

20. Pratley RE, Eldor R, Raji A, et al. Ertugliflozin plus sitagliptin versus either individual agent over 52 weeks in patients with type 2 diabetes mellitus inadequately controlled with metformin: the VERTIS FACTORIAL randomized trial. *Diabetes Obes Metab*. 2018;20(5):1111-1120. doi: 10.1111/dom.13194.
21. Kosiborod M, Cavender MA, Fu AZ, et al; CVD-REAL Investigators and Study Group. Lower risk of heart failure and death in patients initiated on sodium-glucose cotransporter-2 inhibitors versus other glucose-lowering drugs: the CVD-REAL study (comparative effectiveness of cardiovascular outcomes in new users of sodium-glucose cotransporter-2 inhibitors). *Circulation*. 2017;136(3):249-259. doi: 10.1161/CIRCULATIONAHA.117.029190.
22. Zinman B, Wanner C, Lachin JM, et al; EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med*. 2015;373(22):2117-2128. doi: 10.1056/NEJMoa1504720.
23. Roussel R, Duran-Garcia S, Zhang Y, et al. Efficacy and safety of continuing sitagliptin when initiating insulin therapy in subjects with type 2 diabetes mellitus. *Diabetes*. 2018;67(suppl 1):LB32. doi: 10.2337/db18-112-LB.
24. Palmer AJ, Roze S, Valentine WJ, et al. The CORE Diabetes Model: projecting long-term clinical outcomes, costs and cost-effectiveness of interventions in diabetes mellitus (types 1 and 2) to support clinical and reimbursement decision-making. *Curr Med Res Opin*. 2004;20(suppl 1):S5-S26. doi: 10.1185/030079904X1980.
25. Palmer AJ, Roze S, Valentine WJ, et al. Validation of the CORE Diabetes Model against epidemiological and clinical studies. *Curr Med Res Opin*. 2004;20(suppl 1):S27-S40. doi: 10.1185/030079904X2006.
26. McEwan P, Foos V, Palmer JL, Lamotte M, Lloyd A, Grant D. Validation of the IMS CORE Diabetes Model. *Value Health*. 2014;17(6):714-724. doi: 10.1016/j.jval.2014.07.007.
27. Stevens RJ, Kothari V, Adler AI, Stratton IM; United Kingdom Prospective Diabetes Study (UKPDS) Group. The UKPDS risk engine: a model for the risk of coronary heart disease in type II diabetes (UKPDS 56) [erratum in *Clin Sci (Lond)*. 2002;102(6):679. doi: 10.1042/cs1020679]. *Clin Sci (Lond)*. 2001;101(6):671-679. doi: 10.1042/cs1010671.
28. Stratton IM, Adler AI, Neil HA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ*. 2000;321(7258):405-412. doi: 10.1136/bmj.321.7258.405.
29. Kothari V, Stevens RJ, Adler AI, et al. UKPDS 60: risk of stroke in type 2 diabetes estimated by the UK Prospective Diabetes Study risk engine. *Stroke*. 2002;33(7):1776-1781.
30. Wilson PW, Evans JC. Coronary artery disease prediction. *Am J Hypertens*. 1993;6(11, pt 2):309S-313S.
31. Braithwaite RS, Meltzer DO, King JT Jr, Leslie D, Roberts MS. What does the value of modern medicine say about the $50,000 per quality-adjusted life-year decision rule? *Med Care*. 2008;46(4):349-356. doi: 10.1097/MLR.0b013e31815c31a7.
32. Neumann PJ, Cohen JT, Weinstein MC. Updating cost-effectiveness—the curious resilience of the $50,000-per-QALY threshold. *N Engl J Med*. 2014;371(9):796-797. doi: 10.1056/NEJMp1405158.
33. Sanders GD, Neumann PJ, Basu A, et al. Recommendations for conduct, methodological practices, and reporting of cost-effectiveness analyses: Second Panel on Cost-Effectiveness in Health and Medicine [erratum in *JAMA*. 2016;316(18):1924. doi: 10.1001/jama.2016.15518]. *JAMA*. 2016;316(10):1093-1103. doi: 10.1001/jama.2016.12195.
34. Wang L, Wei W, Miao R, Xie L, Baser O. Real-world outcomes of US employees with type 2 diabetes mellitus treated with insulin glargine or neutral protamine Hagedorn insulin: a comparative retrospective database study. *BMJ Open*. 2013;3(4). doi: 10.1136/bmjopen-2012-002348.
35. Medi-Span Price Rx Database. Wolters Kluwer; 2018. pricerx.medispan.com. Accessed September 15, 2018.
36. Beaudet A, Clegg J, Thuresson PO, Lloyd A, McEwan P. Review of utility values for economic modeling in type 2 diabetes. *Value Health*. 2014;17(4):462-470. doi: 10.1016/j.jval.2014.03.003.
37. Evans M, Khunti K, Mamdani M, et al. Health-related quality of life associated with daytime and nocturnal hypoglycaemic events: a time trade-off survey in five countries. *Health Qual Life Outcomes*. 2013;11:90. doi: 10.1186/1477-7525-11-90.
38. Marrett E, Radican L, Davies MJ, Zhang Q. Assessment of severity and frequency of self-reported hypoglycemia on quality of life in patients with type 2 diabetes treated with oral antihyperglycemic agents: a survey study. *BMC Res Notes*. 2011;4:251. doi: 10.1186/1756-0500-4-251.
39. Lauridsen JT, Lønborg, J, Gundgaard J, Jensen HH. Diminishing marginal disutility of hypoglycaemic events: results from a time trade-off survey in five countries. *Qual Life Res*. 2014;23(9):2645-2650. doi: 10.1007/s11136-014-0712-x.
40. Maruthur NM, Tseng E, Hutfless S, et al. Diabetes medications as monotherapy or metformin-based combination therapy for type 2 diabetes: a systematic review and meta-analysis. *Ann Intern Med*. 2016;164(11):740-751. doi: 10.7326/M15-2650.
41. Billings LK, Doshi A, Gouet D, et al. Efficacy and safety of IDegLira versus basal-bolus insulin therapy in patients with type 2 diabetes uncontrolled on metformin and basal insulin: the DUAL VII randomized clinical trial. *Diabetes Care*. 2018;41(5):1009-1016. doi: 10.2337/dc17-1114.
42. Fritsche A, Larbig M, Owens D, Häring HU; GINGER Study Group. Comparison between a basal-bolus and a premixed insulin regimen in individuals with type 2 diabetes—results of the GINGER study [erratum in *Diabetes Obes Metab*. 2010;12(11):1022]. *Diabetes Obes Metab*. 2010;12(2):115-123. doi: 10.1111/j.1463-1326.2009.01165.x.
43. Fonseca V, Gill J, Zhou R, Leahy J. An analysis of early insulin glargine added to metformin with or without sulfonylurea: impact on glycaemic control and hypoglycaemia. *Diabetes Obes Metab*. 2011;13(9):814-822. doi: 10.1111/j.1463-1326.2011.01412.x.
44. Schütt M, Kern W, Krause U, et al; DPV Initiative. Is the frequency of self-monitoring of blood glucose related to long-term metabolic control? multicenter analysis including 24,500 patients from 191 centers in Germany and Austria. *Exp Clin Endocrinol Diabetes*. 2006;114(7):384-388. doi: 10.1055/s-2006-924152.
45. Physician Fee Schedule Search. CMS website. cms.gov/apps/physician-fee-schedule/search/search-criteria.aspx. Accessed September 15, 2018.
46. Kongwatcharapong J, Dilokthornsakul P, Nathisuwan S, Phrommintikul A, Chaiyakunapruk N. Effect of dipeptidyl peptidase-4 inhibitors on heart failure: a meta-analysis of randomized clinical trials. *Int J Cardiol*. 2016;211:88-95. doi: 10.1016/j.ijcard.2016.02.146.
47. Li R, Zhang P, Barker LE, Chowdhury FM, Zhang X. Cost-effectiveness of interventions to prevent and control diabetes mellitus: a systematic review. *Diabetes Care*. 2010;33(8):1872-1894. doi: 10.2337/dc10-0843.
48. Hirth RA, Chernew ME, Miller E, Fendrick AM, Weissert WG. Willingness to pay for a quality-adjusted life year: in search of a standard. *Med Decis Making*. 2000;20(3):332-342. doi: 10.1177/0272989X0002000310
49. Ubel PA, Hirth RA, Chernew ME, Fendrick AM. What is the price of life and why doesn't it increase at the rate of inflation? *Arch Intern Med*. 2003;163(14):1637-1641. doi: 10.1001/archinte.163.14.1637.
50. Hsu PF, Sung SH, Cheng HM, et al. Association of clinical symptomatic hypoglycemia with cardiovascular events and total mortality in type 2 diabetes: a nationwide population-based study. *Diabetes Care*. 2013;36(4):894-900. doi: 10.2337/dc12-0916.
51. Goto A, Arah OA, Goto M, Terauchi Y, Noda M. Severe hypoglycaemia and cardiovascular disease: systematic review and meta-analysis with bias analysis. *BMJ*. 2013;347:f4533. doi: 10.1136/bmj.f4533.

Visit **ajmc.com/link/3944** to download PDF and eAppendix

eAppendix Table.

Cohort Characteristics

Required values	All patients		Units/Range	References/Notes
PATIENT DEMOGRAPHICS	**Mean**	**SD**		
Start age	57.9	11.9	years	GE Centricity[1]
Duration of Diabetes	3	3.6	years	
Prop. Male	0.518		[0-1]	
	All patients			
BASELINE RISK FACTORS	**Mean**	**SD**		
HbA1c	8.37	1.84	%-points	GE Centricity[1]
SBP	130.94	16.90	mmHg	
T-CHOL	181.79	42.81	mg/dL	Merck Data on File[2]
HDL	42.94	11.52	mg/dL	GE Centricity[1]
LDL	99.53	37.21	mg/dL	Merck Data on File[2]
TRIG	143.34	80.88	mg/dL	GE Centricity[1]
BMI	34.40	7.87	kg/m^2	
eGFR	87.200	18.500	$ml/min/1.73m^2$	Merck Data on File[2]
HAEM	13.827	1.237	gr/dl	Merck Data on File[2]
WBC	7.437	1.913	$10^6/ml$	
Heart rate	70.502	10.698	bpm	Merck Data on File[2]
Alcohol consumption	7.54		oz/week	WHO Global status report on alcohol and health 2014[3]
	All patients			
RACIAL CHARACTERISTICS	**Mean**			
Prop. White	0.659		[0-1]	GE Centricity[1]
Prop. Black	0.0126		[0-1]	
Prop. Hispanic	0.00		[0-1]	
Prop. Native American	0.0034		[0-1]	
Prop. Asian/Pacific Islander	0.02		[0-1]	
	All patients			
BASELINE CVD COMPLICATIONS	**Mean**			
Prop. MI	0.029		[0-1]	Merck Data on File[2]
Prop. Angina	0.034		[0-1]	
Prop. PVD	0.003		[0-1]	
Prop. stroke	0.011		[0-1]	
Prop. HF	0.008		[0-1]	
Prop. Atrial filbrillation	0.015		[0-1]	
Prop. LVH	0.005		[0-1]	
	All patients			

BASELINE RENAL COMPLICATIONS	**Mean**		
Prop. MA	0.017	[0-1]	Merck Data on File[2]
Prop. GRP	0.006	[0-1]	
Prop. ESRD	0.000	[0-1]	
	All patients		
BASELINE RETINOPATHY COMPLICATIONS	**Mean**		
Prop. BDR	0.038	[0-1]	Merck Data on File[2]
Prop. PDR	0.000	[0-1]	
Prop. SVL	0.004	[0-1]	
	All patients		
BASELINE MACULAR EDEMA	**Mean**		
Prop. ME	0.0	[0-1]	Merck Data on File[2]; none reported
	All patients		
BASELINE CATARACT	**Mean**		
Prop. cataract	0.063	[0-1]	Merck Data on File[2]
	All patients		
BASELINE FOOT ULCER COMPLICATIONS	**Mean**		
Prop. uninfected ulcer	0.000	[0-1]	Merck Data on File[2] (0= not reported)
Prop. infected ulcer	0.000	[0-1]	
Prop. healed ulcer	0.000	[0-1]	
Prop. history of amputation	0.002	[0-1]	
	All patients		
BASELINE NEUROPATHY	**Mean**		
Prop. neuropathy	0.125	[0-1]	Merck Data on File[2]
	All patients		
BASELINE DEPRESSION	**Mean**		
Prop. depression	0.054	[0-1]	Merck Data on File[2]

Clinical inputs (non-treatment specific)

	Required values	Units/ Range	References/Notes
HbA1c adjustments - Type 2 diabetes			
Risk Reduct for 1%-point lower HbA1c MI T2	14	[0-100]	Stratton et al 2000[4]
Risk Reduct for 1%-point lower HbA1c micro T2	37	[0-100]	Stratton et al 2000[4]
Risk Reduct for 1%-point lower HbA1c PVD T2	22	[0-100]	Adler et al 2002[5]
Risk Reduct for 1%-point lower HbA1c Cataract T2	19	[0-100]	Stratton et al 2000[4]
Risk Reduct for 1%-point lower HbA1c HF T2	16	[0-100]	Stratton et al 2000[4]
Risk Reduct for 1%-point lower HbA1c stroke type 2	12	[0-100]	Stratton et al 2000[4]
Risk Reduct for 1%-point lower HbA1c angina type 2	12	[0-100]	Clarke et al 2004[6]
HbA1c adjustments - Type 1 and -2 diabetes			
Risk Reduct for 1%-point lower HbA1c HD Mort	12	[0-100]	Morioka et al 2001[7]
Risk Reduct for 1%-point lower HbA1c PD Mort	12	[0-100]	Morioka et al 2001[7]
Risk Reduct for 1%-point lower HbA1c RT Mort	0	[0-100]	Wiesbauer et al 2010[4]
Risk Reduct for 1%-point lower HbA1c 1st ulcer	17	[0-100]	Monami et al 2009[8]
SBP adjustments			
Risk Reduct for 10mmHg lower SBP all micro T2	13	[0-100]	Adler et al 2000[9]
Risk Reduct for 10mmHg lower SBP SVL T2	0	[0-100]	Assumption (No data)
MI			
Prop. init CHD event MI Female	0.361	[0-1]	D'Agostino et al 2000[10]
Prop. init CHD event MI Male	0.522	[0-1]	D'Agostino et al 2000[10]
Prop. subseq CHD event MI female	0.474	[0-1]	D'Agostino et al 2000[10]
Prop. subseq CHD event MI Male	0.451	[0-1]	D'Agostino et al 2000[10]
Increased Risk MI if MA	1.00	Multiplier	Assumption (No data)
Increased Risk MI if GPR	1.00	Multiplier	Assumption (No data)
Increased Risk MI if ESRD	1.00	Multiplier	Assumption (No data)
Multiplier for Risk rec MI if DIGAMI intensive control	1.00	Multiplier	Assumption (No data)
Multiplier for Risk pot MI mort if DIGAMI intensive control	1.00	Multiplier	Assumption (No data)
Multiplier Aspirin 1° MI	0.82	Multiplier	Antithrombotic Trialists' (ATT) Collaboration 2009[11]
Multiplier Aspirin 2° MI	0.80	Multiplier	Antithrombotic Trialists' (ATT) Collaboration 2009[11]
Multiplier Statins 1° MI	0.70	Multiplier	Brugts et al 2009[12]
Multiplier Statins 2° MI	0.81	Multiplier	Shepherd et al 2002[13]
Risk Reduct with ACE 1st MI	0.78	[0-1]	Heart Outcomes Prevention Evaluation (HOPE) Study Investigators 2000[14]
Risk Reduct with ACE rect MI	0.78	[0-1]	Heart Outcomes Prevention Evaluation (HOPE) Study Investigators 2000[14]
MI mortality			
p sudden death 1st MI male	0.393	[0-1]	Sonke et al 1996[15]
p sudden death 1st MI female	0.364	[0-1]	Sonke et al 1996[15]
p sudden death rec MI male	0.393	[0-1]	Sonke et al 1996[15]

p sudden death rec MI female	0.364	[0-1]	Sonke et al 1996[15]
Multiplier 12 month mortality MI convent treatment	1.45	Multiplier	Malmberg et al 1995[16]
Multiplier Aspirin mortality 1st year MI	0.88	Multiplier	Antiplatelet Trialists' Collaboration 1994[17]
Multiplier Aspirin mortality 2nd+ years MI	0.88	Multiplier	Antiplatelet Trialists' Collaboration 1994[17]
Multiplier Statins mortality 1st year MI	0.75	Multiplier	Stenestrand et al 2001[18]
Multiplier Statins mortality 2nd+ years MI	1.00	Multiplier	Assumption (No data)
Multiplier Aspirin sudden death MI	1.00	Multiplier	Assumption (No data)
Multiplier Statin sudden death MI	1.00	Multiplier	Briel et al 2006[19]
Multiplier ACE sudden death MI	1.00	Multiplier	Assumption (No data)
Risk Reduct with ACE MI long-term mort	0.64	[0-1]	Gustafsson et al 1999[20]
Risk Reduct with ACE MI 12 month mort	0.64	[0-1]	Gustafsson et al 1999[20]
Stroke			
Mult Stroke MA	1.00	Multiplier	Assumption (no data)
Mult Stroke GRP	1.00	Multiplier	Assumption (no data)
Mult Stroke ESRD	1.00	Multiplier	Assumption (no data)
Multiplier Aspirin 1° stroke	0.86	Multiplier	Antithrombotic Trialists' (ATT) Collaboration 2009[11]
Multiplier Aspirin 2° stroke	0.78	Multiplier	Antithrombotic Trialists' (ATT) Collaboration 2009[11]
Multiplier Statins 1° stroke	0.81	Multiplier	Brugts et al 2009[12]
Multiplier Statins 2° stroke	0.84	Multiplier	The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Investigators 2006[21]
Risk Reduct with ACE 1st stroke	0.67	[0-1]	Heart Outcomes Prevention Evaluation (HOPE) Study Investigators 2000[14]
Risk Reduct with ACE rec stroke	0.72	[0-1]	PROGRESS Collaborative Group 2001[22]
Stroke mortality			
p 30-day death 1st stroke male	0.124	[0-1]	Eriksson et al 2001[23]
p 30-day death 1st stroke female	0.124	[0-1]	Eriksson et al 2001[23]
p 30-day death rec stroke male	0.422	[0-1]	Eriksson et al 2001[23]
p 30-day death rec stroke female	0.422	[0-1]	Eriksson et al 2001[23]
Multiplier Aspirin mortality 1st year stroke	0.84	Multiplier	Antiplatelet Trialists' Collaboration 1994[17]
Multiplier Aspirin mortality 2nd+ years stroke	0.84	Multiplier	Antiplatelet Trialists' Collaboration 1994[17]
Multiplier Statins mortality 1st year stroke	1.00	Multiplier	Manktelow et al 2009[24]
Multiplier Statins mortality 2nd+ years stroke	1.00	Multiplier	Manktelow et al 2009[24]
Multiplier Aspirin sudden death stroke	0.95	Multiplier	Sandercock et al 2008[25]
Multiplier Statin sudden death stroke	1.00	Multiplier	Briel et al 2006[19]
Multiplier ACE sudden death stroke	0.49	Multiplier	Chitravas et al 2007[26]
Risk Reduct with ACE stroke long-term mort	1.000	[0-1]	Asberg et al 2010[27]
Risk Reduct with ACE stroke 12 month mort	1.000	[0-1]	Asberg et al 2010[27]
Angina			
Prop. init CHD event angina Female	0.621	[0-1]	D'Agostino et al 2000[10]

Prop. init CHD event angina Male	0.420	[0-1]	D'Agostino et al 2000[10]
Prop. subseq CHD event angina Female	0.359	[0-1]	D'Agostino et al 2000[10]
Prop. subseq CHD event angina Male	0.301	[0-1]	D'Agostino et al 2000[10]
Mult Angina MA	1.00	Multiplier	Assumption (No data)
Mult Angina GRP	1.00	Multiplier	Assumption (No data)
Mult Angina ESRD	1.00	Multiplier	Assumption (No data)
Congestive heart failure			
Increased Risk HF if MAU	1.00	Multiplier	Assumption (No data)
Increased Risk HF if GPR	1.00	Multiplier	Assumption (No data)
Increased Risk HF if ESRD	1.00	Multiplier	Assumption (No data)
Risk reduct HF if Aspirin	1.00	[0-1]	Assumption (No data)
Risk reduct HF if Statin	1.00	[0-1]	Assumption (No data)
Risk reduct HF if ACE	0.80	[0-1]	Heart Outcomes Prevention Evaluation (HOPE) Study Investigators 2000[14]
Risk reduct HF death if ACE	0.80	[0-1]	Ascencao et al 2008[28]
Multiplier HF death diab male	1.00	Multiplier	Ho et al 1993[29]
Multiplier HF death diab female	1.70	Multiplier	Ho et al 1993[29]
ACE inhibitor adjustments for microvascular complications			
Risk Reduct with ACE BDR T2	0.75	[0-1]	Chaturvedi et al 1998[30]
Risk Reduct with ACE PDR T2	0.19	[0-1]	Chaturvedi et al 1998[30]
Risk Reduct with ACE ME T2	1.00	[0-1]	Assumption (No data)
Risk Reduct with ACE SVL T2	1.00	[0-1]	Assumption (No data)
Risk Reduct with ACE Neuropathy T2	1.00	[0-1]	Assumption (No data)
Probabilities for ACE side effects			
p SEs stopping ACE 1st year	0.000	[0-1]	Assumption (No data)
p SEs stopping ACE 2nd+ years	0.000	[0-1]	Assumption (No data)
Adverse events			
p die major hypo T2	0.000	[0-1]	Ben-Ami et al 1999[31]
p die ketoacidosis	0.027	[0-1]	MacIsaac et al 2002[32]
p die after lactic acidosis	0.430	[0-1]	Campbell 1985[33]
Increased Risk hypo with ACE T2	1.00	Multiplier	Assumption (No data)
Foot ulcer and amputation			
p gangrene to amp with gang	0.181800	[0-1] monthly based	Persson et al 2000[34]
p gangrene to healed amp	0.308200	[0-1] monthly based	Persson et al 2000[34]
p death following onset gangrene	0.009800	[0-1] monthly based	Persson et al 2000[34]
p death with history amputation	0.004000	[0-1] monthly based	Persson et al 2000[34]

p death following healed ulcer	0.004000	[0-1] monthly based	Persson et al 2000[34]
p developing recurrent uninfected ulcer	0.039300	[0-1] monthly based	Persson et al 2000[34]
p amputation following infected ulcer	0.003700	[0-1] monthly based	Persson et al 2000[34]
p infect ulcer->amp healed	0.044500	[0-1] monthly based	Persson et al 2000[34]
p infect ulcer->death	0.009800	[0-1] monthly based	Persson et al 2000[34]
p infect ulcer->gangrene	0.007500	[0-1] monthly based	Persson et al 2000[34]
p infect ulc->uninfect ulc	0.139700	[0-1] monthly based	Persson et al 2000[34]
p recurrent amp	0.008451	[0-1] monthly based	Borkosky et al 2012[35]
p uninfect ulc->death	0.004000	[0-1] monthly based	Persson et al 2000[34]
p uninfect ulc->infect ulc	0.047300	[0-1] monthly based	Persson et al 2000[34]
p uninfect ulc->healed ulc	0.078700	[0-1] monthly based	Persson et al 2000[34]
p developing ulcer with neither neur or PVD	0.000250	[0-1] monthly based	Ragnarson Tennvall et al 2001[36]
p developing ulcer with either neur or PVD	0.006092	[0-1] monthly based	Ragnarson Tennvall et al 2001[36]
p developing ulcer with both neur or PVD	0.006092	[0-1] monthly based	Ragnarson Tennvall et al 2001[36]
Depression			
Mult for all cause death if depression	1.33	Multiplier	Egede et al 2005[37]
Mult for CHF if depression	1.00	Multiplier	Assumption (No data)
Mult for MI if depression	1.00	Multiplier	Assumption (No data)
Mult for depression if neuropathy	3.10	Multiplier	Yoshida et al 2009[38]
Mult for depression if stroke	6.30	Multiplier	Whyte et al 2004[39]
Mult for depression if amp.	1.00	Multiplier	Assumption (No data)
Other			
p BDR->SVL	0.0148	[0-1]	Javitt et al 1994[40]
p reversal of neuropathy	0.000	[0-1]	Assumption (No data)

Other management relevant inputs

	Required values	Units/ Range	References/Notes
Concomitant medication	**Mean**		
Prop 1° prevention ASP	0.575	[0-1]	VanWormer 2014[41]
Prop 2° prevention ASP	0.575	[0-1]	
Prop 1° prevention Statins	0.404	[0-1]	Gamboa 2014[42]
Prop 2° prevention Statins	0.215	[0-1]	Abdallah 2014[43]
Prop 1° prevention ACE-I	0.64	[0-1]	Ali 2013[44]
Prop 2° prevention ACE-I	0.64	[0-1]	
Screening and patient management proportions			
Prop on foot ulcer prevention program	0.714	[0-1]	Ali 2013[44]
Prop screened eye disease	0.734	[0-1]	
Prop screened for renal disease	0.477	[0-1]	Anabtawi 2013[45]
Prop receiving intensive insulin after MI	0.877	[0-1]	McMullin 2004[46]
Prop treated with extra ulcer treatment	0.570	[0-1]	Lyon 2008[47]
Prop screened for depression - no complications	0.830	[0-1]	Jones 2007[48]
Prop screened for depression - complications	0.830	[0-1]	
Other			
Reduction in incidence FU with Prev Program	0.310	[0-1]	O'Meara 2000[49]
Improvement in ulcer healing rate with extra ulcer treatment	1.390	Multiplier	Kantor 2001[50]
Reduction in amputation rate with footcare	0.340	[0-1]	O'Meara 2000[49]
Sensitivity eye screening	0.934	[0-1]	Wilson 2010[51]
Specificity eye screening	0.858	[0-1]	
Sensitivity GRP screening	0.989	[0-1]	White 2011[52]
Sensitivity MA screening	0.87	[0-1]	Wu 2014[53]
Specificity MA screening	0.88	[0-1]	

Economic inputs

	Required values	Units / Range	References/notes
DISCOUNT RATES			
Discount Clinical	3.0	%	Sanders 2016[54]
Discount Costs	3.0	%	
SAMPLING FOR PROBABILISTIC SENSITIVITY ANALYSIS			
Percent variation direct costs	20.0	%	Assumed
Percent variation indirect costs	20.0	%	Assumed
MANAGEMENT COSTS			
c statins	47.67	$	PriceRx 2017[55]
c aspirin	2.82	$	
c ACE	33.22	$	
c screening for MA	28.39	$	
c screening for GRP	25.49	$	
c eye screening	66.75	$	
DIRECT COSTS CVD COMPLICATIONS			
c MI 1st year	16,556.91	$	Yeaw 2014[56]
c MI 2nd+ years	2,004.75	$	
c angina 1st year	3,625.33	$	
c angina 2nd+ years	507.00	$	
c CHF 1st year	12,523.77	$	
c CHF 2nd+ years	6,394.86	$	
c stroke 1st year	7,223.48	$	
c stroke 2nd+ years	1,010.65	$	
c stroke death within 30 days	7,343.84	$	
c PVD 1st year	5,496.51	$	
c PVD 2nd+ years	2,128.86	$	
DIRECT COSTS RENAL COMPLICATIONS			
HD costs 1st year	20,204.70	$	Yeaw 2014[56]
annual costs HD 2+ years	15,302.76	$	
PD costs 1st year	30,901.02	$	
annual costs PD 2+ years	22,241.36	$	
RT costs 1st year	10,149.04	$	
annual costs RT 2+ years	7,166.74	$	
DIRECT COSTS ACUTE EVENTS			
c severe hypo requiring non-medical third party intervention	75.26	$	Foos 2013[57]
c severe hypo requiring medical third party intervention	1,311.30	$	
c non-severe hypo	10.23	$	CMS PFS 2017[58]
c keto event	290.78	$	Yeaw 2014[56]
c lactic acid event	12,889.02	$	
DIRECT COSTS EYE DISEASE			
c laser treatment	982.27	$	CMS PFS 2017[58]

c cataract operation	627.67	$	Yeaw 2014[56]
c following cataract operation	154.85	$	
c blindness - year of onset	1,241.15	$	
c blindness - following years	302.60	$	
DIRECT COSTS NEUROP/FOOT ULCER/AMP			
c Neurop 1st year	2,101.68	$	Yeaw 2014[56]
c Neurop 2nd+ years	709.23	$	
c Amputation (event based)	7,304.32	$	
c Amp Prosthesis (event based)	21,720.47	$	
c Gangrene treatment	15,552.16	$	
c after healed ulcer	3,898.29	$	
c infected ulcer	7,833.17	$	
c standard uninfected ulcer	7,833.17	$	
c healed ulcer history of amputation	3,898.29	$	
QUALITY OF LIFE	**Mean**		
QoL utility T2 no complications	0.7850	[0-1]	Clarke et al 2002[59]
QoL disutility MI event	-0.0550	[-1-0]	
QoL utility post MI	0.7300	[0-1]	
QoL utility angina	0.6950	[0-1]	
QoL utility CHF	0.6770	[0-1]	
QoL disutility stroke event	-0.1640	[-1-0]	
QoL utility post Stroke	0.6210	[0-1]	
QoL utility PVD	0.7240	[0-1]	Bagust et al 2005[60]
QoL utility MA	0.7850	[0-1]	Assumed to be asymptomatic
QoL utility GRP	0.7370	[0-1]	Bagust et al 2005[60]
QoL utility HD	0.6210	[0-1]	Wasserfallen et al 2004[61]
QoL utility PD	0.5810	[0-1]	
QoL utility RT	0.7620	[0-1]	Kiberd 1995[62]
QoL utility BDR	0.7450	[0-1]	Fenwick et al 2012[63]
QoL utility BDR wrongly treated	0.7450	[0-1]	
QoL utility PDR laser treated	0.7150	[0-1]	
QoL utility PDR no Laser	0.7150	[0-1]	
QoL utility ME	0.7450	[0-1]	
QoL utility SVL	0.7110	[0-1]	Clarke et al 2002[59]
QoL utility cataract	0.7690	[0-1]	Lee et al 2012[64]
QoL utility neuropathy	0.7010	[0-1]	Bagust et al 2005[60]
QoL utility healed ulcer	0.7850	[0-1]	Assumed not to have impact on QoL
QoL utility active ulcer	0.6150	[0-1]	Bagust et al 2005[60]
QoL disutility amp event	-0.2800	[-1-0]	Clarke et al 2002[59]
QoL utility post amputation	0.5050	[0-1]	
QoL disutility for major hypo events, non-medical third party assistance	-0.0183	[-1-0]	Marrett et al 2011[65]
QoL disutility for major hypo events, medical third party assistance	-0.055	[-1-0]	Evans et al 2013[66]
QoL for minor hypo events	Lauridsen diminishing disutilities function selected		Lauridsen et al 2014[67] [model autocalculates per line of therapy based on annual rate]

eAppendix References

1. GEHealthcare, Centricity Electronic Medical Record (EMR) 2015.

2. Merck, Data on File. Clinical Study Report P002 VERTIS. 2017.

3. Organization, W.H., Global Status Report on Alcohol and Health 2014. 2014, WHO: Geneva, Switzerland.

4. Stratton, I.M., et al., Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ, 2000. 321(7258): p. 405-12.

5. Adler, A.I., et al., UKPDS 59: hyperglycemia and other potentially modifiable risk factors for peripheral vascular disease in type 2 diabetes. Diabetes Care, 2002. 25(5): p. 894-9.

6. Clarke, P.M., et al., A model to estimate the lifetime health outcomes of patients with type 2 diabetes: the United Kingdom Prospective Diabetes Study (UKPDS) Outcomes Model (UKPDS no. 68). Diabetologia, 2004. 47(10): p. 1747-59.

7. Morioka, T., et al., Glycemic control is a predictor of survival for diabetic patients on hemodialysis. Diabetes Care, 2001. 24(5): p. 909-13.

8. Monami, M., et al., Pulse pressure and prediction of incident foot ulcers in type 2 diabetes. Diabetes Care, 2009. 32(5): p. 897-9.

9. Adler, A.I., et al., Association of systolic blood pressure with macrovascular and microvascular complications of type 2 diabetes (UKPDS 36): prospective observational study. BMJ, 2000. 321(7258): p. 412-9.

10. D'Agostino, R.B., et al., Primary and subsequent coronary risk appraisal: new results from the Framingham study. Am Heart J, 2000. 139(2 Pt 1): p. 272-81.

11. Antithrombotic Trialists, C., et al., Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. Lancet, 2009. 373(9678): p. 1849-60.

12. Brugts, J.J., et al., The benefits of statins in people without established cardiovascular disease but with cardiovascular risk factors: meta-analysis of randomised controlled trials. BMJ, 2009. 338: p. b2376.

13. Shepherd, J., et al., Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. Lancet, 2002. 360(9346): p. 1623-30.

14. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. Heart Outcomes Prevention Evaluation Study Investigators. Lancet, 2000. 355(9200): p. 253-9.
15. Sonke, G.S., et al., Sex differences in case fatality before and after admission to hospital after acute cardiac events: analysis of community based coronary heart disease register. BMJ, 1996. 313(7061): p. 853-5.
16. Malmberg, K., et al., Randomized trial of insulin-glucose infusion followed by subcutaneous insulin treatment in diabetic patients with acute myocardial infarction (DIGAMI study): effects on mortality at 1 year. J Am Coll Cardiol, 1995. 26(1): p. 57-65.
17. Collaborative overview of randomised trials of antiplatelet therapy--I: Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. Antiplatelet Trialists' Collaboration. BMJ, 1994. 308(6921): p. 81-106.
18. Stenestrand, U., L. Wallentin, and C. Swedish Register of Cardiac Intensive, Early statin treatment following acute myocardial infarction and 1-year survival. JAMA, 2001. 285(4): p. 430-6.
19. Briel, M., et al., Effects of early treatment with statins on short-term clinical outcomes in acute coronary syndromes: a meta-analysis of randomized controlled trials. JAMA, 2006. 295(17): p. 2046-56.
20. Gustafsson, I., et al., Effect of the angiotensin-converting enzyme inhibitor trandolapril on mortality and morbidity in diabetic patients with left ventricular dysfunction after acute myocardial infarction. Trace Study Group. J Am Coll Cardiol, 1999. 34(1): p. 83-9.
21. Amarenco, P., et al., High-dose atorvastatin after stroke or transient ischemic attack. N Engl J Med, 2006. 355(6): p. 549-59.
22. Group, P.C., Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack. Lancet, 2001. 358(9287): p. 1033-41.
23. Eriksson, S.E. and J.E. Olsson, Survival and recurrent strokes in patients with different subtypes of stroke: a fourteen-year follow-up study. Cerebrovasc Dis, 2001. 12(3): p. 171-80.
24. Manktelow, B.N. and J.F. Potter, Interventions in the management of serum lipids for preventing stroke recurrence. Cochrane Database Syst Rev, 2009(3): p. CD002091.

25. Sandercock, P.A., et al., Antiplatelet therapy for acute ischaemic stroke. Cochrane Database Syst Rev, 2008(3): p. CD000029.
26. Chitravas, N., et al., Is prestroke use of angiotensin-converting enzyme inhibitors associated with better outcome? Neurology, 2007. 68(20): p. 1687-93.
27. Asberg, S., et al., Ischemic stroke and secondary prevention in clinical practice: a cohort study of 14,529 patients in the Swedish Stroke Register. Stroke, 2010. 41(7): p. 1338-42.
28. Ascencao, R., et al., Drug therapy for chronic heart failure due to left ventricular systolic dysfunction: a review. III. Angiotensin-converting enzyme inhibitors. Rev Port Cardiol, 2008. 27(9): p. 1169-87.
29. Ho, K.K., et al., Survival after the onset of congestive heart failure in Framingham Heart Study subjects. Circulation, 1993. 88(1): p. 107-15.
30. Chaturvedi, N., et al., Effect of lisinopril on progression of retinopathy in normotensive people with type 1 diabetes. The EUCLID Study Group. EURODIAB Controlled Trial of Lisinopril in Insulin-Dependent Diabetes Mellitus. Lancet, 1998. 351(9095): p. 28-31.
31. Ben-Ami, H., et al., Drug-induced hypoglycemic coma in 102 diabetic patients. Arch Intern Med, 1999. 159(3): p. 281-4.
32. MacIsaac, R.J., et al., Influence of age on the presentation and outcome of acidotic and hyperosmolar diabetic emergencies. Intern Med J, 2002. 32(8): p. 379-85.
33. Campbell, I.W., Metformin and the sulphonylureas: the comparative risk. Horm Metab Res Suppl, 1985. 15: p. 105-11.
34. Persson, U., et al., The cost-effectiveness of treating diabetic lower extremity ulcers with becaplermin (Regranex): a core model with an application using Swedish cost data. Value Health, 2000. 3 Suppl 1: p. 39-46.
35. Borkosky, S.L. and T.S. Roukis, Incidence of re-amputation following partial first ray amputation associated with diabetes mellitus and peripheral sensory neuropathy: a systematic review. Diabet Foot Ankle, 2012. 3.
36. Ragnarson Tennvall, G. and J. Apelqvist, Prevention of diabetes-related foot ulcers and amputations: a cost-utility analysis based on Markov model simulations. Diabetologia, 2001. 44(11): p. 2077-87.
37. Egede, L.E., P.J. Nietert, and D. Zheng, Depression and all-cause and coronary heart disease mortality among adults with and without diabetes. Diabetes Care, 2005. 28(6): p. 1339-45.

38. Yoshida, S., et al., Neuropathy is associated with depression independently of health-related quality of life in Japanese patients with diabetes. Psychiatry Clin Neurosci, 2009. 63(1): p. 65-72.
39. Whyte, E.M., et al., Depression after stroke: a prospective epidemiological study. J Am Geriatr Soc, 2004. 52(5): p. 774-8.
40. Javitt, J.C., et al., Preventive eye care in people with diabetes is cost-saving to the federal government. Implications for health-care reform. Diabetes Care, 1994. 17(8): p. 909-17.
41. VanWormer, J.J., A.W. Miller, and H. Rezkalla, Identifying opportunities to improve aspirin utilization for the primary prevention of cardiovascular disease in a regional health care system. WMJ, 2014. 113(5): p. 190-5; quiz 196.
42. Gamboa, C.M., et al., Statin underuse and low prevalence of LDL-C control among U.S. adults at high risk of coronary heart disease. Am J Med Sci, 2014. 348(2): p. 108-14.
43. Abdallah, M.S., et al., Patterns and predictors of intensive statin therapy among patients with diabetes mellitus after acute myocardial infarction. Am J Cardiol, 2014. 113(8): p. 1267-72.
44. Ali, M.K., K.M. Bullard, and E.W. Gregg, Achievement of goals in U.S. Diabetes Care, 1999-2010. N Engl J Med, 2013. 369(3): p. 287-8.
45. Anabtawi, A. and L.M. Mathew, Improving compliance with screening of diabetic patients for microalbuminuria in primary care practice. ISRN Endocrinol, 2013. 2013: p. 893913.
46. McMullin, J., et al., Glycemic control in the ICU: a multicenter survey. Intensive Care Med, 2004. 30(5): p. 798-803.
47. Lyon, K.C., The case for evidence in wound care: investigating advanced treatment modalities in healing chronic diabetic lower extremity wounds. J Wound Ostomy Continence Nurs, 2008. 35(6): p. 585-90.
48. Jones, L.E. and C.C. Doebbeling, Depression screening disparities among veterans with diabetes compared with the general veteran population. Diabetes Care, 2007. 30(9): p. 2216-21.
49. O'Meara, S., et al., Systematic reviews of wound care management: (3) antimicrobial agents for chronic wounds; (4) diabetic foot ulceration. Health Technol Assess, 2000. 4(21): p. 1-237.
50. Kantor, J. and D.J. Margolis, Treatment options for diabetic neuropathic foot ulcers: a cost-effectiveness analysis. Dermatol Surg, 2001. 27(4): p. 347-51.
51. Wilson, P.J., et al., Screening for diabetic retinopathy: a comparative trial of photography and scanning laser ophthalmoscopy. Ophthalmologica, 2010. 224(4): p. 251-7.

52. White, S.L., et al., Diagnostic accuracy of urine dipsticks for detection of albuminuria in the general community. Am J Kidney Dis, 2011. 58(1): p. 19-28.
53. Wu, H.Y., et al., Diagnostic performance of random urine samples using albumin concentration vs ratio of albumin to creatinine for microalbuminuria screening in patients with diabetes mellitus: a systematic review and meta-analysis. JAMA Intern Med, 2014. 174(7): p. 1108-15.
54. Sanders, G.D., et al., Recommendations for Conduct, Methodological Practices, and Reporting of Cost-effectiveness Analyses: Second Panel on Cost-Effectiveness in Health and Medicine. JAMA, 2016. 316(10): p. 1093-103.
55. PriceRx database. 2018, Wolters Kluwer.
56. Yeaw, J., et al., Direct medical costs for complications among children and adults with diabetes in the US commercial payer setting. Appl Health Econ Health Policy, 2014. 12(2): p. 219-30.
57. V., F., Core Diabetes Model User Forum. 2013: Dublin, Ireland.
58. Physician Fee Schedule, C.o.M.a.M. (CMS), Editor. 2018.
59. Clarke, P., A. Gray, and R. Holman, Estimating utility values for health states of type 2 diabetic patients using the EQ-5D (UKPDS 62). Med Decis Making, 2002. 22(4): p. 340-9.
60. Bagust, A. and S. Beale, Modelling EuroQol health-related utility values for diabetic complications from CODE-2 data. Health Econ, 2005. 14(3): p. 217-30.
61. Wasserfallen, J.B., et al., Quality of life on chronic dialysis: comparison between haemodialysis and peritoneal dialysis. Nephrol Dial Transplant, 2004. 19(6): p. 1594-9.
62. Kiberd, B.A. and K.K. Jindal, Screening to prevent renal failure in insulin dependent diabetic patients: an economic evaluation. BMJ, 1995. 311(7020): p. 1595-9.
63. Fenwick, E.K., et al., The impact of diabetic retinopathy and diabetic macular edema on health-related quality of life in type 1 and type 2 diabetes. Invest Ophthalmol Vis Sci, 2012. 53(2): p. 677-84.
64. Lee, W.J., et al., Health-related quality of life using the EuroQol 5D questionnaire in Korean patients with type 2 diabetes. J Korean Med Sci, 2012. 27(3): p. 255-60.
65. Marrett, E., et al., Assessment of severity and frequency of self-reported hypoglycemia on quality of life in patients with type 2 diabetes treated with oral antihyperglycemic agents: A survey study. BMC Res Notes, 2011. 4: p. 251.

66. Evans, M., et al., Health-related quality of life associated with daytime and nocturnal hypoglycaemic events: a time trade-off survey in five countries. Health Qual Life Outcomes, 2013. 11: p. 90.
67. Lauridsen, J.T., et al., Diminishing marginal disutility of hypoglycaemic events: results from a time trade-off survey in five countries. Qual Life Res, 2014. 23(9): p. 2645-50.

eAppendix Figure. PSA Scatterplot and Cost-Effectiveness Acceptability Curve