Value of Personalized Risk Information in Economic Analysis

A thesis submitted by

Natalia Olchanski

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Advisor: David M. Kent, MD

Abstract

Better targeting of medical interventions is ever more important given the aging population in the US, high prices of new technologies and limited budgets of healthcare payers. Cost-effectiveness analysis (CEA) assesses the intervention value, typically by comparing average population health gains to average costs. Because intervention value differs across individuals, this project aims to extend conventional CEA methods to address patient risk heterogeneity (e.g. risk of the primary outcome), when risk can be predicted on the basis of pre-treatment characteristics. Because baseline risk is often an important determinant of an intervention's absolute effects, benefit-harm trade-offs, and costs, we assessed the potential value of targeting interventions based on individual risk. This project includes risk-based CEA of (1) a diabetes prevention program for individuals with pre-diabetes, and (2) duration of dual antiplatelet therapy by bleeding risk after percutaneous coronary intervention in patients with acute coronary syndrome (ACS). We assessed how cost-effectiveness varies by risk stratum and how the risk-based approach may help target patients for intervention. Because the pre-diabetes population is large, targeting of preventive measures may be necessary to address budget and capacity limits. Likewise, there is a large population of ACS patients undergoing interventions, and a need to better target appropriate duration of antiplatelet therapy to minimize the risks and costs of adverse events. A third paper explores how clinical risk prediction model performance may influence the results of individualized economic analysis, and in particular the 'value of misinformation' from miscalibrated models.

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List of Abbreviations

ACS – acute coronary syndrome
BMI – body mass index
CEA – cost-effectiveness analysis
CPM – clinical prediction model
DAPT – dual antiplatelet therapy
DPP – the Diabetes Prevention Program
DPPOS – the Diabetes Prevention Program Outcomes Study
EVIC – expected value of individualized care
GUSTO – the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries study
HbA1c – hemoglobin A1c
ICER – incremental cost-effectiveness ratio
MI – myocardial infarction
NMB – net monetary benefit
QALY – quality-adjusted life year
ST – stent thrombosis
TIMI – The Thrombolysis in Myocardial Infarction (TIMI) bleeding criteria
tPA – tissue plasminogen activator
TVR – target vessel revascularization
WTP – willingness to pay

Chapter 1 : Introduction

The broad idea and promise of personalized medicine is to tailor medical treatment to each individual, to target and prioritize for treatment those who are most likely to benefit based on their personal characteristics.[1-3]

Much of the conversation about “precision” or “personalized” medicine has focused on the field of pharmacogenomics, which studies how a person’s genes influences their response to therapy, with the goal of using genetic markers or genomic profiles to target the use of certain drugs, such as cancer drugs with companion genetic or genomic tests.[4,5] The applications of this type of precision medicine have been relatively specific to rare diseases or certain types of cancer, where the genetic make-up of the disease (rather than the patient) is frequently most relevant (i.e. somatic mutations of a tumor, rather than germline genetic profile).

However, there are many high prevalence and costly conditions, such as heart disease, for which there is no straightforward genetic or genomic determinant of treatment success. Another application of “personalized” medicine can potentially take advantage of the substantial variation among patients – both in terms of their risk of poor outcomes and the effectiveness of interventions – and use individualized information based on abundant and easily obtainable clinical information to target treatment.

1.1. Economic analysis in the era of personalized medicine

While medical decision making has always been “personalized” at the physician’s office, where the clinician makes each treatment decision for each individual patient, policy makers generally consider evidence and make decisions at the population wide level. The recently developed Institute for Clinical and Economic Review (ICER) value framework for evaluating medical technologies calls for consideration of cost-effectiveness and budget impact.[6] Budget impact in particular often depends strongly on the size of the treatment population. Even interventions with very favorable cost-effectiveness may have a staggering budget impact when treatment costs are summed across large populations. Decision making becomes especially difficult when major costs are 'up front' and born from one budget and savings are realized in the future, potentially from a different budget.

With many costly chronic conditions, healthcare investment decisions always involve large and heterogeneous patient populations. There is a growing body of literature that examines the contrast between average effects of interventions, most often reported in clinical trials, and the effects in specific subgroups – especially subgroups that differ in their baseline risk of poor outcomes. Because treatment benefit mathematically depends on baseline risk, individuals at higher risk have the greatest potential benefit from interventions—where benefit (for clinical decision making and economic purposes) is appropriately measured on the risk difference scale. Because in broad populations most individuals often have lower risk than the average in a clinical trial (especially when the outcome rate is low),[7-11] for a large portion of the population the treatment may not confer good value in terms of health gains for the resources invested—even when it is cost-effective on average. Conversely, a policy maker may consider an intervention not cost-effective and not worth offering at all, even though some patients (often high risk patients) may have accrued substantial benefits and value. If on the other hand the policy maker were able to evaluate the economic feasibility or cost-effectiveness at a more granular level, for instance, based on baseline outcome risk, clinicians may be able to selectively target individuals for whom health gains would be sufficiently large to justify costs, improving both outcomes and economic efficiency.

For example, among the 84 million people in the US at increased risk for type 2 diabetes, or those with pre-diabetes, diabetes risk varies substantially. The capacity and utilization of prevention programs lag behind the population needs. Although these programs could prevent diabetes, improve health, and save money, immediately achieving high utilization is infeasible. One way to maximize health gains and economic efficiency would be to prioritize implementation and use of these programs in subpopulations with elevated diabetes risk. Although clinical risk prediction models can help to identify these individuals, no study has yet quantified the benefit of using these models to target diabetes prevention programs in this way.

A second example is the selection of the duration for dual antiplatelet therapy (DAPT) in acute coronary syndrome patients. This therapy decreases the rates of repeat heart attacks, strokes, and other ischemic events on one hand, but increases the chance of a major bleeding event on the other. Clinical guidelines recommend 12 months of DAPT, but add that—depending on bleeding risk—either reducing therapy duration to 6 months, or extending it beyond 12 months may be reasonable. No published analysis has evaluated the cost-effectiveness of DAPT to compare different therapy durations across patients with different bleeding risks, or the economic impact of using personalized risk information to select treatment duration.

In addition to helping to identify that subset of patients for whom a treatment's costs may be justified, granular CEA is also consistent with recent initiatives to promote personalized medicine, the goal of which is to move away from "one size fits all" decisions and towards decisions tailored to each patient based on his or her anticipated response to therapy. Although researchers have described approaches for performing and reporting individualized CEA, [12] analysts have in practice not pursued individualized CEAs.[13]

1.2. Heterogeneity of risk and treatment effect

Clinical trials typically report average treatment effects in the form of relative (e.g. relative risk, odds ratio or hazard ratios), and also test statistically for heterogeneity on this scale. However, the most important measure for economic analyses (and for clinical decision making) is absolute risk differences. Because outcome risk typically varies substantially across the trial population, the risk difference will also typically vary. Indeed, while proportional treatment effects are generally believed to be more stable than absolute risk differences, even relative measures of treatment effects may also vary across groups of patients with different outcome risks. Further, sometimes the risk distributions are skewed in such a way that a small number of high risk participants, receiving a large benefit from treatment, might obscure a relatively large proportion of participants, whose risk is much lower, and who might receive little to no benefit from treatment.[9-11,14] A number of articles report that average clinical trial findings, especially when expressed in terms of absolute risk reduction, often vary across a trial population in clinically important ways.[9,15-18]

To add to the complexity, multiple factors that can vary across patients influence potential net benefit, including outcome risk, treatment effect, life expectancy, patient preferences, and costs. Often different characteristics of a single individual might influence patient outcomes and costs in different directions, for example, older age may be associated with both a higher risk of the primary outcome and shorter life expectancy. Nonetheless, few published CEAs recognize heterogeneity, and even those analyses that have typically do so to a limited extent insufficient to inform decisions.[13,19-21] For example, they may compare the cost-effectiveness across groups that differ in terms of one risk factor (e.g., age or gender) but do not look at how baseline risk, and hence benefit and cost-effectiveness, can vary across multiple characteristics simultaneously.

A review of the cost-effectiveness literature found that few CEAs attempt to estimate cost-effectiveness in patient subgroups.[13] Those that do typically use single risk factor definitions of subgroups – such as gender, age, or a single biomarker. One problem with using such definitions is that in reality any given individual has a combination of characteristics that may in one-way analyses indicate conflicting recommendations for treatment. In a treatment decision considering one risk factor at a time, should the patient's age be given higher priority? Their gender? Their body mass index? Their HbA1c measure? Rather than guessing, data-driven methods can guide these decisions in a systematic manner, estimating risks and treatment outcomes based on the combination of multiple risk factors, as well as helping determine the most appropriate way of subgrouping the patients.[9,11,22-25]

1.3. Clinical risk prediction models

Clinical prediction models (CPMs) estimate baseline risk for each patient as a function of his or her individual and disease characteristics. If the CPMs have good calibration (i.e., they accurately predict risk magnitude) and discrimination (i.e., they correctly identify the patients at greatest risk), then they can help to identify patients who will benefit most from therapy, conserving resources and even averting net harm that might be suffered by patients for whom adverse events would on average outweigh potential therapeutic benefits.

CPMs incorporate the analysis of associations between individual characteristics and outcomes, and have been used in clinical practice to guide clinician decision making and sometimes have been used in the development of clinical care guidelines, to indicate where treatment pathways and outcomes might vary by patient's estimated risk of adverse events, such as stroke.[26-29] CEA incorporating subgroup analysis by patient characteristics or by risk strata, as estimated by CPMs, offers a way to estimate the individual level costs, benefits, and value by risk group, and to assess the value of targeting interventions by risk. However, it may be that poorly performing CPMs may misestimate individual risks and lead to worse decisions, than a strategy based on the population average. At present, it is difficult to gauge whether the use of CPM adds or detracts value, compared with the population-based strategy.

The limitation of traditional CPM evaluation measures, such as discrimination and calibration, is that they do not inform whether an incremental improvement in model performance has a practical impact on a clinically significant measure or more broadly on the value of using the model. Moreover, more recently developed measures of assessment of CPMs used for model-to-model comparisons, such as net reclassification improvement or integrated discrimination improvement index,[30,31] do not incorporate all the relevant dimensions for assessing the impact on value of individualized care, as they ignore the relative consequences of different types of mistakes in treatment assignment and are insensitive to the outcome prevalence. Finally, decision curves,[32,33] a tool that incorporates the relative value of incorrectly assigning treatment, may be difficult to apply and interpret, and they do not offer guidance as to the relevant range for the decision threshold for any specific clinical decision scenario.

In summary, it is important to understand under what circumstances individualized information allows for better decisions and clinically or economically significant impact, using tools that both incorporate the relevant aspects of a decision scenario and provide easily interpretable insights.

1.4. Project aims

This project illustrates incorporation of patient heterogeneity in the risk-based CEA approach using several clinical case-studies and investigates the value of individualized decisions compared with conventional population-based decision making. Our two clinical examples – diabetes prevention options for individuals with pre-diabetes, and selection of DAPT therapy duration after stenting for patients with acute coronary syndrome – substantially influence health for a large number of people and therefore have important implications for resource utilization. These examples also feature populations with a wide range of both disease risk and treatment effectiveness.

While targeting care based on individual information theoretically improves the overall value of care, this project is the first to measure value for specific clinical examples, using state of the art models based on patient level data. Finally, the analysis evaluates a series of scenarios investigating the extent to which performance of the underlying CPM may affect the value that individualized targeting confers over a one-size-fits-all approach. The third case study, which investigates selection of tPA or streptokinase to treat possible myocardial infarction, estimates the relationship between model performance (discrimination and calibration) and the value of targeting, and how this value may also depend on the average outcome prevalence and health benefit valuation.

Chapter 2 : Targeting of the Diabetes Prevention Program leads to substantial benefits when capacity is constrained[1]

[1] Olchanski N, van Klaveren D, Cohen JT, Wong JB, Ruthazer R, Kent D. To be submitted.

2.1. Introduction

An estimated 84 million adults in the US have impaired glucose regulation with an increased risk for developing type 2 diabetes. A number of programs and clinical trials, including the Diabetes Prevention Program (DPP), have investigated diabetes prevention strategies for these individuals. In particular, studies have found that intensive lifestyle intervention, focused on maintaining healthy diet and exercise, or administration of metformin are effective at delaying or preventing diabetes.[34,35] Health-economic studies of these trials have shown these interventions to be cost-effective by reducing the costs, adverse health and adverse quality of life impacts associated with long-term diabetes complications, such as heart disease, stroke, peripheral arterial disease, renal failure, blindness, and neuropathy.[34,35]

Although these interventions have been found to be cost-effective on average, treating all individuals with impaired glucose regulation the same way may not be efficient or feasible. The DPP lifestyle intervention is intensive and requires a major commitment from the patient: a minimum of 6 months of weekly classes and group counseling sessions led by a specially trained lifestyle coach, followed by 6 months of monthly group sessions and continued support in changing lifestyle habits. Despite its proven efficacy, health systems are still working on implementing and ramping up the DPP lifestyle intervention, partnering with community-based organizations, serving tens of thousands of people, but still short of capacity to serve the millions that are eligible.[36-39]

Substantial differences in the extent to which individuals can potentially benefit from DPP also casts doubt on the optimality of its universal application. Previous clinical and economic studies have focused on finding the best cutoff thresholds, such as hemoglobin A1c measures or fasting plasma glucose measures, to determine the population to treat in order optimize cost and benefits of treatment,[40-42] but these results have been difficult to apply in practice, because no single biomarker is able to strongly discriminate between individuals who will develop diabetes from those who will not – even using the 5.5% HbA1c threshold captures only about 70% of diabetes cases over 5 years.[23] Researchers have pointed out that multivariable risk measures provide much more robust ways of predicting the risk of diabetes onset, as well as other patient outcomes.[9,11,22-25] New efforts to pilot the use of multivariate risk prediction tools for decision making in the clinical setting are already under way (Patient-Centered Outcomes Research Institute grant DI-1604-35234). However, only two economic studies of diabetes prevention, one in the US and one in the UK, have previously applied this approach but were limited by using average intervention effectiveness rates across treated populations.[42,43]

When we examine the 3-year risk of developing diabetes, estimated using multivariable prediction models, the risk in the DPP-eligible population ranges from 1% to more than 90%.[44,45] The distribution for this risk is skewed so while its mean is 21%, it is less than 15% for half of the population.[44,45] Because individual risks vary considerably, intervention benefits for individuals also vary. Moreover, many DPP trial participants at low risk have been reported to receive no benefit from metformin and only a modest absolute benefit from lifestyle intervention.[10,44] Thus, treating all individuals with impaired glucose regulation with the same intervention is ineffective in some cases and is hence inefficient. Targeting only those individuals at highest risk might accrue a considerable proportion of the potential population benefits, while substantially reducing costs and treatment burden. Importantly, clinical risk prediction models based on combining demographic and clinical characteristics, such as age and sex, and their lab values (e.g., hemoglobin A1c, fasting glucose, triglyceride, and others) can identify these higher risk individuals.[44,46] To our knowledge, no previous economic study has examined the heterogeneity of treatment effect of DPP by diabetes risk.[22,47,48]

This study aimed to estimate the value of using individualized risk information, based on multivariable modeling and individualized analysis of intervention effectiveness, to target use of either (1) intensive lifestyle intervention to achieve at least 7% weight loss and attain 150 minutes per week of moderate intensity physical activity, or (2) metformin administration, for diabetes prevention versus "usual care" (i.e., no additional intervention).

2.2. Research Design and Methods

2.2.1. Value comparisons

To estimate the value of risk-based targeting, we used the "net monetary benefit" (NMB) metric. We estimated net monetary benefit as the difference between the monetized value of health and the incurred cost of health care. The monetized value of health is the product of the quality adjusted life expectancy and the value of each quality-adjusted life year (QALY). In our base case NMB calculations we monetized the health benefits based on the willingness to pay (WTP) value of $50,000 per QALY gained, per recommendations of the Second Panel on Cost-Effectiveness in Health and Medicine.[49]

Extrapolating the DPP cohort to the approximately 84 million members of the US population satisfying the DPP inclusion criteria, we compared the NMB of either active intervention (lifestyle or metformin) to usual care: (1) treating all population members the same way (either treating all members or treating no members) based on the average NMB of treatment for the entire cohort; and (2) targeting for treatment only those population members whose individual NMB is expected to be positive.

Our second analysis assumed that resource constraints permitted active prevention (either lifestyle or metformin) for only 20% of the US population meeting the DPP criteria (approximately 17 million individuals). We compared administering active prevention to (1) 17 million individuals selected at random from this population and (2) the 17 million individuals projected to gain the most from active prevention.

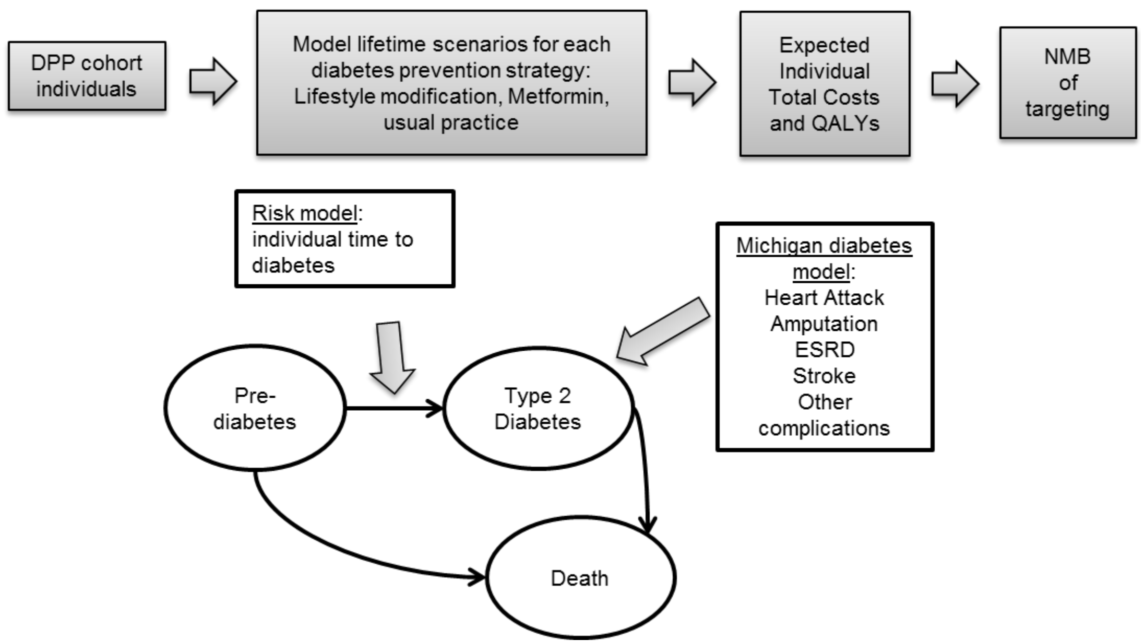
2.2.2. Cost and health benefit estimation

We used a decision-analytic micro-simulation model to project individual care costs and health outcomes for each of the two active prevention strategies and for usual care. In accordance with the recommendations of the Second Panel on Cost-Effectiveness in Health and Medicine,[49] we expressed health outcomes as QALYs, to account for both length and quality of life.

We created a simulated cohort of individuals with impaired glucose regulation and baseline characteristics similar to DPP clinical trial participants (Table 2.1). For each individual, we used a risk model to predict probabilities of diabetes onset at different ages when receiving the lifestyle intervention, metformin, or usual care. In multiple replications, we simulated individuals moving through the model's health states, starting from the initial state of pre-diabetes. Over their lifetime, they might progress to diabetes and develop diabetes-related complications, such as heart disease, stroke, renal impairment, blindness, or neuropathy (Figure 2.1). Individuals accrue associated costs and QALYs based on each specific health state and complication they experience over time. By averaging over the replications, the simulation yields expected total lifetime costs and QALYs for each person under each prevention strategy. We then calculated individual NMB, stratified these values by individual 3-year risk of diabetes, and finally evaluated the population net benefits for the two approaches for selecting the treated individuals: randomly selecting from the population eligible for DPP, or targeting for treatment those DPP-eligible population members with greatest expected net benefit.

The analysis applied a healthcare sector perspective and with costs and health benefits discounted 3% annually per recommendations of the second Panel on Cost-Effectiveness in Health and Medicine.[49] We measured costs in 2014 US Dollars.

Figure 2.1: Overview of Simulation Model



Note: Further methodological details on the simulation models in Chapter 6 Appendix 1

2.2.3. Study population and data sources

We based the study population on the 3-year randomized DPP trial cohort of 3081 individuals who had impaired glucose regulation and were eligible for diabetes prevention programs, but had not progressed to type 2 diabetes (Table 2.1).[50] Starting with the baseline characteristics of the simulated individuals from the DPP patient-level data sets, we projected time-varying measures, e.g., BMI, based on trajectories observed in the trial. We used published estimates for costs and health-related quality of life for the pre-diabetes and diabetes health states and associated complications, mortality rates from the age- and sex-specific US life tables for years 1981-2013[51], and age- and sex-specific medical costs from the Medical Expenditures Panel Survey (MEPS) dataset for 2015 (Table 2.1).[52]

To estimate lifetime costs and QALYs for individuals developing diabetes, we used the publicly available Michigan Diabetes Research Center model[53,54] which assumes standard of care diabetes treatment, with its associated costs, outcomes and adherence rates, and incorporates costs and health-related quality of life impact of adverse outcomes associated with diabetes, including microvascular and macrovascular complications, and mortality (Supplementary Appendix 6.1).

Table 2.1: Study cohort description and simulation model assumptions

DPP trial cohort at baseline (n=3081)	**Mean or number**	**SD or %**
Age, years	50.6	9.0
Female sex	2053	66.6%
Race/ethnicity		
White	1768	57.4%
Black	644	20.9%
Hispanic	508	16.5%
Diagnosis of hypertension	835	27.1%
BMI	33.5	5.8
Hemoglobin A1c, %	5.9	0.5
Triglycerides, mg/dL	162.9	93.5
Fasting plasma glucose, mg/dL	107.2	7.7
History of high blood glucose	614	19.9%
Waist to hip ratio	0.9	0.1
Waist circumference, cm	105.0	14.6

Simulation Model Input Assumptions		
Costs of DPP interventions (Herman et al.[35])	**Initial 4 years**	**Maintenance annual cost**
Lifestyle intervention	$4,000	$140
Metformin	$1,416	$160
Costs of diabetes treatment and complications*	**One-time event**	**Ongoing**
Baseline annual cost with no complications		$2,315
Nonproliferative retinopathy	$103	$103
Macular edema or proliferative retinopathy	$1,101	$103
Blindness	$2,951	$2,951
Microalbuminuria	$437	$437
Proteinuria	$748	$748
End-stage renal disease with hemodialysis	$99,046	$99,046
End-stage renal disease with renal transplant	$138,071	$44,331
Clinical neuropathy	$511	$511
Amputation	$42,929	$1,500
Angina	$8,282	$2,139
Myocardial infarction	$41,744	$2,307
Percutaneous transluminal coronary angioplasty	$8,282	$2,139
Coronary artery bypass graft	$60,685	$2,307
Myocardial infarction with coronary artery bypass graft	$60,685	$2,307
Congestive heart failure	$34,635	$7,620
Ischemic stroke	$55,278	$18,448
Acute metabolic complication: Hypoglycemia requiring hospitalization	$16,991	
Health utilities		
Impaired glucose regulation	0.77	Palmer et

		al.[55]
Diabetes (intercept, adjusted by disutilities for complications and comorbidities, not shown)	0.69	Zhou et al.[54]

* Full details on the Michigan Model for Diabetes structure and input assumptions are available in the model manual (accessed at *http://diabetesresearch.med.umich.edu/peripherals/DiseaseModel/MDRTC%20Diabetes%20Model/UserManual_MichiganModel_for_Diabetes_ver2.pdf*)

Note: all costs shown in 2014 US dollars

2.2.4. Prediction of progression to diabetes

To predict the risk of developing diabetes and time to progression in adults with impaired glucose regulation, given baseline characteristics and a pre-specified prevention strategy, we used a Cox proportional hazards model. Starting with a previously published short-term prediction model[44] derived from individuals enrolled in the DPP trial and their 3-year outcomes, we extended the model (Supplementary Appendix 2) using long-term patient level follow-up data from the Diabetes Prevention Program Outcomes Study (DPPOS), a 7-year open-label follow-up of 2,766 participants from the DPP trial who were offered the effective lifestyle intervention after the DPP randomized trial ended.[56] In this model, treatment effect was estimated at each level of diabetes risk, taking into account the statistically significant interaction between diabetes risk and diabetes onset hazard reduction for metformin (further detail in Supplementary Appendix 2).

Published literature suggests that treatment efficacy for diabetes prevention varies over time with substantial uncertainty.[47,57] The initial 4 years of DPP trial data suggest that the treatment effect was strongest during the first 24 months, with hazard ratios declining over the subsequent 24 months. To estimate efficacy beyond year 4, as recommended by the second Panel on Cost-Effectiveness in Health and Medicine for cost-effectiveness modeling,[49] we developed two alternative scenarios – a conservative, or short-term treatment effect scenario, which assumes that beyond the first 48 months, interventions do not provide any reduction in hazard of diabetes onset; and a second, more optimistic, long-term treatment effect scenario assuming a constant hazard reduction for diabetes onset over time, based on the hazard observed during months 24-48.

2.2.5. Sensitivity analysis

For each treatment effect duration scenario we tested the impact of different values of a QALY, different levels of discounting, duration of intervention costs, and the utility values assigned to the pre-diabetes and diabetes health states (Supplementary Appendix 3).

Additional sensitivity analyses tested alternative assumptions for mortality rates, increasing general population estimates for age- and sex-specific mortality to account for potentially higher mortality risk in the population with pre-diabetes. In general, when individualizing cost effectiveness estimates, life expectancy estimates should be modeled at the same level of disaggregation as short-term risk and benefit estimates, although in practice the detailed information needed to adjust appropriately for these longer term estimates may not be available.[58,59] Thus, in sensitivity analysis, besides examining an identical increased mortality rate due to pre-diabetes across the entire cohort, we also explored a differential adjustment to age- and sex- specific mortality rates by baseline diabetes risk. Assuming that mortality rates would be positively associated with risk of diabetes, we applied mortality rates similar to general population for individuals at lowest diabetes risk and added a penalty equivalent to being 5 years older for individuals with pre-diabetes in the highest diabetes risk quintile with a reduced intermediate penalties for individuals in the intermediate risk quintiles, linearly extrapolated from 5 to 1 year.[58] This adjustment has the net effect of attenuating the contrast between the pre-diabetic state and the diabetic state, particularly for those at the higher risk end of the pre-diabetic spectrum and minimizes the relative benefit of diabetes prevention from the pre-diabetic state.

Finally, medical literature indicates that some individuals experience significant "treatment burden" of metformin—i.e. the impact of taking a daily medication on health-related quality of life and adverse events from metformin as a preventive treatment.[60,61] We examined how this treatment burden could affect the overall net benefits of metformin by applying an annual absolute reduction of health utility value, or disutility, ranging from 0.002-0.05 based on published estimates.[60,61] In the absence of patient-level data linking patient preferences with other characteristics and outcomes, our sensitivity analysis applied the disutility uniformly across the modeled population.

We performed statistical analysis in SAS and R and implemented the decision model in Excel. The Michigan simulation model is implemented in Python using the Michigan Model for Diabetes version 2.1 and IEST 0.85 available from the Michigan Diabetes Research Center (*http://diabetesresearch.med.umich.edu/Core_MCDTR_Methods_DM_MMD.php*).

2.3. Results

2.3.1. Treating the entire eligible population

When compared to usual care, metformin delayed the onset of diabetes by a mean of 1.3 years in the short-term treatment effect scenario and 2.0 years with the long-term effect scenario, while lifestyle delayed it by a mean of 3.1 and 7.3 years, respectively. These averages, however, obscured substantial heterogeneity. Individuals in the lowest risk quintile did not benefit from metformin, while mid- to high-risk individuals benefitted considerably. For individuals in the lowest risk quintile, metformin did not delay diabetes onset versus usual care, but in the highest quintile delayed it by 2.7 years in the short treatment effect scenario. Compared with usual care metformin was not cost-effective in the lowest diabetes risk quintile, but was cost-saving for higher risk patients (Table 2.2). In contrast, the lifestyle intervention delayed diabetes onset by 1.7 years in the lowest risk quintile, and 4.1 years in the highest quintile (Supplementary Appendix figure 6.4). Lifestyle intervention was cost-saving across all risk quintiles.

Table 2.2: Incremental costs, health benefits, and incremental cost-effectiveness ratios (ICERs) by diabetes risk quintile

Diabetes risk quintile	Short treatment effect			Long treatment effect		
	∆cost	**∆QALY**	**ICER**	**∆cost**	**∆QALY**	**ICER**
Metformin vs usual care						
1	$2,754	0.01	$275,400	$3,917	-0.01	dominated
2	$1,141	0.05	$22,820	-$335	0.08	cost-saving
3	-$469	0.09	cost-saving	-$3,127	0.14	cost-saving
4	-$3,042	0.16	cost-saving	-$6,376	0.25	cost-saving
5	-$8,953	0.34	cost-saving	-$9,927	0.45	cost-saving
Lifestyle vs metformin						
1	-$2,758	0.17	cost-saving	-$18,238	0.22	cost-saving (vs usual care)
2	-$4,156	0.19	cost-saving	-$21,024	0.34	cost-saving
3	-$4,624	0.20	cost-saving	-$18,312	0.32	cost-saving
4	-$5,380	0.23	cost-saving	-$16,712	0.37	cost-saving
5	-$4,986	0.25	cost-saving	-$13,118	0.36	cost-saving

NMB provides additional insights for comparing the value of cost-saving strategies. Compared with usual care, average NMB per person over the entire population was positive, suggesting good value, for both interventions: ranging from $7,415-$20,190 for metformin, and $21,258-$45,290 for lifestyle, depending on treatment effect duration. However, risk-stratified NMB largely reflected the heterogeneity of diabetes risk and intervention treatment effect seen across risk quintiles. In both the short-term and long-term treatment effect scenarios, lifestyle intervention had positive increasing value across 3-year diabetes risk quintiles. In contrast, metformin had a negative value in the lowest risk quintile, with progressively increasing positive values in higher risk quintiles (Figure 2.2).

2.3.2. Targeting treatment strategies

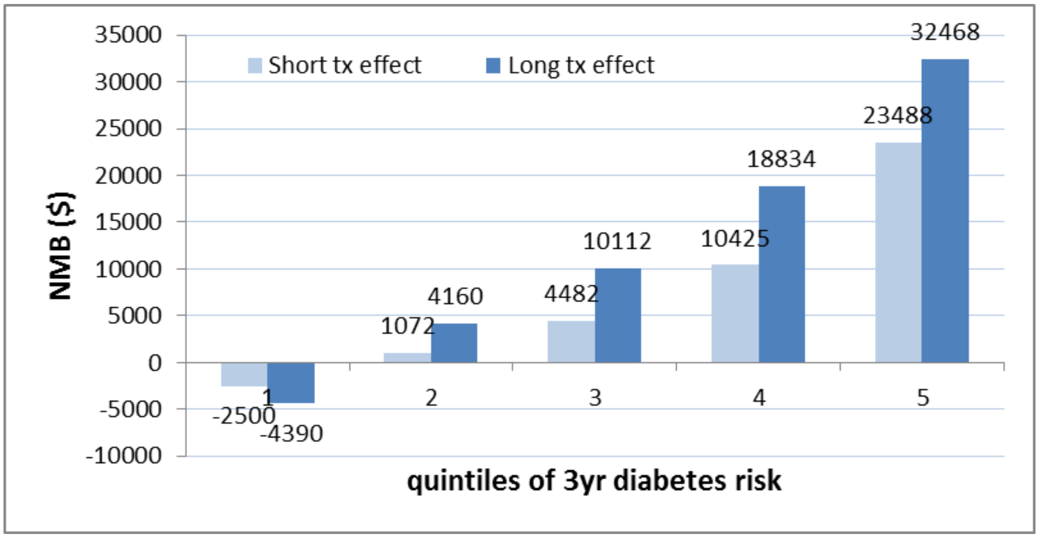
For the DPP lifestyle intervention, there was no difference between strategies of treating everyone and treating only those with a positive expected NMB, since this intervention had a positive expected NMB for all individuals in the cohort. When treated with metformin, 75% of the population had positive expected NMB for the short-term treatment effect assumption. Targeting treatment to only these individuals yielded a NMB gain of $523 per person, or 7% of NMB of treatment without targeting. Assuming a long-term treatment effect, targeting metformin to those 81% with positive expected NMB increased NMB by $880 or 7% per person.

In the case of total DPP program capacity of 17 million people, or 20% of the eligible population, targeting treatment to individuals in the highest diabetes risk quintile, which had the highest predicted NMB, increased average NMB per person substantially. The benefits of targeting lifestyle intervention, or the difference in NMB between allocating prevention in a targeted fashion versus randomly selecting qualifying patients with pre-diabetes, ranged from $14,000 to $18,000 per person on average, depending on assumptions of treatment effect duration. The benefits of targeting treatment with metformin ranged from $16,000 to $20,000 per person (Figure 2.3).

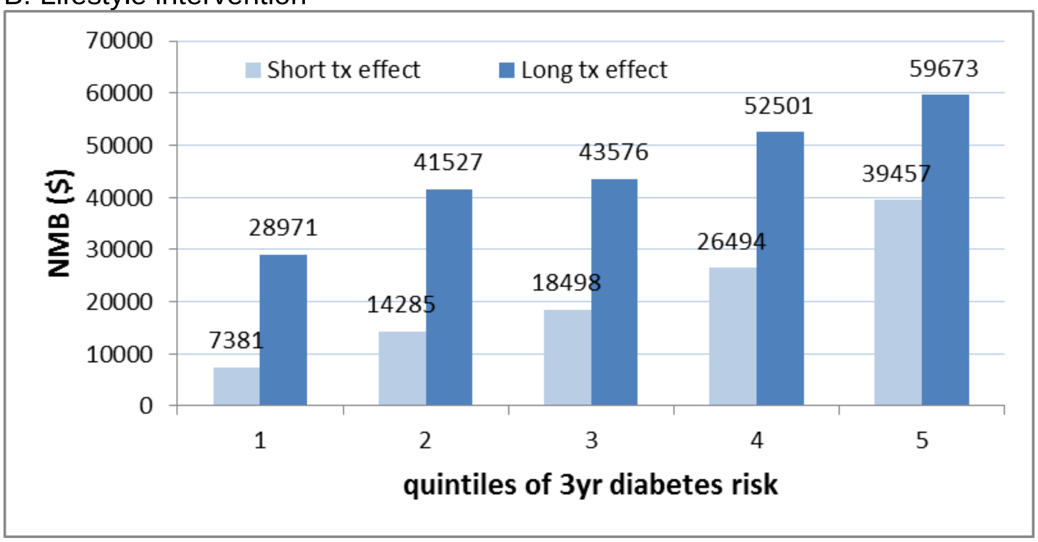
Figure 2.2: Population net monetary benefit (NMB) for each treatment by quintile of 3 year diabetes risk with alternative assumptions of treatment effect duration.

The short treatment effect scenario assumes diabetes onset hazard reduction in the first four years only, and extended treatment effect scenario assumes diabetes onset hazard reduction extends over the entire lifetime.

A: Metformin

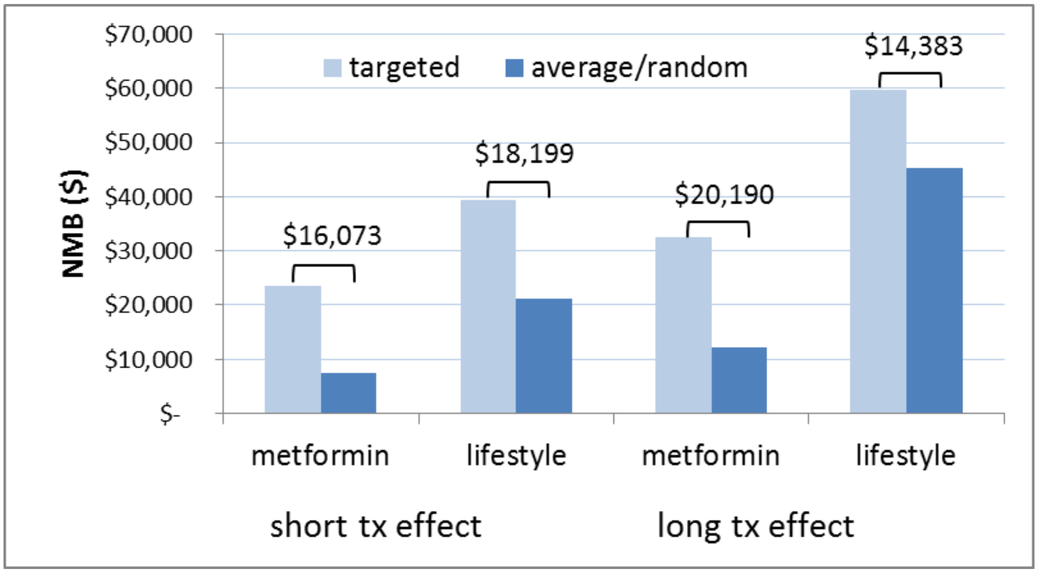


B: Lifestyle intervention



Note: NMB calculated compared to usual care, based on $50,000 WTP threshold

Figure 2.3: Average net monetary benefit (NMB) per person, a comparison of targeting treatment to those with highest expected benefit versus randomly sampling from the entire eligible population for a subset of 17 million (20%) of the eligible population of adults with impaired glucose regulation.



<u>2.3.3. Sensitivity analysis</u>

In sensitivity analyses the patterns of NMB across diabetes risk quintiles remained stable, with metformin having negative values for the lowest diabetes risk quintile, and becoming positive and increasingly positive with greater risk of diabetes (Supplementary Appendix 3). For the lifestyle intervention, all risk quintiles had positive NMB across the tested variable ranges. For most tested scenarios, the value of targeting remained stable in the range of 5-10% NMB gain. When assuming long-term treatment effect, active interventions provided greater NMB, a higher proportion of patients with positive NMB, and greater absolute NMB increase from targeting, compared to scenarios assuming short-term treatment effect.

Treatment burden from daily metformin administration had a strong effect in decreasing NMB of metformin, and the proportion of patients with positive NMB, amplifying the value of targeting treatment (107-145%). Increasing the discount rate tended to reduce all net benefits, with greatest impact on lower risk individuals, when assuming a long-term treatment effect, suggesting that more of the QALY benefits occurred in the future.

2.4. Discussion

Our model found that targeting active diabetes prevention to those patients at highest risk could improve health outcomes and reduce costs compared to providing the same intervention to a similar number of patients with pre-diabetes without targeted selection. While on average both metformin and the DPP lifestyle intervention appeared to be cost-saving (compared to usual care), the value of these interventions varied considerably over the DPP-eligible population.

In a scenario in which a healthcare system can treat the entire eligible population of adults with impaired glucose regulation, our results suggest it is worthwhile to offer the lifestyle intervention to all. However, if programs can afford to treat only a fraction of eligible individuals, societal value could be increased by prioritizing lifestyle intervention based on diabetes risk, because greatest value is achieved in individuals in higher diabetes risk quintiles.

In contrast to the lifestyle intervention, preventive use of metformin may not be worth the cost for individuals in the lowest diabetes risk quintile, because these individuals did not appear to benefit from the therapy, particularly when treatment burden and costs were factored in. For patients unable or unwilling to participate in the lifestyle intervention, our analysis suggests that prioritization of metformin prevention to higher risk individuals – i.e., those in whom the net benefit is positive – would confer higher value to society.

The National DPP, an ambitious program to provide a complex intervention to a large population, has faced many challenges while scaling up from research program to the real world settings. Further, improvements in delivery efficiency should have an important impact. The types of lifestyle programs shown to be effective are resource-intensive, involving multiple one-on-one sessions with case managers to educate patients about diet, exercise, and behavior modification, as well as ongoing monthly individual and group sessions to support a healthy lifestyle. Even with current nationwide efforts to expand participation in the National DPP program, many eligible individuals are not participating. As the program has ramped up, patients have encountered many barriers, such as long waiting times, poor accessibility, and a lack of programs in their native languages.[36-39,62] Further, even with substantial progress to build capacity, involve more organizations and healthcare providers, and create programs in multiple languages and with virtual modalities, substantial additional investment is needed to maintain participant engagement and retention. Prioritizing efforts and resources towards engaging highest risk participants should confer higher program value.

Conclusions of this study should reasonably generalize to the US population eligible for DPP programs. The eligibility criteria for the National DPP program are slightly less restrictive, than the enrollment criteria for the DPP trial. The criteria for fasting plasma glucose 100-125 mg/dL and 2 hour plasma glucose 140-199 mg/dL remain the same, but the National DPP program criteria now include individuals with hemoglobin A1c levels of 5.7%–6.4%, as well as all individuals with prior gestational diabetes. The program also allows participation starting at age 18, rather than 25 in the trial, and for persons who are slightly more overweight (body mass index 25, rather than 24, or higher). Based on these less restrictive criteria, we expect the National DPP eligible population contains more individuals at low risk of diabetes than the DPP trial population that underlies our analysis. If so, prioritization should confer even greater value than our current model estimates.

One of the strengths of the modeling approach is the ability to project outcome scenarios beyond the observed data in clinical trials and observational studies. In this study we estimated outcomes for hypothetical treatment scenarios with different diabetes prevention alternatives and projected the outcomes over lifetime horizons. Rather than using average clinical trial results as are often reported in the literature, we had access to detailed patient-level data, and were able to not only model risk using patient-level data, but also project costs and outcomes for each individual in the clinical trial, using microsimulation based on their specific detailed baseline characteristics. Importantly, our analyses stratified patients along a multivariable measure of risk, rather than a single parameter subgroup, such as gender, or a single risk factor for diabetes onset, such as hemoglobin A1c level. For example, based on our analysis of the DPP trial participants, of the individuals with the high nondiabetic HbA1c of 5.7%-6.4% 13% are in the lowest quintile of risk to develop diabetes in 3 years, and conversely, of those with HbA1c levels below 5.5% - 3% are in the highest diabetes risk quintile. Because multivariable risk measures correlate better than univariate ones with patient outcomes, researchers have advocated for this approach; however, to date it is still underutilized.[9,11,22-25] Our models for the risk of diabetes onset over time accounted for the diminishing impact of baseline covariates, and we estimated several scenarios for the effects of DPP, both a short-term treatment effect, as well as one continuing over time. This is consistent with the uncertainty in the durability of DPP efficacy found in a recent meta-analysis, which also showed that the effects of medication therapy were less durable than lifestyle interventions.[57]

Prior analyses of DPP data have been generally consistent with our findings for the population on average, although none have presented effectiveness or cost-effectiveness by diabetes risk. One analysis estimated the median delay in diabetes onset to be 11 years with lifestyle intervention and 3.4 years with metformin.[35] These estimates appear more positive than our extended treatment effect scenario, and are based on an assumption of a greater treatment effect and hazard ratios for 0-48 months, which include the highest treatment effect when patients first start their treatment during months 0-24. Additionally, unlike prior analyses, our study incorporates the patient-level heterogeneity of treatment effect, using diabetes risk-based hazard ratios, rather than population-wide average hazard ratios. Because of the significant interaction between diabetes risk and intervention effectiveness, incorporating it into analysis substantially affects the results.

A limitation of our analysis is that we estimated the effects of lifestyle intervention on health outcomes and costs that are directly related to prevention or delay of diabetes onset, based on the assumption that delaying development of diabetes postpones the eventual onset of diabetic complications. Since better diet and exercise habits may have other far reaching effects on overall health and complication risks, our analysis likely underestimated the value of successful lifestyle interventions.

Consistent with other analyses of heterogeneity of treatment effect,[13,59] we found that NMB or cost-effectiveness varies by diabetes risk strata, based on the heterogeneity in diabetes risk and the patterns of treatment effect for DPP interventions across the population of adults with impaired glucose regulation. Individual level information may be helpful in prioritizing or targeting treatment to those who benefit most and avoid the costs of treatment in individuals who derive little to no benefit. Our analyses showed that while lifestyle intervention provides health benefits at reasonable societal cost to all adults in the cohort, the greatest expected gains occur in higher risk individuals, and—where capacity is limited—these individuals should be targeted. Additionally, according to our analyses metformin administration should be targeted to high risk individuals, since patients in the lowest risk quartile do not appear to benefit.

2.5. Contribution statement

All authors contributed to the research design, interpretation of the results, and critically revising the manuscript. N.O. drafted the manuscript, N.O. and D.vK. contributed to the data analysis. All authors have approved the submission of this manuscript. N.O. is the guarantor of this research.

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Chapter 3 : Dual anti-platelet therapy after coronary stenting in patients with acute coronary syndrome (ACS): costs and benefits of selecting therapy duration by individual bleeding risk [2]

[2] Olchanski N, van Klaveren D, Cohen JT, Kent D. To be submitted to *JACC*.

3.1. Introduction

With 1.7% of the Medicare population receiving a new acute coronary syndrome (ACS) diagnosis annually,[63,64] more than 800,000 ACS patients undergo coronary stenting and subsequent medical treatment. While dual antiplatelet therapy (DAPT) reduces the risk of ischemic events and stent thrombosis after stent implantation in these patients, it increases the risk of bleeding. The baseline risk of bleeding and the risk of ischemic events vary considerably in this patient population, and both US and European clinical guidelines recommend taking into consideration individual patient characteristics when deciding the duration of DAPT therapy.[65,66]

While guidelines recommend DAPT consisting of ticagrelor and aspirin for ACS patients after coronary stent implantation, the optimal duration of therapy is uncertain.[65-68] Clinical guidelines recommend 12 months of DAPT, but state that it is reasonable to limit therapy to 6 months for high risk individuals, or extend it beyond 12 months for low risk individuals.[65,66] The guidelines do not offer clear direction as to how clinicians should quantify and use bleeding risk to select appropriate treatments, nor is there consensus on how to best quantify bleeding risk.[69] The US guidelines discuss the use of clinical predictive modeling to estimate a patient's risk of adverse events.[66] One potential tool is the precise-DAPT score, a validated score predicting bleeding risk.[70]

DAPT cost-effectiveness depends on balancing the risks and costs of ischemic events, bleeding events, and therapy. Accounting for bleeding risk when selecting the best therapy for a patient is important, because it influences the effectiveness of prolonged DAPT.[70] In particular, individuals with a lower risk of bleeding have a much more favorable tradeoff between the risks of bleeding and ischemic events with longer DAPT therapy, compared to individuals with higher bleeding risk. While bleeding event rates increased with duration of DAPT therapy across all bleeding risk levels, longer DAPT therapy was associated with reducing ischemic event rates only in low to moderate risk individuals, and not in high risk individuals.70

The cost of ticagrelor is substantial in the US, and the literature suggests that the cost-effectiveness of prolonged DAPT with ticagrelor compared to aspirin alone is $96,000 per quality adjusted life year (QALY) gained across the population.[71] This average cost effectiveness falls in a range that is considered to be roughly at the benchmark representing reasonable value. Because the average ratio is close to the benchmark, understanding how it varies across the patient population might be especially informative, since the cost effectiveness may compare very favorably to other accepted therapies for some patients but very unfavorably for others.[72] To date, no published health-economic studies have compared different therapy durations across patients with different bleeding risks, and no cost-effectiveness analysis has evaluated strategies that tailor DAPT duration based on individual bleeding risk.

This study aims to quantify the economic impact of using the precise-DAPT bleeding risk score to tailor the duration of DAPT therapy, compared to treating all ACS patients with 12 months of DAPT with ticagrelor, per the standard recommendations.

3.2. Methods

We constructed a decision model to evaluate the lifetime costs and health outcomes for three different DAPT therapy durations – 6 months, 12 months or 24 months – in patients by bleeding risk quartile. In order to assess the value of different durations of DAPT, we estimated net monetary benefit (NMB) as the difference between the monetized value of health and the incurred cost of health care. The monetized value of health is the product of the quality adjusted life expectancy and the value of each quality-adjusted life year (QALY). We then evaluated the strategy of selecting the DAPT therapy duration with the highest NMB, based on the patient's bleeding risk, compared to the strategy of treating all ACS patients with 12 months of DAPT therapy, as recommended by clinical guidelines.

Figure 3.1: Decision Model structure

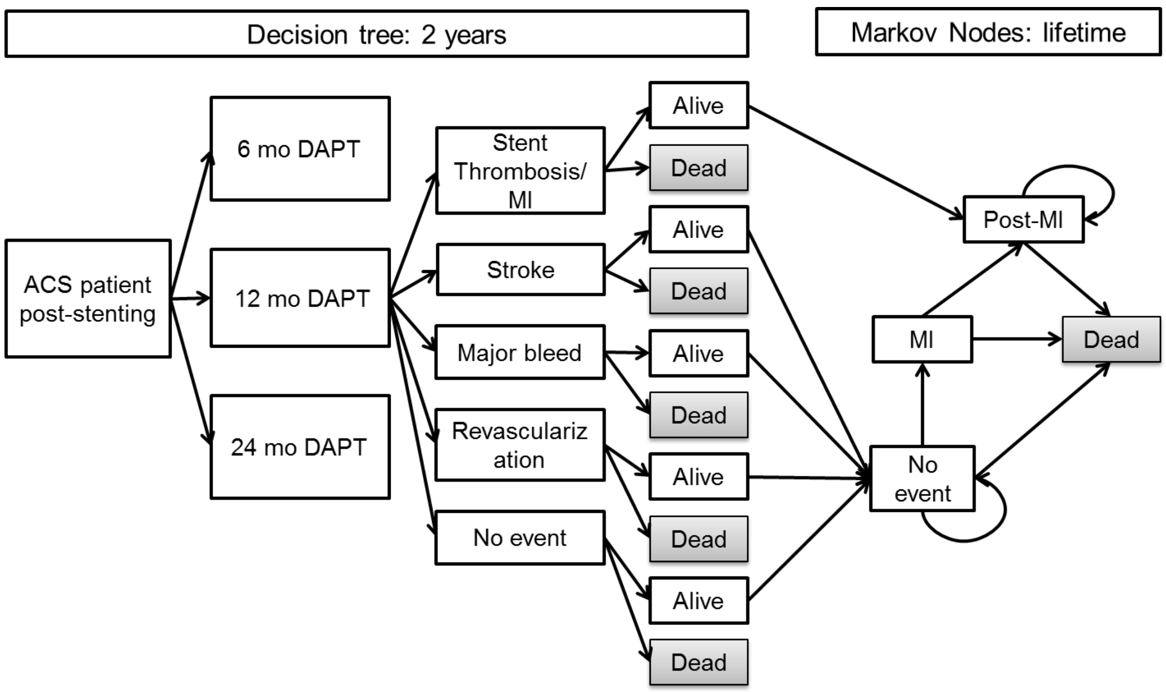


Figure 3.1 illustrates the simulation model used to project outcomes for each DAPT duration. Patients start at the left of the figure at the point just after experiencing ACS and undergoing stenting. They then proceed to the right, undergoing 6, 12, or 24 months of DAPT. During treatment patients may experience stent thrombosis, MI, stroke, a major bleed, revascularization, or no event. The model first estimates patient outcomes at 2 years after initial stenting, for each of the bleeding risk quartiles.

At the end of the initial two years following the ACS and stenting, the patients are either alive or dead. No patients remain on DAPT after two years, and we used a time-varying

Markov model to project their progression through a series of health states, including no event, MI, and post-MI, until death (Figure 3.1). The Markov model incorporated age and sex-specific myocardial infarction (MI), stroke, and all-cause mortality rates. The transition probabilities for events beyond the first 2 years were assumed to be the same across the range of bleeding risk.

3.2.1. Health outcome modeling assumptions

Tables 3.1 and 3.2 summarize our model assumptions, which reflect estimates for contemporary PCI and stenting practices in the ACS patient population, and DAPT therapy using ticagrelor and aspirin as recommended by current ESC and ACC clinical guidelines.[65,66] Following discontinuation of DAPT, patients stopped ticagrelor, but continued on aspirin indefinitely.

Table 3.1 shows the assumptions for bleeding risk-stratified patient demographics and clinical event rates during the first 2 years after the initial stenting procedure. We estimated event rates using a pooled data set from a published meta-analysis combining 5 randomized clinical trials and stratified them according to the precise-DAPT bleeding score quartiles.[70] For our model we made one adjustment of the published data: in the original publication the highest bleeding risk quartile patients had a higher rate of ischemic events in the longer DAPT arm than in the shorter DAPT arm – a counterintuitive result that implied that extended DAPT is less effective in this patient group. Because this difference was not statistically significant, in our model we assumed that there was no difference in DAPT effectiveness. We also tested a scenario per event rate differences as published in a sensitivity analysis.

Table 3.1: Bleeding risk-specific decision model input parameters

	Bleeding risk quartiles				
	Very low	**Low**	**Moderate**	**High**	**Mean**
Cohort characteristics					
Age (average)*	60	65	70	75	65
Sex (% male)*	50%	50%	50%	50%	50%
2 year event rates					
MI or stent thrombosis					
6 mo DAPT	0.8%	0.9%	0.9%	4.3%	1.7%
12 mo DAPT	0.4%	0.5%	0.5%	4.3%	1.4%
24 mo DAPT	0.2%	0.4%	0.4%	3.7%	1.2%
Revascularization**					
6 mo DAPT	4.9%	6.0%	6.7%	6.7%	6.1%
12 mo DAPT	2.7%	2.8%	2.8%	2.8%	2.8%
24 mo DAPT	1.1%	2.1%	2.1%	2.1%	1.9%
Stroke					
6 mo DAPT	0.2%	0.7%	1.9%	2.1%	1.2%
12 mo DAPT	0.1%	0.4%	1.1%	2.1%	0.9%
24 mo DAPT	0.1%	0.4%	1.1%	2.1%	0.9%
TIMI major or minor bleeding					
6 mo DAPT	0.9%	1.2%	1.6%	4.5%	2.0%
12 mo DAPT	1.2%	1.5%	2.0%	5.9%	2.6%
24 mo DAPT	1.6%	2.0%	2.6%	7.7%	3.5%
TIMI major bleeding					
6 mo DAPT	0.3%	0.3%	0.4%	1.5%	0.6%
12 mo DAPT	0.4%	0.4%	0.6%	2.3%	0.9%
24 mo DAPT	0.7%	0.7%	1.0%	3.8%	1.6%

Source: pooled multi-trial data set from Costa et al 2017[70], adjusted using ticagrelor to clopidogrel event specific odds ratios.
*Assumed for model, based on age differences by bleeding risk in Zocca et al.[69]
** Revascularization rates are based on target vessel revascularization (TVR) endpoints in the pooled dataset from Costa et al.[70]
DAPT = dual antiplatelet therapy; MI = myocardial infarction; TIMI = The Thrombolysis in Myocardial Infarction (TIMI) bleeding criteria[73]

Since the data set included trials that studied different durations of clopidogrel regimens, and a similar risk-stratified analysis was not available for patients who received ticagrelor, we adjusted clopidogrel-specific event rates to approximate the rates for ticagrelor treatment. For this adjustment we applied risk ratios of ticagrelor vs clopidogrel for each type of event drawn from published meta-analyses (Table 3.3).[74-79]

To characterize background mortality, we used US life tables for estimates of age and sex specific mortality rates,[51] adjusted for increased risk of mortality post-MI.[71] Further, we estimated a probability of death after each type of clinical event during the first 2 years based on published estimates of case fatality rates (Table 3.2). We found a range of estimates of case fatality rates of bleeding events, depending on the specific definition of bleeding. Our outcome rates were according to the Thrombolysis in Myocardial Infarction (TIMI) bleeding criteria,[73] and we made a conservative assumption of 11% for case fatality rates of major bleeding, based on the reported range from 11% to 14% (Table 3.2).

In accordance with the recommendations of the Second Panel on Cost-Effectiveness in Health and Medicine,[49] we expressed health outcomes as QALYs, to account for both length and quality of life. We used published health state utility values to make the QALY estimates (Table 3.2).

Table 3.2: Overall decision model input parameters

	Parameter estimate	**Source**
Markov Node inputs		
Annual transition probabilities		
No event to MI	0.013	67,80,81
No event to death	Age and sex specific mortality rates from life tables	51
MI to death	Male: 0.321 for age<75, 0.4 for ages 75-84, 0.67 for ages 85 and over Female: 0.28 for age<75, 0.5 for ages 75-84, 0.54 for ages 85 and over	82-85
Post-MI to death	Age and sex specific mortality rates from life tables, modified for increased mortality risk post MI	51,71
Decision tree probabilities		
Probability of death given MI	0.3	82-86
Probability of death given stroke	0.22	87
Probability of death given major TIMI bleed	0.11	86,88-91
Probability of death given major or minor TIMI bleed	0.026	90,92
Costs		
No event	$10,545 (average annual health care costs for persons aged over 65)	52
Revascularization	$33,342	93,94
MI	$53,626	93,94
Stroke	$68,200	93,94
Major bleeding	$33,342	93,94
Bleeding	$30,765	93,94
60mg Ticagrelor	$5.88	95
Health state utilities		

No event	0.794	[93,94]
MI	0.778	[93,94]
Post-MI	0.794	[93,94]
Stroke	0.768	[93,94]
Bleeding	0.778	[93,94]

Note: costs expressed in 2018 US dollars
MI = myocardial infarction; TIMI = The Thrombolysis in Myocardial Infarction (TIMI) bleeding criteria[73]

3.2.2. Cost modeling assumptions

We used published estimates for cost inputs for each of the clinical events in the model, based on Medicare inpatient hospitalization payment rates.[93] Additionally, for background medical costs we applied annual age and sex-specific medical care expenditures from the Medical Expenditures Panel Survey (MEPS) dataset for 2015.[52] We based the DAPT costs on the FDA approved regimen of 60mg of ticagrelor twice daily and the average wholesale acquisition cost (WAC) of $5.88 in 2018[95] (Table 3.2). Using the medical care services component of the US Consumer Price Index (CPI), we adjusted all costs to 2018 US Dollars.

In sensitivity analyses we also examined alternate scenarios, which included major and minor bleeds, rather than only major bleeding events, the effects of varying input parameter values, such as event costs, baseline age, clinical event rates (in terms of risk reduction between different DAPT durations), severity of bleeds in terms of case fatality rates, and discount rates. We also examined the impact of the price of ticagrelor coming down to levels similar to the price of generic clopidogrel.

Table 3.3: Conversion from clopidogrel to ticagrelor outcomes

Event	Odds Ratios for events at 12 months Ticagrelor vs clopidogrel	Source
MI/Stent Thrombosis	0.85	Shah network meta-analysis[74]
Bleed (major or minor TIMI)	1.05	Shah network meta-analysis[74]
Major TIMI bleed	1.03	PLATO trial[67]
Stroke	1	Multiple meta-analyses (Zhang, Bavishi, Tan)[75,76,78]
Death (all cause)	0.88	Shah network meta-analysis[74]
TVR (hbr)	*0.82*	*Change-DAPT observational study (HR)[69]*
TVR (non hbr)	*1.57*	*Change-DAPT observational study (HR)[69]*

Note: We did not adjust target vessel revascularization (TVR) rates for ticagrelor for our base case analysis, as the only source for comparison between ticagrelor and clopidogrel was the Change-DAPT study, which did not provide robust enough estimates that could be applied in our analysis.
Hbr = high bleed risk, the definition in the Change-DAPT study was very different from our definition, based on the clinical risk prediction tools. Patients were considered hbr if fulfilled one of 3 criteria: (1) age ≥75, (2) hemoglobin <11g/dl, (3) platelet count b 100.000/mm3; 4) hospital admission for gastro-intestinal bleeding in the previous 12 months; 5) stroke during the previous 12months; 6) any previous intracranial hemorrhage; 7) creatinine clearance b40 ml/min/1.73m2 (calculated from serum creatinine, using the Modification of Diet in Renal Disease [MDRD] equation); 8) cancer (except skin) diagnosed in the previous 3 years; and 9) non-steroidal anti-inflammatory drug use at discharge. As 10) the use of oral anticoagulation at baseline and 11) planned major surgery in the next 6 months after the index PCI had been exclusion criteria of the CHANGE DAPT study [10], none of the CHANGE DAPT patients fulfilled HBR criteria 10 or 11.

The analysis applied a healthcare sector perspective with a base case willingness to pay (WTP) of $100,000 per QALY gained and with costs and health benefits discounted at 3% annually per recommendations of the second Panel on Cost-Effectiveness in Health and Medicine.[49] We used R version 3.5.1 for statistical analysis and decision model implementation.

3.3. Results

Table 3.4 shows the lifetime outcomes and costs of patients undergoing DAPT for each of the pre-specified durations, stratified by bleeding risk. For patients in very low to moderate bleeding risk quartiles, the overall balance of risks and benefits appeared to favor DAPT with the 12 month duration. The health benefits were slightly better with 12 months of DAPT, and costs were similar but slightly lower with 12 months of DAPT. For these patient groups, where both incremental costs and incremental QALYs were negative, to be considered cost-effective, incremental cost-effectiveness ratios (ICERs) have to fall *above* the cost-effectiveness threshold, which is typically $100,000-150,000/QALY.[96,97] In this case 6 months of DAPT would be considered not cost-effective compared to 12 months in very low to moderate bleeding risk patients.

Unlike the other risk groups, the highest bleeding risk quartile patients derived the greatest benefit from decreasing therapy duration from 12 months to 6 months. There was no difference in overall health benefits, and decreases in costs resulted in an overall increase in value, and a cost-saving ICER.

Extending DAPT duration to 24 months resulted in slight increases in both QALYs and costs across all bleeding risk quartiles. However, the ICERs ranged from $370,800/QALY to dominated, and the NMB values were negative in all quartiles.

NMB were not monotonic as bleeding risk increased, suggestive of some noise in the data, and in sensitivity analyses some of the time the very low bleeding risk quartile also

Table 3.4: Lifetime costs, quality adjusted life years (QALYs), incremental cost-effectiveness ratios (ICERs), and net monetary benefits (NMB) of ACS patients undergoing different durations of DAPT compared with guideline-recommended 12 months, stratified by bleeding risk

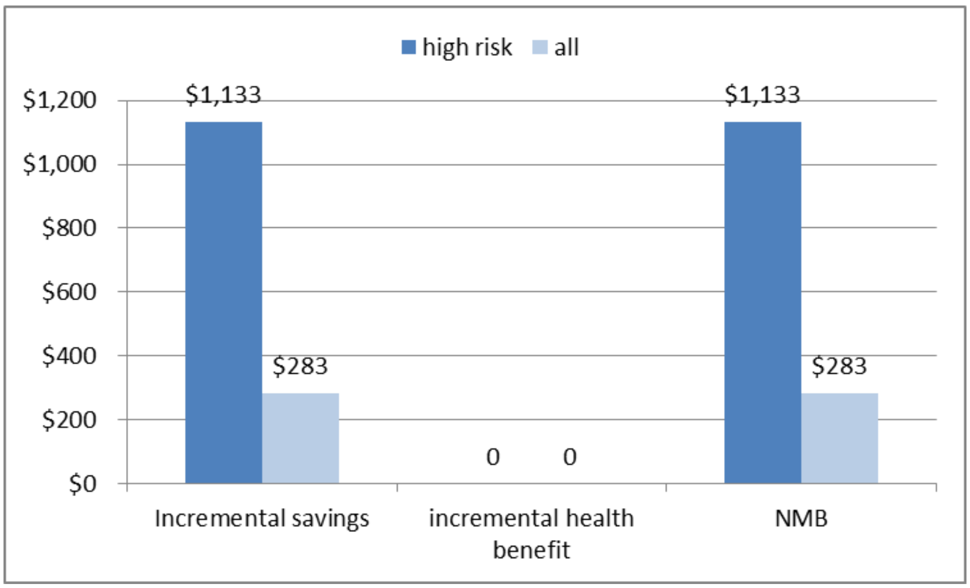
	Bleeding Risk Quartiles				
	Very low	**Low**	**Moderate**	**High**	**Average**
12 months of DAPT therapy					
Costs	$136,258	$117,032	$97,911	$82,047	$108,312
QALYs	10.21	8.86	7.49	6.13	8.17
6 months of DAPT therapy					
Costs	$134,885	$116,110	$97,473	$80,914	$107,346
Δcosts	-$1,373	-$922	-$438	-$1,133	-$967
QALYs	10.2	8.84	7.46	6.13	8.16
ΔQALYs	-0.01	-0.02	-0.03	0	-0.015
ICERs	$137,300	$46,100	$14,600	Cost-saving	$64,433
NMB	$373	-$1,078	-$2,562	$1,133	-$534
24 months of DAPT therapy					
Costs	$139,966	$120,913	$101,954	$86,278	$112,278
Δcosts	$3,708	$3,881	$4,043	$4,231	$3,966
QALYs	10.22	8.87	7.49	6.14	8.18
ΔQALYs	0.01	0.01	0	0.01	0.0075
ICERs	$370,800	$388,100	dominated	$423,100	$528,767
NMB	-$2,708	-$2,881	-$4,043	-$3,231	-$3,216

Note: costs expressed in 2018 US dollars, QALY valued at $100,000/QALY
Incremental costs, QALYs, ICERs, and NMB are comparative to 12 month duration for each patient bleeding risk group.

had a negative NMB, depending on the age at presentation with ACS and the value of a QALY.

Next we compared a targeted approach to treating everyone with 12 months of DAPT. Our findings suggested that the targeted approach would treat patients at very low to moderate bleeding risk with 12 months of DAPT and high risk patients with 6 months of DAPT. We found that the strategy of using bleeding risk information for guiding the optimal DAPT duration resulted in a positive NMB of $1,133 per person in the high bleeding risk group, or $286 per person across the population (Figure 3.2), resulting in an annual savings of $226.6 million across the country, based on the incidence of ACS in the Medicare population alone.

Figure 3.2: Incremental cost savings, health benefits, and net monetary benefit (NMB) of DAPT duration selection based on optimizing bleeding risk quartile specific value – 12 months of DAPT for patients at very low to moderate bleeding risk and 6 months for patients at high bleeding risk, compared with 12 months of DAPT for all patients



Note: costs expressed in 2018 US dollars, QALY valued at $100,000/QALY

Sensitivity analyses (Table 3.5) showed that the model results were most sensitive to the assumptions about the event rates while on ticagrelor – for both ischemic and bleeding events. Additionally, what types of bleeds were considered in the analysis, and their impact on mortality outcomes, also had a minor impact on the value derived from targeting based on bleeding risk. The effectiveness of DAPT in reducing the ischemic event rates, bleeding event rates, and relative differences between DAPT at different durations were the key driver of both health and economic outcomes, and consequently value, or NMB. For these variables, most of the uncertainty lies in comparing event rates, or relative effectiveness, with different durations of DAPT.

Table 3.5: Sensitivity Analysis Results

Scenario	**Value of targeting**	**% difference vs. base case**
Base case	$283	
Cost of ticagrelor assumed the same as generic clopidogrel ($12 per month[94])	None	-100%
Ticagrelor assumed less effective at reducing ischemic events in high bleeding risk patients (per trend shown in Costa et al.[70])	$1,392	391%
Costs of events increased 10%	$257	-9%
Costs of events decreased 10%	$309	9%
Varying the starting age of each bleeding risk quartile subgroup (60, 65, 70, 75)	$283	0%
Including both minor and major bleeds in analysis	$344	21%
Low case fatality rate from major bleed (0.026)	$295	4%
High case fatality rate from major bleed (0.15)	$312	10%
Discounting (1%, 5%, 10%)	$283	0%

Increasing the costs of events in the model resulted in an overall decrease in the value of targeting DAPT duration by bleeding risk quartile. And conversely decreasing those input assumptions resulted in a commensurate increase in value.

When we modeled what would happen if the price of ticagrelor were to decrease to the same level as generic clopidogrel, we obtained a similar result to prior cost-effectiveness analyses of extended clopidogrel.[94] In this scenario, the most cost-effective option was extending DAPT treatment to 24 months in all bleeding risk quartiles. The ICERs ranged from cost-saving in the lowest risk quartiles to $1,700/QALY in moderate risk and $26,700/QALY in the high risk quartiles, with a cost-saving ICER on average for the entire population. NMB were positive in all quartiles and ranged from $337 to $1,151.

3.4. Discussion

In this study we found that for the highest bleeding risk patients with ACS reducing DAPT durations from 12 to 6 months may be the most cost-effective strategy – reducing costs and improving health outcomes, while for the low to moderate bleeding risk patients 12 months of DAPT provides better outcomes that are worth the additional cost of longer therapy. Using a validated bleeding risk prediction tool with reasonable prediction accuracy has the potential to improve the efficiency and cost-effectiveness of treatment, by allowing clinicians to select the most appropriate DAPT duration based on the patient's individual risk. In our study we estimated a potential lifetime cost-saving of nearly a quarter of a billion dollars for the risk-based selection strategy compared with 12 months of DAPT with ticagrelor for all annual incident ACS patients, using stratification by the precise-DAPT bleeding risk score.[70]

Extending DAPT beyond 12 months appears to confer a small health benefit, due to the reduction of ischemic events; however, given the cost of therapy with ticagrelor, it was not cost-effective in any of the bleeding risk groups. If ticagrelor's price drops down to the same level as generic clopidogrel, which is a possibility when ticagrelor comes off patent in 2021, then the most cost-effective strategy would be to prolong DAPT therapy. Even in the high bleeding risk patient quartile the added costs of bleeding events are not large enough to bring the ICER close to the cost-effectiveness threshold. In this study we reported the longest duration of 24 months of DAPT. Due to the lack of data for risk stratified outcomes with 30 months of DAPT, we chose not to model this duration explicitly, but we can extrapolate that the findings would be similar to our results with 24 months of DAPT.

So far the optimal duration of DAPT is uncertain – and in practice patients may remain on therapy more according to regional practice variations and patient preferences, rather than specific evidence around expected outcomes. There are many complicating factors that make the decision difficult, such as differences in individual patient risk of bleeding events, ischemic events, the choice of different DAPT drugs, the initial decision-making at the time of presentation with ACS, the complexity of the original stenting procedure and the type and size of stent used, lack of consensus on the definition and severity of bleeding,[98] and the interaction of all these factors.[99,100] Further, there is no clear standard for how to best select treatment duration to account for individual risk. The US guidelines discuss the DAPT score – a combination of two clinical risk prediction models, one predicting bleeding events, and the other predicting ischemic events.[66,101] However, the DAPT score was developed on a mixed cohort of patients, including both ACS and stable coronary artery disease patients, who have different risk profiles and outcome rates, and to date no validation of the DAPT score on ACS patients has been reported.

We used precise-DAPT for our stratification because this tool provided the only report of ACS patient outcomes with different durations of DAPT by bleeding risk.[70] Future research should examine the value of other bleeding risk scores for guiding DAPT duration selection, but it will require reanalysis of patient-level data to evaluate ACS patient outcomes stratified according to bleeding risk.

Decision modeling rigorously compares strategies over a long period of time. These comparisons are difficult to address using empirical studies alone because with many rapidly evolving therapies in this space, the findings are often no longer relevant by the time long term follow up data collection is complete. The modeling approach enables us to combine the best available information from multiple studies, and simulation modeling allows makes it possible for us to see if our findings change when we revise our assumptions. In this way, simulation modeling allows us to explore how robust the results are in the face of uncertainty.

A potential limitation is that our DAPT effectiveness estimates may be biased because of different levels of adherence in different trial treatment groups. There is some evidence that patients with increased bleeding risk have lower adherence to DAPT at 12 months – as shown in a systematic review of observational studies.[102] To the extent that adherence to DAPT in clinical trials also reflects the same pattern, our model inputs for event rates and DAPT effectiveness measures reflect the differential adherence. The value of reducing DAPT duration in patients with increased bleeding risk may be slightly attenuated if these patients are in reality even less likely to adhere to therapy beyond 6 months.

Additional future directions to develop our model would be to reanalyze pooled clinical data at the individual level to obtain less noisy estimates of the effectiveness of different durations of DAPT. One way to do this is to include in the model the interaction between treatment effectiveness (risk reduction of ischemic and bleeding events) and individual bleeding risk, and to model event rates and risk reductions as a function of individual bleeding risk. Individual level statistical modeling should allow us to reduce the noise in the data that is apparent in our quartile level analysis. However, even quartile level analysis of NMB indicates a robust value improvement from reducing DAPT from 12 to 6 months in the highest bleeding risk individuals.

3.5. Conclusions

In conclusion, a risk-based approach to selecting the most appropriate DAPT treatment for each patient should improve the efficiency and value of therapy. Furthermore, this approach is in line with the clinical guidelines that recommend taking into account individual patient characteristics when assigning medical treatment and its duration after stenting. Future clinical trials should make efforts to examine and report the effectiveness of therapy stratified by risk in order to enable clinicians and analysts to take into account its impact on patient outcomes and value of treatment. Additional work is necessary to validate bleeding risk prediction scores and improve their applicability and usability in practical clinical decision making for ACS patients.

3.6. Acknowledgments

All authors contributed to the research design, interpretation of the results, and revising the manuscript. N.O. drafted the manuscript, N.O. and D.vK. contributed to the data analysis. Financial support for this study was provided by a grant from the National Center For Advancing Translational Sciences of the National Institutes of Health under Award Number TL1TR001062. N. Olchanski was also supported by a Pre-Doctoral Fellowship in Health Outcomes from PhRMA Foundation.

Chapter 4 : Understanding the value of individualized information: the impact of poor calibration or discrimination in outcome prediction models[3]

[3] Olchanski N, Cohen JT, Neumann PJ, Wong JB, Kent D. Understanding the Value of Individualized Information: The Impact of Poor Calibration or Discrimination in Outcome Prediction Models. *Medical Decision Making*. 2017; 37(7):790-801. PubMed PMID: 28399375.

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4.1. Introduction

It has become more widely appreciated that patients enrolled in clinical trials may vary greatly in their risk of the outcome of interest and that, because of this, the average trial results (especially when expressed as an absolute risk reduction) typically do not apply to all enrolled patients[9,15-18]. Thus, the optimal clinical approach can vary across patients, particularly when a therapy is associated with some treatment-related harm or substantial cost. Hence, recommendations tailored to the individual, based in particular on individual patient risks, hold potential for improving care compared to “one-size-fits-all” recommendations (e.g., “treat all” or “treat none”). It is unclear how much of an improvement in specific treatment decisions can be made with currently available information incorporating individualized risk estimates. Key outstanding questions include: (1) how great are the incremental benefits of individualizing care compared to a treat all or treat none approach, (2) under what conditions are these benefits greatest, and (3) when might targeted strategies result in net harm?

This study uses simulation to explore how the underlying characteristics of a decision scenario can influence the additional benefits to be derived from an individualized (risk-based) approach versus a “one-size-fits-all” approach, based on calculating the expected value of individualized care (EVIC)[103]. In particular, we explore how changes in the clinical risk prediction model performance (such as predictive model discrimination and calibration) might influence the EVIC. At the same time we assess the impact of different levels of the willingness to pay and the average population risk. Our goal is to understand the decisional context for which an individualized tailored risk-based approach is most likely to add value, as well as when it might lead to harm.

4.2. Theory

4.2.1. Expected Value of Individualized Care

In this study we use a previously developed framework known as the Expected Value of Individualized Care (EVIC)[103-105]. EVIC is the difference between the expected value of the best population-wide strategy – i.e., either treating every population member or treating no one – and the expected value of selecting treatment for each population member individually.

4.2.1.1. Identifying and valuing the best population-wide strategy: By convention, we designate the expected value of treating no one to be zero. The incremental value of treating everybody is therefore the monetized treatment benefit for the population (where benefits are monetized based on the "willingness to pay" (WTP) threshold) minus treatment costs, averaged over the entire population. If this incremental net benefit value is positive, treating everyone is the optimal population-wide strategy. Otherwise, treating nobody (value of zero) is the optimal population-wide strategy.

The analysis in this paper estimates each individual's treatment benefit by assuming it is proportional to the product of three quantities: (1) the baseline risk of the adverse event for individual i in the absence of treatment, designated $R_{i,baseline}$; (2) the risk reduction conferred by treatment, designated $(1 - RR_{tx})$, where RR_{tx} is the relative risk of the adverse event with treatment; and (3) the QALY gain associated with averting the adverse outcome, designated $\Delta QALY$. Hence, the expected QALY gain from treatment of individual i is $R_{i,baseline} \times (1 - RR_{tx}) \times \Delta QALY$. Note that this formulation assumes that both RR_{tx} and $\Delta QALY$ are the same for all members of the population; only baseline outcome risk ($R_{i,baseline}$) differs across individuals. This is a simplification that does not change the overall results of the framework presented. Each individual's outcome in the absence of treatment is not known ex ante, but the baseline outcome risk can be estimated using a predictive model on the basis of baseline characteristics of the individual.

Multiplying the expected QALY gain by WTP (the willingness to pay for one QALY) yields the expected monetized treatment benefit. If this benefit exceeds the treatment cost on average, then treating everyone is the optimal population-wide strategy, and its expected per-person value is $WTP \times \bar{R}_{baseline} \times (1 - RR_{tx}) \times \Delta QALY - Cost_{Tx}$. Here, $\bar{R}_{baseline}$ is the average population baseline risk and $Cost_{Tx}$ is the per-patient treatment cost. Otherwise, the optimal population strategy is treating nobody and its monetized value is zero, by convention.

4.2.1.2. Valuing individualized care: We again estimate benefits minus costs for all members of the population. In this case, however, individuals receive treatment only if their monetized benefits exceed costs. For individuals receiving treatment, treatment value is $WTP \times R_{i,baseline} \times (1 - RR_{tx}) \times \Delta QALY - Cost_{Tx}$, exactly as above; for others (who remain untreated), it is zero.

Assuming that the individualized decisions are based on accurate estimates, EVIC cannot be negative; that is, individualized care must be at least as good as the best population-wide strategy, because it only eliminates treatments in those patients for whom treatment has a negative value. At worst, EVIC is zero when the optimal decision does not vary across individuals and thus decision-making is the same for both the individualized and "one-size-fits-all" approaches.

4.2.2. Perfect risk prediction

Consider a hypothetical clinical prediction model that perfectly predicts which population members will experience an adverse outcome in the absence of treatment. Under this condition, only that group which would benefit from treatment would receive it (assuming the therapy provides overall benefit to them, and they would not have a good outcome regardless of therapy).

If the optimal population-wide strategy is to treat everyone, then EVIC is the difference between the value of targeting individuals who will experience the adverse outcome in the absence of treatment, and the value of treating everyone (including those who will not benefit from treatment or do well even if untreated). In the absence of treatment harm, the treatment benefit is the same for both strategies since both strategies treat all members of the population who could benefit. The costs differ, however. For the targeted strategy, costs are $N \times \bar{R}_{baseline} \times Cost_{Tx}$. For the "treat all" strategy, costs are $N \times Cost_{Tx}$. EVIC is the difference between these two values, or $(1 - \bar{R}_{baseline})N \times Cost_{Tx}$ and is maximized when $\bar{R}_{baseline}$ is small, since a smaller number of patients would need to be treated with individualized care.

If the optimal population-wide strategy is "treat none" (value of zero by convention), then EVIC is the treatment benefits minus the treatment costs. That is, EVIC is $N \times \bar{R}_{baseline} \times [WTP \times \Delta QALY \times (1 - RR_{tx}) - Cost_{Tx}]$. Note that as $\bar{R}_{baseline}$ increases, EVIC also grows, since we would be changing the treatment strategy on progressively more individuals. This relationship may not be monotonic because at some value of $\bar{R}_{baseline}$ the optimal population strategy can switch between "treat all" and "treat none".

4.2.3. Imperfect risk prediction

We are interested in EVIC in more typical circumstances in which risk prediction is imperfect. Below we consider briefly how EVIC might change when model discrimination is imperfect and also when a model is miscalibrated.

4.2.4. Imperfect discrimination

"Risk" refers to the *ex ante* probability that a particular member of a population will ultimately experience an adverse outcome. Discrimination refers to a model's ability to assign higher risks to subjects who will ultimately experience the adverse outcome than to subjects who will not. Formally, discrimination is measured in terms of the c-statistic, which represents the proportion of all possible discordant subject pairs (i.e., pairs in which exactly one subject will experience the adverse outcome) that the model correctly orders by risk. That is, in a correctly ordered pair, the model predicts a higher risk for the subject who will experience the adverse outcome than it predicts for the subject who will not.

A model with perfect discrimination will always assign a higher risk to the subject who will experience the adverse outcome, so a model with perfect discrimination has a c-statistic value of 1.0 (100% of the pairs are correctly ordered). A model with no discriminatory power effectively "flips a coin" and hence has a 50% chance of correctly assigning a higher risk to the subject who will ultimately experience the adverse outcome. Therefore, a model with no discriminatory power has a c-statistic of 0.5 (50%). Note that the c-statistic says nothing about the relative magnitude of the risks assigned by the model to individuals who do and do not experience the adverse outcome. Only the order matters.

Figure 4.1 illustrates empirically derived risk distributions corresponding to c-statistic values ranging from 0.5 (model predictions are no better than chance) to 1.0 (model achieves perfect discrimination). At c-statistic values modestly exceeding 0.5 (e.g., c-statistic = 0.6), modeled risk estimates for population members cluster around the value of $\bar{R}_{baseline}$ (risk values for some individuals are slightly above $\bar{R}_{baseline}$, while others are a bit below). That is, models with low c-statistic values typically predict that all subjects face similar risks, and these risks are roughly equal to the prevalence of the adverse outcome in the population. As the c-statistic increases, the resulting risk heterogeneity across the population increases because of improvements in the model's ability to discriminate high from low risk individuals. At c-statistic values closer to 1.0 (e.g., c-statistic = 0.8 or 0.9), the model-predicted risk for a portion of the population is large (eventually approaching 1.0 as the c-statistic grows), while for the remainder of the population, the model-predicted risk is small (approaching zero as the c-statistic grows). That is, at high c-statistic values, the model distinguishes individuals very likely to experience the adverse outcome from those very likely not to.

In this paper we use simulations to explore the relationship between the predictive model's c-statistic and the EVIC.

4.2.5. Imperfect calibration

Calibration measures the extent to which model-predicted prevalence approximates the actual outcome prevalence, typically across some subgrouping specification (e.g., risk deciles). When calibration is perfect, the model is unbiased, and treatment decisions made for each member of the population individually are at least as good as the population-wide optimal treatment, regardless of how good or poor model discrimination is[106]. Hence, in these circumstances, EVIC is non-negative.

Often, risk models do not accurately predict risk for individuals outside the population used to construct the model. They may overestimate risk across quantiles, underestimate risk across quantiles, be “overfit” (under-estimate in low risk and over-estimate in high risk patients), be “underfit” (over-estimate low risk, under-estimate high risk) or have various other patterns. The risk prediction model in these situations can be said to have poor “external validity”, or to be “miscalibrated” or “biased”.

A miscalibrated model can incorrectly classify members of the population with regard to whether their expected benefit from treatment exceeds the treatment costs because the expected benefits are inaccurate. Misclassification can, in turn, produce erroneous treatment recommendations. Because the model recommendation might be erroneous, model-based recommendations for individuals can be worse than the optimal population-wide treatment recommendation. As a result, for misclassified models, the EVIC can be negative.

Finally, miscalibration is a potential problem not just when risk models are used to individualize treatment decisions, but anytime external evidence is applied to a population. Indeed, whenever applying clinical trial results to a population in actual practice, the degree of bias in the effect estimates is generally unknown, and thus population-wide recommendations can also yield sub-optimal population-wide decisions.

4.3. Illustrative Clinical Example

4.3.1. Methods

We illustrate the concepts described above through a case study based on the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (*GUSTO*) trial, a large multicenter randomized clinical trial. The GUSTO trial showed that a newer more expensive thrombolytic agent, tissue plasminogen activator (tPA), conferred a survival benefit compared to the contemporaneous standard agent, streptokinase, for the treatment of acute myocardial infarction (MI)[107].

4.3.1.1. Assumptions: We based outcome rate and cost estimates for our simulations on the GUSTO trial[107]. We defined the adverse outcome event to be 30-day mortality. We assumed the average population risk $\overline{(R_{baseline}})$ for this outcome is 7%, that tPA achieves a 15% relative risk reduction ($RR_{Tx} = 0.85$) for mortality compared with streptokinase, and that the total cost difference for patients treated with tPA vs. streptokinase ($Cost_{Tx}$) is \$2000. This difference incorporates the short term direct medical costs. We assumed that the QALY gain due to averting death at 30 days is 12 additional QALYs, an estimate corresponding to average survival duration for acute MI survivors [108-110], but that there is no additional difference in QALYs due to treatment choice. Further, to simplify interpretation, we excluded future health care costs for MI survivors, beyond the costs of tPA and streptokinase treatment. We investigated the impact of altering some of these assumptions, using ranges detailed in Table 4.1.

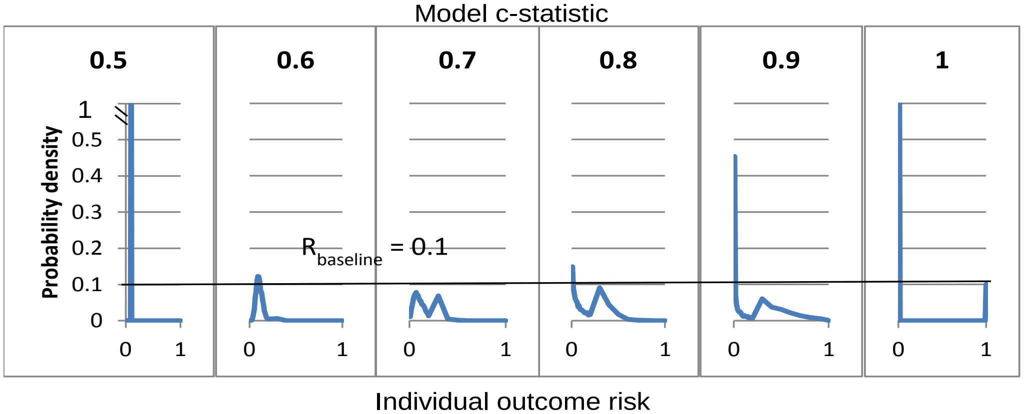
4.3.1.2. Identifying the optimal population-wide strategy: In addition to a treatment's effectiveness and cost, the optimal population-wide strategy ("treat all" or "treat none") depended on several factors. These factors were the expected prevalence of the adverse outcome (in this example, the 30 day mortality rate $\bar{R}_{baseline}$), and the monetized value of each QALY gained (i.e., the decision maker's WTP threshold). Specifically, $Net\ Benefit = WTP \times \bar{R}_{baseline} \times (1 - RR_{tx}) \times \Delta QALY - Cost_{Tx}$. If $R_{Baseline} = 0$, treatment can have no benefit, and net benefits cannot exceed zero (if treatment incurs any cost, net benefits will be negative). As $R_{Baseline}$ increases, net benefits increase with a slope of $WTP \times (1 - RR_{tx}) \times \Delta QALY$ (see Figure 4.1). For $\bar{R}_{baseline} = \frac{Cost_{Tx}}{WTP \times (1 - RR_{Tx}) \times \Delta QALY}$, net benefit is zero.

Table 4.1: Illustrative example assumptions

Symbol	Meaning	Values
$\Delta QALY(R_{Death})$	Expected QALY gain with tPA vs. streptokinase in MI as a function of baseline risk of death	
R_{Death}	Baseline risk of death	0.05 – 0.2
RR_{tPA}	Relative risk of death with tPA vs. streptokinase in MI	85%
$\Delta Q_{NoDeath}$	Incremental QALYs gained if death averted	12 QALYs
ΔQ_{tPA}	Incremental QALY loss from treatment, independent of outcome	0
$\boldsymbol{\Delta} Cost(R_{Death})$	Expected cost with tPA vs. streptokinase in MI as a function of baseline risk of death	
$\Delta Cost_{NoDeath}$	Savings if death averted	\$0
$\Delta Cost_{tPA}$	Cost of tPA vs. streptokinase in MI, independent of outcome	\$2,000

4.3.1.3. Generating baseline risk values for each simulated population member: We assigned each member of our simulated population a baseline risk value drawn from a beta probability distribution. We created a series of baseline risk probability distributions, each corresponding to assumed values for (1) the population adverse event prevalence ($R_{Baseline} = 5\%, 7\%, 10\%, or\ 20\%$), and (2) the c-statistic (values ranging from 0.5 - no discriminatory power - to 0.9 - high discriminatory power).

Figure 4.1: Individual Outcome Risk Distribution by C-statistic



In summary, a different risk distribution corresponds to each combination of values for $\bar{R}_{baseline}$ and the c-statistic, and can be modeled for a given population and predictive model, as previously shown in an analysis of 32 large clinical trials by Kent et al[10]. We described each distribution as a beta distribution with parameters that depend on the assumed values for the c-statistic and population prevalence, $\bar{R}_{baseline}$, in our simulations. We estimated the beta distribution parameters from empirical relationships across multiple clinical trials, derived previously[10]. To characterize the beta distribution, we first estimated the alpha parameter using ordinary least squares regression applied to alpha values derived for specific beta distributions fitted to each clinical trial in a set of 25 large randomized clinical trials (including ACCORD[111], AFFIRM[112], ALLHAT[113,114], AMIS[115], BARI[116], BEST[117], BHAT[118], CAST[119], CPPT[120], DCCT[121], DIG[122], DPP[123], ENRICHD[124], FAVORIT[125], HALTC[126], HDFP[127], HEMO[128], MRFIT[129], MTOPS[130], OAT[131], PEACE[132], ROC[133,134], SHEP[135], SOLVD[136,137], TIMI II[138].) The resulting relationship was $ln\alpha = 9.35 - 12.15c$, where c is the c-statistic. The R^2 for this regression was 0.90. After estimating α, we estimated β from the relationship $\frac{\alpha}{\alpha+\beta} = p$, where p is the population prevalence of the adverse outcome (equal to $\bar{R}_{baseline}$). Because the clinical trials in our sample had c-statistic values ranging from 0.58 to 0.75, our characterization of the population baseline risk distribution is least uncertain in this range.

We simulated a cohort of 5,000 individuals for each scenario (i.e., for each combination of c-statistic and $\bar{R}_{baseline}$ values). For each scenario, we reported the EVIC and the population distribution of cost-effectiveness ratios. By comparing scenarios, we described how the cost-effectiveness distribution changes in response to changes in the assumed discriminatory power of the risk model.

4.3.1.4. EVIC when risk estimates are well calibrated: To calculate EVIC, we first identified the optimal "one-size-fits-all" population strategy (treat all or treat none) for each scenario. We then identified the optimal strategy for each population member based on his or her baseline 30-day mortality risk. Specifically, we identified tPA to be the optimal treatment for individual i if $WTP \times \bar{R}_{i,baseline} \times (1 - RR_{tx}) \times \Delta QALY > Cost_{Tx}$, where $\bar{R}_{i,baseline}$ is the baseline 30-day mortality risk for that individual, $(1 - RR_{tx})$ is the relative risk conferred by tPA, and $Cost_{Tx}$ is the incremental cost of tPA compared to the streptokinase treatment. Finally, we estimated EVIC by summing the monetized gains accrued for all population members for whom the individualized treatment differed from the optimal population-wide strategy, and averaging them across the population. For example, if the optimal population-wide strategy was "treat none", the EVIC was the sum of the monetized net gains accrued for all population members who, based on an individualized care, switched to treatment.

4.3.1.5. EVIC when risk estimates are miscalibrated: For this scenario, we first characterized the "<u>true</u>" baseline risk distribution using the approach described above for the perfect calibration scenario. We then calculated a <u>reported</u> baseline risk value for each member of the simulated cohort – the value that would be observed in the "real world" – by multiplying that individual's simulated "true" baseline risk value by a miscalibration factor that ranged from 0.5 (underestimate) to 2.0 (overestimate). Next, we identified a putative optimal treatment for each individual by plugging that individual's reported baseline risk value into the benefit expression ($WTP \times \bar{R}_{i,baseline} \times (1 - RR_{tx}) \times \Delta QALY$) and comparing it to tPA's incremental cost. EVIC was calculated based on the "true" underlying costs and benefits of the selected treatment for each individual.

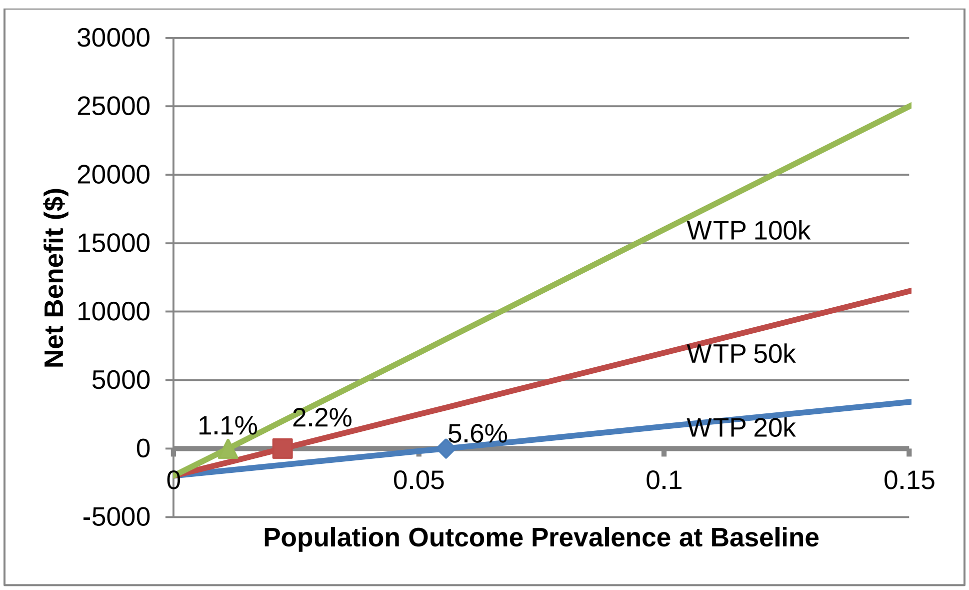
4.3.2. Results

4.3.2.1. Mortality risk and cost-effectiveness of population-wide treatment: Figure 4.2 illustrates the relationship between the net benefit of treating all patients with MI with tPA (vertical axis) when assumptions about 30-day mortality (horizontal axis) are varied. As expected, the net benefit is negative when the 30-day mortality is low; the net benefit is greatest when the 30-day mortality is highest. As illustrated in Figure 2, if a QALY is worth \$100,000, net benefits are zero when population 30 day mortality is assumed to be 1.1% (i.e., $\mathrm{P}_{100\mathrm{k}} = 1.1\%$). The corresponding break-even points for QALY values of \$50,000 and \$100,000 are $P_{50k} = 2.2\%$, and $\mathrm{P}_{20\mathrm{k}} = 5.6\%$, respectively. When the population-wide mortality risk falls below these thresholds, the optimal population-wide strategy is to treat none (i.e. use streptokinase in all patients); when the average mortality risk is higher, the optimal population-wide strategy is to treat all.

For example, if the QALY value (WTP) = \$50,000/QALY, the EVIC for a model with a c-statistic of 0.8 is \$200 per population member when $\bar{R}_{baseline}$ = 20%. The per-person EVIC of the same model increases to \$500 in a population with a $\bar{R}_{baseline} = 5\%$ because $\bar{R}_{baseline} = 5\%$ is closer to the break-even risk value of 2% (Figure 4.2). Similarly, when WTP = \$20,000/QALY, the break-even average 30-day mortality is approximately 6%, and the EVIC is in fact highest when $\bar{R}_{baseline}$ is between 5% and 7%.

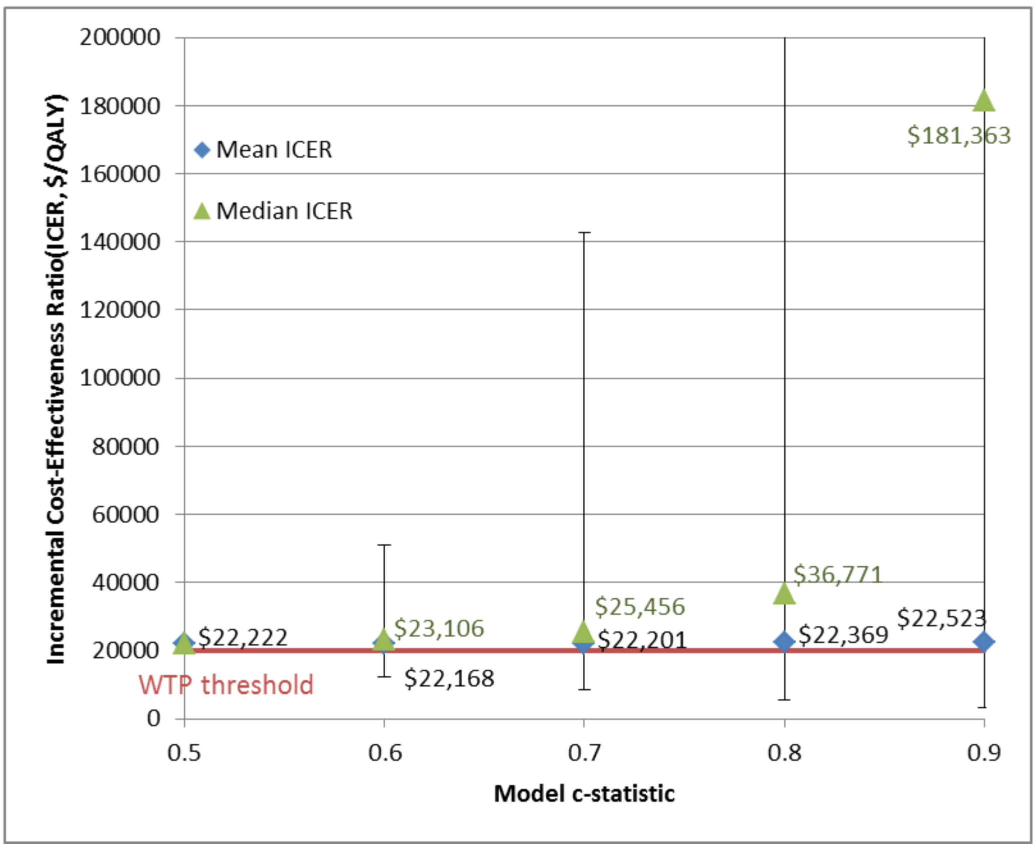
Holding $\bar{R}_{baseline}$.constant and instead changing the assumed monetized value of a QALY (WTP) likewise influences EVIC for analogous reasons. As WTP becomes smaller (e.g., reducing it from \$100,000/QALY to \$20,000/QALY), EVIC increases from \$350 per subject to \$700 per subject. Note that in both scenarios, the optimal population-wide strategy is to treat all with tPA. But as the value for WTP falls, the less expensive streptokinase therapy becomes the optimal strategy for a growing number of population members because individualized care accrues benefits for this growing number of individuals (by switching these patients from tPA to streptokinase) so that EVIC increases.

Figure 4.2: Net benefit of treating all members of the population compared to no treatment as a function of population outcome prevalence and the willingness-to-pay (WTP) threshold



4.3.2.2. Changes in individualized ICER with changes in discrimination: Figure 4.3 illustrates individualized cost-effectiveness value distributions corresponding to different assumptions regarding the risk model's discriminatory power. Because a well-calibrated model with low discriminatory power (c statistic) yields similar baseline risks for all members of the population, individualized cost-effectiveness estimates are likewise similar for all members of the population and the mean and median cost-effectiveness estimates do not substantially differ. As discriminatory power improves, predicted risk varies across population members and so do the individualized ICERs. The individualized cost-effectiveness of tPA for some patients (i.e. those at low risk for mortality) becomes highly unfavorable (very large) as the incremental benefit in the cost-effectiveness ratio denominator becomes small; for others (i.e. those at high risk), tPA's cost-effectiveness ratio becomes more favorable (relatively small) as the incremental benefit in the ratio's denominator grows. Because the resulting distribution of cost-effectiveness ratios is skewed, the mean and median diverge, making tPA less worthwhile in the typical patient.

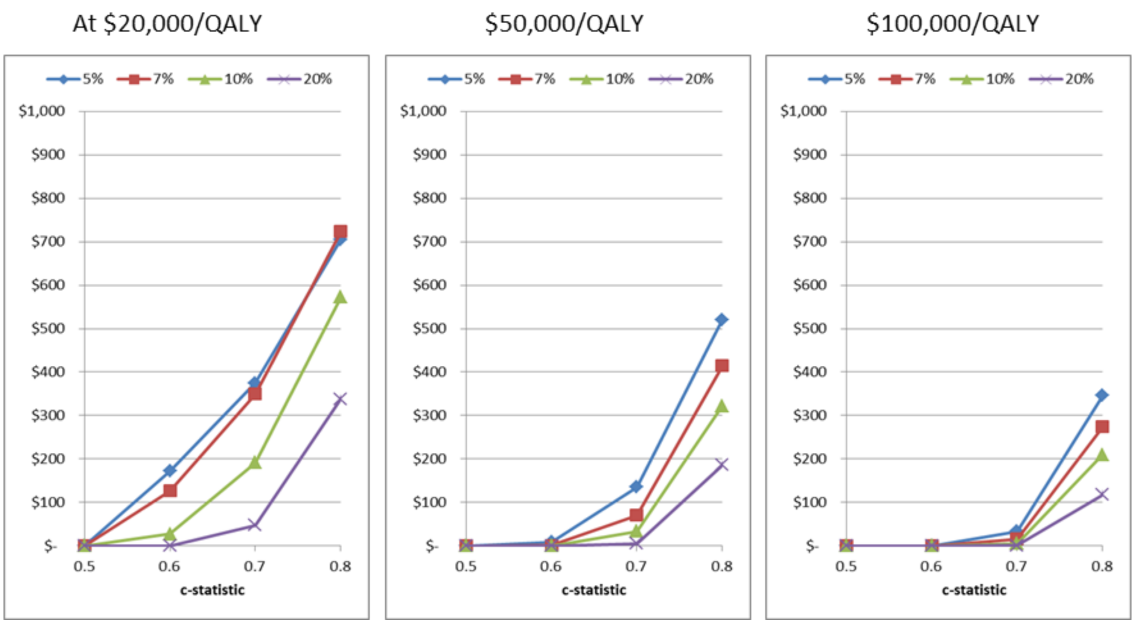
Figure 4.3: ICER distribution changes with c-statistic



Note: ICERs for model c-statistic 0.8 and 0.9 range up to $3.4 million and $4 trillion per QALY, respectively.

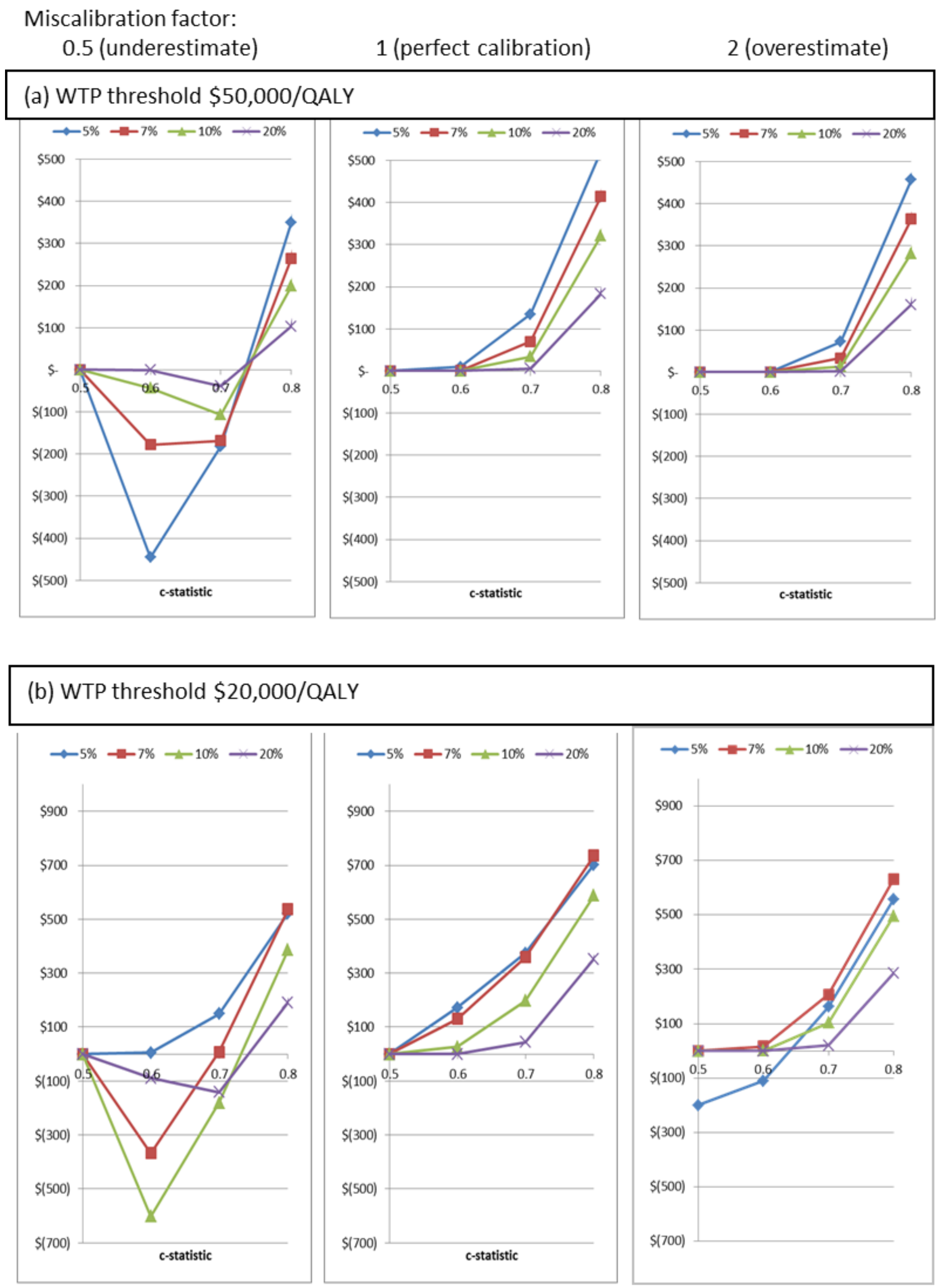
4.3.2.3. EVIC when risk estimates are perfectly calibrated: Figure 4.4 illustrates our EVIC calculations for the simulated cohorts. The EVIC ranges from 0 to $700 per person, with better discrimination (higher c-statistic values) yielding higher EVIC values. The association between discriminatory power and EVIC persists across different assumed values for baseline average 30-day mortality $(\overline{R}_{baseline})$ and the monetized value for a QALY (WTP).

Figure 4.4: EVIC as a function of c-statistic at several levels of mortality risk and WTP thresholds



4.3.2.4. EVIC when risk estimates are miscalibrated: Figure 4.5 illustrates our findings for scenarios in which the prediction models produce miscalibrated individual risk estimates. Under the assumptions in our study, EVIC ranged from -$600 to $700 per person, reflecting lower value for individualized care compared to optimal population-wide decisions in some circumstances. The most striking feature of these results is evident in the plots on the left (miscalibration factor of 0.5, meaning that the model-reported risk underestimates each individual true 30-day mortality probability by one-half). In those plots, improvements in discrimination were non-monotonically related to

Figure 4.5: Predictive model miscalibration compared to perfectly accurate population ICER: EVIC values at different levels of c-statistic, mean mortality risk, and miscalibration



changes in EVIC. Increasing discriminatory power lowered EVIC when discrimination was low (i.e. as the c-statistic improved from 0.5 to between 0.6 and 0.7) but then increased EVIC when the c-statistic was higher (i.e. as the c-statistic improves to between 0.8 and 0.9).

4.3.3. Discussion

Cost-effectiveness analyses are typically performed at a population level, yet most medical decisions are made, and most resources are allocated, one patient at a time. Therefore, cost-effectiveness analyses are generally at a level that is incongruent with medical decision making, and individual cost-effectiveness estimates can vary substantially from the overall average cost-effectiveness[12,110,139]. In the simulations reported we examine the value of individualizing information based on estimates of individual patient risk. Our results suggest that individualizing treatment decisions may yield substantial value, but also has the potential for harm. We have verified what others have observed for well calibrated models: EVIC increases as discriminatory power increases[106]. As model discrimination improves, risk heterogeneity increases, and consequently there is also greater heterogeneity in individual ICER estimates. Because these individual ICER estimates may diverge substantially from the population average (and the ICER for the typical patient may be quite different from the population average), the optimized individualized strategy may diverge substantially from the optimized strategy based on a population average. Our simulations, based on a simplified version of a classic cost-effectiveness analysis, suggest that moderate improvements in discrimination can add substantial value, equivalent to several hundred dollars on a per person basis in some scenarios.

When models are well calibrated, individualized risk based decisions are, at worst, non-harmful. This is consistent with other work using a decision analytic framework[106]. We also found that well calibrated risk models are of greatest value to decisions when the overall prevalence places a population-wide strategy near the decision threshold and when model discrimination is good. When the mortality risk yields an incremental cost-effectiveness ratio that is far from the WTP decision threshold, the optimal population-wide and individualized strategies will be the same and EVIC will be near-zero, except when model discrimination is very good.

The EVIC is higher when the population baseline risk estimate ($\bar{R}_{baseline}$) is closer to the "break-even" value that makes the expected net benefit or incremental monetized value of tPA close to zero. In this circumstance, there is no clear advantage to either the "treat all with tPA" or "treat none with tPA" strategy (see Figure 4.1). This balance implies that the break-even risk value is near the middle of the population risk distribution, and that the optimized individualized strategy will differ from the best population-wide option (either treat all with tPA or treat none with tPA) for many. Hence, individualized care will result in a substantial number of treatment switches, and because gains from individualized care accrue only in these switched cases, EVIC can grow larger as discrimination improves and the risk distribution broadens.

Our analysis goes beyond past work by carefully examining what happens when models are miscalibrated. That scenario is important because in the real world, models are typically developed on one population and applied to others.

When models are miscalibrated, EVIC can be negative and improvements in model discrimination can paradoxically decrease the value of individualizing care in some circumstances. We explored the impact of individualization based on miscalibrated predictive models, which can lead to treatment assignment “mistakes”. When the population average ICER is near the WTP threshold, decision making is more sensitive to miscalibration and these treatment assignment mistakes are more common (making EVIC more negative). This can be explained by looking at the distribution of individual ICERs (Figure 4.3). The effect of model miscalibration in our simulation was to shift the ICERs of some individuals across the WTP threshold, leading to the wrong decision for those patients, thus lowering the overall EVIC. When the WTP threshold is not close to the population ICER, the change in individual ICERs does not affect the treatment decision, and there is no effect on the overall EVIC. Interestingly, a poor c-statistic can sometimes protect from misclassification due to bias, which becomes revealed only when the c-statistic improves; thus, greater discriminating power can paradoxically reduce the EVIC under some circumstances.

These simulations were based on several simplifying assumptions. Most importantly, we assumed the following parameters were independent of baseline risk: treatment effect (measured as relative risk reduction); treatment costs; and QALYs gained conditioned on outcome. It is likely that long term costs and life expectancy or QALYs are correlated with the short-term outcome risk. For example, individuals at higher risk of a cardiovascular death are also more likely to be older and have more severe heart attacks and other risk factors or health conditions that would impact their long-term life expectancy. Including the correlations between short-term risk and long-term benefit in the decision model is likely to attenuate the heterogeneity of individualized benefits across the population (and diminish EVIC), although it may be difficult to generalize whether this would be true across other conditions. A further complicating factor not included in this analysis is heterogeneity of treatment-related harm (i.e., intracranial bleeding)[109], especially its interplay with the heterogeneity of the individual outcome risk and benefit from treatment. These issues underscore the heavy data and analytic burdens of more individualized cost effectiveness studies.

4.4. Conclusions

Individualized estimates can help determine treatment course. However, predictive models should be used with care and an understanding of the model's applicability. First, if the treatment's average cost-effectiveness is far from any important decision threshold, there is a high probability that the optimal population-wide strategy is the right course for any individual. When the net benefit of a population wide strategy is near zero, individualized information may be very helpful in assigning the best treatment strategy. Second, if a predictive model has poor discriminating power, it may be of very low value. Finally, poorly calibrated models may provide misleading predictions and cause patient harm, reducing EVIC. These results emphasize the importance of paying special attention to the decisional context in which models will be deployed and to model calibration, an often neglected aspect of predictive model validation. Caution is needed when transporting risk models to new settings. In general, models developed on local samples are anticipated to be better calibrated than models developed on "different but related" samples. Whenever possible, risk models should be updated and recalibrated to ensure the accuracy of the risk information they yield. While the potential for miscalibration is ubiquitous, more research is needed to determine those situations in which risk models are especially likely to be vulnerable to miscalibration.

4.5. Acknowledgments

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Chapter 5 : Discussion

5.1. Summary

The preceding chapters developed individualized cost-effectiveness and net benefit estimates to quantify the value of risk-based targeting of type 2 diabetes prevention programs and selection of DAPT therapy durations for ACS patients post-PCI. The diabetes prevention model made individual level estimates for costs and health effects and the DAPT model made risk quartile-specific estimates. In both case studies, targeting achieves value gains, and even stratifying by risk quartile provides valuable insight that enables the decision maker to assess whether the magnitude of risk heterogeneity in the population and its effect on outcomes and costs justifies targeting an intervention by risk.

For example, in the case of DPP, both lifestyle and metformin interventions conferred best value when administered to individuals with the highest diabetes risk. However, the analysis also showed that among patients in the lowest risk quintile, metformin provided no clinical benefit; indeed, for this group, the net benefit was negative, meaning that its costs exceeded the monetized value of the gained health benefits.

The DAPT analysis showed that individuals in the highest bleeding risk quartile derived the most benefit from reducing therapy duration to 6 months from the standard 12 month duration. The remaining lower risk quartiles in this case were fairly similar in terms of outcome risks and treatment effects. For all of these groups, the optimal strategy was 12 months of DAPT therapy. Because results for these groups were similar, there was no need to differentiate them. Instead, decision makers could use the pooled “moderate to low risk” subgroup results to identify the optimal treatment duration for these groups.

As expected, the third paper found that for decisions based on well calibrated models, i.e., models that do not over or underestimate predicted vs observed event risk, individualized care conferred more value than population-level care; that is, the expected value of individualized care (EVIC), was positive. Better discrimination (higher c-statistic values) yielded progressively higher EVIC values. Interestingly, for decisions based on poorly calibrated models, the EVIC can under some circumstances still be positive. In other circumstances, they may have the potential for net harm. Our simulations revealed some general tendencies that can help promote the appropriate use of risk models for clinical decision making. First, if the treatment's average cost-effectiveness is far from any important decision threshold, there is a high probability that the optimal population-wide strategy is the right course for any individual. When the net benefit of a population wide strategy is near zero, individualized information may be very helpful in assigning the best treatment strategy. Second, if a predictive model has poor discriminating power, it may have very little value. Finally, poorly calibrated models may provide misleading predictions and cause patient harm, reducing EVIC.

These results emphasize the importance of paying special attention to the decision context in which models will be deployed and to model calibration, an often neglected aspect of predictive model validation. Even a validated model, when applied to a different population – by patient characteristics or geographic region with different disease prevalences – may generate risk predictions that are substantially different from the actual population risk – or be miscalibrated when applied to a new population. It is important to check that the CPM is based on an appropriate and relevant population, as relates to the target population for the decision. Moreover, methods to adjust and recalibrate models can help adjust the model and improve calibration for a new setting.[140]

5.2. Future research directions

There are multiple reasons why individualized approach has not been widely adopted in conducting CEA. While such analyses are more complex, the biggest obstacle has been the lack of data. Patient-level data are rarely available to analysts, and clinical trial results are typically reported as either the averages across the study population, or by single factor subgroups. However, there is increased awareness of the limitations of such outcome measures in settings where risk or outcome heterogeneity is high. There are calls for more trials to include risk-based subgroup reporting, which should enable health economists in turn to perform risk-based CEA.[16,141] However, in addition to clinical outcome data, many other factors in an individualized CEA should reflect patient level heterogeneity. Unfortunately, it is still difficult to obtain estimates of resource use, costs, or patient preferences stratified by disease risk, or other relevant outcome risk. Future efforts should focus on developing estimates that will enable more accurate individualized modeling.

In addition to all trials reporting on the range of risk and risk-stratified treatment effects within the trial follow up period, additional data are necessary. For instance, in addition to stratification or prediction of short term outcomes, researchers and analysts need a better understanding of how long term outcomes are associated with individual characteristics at baseline. Usually they cannot be estimated in the same individualized way as short term outcomes because longitudinal data do not provide long enough follow up times, and at the same time, long term data sets typically do not allow individual level linkage with baseline characteristics. While future data sources may provide richer and longer-term data, they should also provide ways to link at the individual level through time. This is especially important for major endpoints such as mortality.

Another area for future research and a major source of individual level variation in impacts of therapies is the individual preferences around medication taking and other types of interventions. As our analyses showed, these preferences have a substantial impact on the QALYs derived from an intervention – firstly though the effect on the patient's quality of life, and secondly, through reduced effectiveness, if mismatch with preferences leads to poor adherence or discontinuation of treatment. In conducting our studies, we found a critical lack of data in this area.

Chapter 6 : APPENDIX Supplemental Materials for Manuscript “Targeting of the Diabetes Prevention Program leads to substantial benefits when capacity is constrained”

6.1. Appendix 1: Simulation model

6.1.1. Simulating individual costs and outcomes

Individuals with impaired glucose regulation progressed over time, accruing annual costs based on national average age- and sex-specific estimates, and the costs of diabetes prevention, based on data from the DPP study[35] (Table 1). The model assumed that patients maintained each DPP intervention until they either progressed to diabetes or died, incurring annual treatment and complication costs. The scenarios where patients received no DPP intervention assumed no associated prevention costs. To estimate QALYs, we applied a published utility weight for impaired glucose tolerance of 0.77, supported by additional published estimates ranging from 0.7 to 0.8.[55,142-144] The duration of time spent in this health state derived from the mean of the distribution of individualized mortality-adjusted probabilities of time to diabetes onset for each of the three strategies. After diabetes onset, the model calculated the individual utility weights based on sex, BMI, complications and comorbidities, where a male with uncomplicated diabetes had a weight of 0.69.[54]

Given each individual’s age of diabetes onset and other characteristics, we used the publicly available Michigan Diabetes Research Center model[53,54] to estimate the lifetime costs and QALYs of individuals developing diabetes. The model assumes standard of care diabetes treatment and incorporates treatment costs, risks, and quality of life impact of adverse outcomes, including microvascular and macrovascular complications, and mortality. The model has been previously described and validated.[53,54,145-147]

In order to estimate the lifetime costs and QALYs after onset of diabetes, we ran each person in the study cohort through the Michigan simulation model given diabetes onset at different ages, with 100 simulation runs per scenario. We used the baseline characteristics from the DPP cohort to generate the initial characteristics of the study cohort at different possible times of diabetes onset, with scenarios where all individuals develop diabetes immediately, or at 5 year increments from year 0 to year 40 from baseline. In scenarios with later diabetes onset times, we projected age, BMI, and HbA1c at a future time of diabetes onset based on a multivariable analysis of the trajectories of these measures in DPP study participants who developed diabetes. We then weighted the mean lifetime costs and QALYs per individual by the individual mortality-adjusted probability of diabetes onset for each scenario to obtain overall mean lifetime costs and QALYs per individual for each prevention strategy (Figure 1).

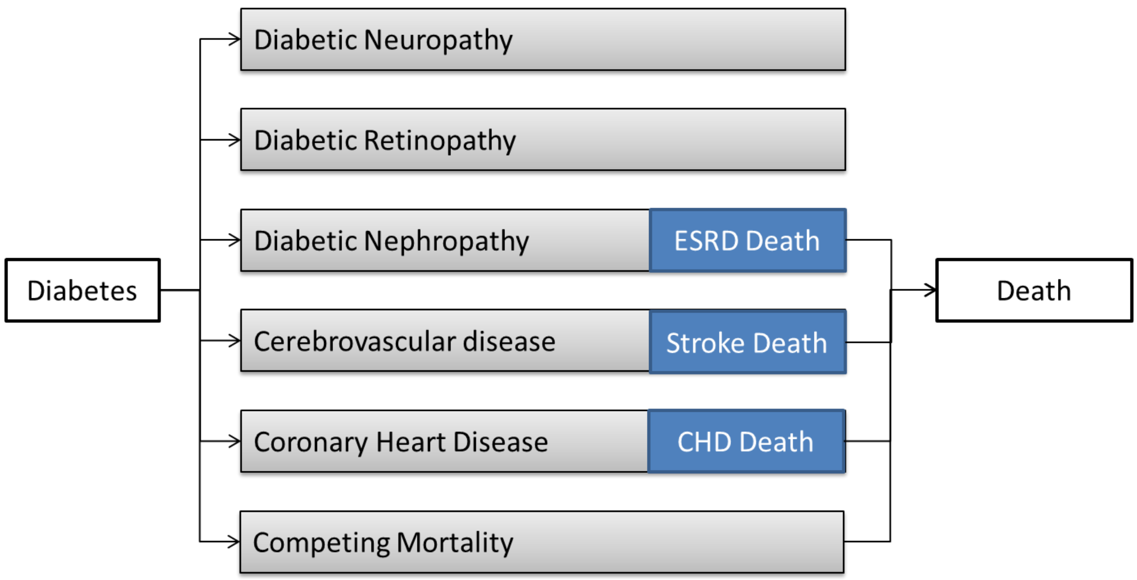
6.1.2. Michigan Model for Diabetes

Michigan Model for Diabetes is a computer simulation model that projects the medical costs of diabetes and patient outcomes in terms of survival and health-related quality of life.

In brief, the Michigan model simulates the lifetime progress of individuals with diabetes, receiving contemporary therapy, and includes changes over time in blood pressure, BMI, HbA1c, and other biomarkers, the possibility of developing coronary heart disease and congestive heart failure, cerebrovascular disease and stroke, nephropathy and end-stage renal disease, retinopathy and blindness, neuropathy and amputation, and mortality related to diabetes complications and other causes (Appendix 1 figure 1).

The simulation takes into account individual baseline characteristics, and generates transition probabilities for health states associated with diabetes complications and comorbidities, based on a synthesis of published literature. The simulation tracks the trajectory of each subject in annual cycles for a set number of years or until death, and each cycle recalculates risk factors and transition probabilities based on the subject's health state at the time. Further methodological details have been described elsewhere.[53,54,145-147]

Figure 6.1: Overall structure of the Michigan model



6.2. Appendix 2: Modeling time to diabetes onset

For the initial 4 years, we applied the previously published DPP model.[44] Full details of model building and validation have been described previously.[44] This original model included 7 independent variables (height, waist to hip ratio, waist circumference, fasting plasma glucose, history of high blood glucose, and serum levels of HbA1c and triglycerides) to predict the 3-year risk of diabetes, and also incorporated the effects of the diabetes prevention intervention and the interaction between linear predictor of 3-year diabetes risk and metformin therapy to account for variation in the treatment effect by risk (higher relative benefit for higher risk patients). The lifestyle intervention had a consistent relative effect across all risk quantiles. The final model had a good discrimination with a c-statistic of 0.73.

For long-term predictions beyond the first 4 years, we used the additional 7 year follow-up data from DPPOS to extend the model and to estimate the impact of the baseline covariates on outcomes at time periods beyond year 4. The DPPOS data allows us to accurately estimate the risk distribution of diabetes onset for the group receiving initial and then continued lifestyle intervention, but for the other two arms, we needed to account for treatment cross-over to lifestyle for the metformin and placebo arms in the study. Published literature suggests a wide range of uncertainty about the treatment duration for diabetes prevention.[47,57] The initial 4 years of DPP trial data suggest that the treatment effect was highest during the first 24 months, with hazard ratios declining over the subsequent 24 months. To make efficacy estimates beyond year 4, as suggested by the second Panel on Cost-Effectiveness in Health and Medicine,[49] we assumed two alternative models – a conservative, or short treatment effect scenario, where after the first 48 months, interventions do not provide any additional reduction in hazard of diabetes onset and the cumulative hazards continue parallel to each other over time; and a second, more optimistic, extended treatment effect scenario, assuming constant hazard reduction for diabetes onset over time. For making our long-term estimates, we assumed that the baseline hazard ratio for treatment effect continues the same as in the months 24-48 of follow up with preserved randomization (Appendix 2 figure 1). These two scenarios present two extreme assumptions around treatment effect duration that bound our estimates of the outcomes.

In the extended treatment effect scenario, the lifestyle intervention curve remained the same as in the short effect scenario – anchored by data observed in individuals receiving continuing lifestyle intervention in DPPOS. In this scenario the metformin and usual care curves show sharper declines relative to the lifestyle intervention, since treatment effect is assumed to continue beyond the first 4 years (Appendix 2 figure 2).

6.2.1. Extended model to predict time to diabetes onset

Based on previous 3-year analysis of the DPP trial data,[44] we used the same predictor variables to generate a 3 year diabetes risk linear predictor (LP): height, waist to hip ratio, waist circumference, fasting plasma glucose, history of high blood glucose, and serum levels of HbA1c and triglycerides. For long term individualized predictions we combined several models for each time period.

For 0-48 months the Cox proportional hazards model included the LP above, the treatment arm (lifestyle and metformin), and an interaction term between LP and metformin.

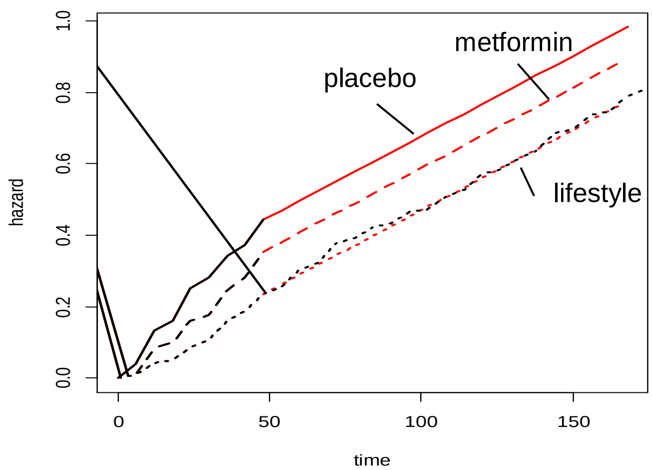
For 48-96 months we extended the prediction using a parametric proportional hazards model with exponential survival, including covariates: LP generated above, lifestyle treatment to estimate the scale parameter, or slope, based on the lifestyle group follow up data for 48-96 months.

Similarly, beyond 96 months we used the same model as 48-96 months, adjusting the covariate effects based on data beyond 96 months.

Figure 6.2: Cumulative hazard functions for time to diabetes.

For all scenarios long term hazard for lifestyle arm was fitted to observed data from DPPOS. In order to capture the significant heterogeneity of metformin treatment effect on the relative scale seen in the DPP trial, multivariable models for derivation of individual hazard ratios incorporated an interaction term between treatment and short term diabetes risk. Red lines represent modeled data and black lines – observed data.

Panel A: Short-term treatment effect scenario assumed no additional treatment effect in metformin and placebo arms after the initial 4 years, that is, diabetes onset hazard ratios for metformin and placebo relative to the slope of the observed data in the lifestyle arm (black dotted line) were set constant over time.



Panel B: Long-term treatment effect scenario assumed hazard reduction continued based on the slopes of the hazards in months 24-48. The models beyond 48 months included an interaction term between LP and metformin treatment arm in order to capture the heterogeneity of the hazard ratios for metformin treatment by LP.

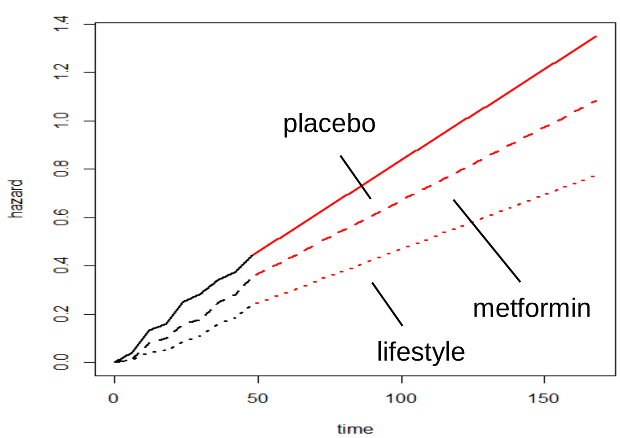
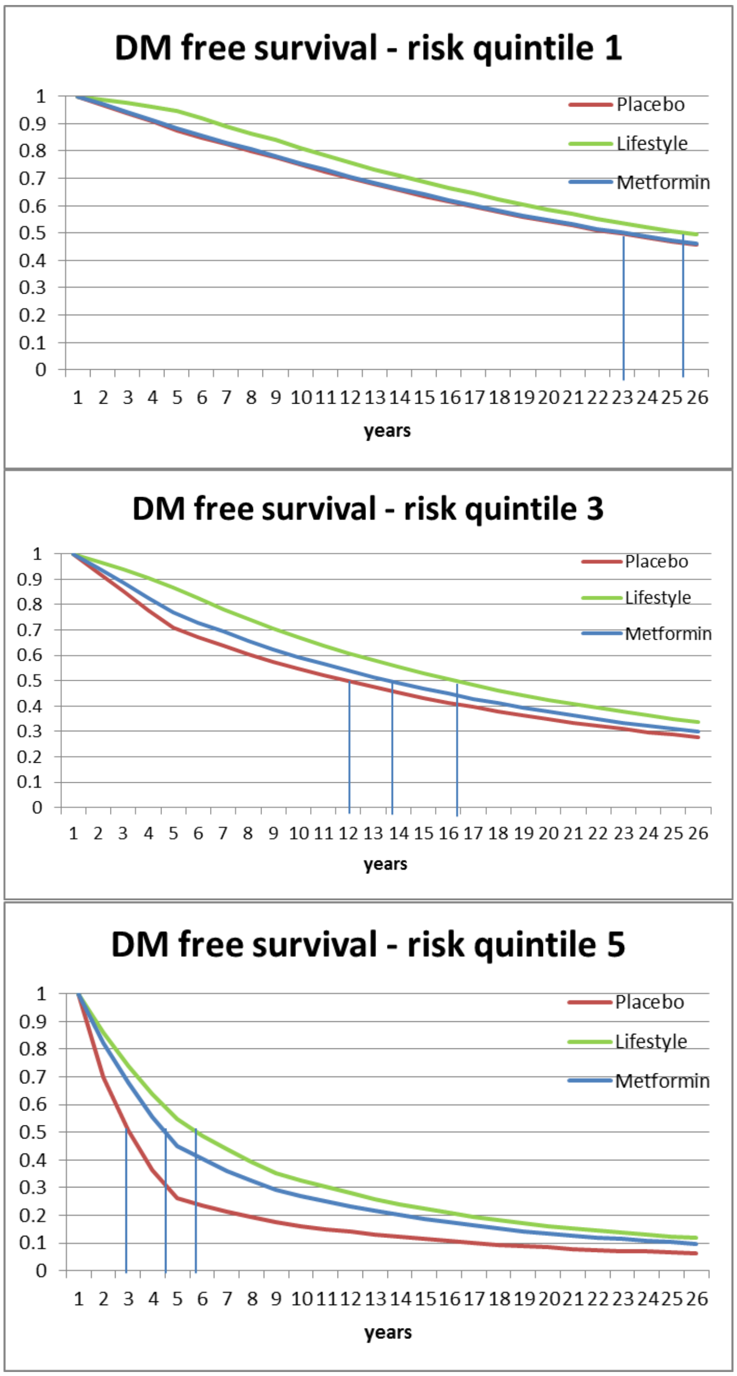


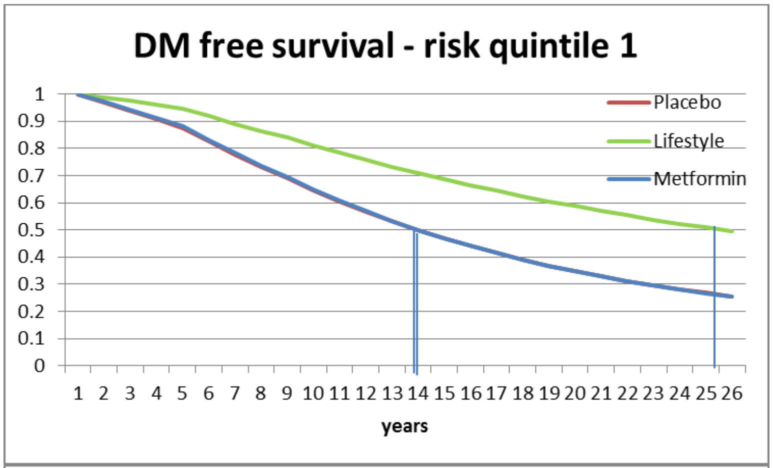
Figure 6.3: Predicted diabetes-free survival by 3 year diabetes risk quintile (from low risk to high risk) with alternative assumptions of treatment effect duration.

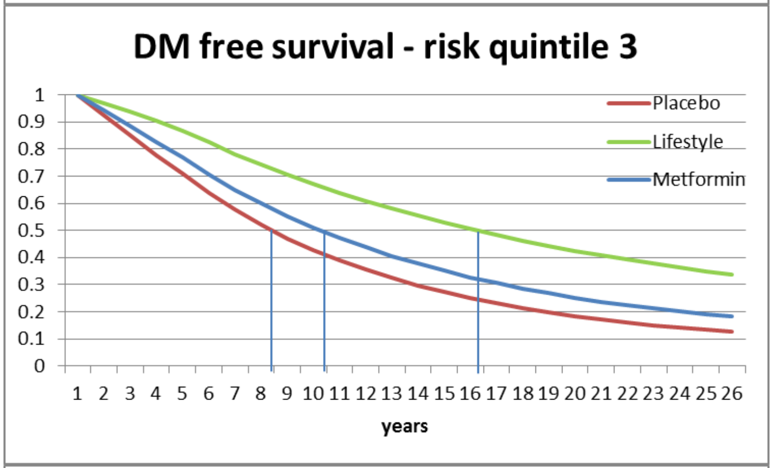
The short-term treatment effect scenario assumes diabetes onset hazard reduction in the first four years only, and long-term treatment effect scenario assumes diabetes onset hazard reduction extends over the entire lifetime. Blue vertical lines indicate median DM free survival.

A: Short duration of treatment effect



B: Extended duration of treatment effect





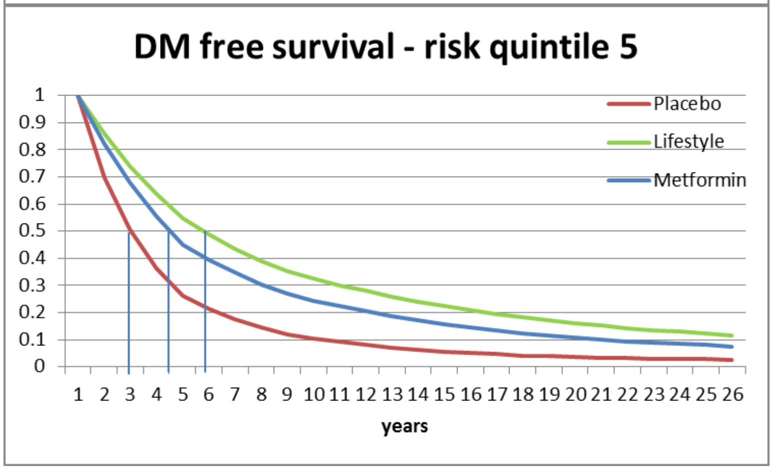
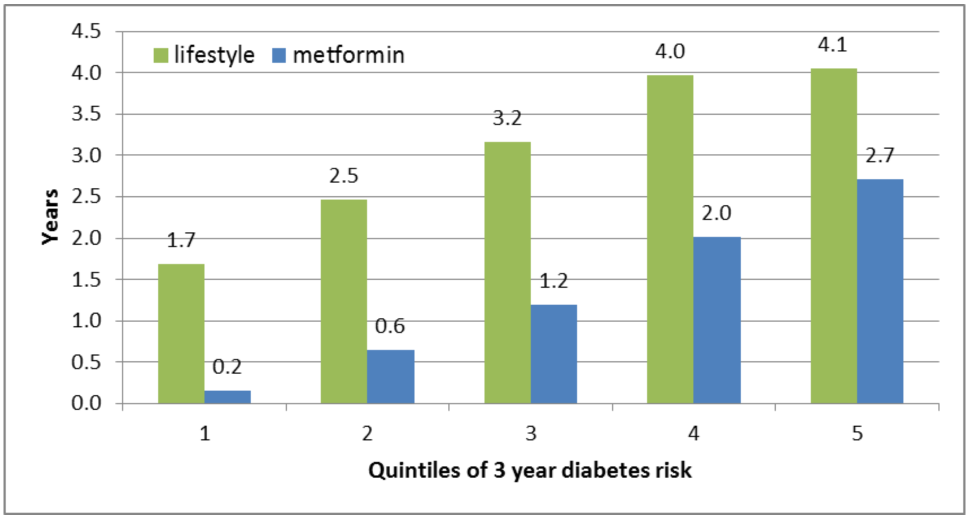


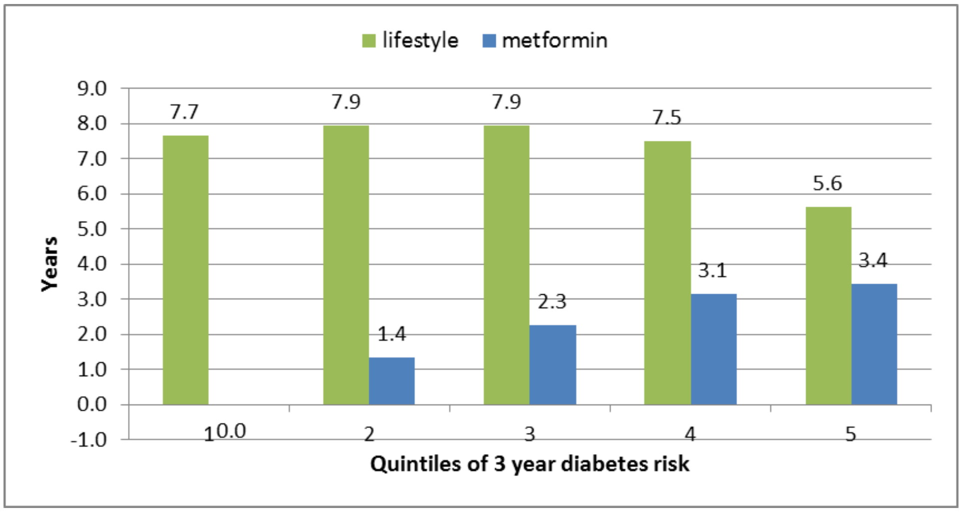
Figure 6.4: Mean delay in years to diabetes onset by 3 year diabetes risk quintile (from low risk to high risk) with alternative assumptions of treatment effect duration.

The short-term treatment effect scenario assumes diabetes onset hazard reduction in the first four years only, and long-term treatment effect scenario assumes diabetes onset hazard reduction extends over the entire lifetime. These values represent the area between the curves shown in Figure 6.3.

A: Short-term duration of treatment effect



B: Long-term duration of treatment effect



6.3. Appendix 3: Sensitivity Analysis

In the real world, there is much uncertainty about treatment effects over time and real world adherence to a diabetes prevention program. The effectiveness and duration of effect of the DPP (lifestyle intervention) vary by program specifics and settings, as well as treatment adherence.[45,47,57] There are many factors, both system level and patient-specific, that influence adherence to DPP, and it is beyond the scope of this study to fully account for these variables. Further, prior analysis of DPP data estimated the median delay in diabetes onset to be 11 years with lifestyle intervention and 3.4 years with metformin.[35] These estimates appear more positive than our extended treatment effect scenario, and are based on an assumption of a greater treatment effect, where the hazard ratios for the first 48 months were extrapolated over a lifetime.

While the lifestyle intervention shows greatest benefits and cost-savings in our models, there may be additional considerations which might make metformin therapy more favorable, especially in high risk individuals. Since compliance will likely vary by the intervention utilized and personal preferences, some individuals may find medication easier to adhere to than lifestyle change, and greater adherence would also improve the benefits and value of the treatment.[45] We have included a measure of the impact of patient preferences and treatment burden of taking a daily medication in our sensitivity analyses. Our results indicate that the value of metformin is highly sensitive to an individual patient's preference and perceived burden of taking a medication daily, as well as the potential for experiencing side effects of metformin.

The short term risk of diabetes may be associated with long-term outcomes, such as mortality and life expectancy. Our use of age- and sex-specific life tables for mortality rates in individuals with impaired glucose regulation, rather than more individualized estimates, as in the diabetes models, may exaggerate effects of heterogeneity.

Previous literature has shown that combining long-term outcome models with differing levels of granularity of individual characteristics may lead to biased estimates.[58,59] Unfortunately, we know of no data that would link short term diabetes risk with such long-term outcomes. To examine the effects of positive association of mortality rates with short term diabetes risk, we conducted sensitivity analyses, which indicated that at low diabetes risk expected NMB of treatment is lowest, it increases in middle diabetes risk groups, and decreases again in those with highest diabetes risk. The resulting inverted u-shaped distribution has been found in previously published studies, indicating that for individuals at higher risk, increased competing mortality reduces expected benefits.[14]

Table 6.1: Sensitivity Analysis Results

Sensitivity analyses:	**Average NMB**	**Lowest risk Quintile NMB**	**Highest risk Quintile NMB**	**Percent with NMB>0**	**Incremental NMB from targeting***
Short-term treatment effect scenario					
Base case: lifestyle	$21,258	$7,381	$39,457	100%	0
Base case: metformin	$7,415	($2,500)	$23,488	75%	$523 (7%)
Discounting 0%: lifestyle	$33,417	$15,581	$54,893	100%	0
Discounting 0%: metformin	$11,086	($3,027)	$32,000	80%	$615 (6%)
Discounting 5%: lifestyle	$18,604	$7,133	$33,418	100%	0
Discounting 5%: metformin	$6,417	($2,221)	$20,046	76%	$456 (7%)
WTP $100,000: lifestyle	$37,917	$15,239	$68,759	100%	0
WTP $100,000: metformin	$13,848	($2,263)	$40,579	81%	$468 (3%)
Impaired glucose regulation utility of 1:	$34,382	$14,202	$60,546	100%	0

lifestyle					
Impaired glucose regulation utility of 1: metformin	$12,309	($2,311)	$35,712	82%	$468 (4%)
Treatment burden of metformin (disutility 0.002)	$6,416	($3,757)	$22,749	68%	$856 (13%)
Treatment burden of metformin (disutility 0.05)	($17,570)	($33,529)	$5,005	14%	$18,867 (107%)
WTP $100,000 and impaired glucose regulation utility of 1: lifestyle	$64,165	$28,880	$110,937	100%	0
WTP $100,000 and impaired glucose regulation utility of 1: metformin	$23,636	($1,853)	$65,026	85%	$461 (2%)
Increased mortality for pre-diabetes (flat): lifestyle	$17,247	$9,171	$24,998	100%	0
Increased mortality for pre-diabetes (flat): metformin	$5,078	($2,549)	$14,892	75%	$531 (10%)
Increased mortality for pre-diabetes (differential by diabetes risk): lifestyle	$17,112	$7,121	$24,998	100%	0
Increased mortality for pre-diabetes (differential by diabetes risk): metformin	$5,298	($2,513)	$14,892	74%	$528 (10%)
Long-term treatment effect scenario					
Base case: lifestyle	$45,290	$28,971	$59,673	100%	0
Base case: metformin	$12,278	($4,390)	$32,468	81%	$880 (7%)
Discounting 0%: lifestyle	$96,846	$97,606	$92,698	100%	0
Discounting 0%:	$19,274	($8,691)	$46,246	83%	$1,774

metformin					(9%)
Discounting 5%: lifestyle	$48,184	$44,366	$51,704	100%	0
Discounting 5%: metformin	$10,407	($4,826)	$27,269	82%	$967 (9%)
WTP $100,000: lifestyle	$70,650	$40,186	$100,085	100%	0
WTP $100,000: metformin	$21,369	($4,864)	$55,010	83%	$1,016 (5%)
Impaired glucose regulation utility of 1: lifestyle	$73,433	$52,905	$91,176	100%	0
Impaired glucose regulation utility of 1: metformin	$19,577	($5,636)	$49,074	83%	$1,162 (6%)
Treatment burden of metformin (disutility 0.002)	$11,453	($5,380)	$31,812	78%	$1,075 (9%)
Treatment burden of metformin (disutility 0.05)	($8,353)	($29,134)	$16,055	28%	$12,084 (145%)
WTP $100,000 and impaired glucose regulation utility of 1: lifestyle	$126,935	$88,053	$163,091	100%	0
WTP $100,000 and impaired glucose regulation utility of 1: metformin	$35,967	($7,355)	$88,221	84%	$1,611 (4%)
Increased mortality for pre-diabetes (differential by diabetes risk): lifestyle	$35,772	$28,336	$24,998	100%	0
Increased mortality for pre-diabetes (differential by diabetes risk): metformin	7,987	($4,321)	$14,892	81%	$866 (11%)

Note: all NMB shown per person, with usual care as the comparator. Targeting here refers to treating only individuals with NMB>0 across the entire eligible population. WTP = willingness to pay, or value assigned to, a QALY, or quality-adjusted life year.

Chapter 7 : APPENDIX: Literature Review: Effects of targeting diabetes prevention programs by risk of diabetes onset

Table 7.1: Literature Review: Effects of targeting diabetes prevention programs by risk of diabetes onset

Clinical Outcomes in Diabetes Prevention		
Reference	**Title**	**Summary**
Sussman et al, BMJ 2015[44]	Improving diabetes prevention with benefit based tailored treatment: risk based reanalysis of Diabetes Prevention Program	Analysis of the original DPP data with stratification by 3 year risk of diabetes as estimated using a clinical prediction model. Although the lifestyle intervention provided a sixfold greater absolute risk reduction in the highest risk quarter than in the lowest risk quarter, patients in the lowest risk quarter still received substantial benefit (three year absolute risk reduction 4.9% v 28.3% in highest risk quarter; numbers needed to treat of 20.4 and 3.5, respectively). The benefit of metformin, however, was seen almost entirely in patients in the top quarter of risk of diabetes. No benefit was seen in the lowest risk quarter. Participants in the highest risk quarter averaged a 21.4% three year absolute risk reduction (number needed to treat 4.6). ***Clinical outcomes.*** **We extend this analysis using longer term follow up data from DPP-OS, and add an economic analysis.**
Herman et al, 2017[45]	Impact of Lifestyle and Metformin Interventions on the Risk of Progression to Diabetes and Regression to Normal Glucose Regulation in Overweight or Obese People With Impaired	This study evaluated the oucomes based on the adherent participants in DPP and DPP-OS studies. Findings: Compared with adherent placebo participants at lowest risk of developing diabetes, participants at lowest risk of developing diabetes who adhered to a lifestyle

	Glucose Regulation	intervention had an 8% absolute risk reduction (ARR) of developing diabetes and a 35% greater absolute likelihood of reverting to NGR. Participants at lowest risk of developing diabetes who adhered to a metformin intervention had no reduction in their risk of developing diabetes and a 17% greater absolute likelihood of reverting to NGR. Participants at highest risk of developing DM who adhered to a lifestyle intervention had a 39% ARR of developing diabetes and a 24% greater absolute likelihood of reverting to NGR, whereas those who adhered to the metformin intervention had a 25% ARR of developing diabetes and an 11% greater absolute likelihood of reverting to NGR. **This study argues for use of individual level risk, determined through a combination of risk factors, but stops short of performing economic analysis, as contributed by our study.**
DPP Research Group, NEJM 2002[123]	REDUCTION IN THE INCIDENCE OF TYPE 2 DIABETES WITH LIFESTYLE INTERVENTION OR METFORMIN	The original report of the DPP trial results – outcomes by one-way subgroups, no stratification by diabetes risk. **Clinical outcomes only.**
Aroda et al, J Clin Endocrinol Metab 2015[148]	The Effect of Lifestyle Intervention and Metformin on Preventing or Delaying Diabetes Among Women With and Without Gestational Diabetes: The Diabetes Prevention Program Outcomes Study 10-Year Follow-Up	Based on DPP-OS, over 10 years, women with a history of gestational diabetes mellitus (GDM) assigned to placebo had a 48% higher risk of developing diabetes compared with women without a history of GDM. In women with a history of GDM, lifestyle and metformin reduced progression to diabetes compared with placebo by 35% and 40%, respectively. Among women without a history of GDM, lifestyle reduced the progression to diabetes by 30%, and metformin did not reduce the

		progression to diabetes. **Note: if we take the history of GDM as a marker of "high risk", these findings mirror ours – showing that in "low risk" persons, lifestyle is effective in delaying or preventing diabetes, but metformin is not, and in "high risk" persons, both interventions are effective.** ***Clinical outcomes, no economic analysis*** **Our study contributes economic analysis with a broader set of risk factors.**
Perreault et al, the Lancet 2012[149]	Effect of regression from pre-diabetes to normal glucose regulation on long-term reduction in diabetes risk: results from the Diabetes Prevention Program Outcomes Study	Analysis of diabetes onset rates in DPP-OS comparing individuals who reverted to normal glucose regulation during DPP with those who didn't. Those who reverted to normal glucose regulation had lower risk of diabetes onset over 10 years. Diabetes risk during DPPOS was 56% lower for participants who had returned to normal glucose regulation versus those who consistently had pre-diabetes (hazard ratio [HR] 0.44, 95% CI 0.37–0.55, p<0.0001). Among participants who did not return to normal glucose regulation in DPP, those assigned to the intensive lifestyle intervention had a higher diabetes risk (HR 1.31, 95% CI 1.03–1.68, p=0.0304) and lower chance of normal glucose regulation (OR 0.59, 95% CI 0.42–0.82, p=0.0014) than did the placebo group in DPPOS. ***Clinical outcomes only*** **This study reports average effectiveness findings and is not directly relevant to our research**

		question.
Haw et al, JAMA Internal Med 2017[57]	Long-term Sustainability of Diabetes Prevention Approaches A Systematic Review and Meta-analysis of Randomized Clinical Trials	Review and meta-analysis of clinical outcomes of various diabetes prevention interventions. **Only average outcomes reviewed, no discussion of stratification or heterogeneity by diabetes risk.**
Economic Analysis of Diabetes Prevention		
Sullivan et al, J Med Econ 2011[43]	Cost-effectiveness of risk stratification for preventing type 2 diabetes using a multi-marker diabetes risk score	Markov model over 10 years, US payer perspective, to evaluate diabetes prevention in individuals with impaired fasting glucose (IFG), vs targeting IFG patients in high risk group according to PreDX Diabetes Risk Score. Conclusions: IFG alone is less cost-effective, risk stratification has ICER $17,000/QALY at 5 years and cost-saving at 10 years. There are indications that stratifying by diabetes risk has important impact on value. Intervention was based on the average effectiveness of metformin arm of DPP study. ***Economic outcomes: ICERs, NNT to prevent a case of diabetes*** **Our study provides analysis using more recent detailed patient level data, allowing analysis of the interaction of intervention effectiveness with diabetes risk. We also specifically estimate both lifestyle and metformin interventions.**
Zhuo et al, Am J Prev Med 2012[41]	Alternative HbA1c Cutoffs to Identify High-Risk Adults for Diabetes Prevention: A Cost-Effectiveness	Simulation model study to assess cost-effectiveness of different HbA1c thresholds for diabetes prevention, with lifetime time horizon and for US

	Perspective	healthcare system perspective. (same as Herman model) Interventions: lifestyle intervention per DPP trial, average effect in the first 3 years, assumed to continue thereafter. Findings: Lowering the HbA1c cutoff would increase the health benefits of the preventive interventions at higher costs. Lowering the HbA1c cutoff for pre-diabetes leads to less cost-effective preventive interventions. Assuming a conventional $50,000/QALY cost-effectiveness benchmark, the HbA1c cutoffs of 5.7% and higher were found to be cost effective. Lowering the cutoff from 5.7% to 5.6% also may be cost-effective, however, if the costs of preventive interventions were to be lowered. The diabetes incidence by A1c level was based on ARIC observational study. ***Economic outcomes: ICERs*** **Our study answers a different question. While this study focuses on HbA1c threshold alone as the marker for diabetes risk and indication for prevention therapy, we evaluate a multifactorial risk score approach for targeting prevention. We also evaluate both the lifestyle and metformin interventions using the most long term and up-to-date data from DPP-OS, which allows for specific individual-level analysis of intervention effectiveness and long term risk of diabetes onset, rather than assuming population average effectiveness.**
Zhuo et al, Diabetes Care 2013[40]	Cost-Effectiveness of Alternative Thresholds of the Fasting	Simulation model study to assess cost-effectiveness of different fasting plasma glucose (FPG) thresholds for diabetes prevention, with lifetime time horizon and

	Plasma Glucose Test to Identify the Target Population for Type 2 Diabetes Prevention in Adults Aged ≥45 Years	for US healthcare system perspective. (same as Herman model and Zhuo et al 2012 paper) CONCLUSIONS: Lowering the FPG threshold leads to a greater health benefit of diabetes prevention but reduces the cost-effectiveness. Using the conventional benchmark of $50,000 per QALY, a threshold of 105 mg/dL or higher would be cost effective. A lower threshold could be selected if the intervention cost could be lowered. Methodology and approach are substantially the same as Zhuo 2012 paper. ***Economic outcomes: ICERs*** **Our study answers a different question. While this study focuses on FPG threshold alone as the marker for diabetes risk and indication for prevention therapy, we evaluate a multifactorial risk score approach for targeting prevention. We also evaluate both the lifestyle and metformin interventions using the most long term and up-to-date data from DPP-OS, which allows for specific individual-level analysis of intervention effectiveness and long term risk of diabetes onset, rather than assuming population average effectiveness.**
Gregg et al, Am J Prev Med 2013[23]	Implications of Risk Stratification for Diabetes Prevention: The Case of Hemoglobin A1c	This paper is a discussion of various HbA1c-based risk-stratification approaches for diabetes prevention. HbA1c predicts diabetes and related outcomes across a wide range of HbA1c values. However, the authors estimate that, among

		U.S. adults, the top 15% of the nondiabetic HBA1c distribution (HbA1c of 5.7%–6.4%) accounts for 47% of diabetes cases over 5 years, and the top 30% (5.5%– 6.4%) accounts for about 70% of cases. Although this clustering of eventual cases at the high end of the HbA1c risk distribution means that intervention resources will be more efficient when applied to the upper end of the distribution, no obvious threshold exists to prioritize people for preventive interventions. **Note: HbA1c represents a single risk factor associated with diabetes onset, but extensive literature has shown that diabetes risk prediction is more robust when multiple risk factors are considered in a multivariate risk model approach. Our study uses a multivariate estimate of diabetes risk, rather than relying on HbA1c level alone, and further estimates individual level outcomes, which take into account the effect of diabetes risk on intervention effectiveness.**
Breeze et al, Diabetic Medicine 2017[42]	The impact of Type 2 diabetes prevention programmes based on risk-identification and lifestyle intervention intensity strategies: a cost-effectiveness analysis	Cost-effectiveness of diabetes prevention programs in subgroups, a UK NHS perspective. Subgroups included: age 40-65, low socioeconomic status, HbA1c > 6%, Finnish Diabetes Risk score > 0.1, BMI ≥ 35, South Asian ethnicity. Intervention: lifestyle intervention (based on meta-analysis of multiple programs), restricted to 2% of general population. Outcomes at 15 years and lifetime. Finding: most cost-effective to target individuals with HbA1c > 6%, Finnish

		Diabetes Risk score > 0.1, BMI ≥ 35. (in that order) ***Economic outcomes: incremental costs, qalys, nmb, icers, diabetes diagnoses*** **This paper is a simulation model analysis of a hypothetical lifestyle intervention in the UK, showing that targeting to certain higher risk subgroups of the general population, compared with doing nothing, is cost-effective using a 1-way subgroup or FDRS risk score.** **Our study is US-based, and focuses both on a well-described specific lifestyle intervention and metformin administration. We use a different risk score, and estimate outcomes by risk strata within the pre-diabetic population.**
Watson et al, Appl Health Econ Health Policy 2014[22]	Modelling the Economics of Type 2 Diabetes Mellitus Prevention: A Literature Review of Methods	Systematic review of issues and methods used in economic evaluation of diabetes prevention. The review suggested that existing models are structurally limited for evaluating cost-effectiveness by only defining one-way type subgroups as the target populations. The authors further suggested that modelers should use a multivariate risk equation for diabetes to overcome this limitation. **Based on the conclusions of this review, our study adds to the current knowledge by evaluating economic outcomes stratified by a multivariate measure of diabetes risk.**
Jacobs-van der Bruggen et al, Diabetes	Lifestyle Interventions Are Cost-Effective in People With Different Levels of Diabetes Risk	Dutch modeling study evaluated community lifestyle intervention and a healthcare setting lifestyle intervention (for those at high risk? This is not clearly described) in the general population. It is

Care 2007[150]		unclear how the model incorporated the effectiveness of intervention at different diabetes risk levels. In fact <u>no results by diabetes risk are reported, only average population results for the two interventions</u>. Paper concludes that both interventions are cost-effective, with ICERs ranging from €3,100-5,500/QALY. ***Economic outcomes: ICERS*** **Our study is US-based, covering different interventions and analyzing and reporting outcomes by risk strata.**
Roberts et al, BMJ Open 2017[47]	Preventing type 2 diabetes: systematic review of studies of cost-effectiveness of lifestyle programmes and metformin, with and without screening, for pre-diabetes	This is a systematic review of economic evaluations of various diabetes prevention programs. Conclusions: The economics of preventing diabetes are complex. There is some evidence that diabetes prevention programmes are cost effective, but the evidence base to date provides few clear answers regarding design of prevention programmes because of differences in denominator populations, definitions, interventions and modelling assumptions. It appears that lifestyle programmes and metformin appeared to be cost effective in preventing diabetes in high-risk individuals (median ICERs of £7490/QALY and £8428/QALY, respectively) but economic estimates varied widely between studies. Most studies use one-way measures to quantify risk – such as HbA1c or FPG levels; only two studies examined the use of a diabetes risk score, none have examined outcomes stratified by diabetes risks.

		Economic outcomes: ICERS **Based on this systematic review, no prior economic studies have estimated the economic impact of diabetes prevention by diabetes risk.**
Li et al, Ann Intern Med 2015[48]	Economic Evaluation of Combined Diet and Physical Activity Promotion Programs to Prevent Type 2 Diabetes Among Persons at Increased Risk: A Systematic Review for the Community Preventive Services Task Force	Twenty-eight studies were included. Costs were expressed in 2013 U.S. dollars. The median program cost per participant was $653. Costs were lower for group-based programs (median, $417) and programs implemented in community or primary care settings (median, $424) than for the U.S. DPP (Diabetes Prevention Program) trial and the DPP Outcomes Study ($5881). Twenty-two studies assessed the incremental cost-effectiveness ratios (ICERs) of the programs. From a health system perspective, 16 studies reported a median ICER of $13 761 per quality-adjusted life-year (QALY) saved. Group based programs were more cost-effective (median, $1819 per QALY) than those that used individual sessions (median, $15 846 per QALY). No cost–benefit studies were identified. Diet and physical activity promotion programs to prevent type 2 diabetes are cost-effective among persons at increased risk. Costs are lower when programs are delivered to groups in community or primary care settings. **No risk-stratified economic outcomes were presented, several studies reported cost-effectiveness by age-based subgroups, which are not strongly predictive of diabetes risk.**
Herman et al, Ann Intern Med 2005[35]	The Cost-Effectiveness of Lifestyle Modification or Metformin in Preventing	Simulation model to estimate lifetime cost-effectiveness of DPP interventions based on the DPP clinical trial.

	Type 2 Diabetes in Adults with Impaired Glucose Tolerance	Compared with the placebo intervention, the cost per QALY was approximately $1100 for the lifestyle intervention and $31 300 for the metformin intervention. From a societal perspective, the interventions cost approximately $8800 and $29 900 per QALY, respectively. From both perspectives, the lifestyle intervention dominated the metformin intervention. **Beyond this study, we incorporate individual risk heterogeneity and interaction between risk and DPP effectiveness, as well as long term data from DPP-OS to drive modeling assumptions.**
THE DPP RESEARCH GROUP, Diabetes Care 2012[151]	The 10-Year Cost-Effectiveness of Lifestyle Intervention or Metformin for Diabetes Prevention: An intent-to-treat analysis of the DPP/DPPOS	10 year US cost-effectiveness analysis of metformin and lifestyle interventions in the DPP population, quantifying the resource use data from DPP-OS. Conclusions: Over 10 years, from a payer perspective, lifestyle was cost-effective and metformin was marginally cost-saving compared with placebo. Investment in lifestyle and metformin interventions for diabetes prevention in high-risk adults provides good value for the money spent. **Analysis did not include any stratification by diabetes risk.** **Our study contributes individual risk stratification and a lifetime time horizon for the economic analysis.**
Herman et al, Am J Manag	Effectiveness and Cost-Effectiveness of Diabetes	Cost-effectiveness for average adherent participant in DPP over 10 years, US

Care 2013[34]	Prevention among Adherent Participants	healthcare system perspective. Concluded that over 10 years lifestyle and metformin were cost-saving compared to placebo. **This study does not incorporate individual risk heterogeneity or interaction between risk and DPP effectiveness. Also our analysis contributes a lifetime perspective.**
Palmer et al, Clin Ther 2004[152]	Intensive Lifestyle Changes or Metformin in Patients with Impaired Glucose Tolerance: Modeling the Long-Term Health Economic Implications of the Diabetes Prevention Program in Australia, France, Germany, Switzerland, and the United Kingdom	Non-US study of cost-effectiveness of lifestyle and metformin interventions. In this model analysis, incorporation of the DPP interventions into clinical practice in 5 developed countries was projected to lead to an increase in DM-free years of life, improvements in life expectancy, and either cost savings or minor increases in costs compared with standard lifestyle advice in a population with IGT. **Study does not incorporate risk stratification of any kind.**
Gillies et al, BMJ 2008[143]	Different strategies for screening and prevention of type 2 diabetes in adults: cost effectiveness analysis	Study evaluates cost-effectiveness of screening and lifestyle and pharmacologic prevention. Conclusion: Screening for type 2 diabetes and impaired glucose tolerance, with appropriate intervention for those with impaired glucose tolerance, in an above average risk population aged 45, seems to be cost effective. The cost-effectiveness of a policy of screening for diabetes alone, which offered no intervention to those with impaired glucose tolerance, is still uncertain. Results for specific ethnic groups were also included. **No multivariate risk stratification was done.**

		Our study contributes analysis stratified by diabetes risk, as determined by a multivariate risk estimation.
Caro et al, Diabetic Medicine 2004[153]	Economic evaluation of therapeutic interventions to prevent Type 2 diabetes in Canada	Cost-effectiveness of lifestyle and metformin interventions in Canada. The results of this model suggest that the treatment of IGT in Canada is a cost-effective way to prevent diabetes and may generate savings. While pharmacological treatments tended to be less costly, intensive lifestyle modification, if maintained, led to the greatest health benefits at reasonable incremental costs. **No analysis of diabetes risk heterogeneity or stratification using risk.**
General Policy Literature		
Zhuo et al, Health Affairs 2012[154]	A Nationwide Community-Based Lifestyle Program Could Delay Or Prevent Type 2 Diabetes Cases And Save $5.7 Billion In 25 Years	Evaluation of a general population (ages 18-84) screening and community based lifestyle intervention program (based on DPP – average effects). Simulation model over 25 years in the US, healthcare system perspective. No risk stratification was done. **Our study advances the evaluation of costs and benefits of DPP by incorporating the individual level risk stratification and interaction between diabetes risk and DPP effectiveness, also by analyzing both lifestyle and metformin interventions.**
Rich et al, Clinical Diabetes 2013[24]	Using a quantitative measure of diabetes risk in clinical practice to target and maximize diabetes	This is a brief review and case series describing the PreDx test which generates a diabetes risk score based on seven biomarkers.

	prevention interventions	**This article outlines the use of a multifactorial risk estimate for targeting individuals for diabetes prevention, without quantifying economic outcomes for the population.**
Davidoff, Ann Intern Med 2016[11]	Can Knowledge About Heterogeneity in Treatment Effects Help Us Choose Wisely?	Perspective piece on heterogeneity of treatment effects and the need for trials to report outcomes stratified by patients' baseline risk, rather than one-variable at a time subgroups.
Kim et al, Health Affairs 2019[155]	Targeted Incentive Programs For Lung Cancer Screening Can Improve Population Health And Economic Efficiency	Incentivising use of lung cancer screening modalities by individuals who are most likely to benefit (according to baseline risk) can improve population health and economic efficiency. **Note: application of risk-based targeting in the area of oncology**

In the news:

National efforts in the US, identifying pre-diabetes, no risk stratification beyond that.

> Targeting populations to overcome barriers in diabetes prevention, by Sara Berg, AMA, JULY 23, 2018 (https://www.ama-assn.org/delivering-care/diabetes/targeting-populations-overcome-barriers-diabetes-prevention)

AMA launches multi-state effort to prevent type 2 diabetes, NOVEMBER 9, 2017 (https://www.ama-assn.org/press-center/press-releases/ama-launches-multi-state-effort-prevent-type-2-diabetes)

Framework in Scotland – promoting risk stratification beyond simple pre-diabetes

> A Healthier Future: type 2 Diabetes prevention, early detection and intervention: framework, 16 Jul 2018 (https://www.gov.scot/publications/healthier-future-framework-prevention-early-detection-early-intervention-type-2/pages/7/)

Chapter 8 : APPENDIX: Literature review of economic analysis of DAPT therapies

Table 8.1: Literature review summary on economic analysis of DAPT therapies

Reference	Year	Strategies/Population	Subgroup or stratification	Note
Wang[156]	2018	(i) generic clopidogrel or ticagrelor based on CYP2C19*2 genotype, (ii) universal use of generic clopidogrel or (iii) universal use of ticagrelor for all patients.		China
Okere[81]	2018	Genetically guided antiplatelet therapy	None	US
Magnuson[71]	2017	Pegasus-TIMI 54	One-way subgroups	US, High risk of ischemia
Reynard	2017	Patients with ACS	Clinical decision tool for antiplatelet therapy	US, conference abstract
Jiang[94]	2017	30-month vs 12-month clopidogrel and aspirin after drug-eluting stents in patients with ACS	None	US
Jiang[93]	2017	Same as Wang	None	US
De la Puente	2017	Ticagrelor vs clopidogrel	None	Chile
Zhao[157]	2016	Ticagrelor vs clopidogrel	None	Singapore
Jiang[158]	2016	Same as Wang	None	US
De la Puente	2016	Ticagrelor vs clopidogrel	None	Chile
Jiang	2016	Same as Wang	None	US
Abdel-Qadir[159]	2015	Ticagrelor vs clopidogrel	None	Canada
Mejia[160]	2015	Ticagrelor vs clopidogrel	None	Colombia

Cowper[80]	2015	PLATO/ Ticagrelor vs clopidogrel	None	US
Jiang	2015	Same as Wang	None	US
Janzon[161]	2015	PLATO/ Ticagrelor vs clopidogrel	None	Europe and Brazil
Yamwong[162]	2014	PLATO/ Ticagrelor vs clopidogrel	None	Thailand
Henriksson[163]	2014	PLATO/ Ticagrelor vs clopidogrel	None	Sweden, Denmark
Kazi[164]	2014	Same as Wang	None	US
Paweska[165]	2014	PLATO/ Ticagrelor vs clopidogrel	None	Poland
Gouveia	2014	PLATO/ Ticagrelor vs clopidogrel	None	Portugal
Grima[166]	2014	PLATO/ Ticagrelor vs clopidogrel	None	Canada
Coleman[167]	2014	(i) generic clopidogrel or ticagrelor based on platelet reactivity assay, (ii) universal use of generic clopidogrel or (iii) universal use of ticagrelor for all patients.	None	Multi-country
Sorich[168]	2013	Same as Wang	None	Australia
Gasche[169]	2013	PLATO/ Ticagrelor vs clopidogrel	None	Switzerland
Liew[170]	2013	PLATO/ Ticagrelor vs clopidogrel	None	Australia
Coleman[171]	2013	(i) generic clopidogrel or ticagrelor based on platelet reactivity assay, (ii) universal use of generic clopidogrel or (iii) universal use of ticagrelor for all patients.	None	US
Chin[172]	2013	PLATO/ Ticagrelor vs clopidogrel	None	Singapore
Theidel[173]	2013	PLATO/ Ticagrelor vs clopidogrel	None	Germany
Nicolic	2012	PLATO/ Ticagrelor vs clopidogrel	None	Sweden

Chapter 9 : Bibliography

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