Overcoming Overuse One Decision at a Time: An Evidence Based Medicine Approach

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This is to acknowledge that Anil Makam, MD has disclosed that he does not have any financial incentives or other relationships with commercial concerns related directly or indirectly to this program. Dr. Makam will not be discussing off-label uses in his presentation. However, he will challenge existing paradigms of treatment.

BIOSKETCH: Anil N. Makam, MD, MAS completed a combined BS/MD program through Lehigh University and Drexel University College of Medicine. He completed his internal medicine residency at UT Southwestern Medical Center. Following his medicine residency he completed a research fellowship at the University of California San Francisco. Dr. Makam joined the faculty at UT Southwestern in 2013 and is currently an Assistant Professor in the Divisions of General Internal Medicine and Outcomes & Health Services Research. Dr. Makam is a health services researcher and practices general internal medicine at Parkland Health & Hospital System, with a focus in hospital medicine. His research interests include post-acute care in the elderly, hospital readmissions, and high value care. Dr. Makam's research is currently supported by the NIH (NCATS, NHLBI) and AHRQ. His clinical and medical education interests include evidence-based medicine (EBM) and critical appraisal of the literature. Locally, he serves on the Department of Internal Medicine's High Value Care Committee and co-directs the Internal Medicine residency's EBM curriculum and journal club at UT Southwestern. Nationally, he is an Associate Editor for the *Journal of Hospital Medicine*.

PURPOSE AND OVERVIEW: Overuse is rampant and leads to potential harms and waste in healthcare. This presentation aims to discuss how an evidence-based medicine (EBM) approach to clinical decision making can overcome overtreatment and promote high value care. To illustrate the applicability of this approach to clinical practice, the EBM principles discussed will be presented in the context of intensive glycemic control through pharmacologic therapies for type 2 diabetes. However, this approach is not unique to glycemic control and can be broadly applied to any treatment for any disease.

EDUCATIONAL OBJECTIVES:

1. Understand the pitfalls of using relative risks and why absolute risks are a more meaningful measure to inform treatment decisions
2. Understand the importance of balancing risks and benefits to guide treatment decisions
3. Learn how to incorporate time horizon to benefit into treatment decisions
4. Understand that overtreatment of hyperglycemia in diabetes is an epidemic

INTRODUCTION: AN OVERVIEW OF OVERUSE

Overuse is defined by the Institute of Medicine as the use of a health care service even when the potential risks exceed the possible benefits.[1] Overuse is pervasive in medicine and is not limited to a single diagnostic or therapeutic category.[2] Overuse accounts for approximately 20% of the estimated $750 billion of wasteful spending in health care in the United States.[3]

Overuse is not only a national issue, but is also local issue with important implications for health care delivered in north Texas. Analysis of Medicare data by the Dartmouth Atlas group has shown that the Dallas is the 4th most expensive region for health care spending in the country.[4]

Aside from the excess costs resulting from overuse, many physicians in the United States believe their own patients are receiving too much medical care that is potentially harmful. In a nationally representative survey study of US primary care physicians (PCPs), 42% believed patients in their own practice were receiving too much care.[5] Even more were concerned about overly aggressive practice among nurse practitioners/physician assistants (47%) and medical subspecialists (61%).[5]

Overuse has many drivers, including several external factors that influence decisions, including financial incentives, malpractice concerns, performance metrics, practice culture, and time constraints. One potential solution to overuse is to leverage evidence-based medicine (EBM) approaches to promote "right" care, independent of the external factors that may lead to overuse. The focus of today's talk is to specifically focus on applying EBM principles to overcoming overtreatment. Overtesting, which is another important area of health care waste and potential harm to patients, will not be discussed today given that the relevant EBM principles to promote Bayesian clinical decision making are distinct from those that govern the prevention of overtreatment.

USING AN EBM APPROACH TO OVERCOME OVERTREATMENT

The reason to use an EBM approach for clinical decision making is simple—there is no better alternative method.[7] In the words of the late David Sackett, one of the founding fathers of EBM and clinical epidemiology, EBM is the "conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients."[6] The practice of EBM means integrating best available evidence with a clinician's judgment and expertise, and the patient's values and preferences (**Figure 1**).

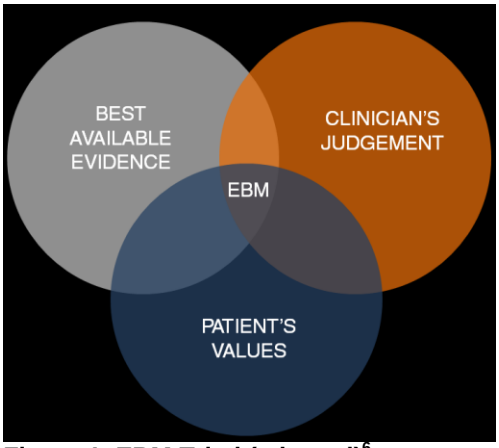


Figure 1. EBM Triad (adapted)[6]

Practicing EBM is not "cookbook" medicine, but truly an art. There are two key reasons for why practicing EBM is not synonymous with

the delivery of uniform healthcare (i.e. top-down "cookbook" medicine). First, many recommendations and guidelines are based on weak evidence, and as such, should not be indiscriminately applied and disseminated to the general public.[8] For example, among the American College of Cardiology (ACC) and the American Heart Association (AHA) practice guidelines, only 11% of the 2,711 recommendations are classified as level of evidence A (i.e. supported by multiple randomized trials or meta-analyses).[9] Furthermore, among the 1,305 class I ACC/AHA guideline recommendations, which indicate general consensus that a particular health care service is useful and effective, only 19% have level of evidence A.[9] As such, approximately 20% of class I ACC/AHA guideline recommendations were downgraded, reversed, or omitted within a decade, suggesting questionable durability in the absence of strong evidence.[10] The proliferation of recommendations based on a weak or non-existent evidence base is not only an issue for practice guidelines, but is a phenomenon observed among popular online evidence-based resources. Approximately 2/3^{rds} of the 9,400 graded recommendations in UpToDate are supported by weak evidence (i.e. absence of clinical trials or robust observational studies).[8]

The second and more compelling reason for why EBM is not synonymous with "cookbook" medicine is that even for recommendations based on strong evidence, decisions in clinical practice are still ultimately value judgements.[6,8] Science can inform decisions, but ultimately cannot make value judgements for us. Thus, EBM requires a bottom-up approach that incorporates the best available evidence with both the clinician's expertise and judgement and the patient's values and preferences.

Using an EBM Approach to Overcoming Overtreatment: Specific Objectives

1. Understand the pitfalls of using relative risks and why absolute risks are a more meaningful measure to inform treatment decisions
2. Understand the importance of balancing risks and benefits to guide treatment decisions
3. Learn how to incorporate time horizon to benefit into treatment decisions

To illustrate the applicability of EBM to clinical decision making, the three objectives listed above will be presented in the context of intensive glycemic control using pharmacologic therapies for type 2 diabetes mellitus (which will henceforth interchangeably be referred to as diabetes). While using an EBM approach is not unique to a particular treatment or disease, diabetes is an ideal disease model to illustrate how an EBM approach can overcome overtreatment because: 1) diabetes is highly prevalent; 2) the strategy of intensive glycemic control has been thoroughly investigated, and there is a large body of evidence on the harms versus benefits of this treatment strategy; 3) the decision to pursue glycemic control is less dependent on external motivators of overuse such as financial incentives and malpractice concerns compared to other conditions (e.g. percutaneous coronary intervention for stable angina); and 4) applying an EBM approach to the treatment of hyperglycemia in type 2 diabetes challenges an existing paradigms of treatment.

1. The Pitfalls of Relative Risks and Why Absolute Risks Are a More Meaningful Measure to Inform Treatment Decisions

To understand the pitfalls of using relative risks to inform treatment decisions and why absolute risks are a more meaningful and preferred measure of treatment efficacy, it is first necessary to review how the these various estimates of treatment effect sizes are computed.

In a hypothetical randomized controlled trial of drug X versus placebo administered for one year, where the primary outcome of myocardial infarction occurred in 10% of individuals in the treatment group (risk 1) versus 15% in the placebo group (risk 2), the treatment effect size can be presented in either relative or absolute terms as illustrated in ***Table 1****.*

Table 1. Calculating Relative versus Absolute Risk

Relative risk		**Absolute risk**	
Relative risk ratio	**Relative risk reduction**	**Absolute risk reduction**	**Number needed to treat**
Risk 1/Risk 2	1 – (Risk 1/Risk 2)	Risk 2 – Risk 1	1/(Risk 2 – Risk 1)
0.10/0.15 = 0.66	1 – 0.66 = 0.34 or 34%	0.15 – 0.10 = 0.05 or 5%	1/0.05 = 20

A number needed to treat (NNT) of 20 in this example means that you would need to treat 20 individuals with drug X for 1 year to prevent 1 additional myocardial infarction compared to placebo. Notably, a NNT of 20 also implies that for 20 people treated with drug X, 19 people derive *no benefit* with respect to preventing myocardial infarction compared to being prescribed placebo. Although both approaches to conveying absolute risk are valid, the NNT more clearly illustrates that the benefits of treatment are not shared equally by each individual in the treatment group, and that most individuals in this example will not derive any benefit after one year of therapy, even for what many would consider a clinically meaningful effect size.

In summary, for the hypothetical example presented above, a relative risk of 0.66, a relative risk reduction of 34%, an absolute risk reduction of 5%, and a NNT of 20 are all statistically valid ways to convey treatment effect size. However, through the context of glycemic control for diabetes, the advantages of conveying risk in absolute terms will become more evident.

Relative Benefits of Intensive Glycemic Control for Diabetes

Table 2. Relative Benefits of Intensive Glycemic Control

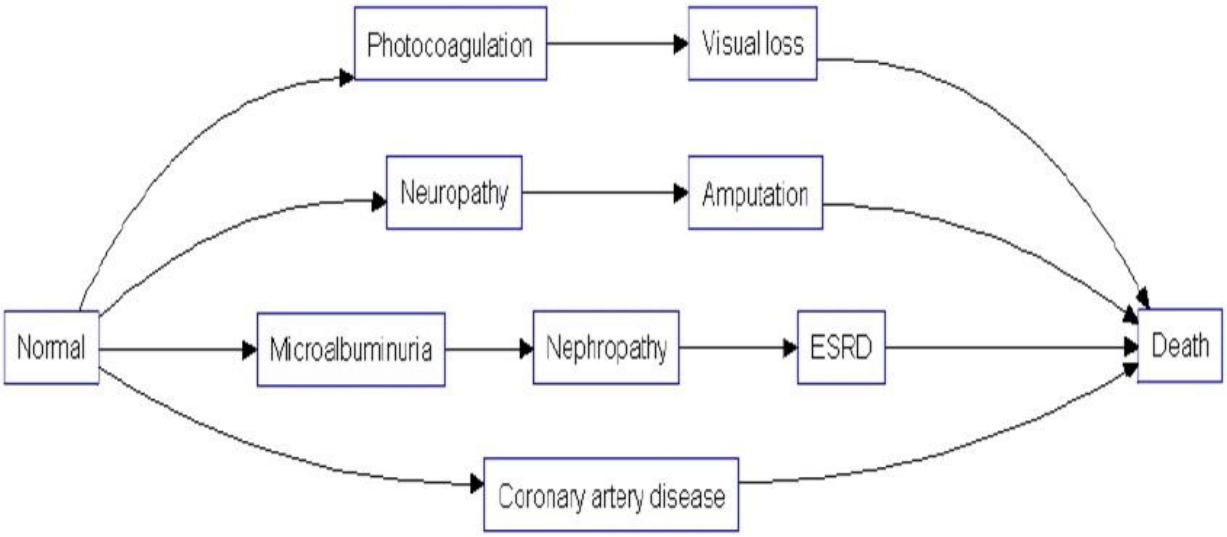
Outcome	**Relative risk reduction**	**Source**
Retinopathy	29% per 0.9% ↓ A1c	UKPDS[11]
Neuropathy	19% per 0.9% ↓ A1c	UKPDS[11]
Microalbuminuria	33% per 0.9% ↓ A1c	UKPDS[11]
Non-fatal myocardial infarction	15% per 1.0% ↓ A1c	Boussageon et al.[12]

The relative benefits of intensive glycemic control (A1c 6.4-7.0%) versus conventional glycemic control (A1c 7.9-8.4%) in type 2 diabetes are summarized in **Table 2**. In the

landmark UKPDS trial, the relative benefits of 10 years of intensive glycemic control for newly diagnosed type 2 diabetics were only demonstrated for intermediate microvascular outcomes, and not for patient-centered complications due to microvascular disease (e.g. visual loss, amputation, or end-stage renal disease).[11] While the benefits of intensive glycemic control for reducing intermediate microvascular outcomes have been consistently observed in subsequent trials,[12] the 15% relative reduction in non-fatal myocardial infarction (MI) is less certain. Whereas each of the four landmark trials on intensive glycemic control (UKPDS, VADT, ACCORD, and ADVANCE) did not show a statistically significant reduction in non-fatal MIs, the results of a meta-analysis more clearly supported this 15% reduction.[12]

While intensive glycemic control has not been shown to directly reduce all-cause mortality (RR 1.04, 95% CI, 0.91-1.19),[12] intensive glycemic control indirectly reduces mortality through improving intermediate microvascular outcomes and non-fatal myocardial infarctions (**Figure 2**).[13]

Figure 2. Schematic Representation of Diabetes (Adapted from Vijan et al.)[13]



Absolute Benefits of Intensive Glycemic Control for Diabetes

Since trials have not shown a direct reduction in patient-centered microvascular endpoints or all-cause mortality, in order to estimate the potential absolute benefits of glycemic control it is essential to rely on a simulation model. In a well-designed study, Vijan and colleagues used a Markov simulation model to estimate the absolute benefits of glycemic control using simulated patients based on the actual adults with diabetes sampled in the National Health and Nutrition Examination Study (NHANES), a nationally representative survey. As shown in the schematic in **Figure 2**, the authors modeled the risk of progression from a "normal" diabetic state to intermediate steps using the relative risk reductions in intermediate outcomes with intensive glycemic control observed in clinical trials (see Table 2), and then estimated the likelihood of progression from intermediate to end-stage complications (i.e. ESRD) using findings from other

randomized controlled trials and observational studies using large US-based population cohorts.

Using this model, the authors simulated two treatment scenarios commonly encountered in clinical practice to estimate the absolute risk reduction in more clinically meaningful microvascular endpoints. Treatment scenario #1 consisted of a newly diagnosed diabetic with a hemoglobin A_{1c} (HbA_{1c}) of 8.5% who is prescribed metformin and experiences a reduction in the HbA_{1c} level of 1.5 points to 7.0%, and remained at this level over the course of the person's life. Treatment scenario #2 was the initiation of insulin therapy for the same patient in treatment scenario #1, after 10 years of oral glucose-lowering therapy after a gradual rise in HbA_{1c} level back to 8.5%. In this scenario, insulin therapy reduced the HbA_{1c} level to 7.5% and remained at this level over the remainder of the person's life. The lifetime absolute benefits of intensive glycemic control for each scenario, varying the age at which diabetes was initially diagnosed, are shown in **Table 3**.

Table 3. Absolute Benefits of Intensive Glycemic Control for Two Treatment Scenarios

	Lifetime Absolute Risk Reduction (NNT)		
Age at Diagnosis, years	**ESRD**	**Vision loss**	**Amputation**
Treatment scenario #1: initiation of metformin at diagnosis to reduce HbA_{1c} from 8.5% to 7%			
45	6.5% (16)	2.1% (48)	2.7% (38)
55	4.2% (24)	1.6% (63)	2.2% (46)
65	2.1% (48)	1.0% (100)	1.5% (67)
75	0.7% (143)	0.5% (200)	0.8% (125)
Treatment scenario #2: initiation of insulin at 10 years after diagnosis to reduce HbA_{1c} from 8.5% to 7.5%			
45	1.3% (77)	0.4% (250)	0.4% (250)
55	0.7% (143)	0.2% (500)	0.3% (334)
65	0.3% (334)	0.1% (1000)	0.2% (500)
75	0.1% (1000)	0.0% (∞)	0.1% (1000)

In both treatment scenarios, the NNT greatly declines with age (more to come on this in the section on time horizon to benefit). For an average 75 year old with newly diagnosed diabetes initiating metformin (treatment scenario #1), the NNT for preventing ESRD, vision loss, and amputation over one's remaining lifetime are estimated to be 143, 200, and 125 respectively. For adults 55 years of age or older diagnosed with diabetes and initiated on insulin 10 years later for "poorly controlled" diabetes (HbA_{1c} of 8.5% on oral therapy), the NNT are well above 100 for each endpoint. In other words, greater than 99% of older adults initiated on insulin therapy to achieve intensive glycemic control will not derive any meaningful benefit within their lifetime.

The findings shown in **Table 3** illustrate the stark differences in using relative versus absolute risks to inform treatment decisions. Despite using fixed relative risk reductions for intermediate microvascular outcomes, the absolute risk reductions for end-stage microvascular endpoints are vastly different for individual patients with different baseline risk and life expectancies. Thus, relying on relative risks to evaluate treatment efficacy can lead to vastly overestimating benefits, and is the reason why absolute risks are the preferred method to inform treatment decisions.

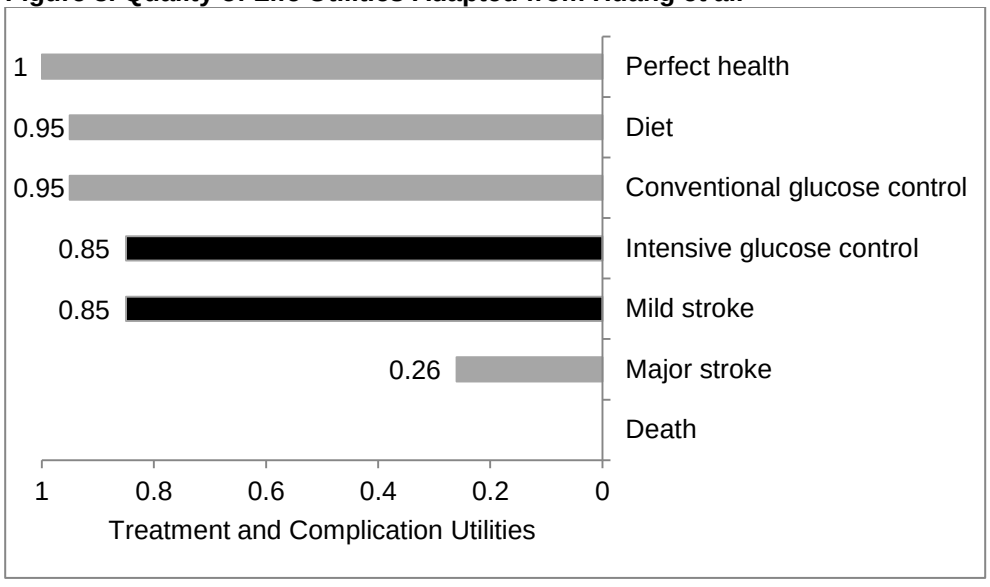
2. Balancing Risks and Benefits to Guide Treatment Decisions

Given that overuse is defined as the imbalance between risks and benefits, it is not enough to focus only on the benefits of therapy. Not considering the harms of therapy would lead one to always favor treatment, even if the NNT is 1000!

In the case of intensive glycemic control for type 2 diabetes, there are several important risks to consider before prescribing glucose-lowering therapy. While risks are unique to particular pharmacologic therapies, the most common side effects reported for patients randomized to the strategy of intensive glycemic control in clinical trials were severe hypoglycemia and weight gain, which were largely attributable to the higher rates of insulin use among these patients.[12,14] Severe hypoglycemia occurred in 4.9% of patients assigned to intensive glycemic control compared to only 2.0% of patients assigned to conventional glycemic control (absolute risk increase=2.9%; NNH=35; RR=2.33).[12] Intensive glycemic control increased body weight by approximately 3% (95% CI, 2% to 4%).[14]

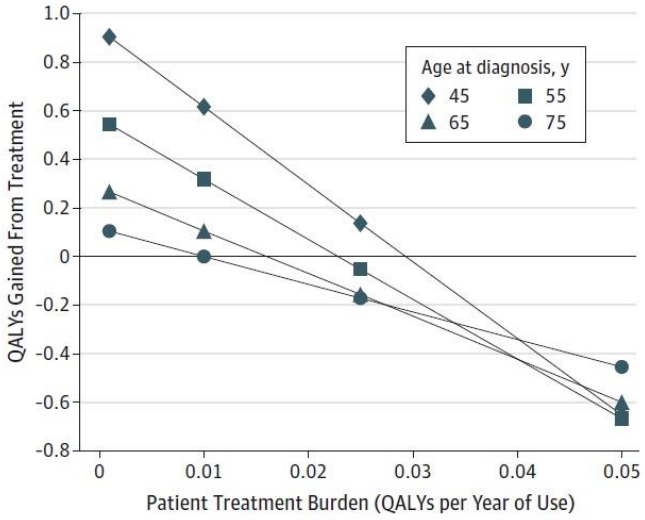
In addition to hypoglycemia and weight gain, an important but often overlooked harm of intensive glycemic control is the decrease in a patient's overall quality of life due to the burden of the treatment itself. Due to the burden of polypharmacy, insulin injections, blood glucose monitoring, and frequency of health care visits that accompany intensive glycemic control, this treatment strategy is perceived by patients to have a median quality of life utility of 0.85 (mean of 0.67 ± 0.34) on a scale where perfect health is 1 and death is 0.[15] A utility of 0.85 (also referred to as a disutility of 0.15) means patients equate living 10 years with intensive glycemic control the same as living 8.5 years in perfect health. Notably, the decrease in quality of life due to intensive glycemic control is perceived by patients to be of the same magnitude as that of a mild stroke (**Figure 3**).

Figure 3. Quality of Life Utilities Adapted from Huang et al.[15]



One commonly used approach to balance the benefits of intensive glycemic control in reducing disease complications and the harms due to treatment is to estimate the net quality-adjusted life years (QALYs) associated with therapy. In the Markov simulation model described above, Vijan and colleagues assigned quality of life utilities to different disease states along the spectrum from a "normal" diabetic state to death (as depicted in the simplified schematic in **Figure 2**) based on prior quality of life literature on diabetes complications to estimate the net QALYs gained or lost.[13] The authors examined the effect of treatment burden on net lifetime QALYs across a range of disutilities for intensive glycemic control using a treatment scenario where a patient was prescribed a glucose-lowering therapy that led to a 1% reduction in HbA_{1c} from 8.5% to 7.5%. Overall, in this treatment scenario the level of treatment burden has a profound impact on the net QALYs achieved from treatment (**Figure 4**). If a patient experiences no treatment burden whatsoever due to intensive glycemic control (i.e. assigning a treatment burden of 0), in this scenario, glucose-lowering therapies would yield net benefits for patients across all four age groups shown in Figure 4 (estimated lifetime net QALYs gained range from 0.1 for an average 45 year old adult to 0.9 for an average 75 year old). However, a treatment burden (i.e., disutility) as modest as 0.04 (i.e. 0.96 utility) outweighs all benefits of glycemic control across all age groups. Notably, the authors' optimistic assumptions of a 15% risk reduction in non-fatal myocardial infarction events and relatively low treatment disutilities (capped at 0.05) bias the results in favor of glucose-lowering treatment. Thus, the net loss in quality of life is likely to be greater for patients than the scenario modeled in this study suggests.

Figure 4. QALYs Gained or Lost by Treatment Burden[13]



Quality-adjusted life years gained or lost by a treatment that leads to a 1% reduction in hemoglobin A_{1c} level (from 8.5% to 7.5%) across 4 age groups and views of the burden of treatment.

This scenario highlights the importance of balancing the risks and benefits in therapeutic decisions. If glucose-lowering therapies are considered to have no risks (i.e., disutility of treatment burden = 0), then they are universally beneficial for all patients (lifetime QALYs gained from treatment = 0.1-0.9), albeit modestly. However, when one takes into account the risks, even a modest treatment burden (disutility=0.04) results in a net decrease in quality of life (QALYs gained from treatment <0 for all age groups). In summary, given that patient treatment burden can potentially negate any benefit gained from treatment, it is essential to elicit patients' perceived and observed treatment burden and use this information to inform treatment decisions.

3. Incorporating Time Horizon to Benefit Into Treatment Decisions

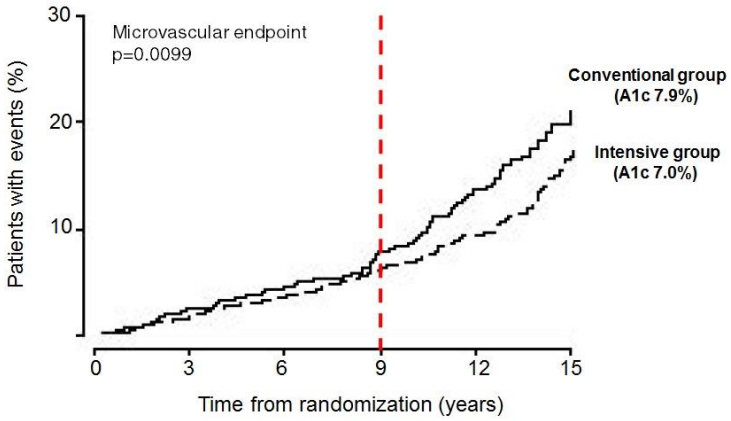
Although measures of absolute risk are preferable to measures of relative risk, one of the key limitations of using absolute risk is that they do not capture the full effect of time.[16] Absolute measures of risk must always be accompanied by a specific time interval to facilitate proper interpretation because they are estimated at a specific point in time. Typically, measures of absolute risk are reported at the end of a study's pre-specified follow-up period.

As a consequence of not incorporating time, absolute measures of risk do not consider the possibility of a beneficial postponement of an outcome. For example, consider a hypothetical trial of adults with a 100 year follow-up period where the primary outcome is mortality. Given the extremely long follow-up period, the intervention will essentially yield an absolute risk reduction of 0 (and a NNT of infinity) at the conclusion of the trial since all participants will have died due to the biological limits of human life expectancy. In this study, relying solely on the absolute risk reduction or NNT as measures of effect size may fail to capture a potential benefit of treatment if therapy postponed the inevitable outcome of death for a clinically meaningful amount of time.

Similarly, absolute measures of risk do not consider the time horizon to benefit—that is the time that must be accrued on treatment until a meaningful benefit emerges. This is a more commonly encountered issue than postponement of an outcome since study follow-up periods tend to be limited in duration due to cost and resource constraints. The implication for a treatment with a sufficiently long time horizon to benefit is that patients with a limited life expectancy may never stand to benefit. Thus, it is essential to always consider the context of the patient, because if patients with limited life expectancy are being treated with therapies that have time horizons to benefit that exceed their anticipated life expectancy, then the patient will be exposed to the potential harms of therapy with only a marginal chance of benefit.

The time horizon to benefit can be estimated in clinical research studies by calculating the difference in the area between the survival curves. However, unlike for magnitude of benefit, measures of time are infrequently reported. If quantitative estimates of the time horizon to benefit are not reported, the time horizon to benefit can be estimated by reviewing the Kaplan-Meier survival curves for the intervention and control

Figure 5. Time horizon to benefit for intensive glycemic control (adapted from UKPDS)[11]



groups.[17] The point at which the two curves diverge provides a qualitative estimate of the time horizon to benefit for a given treatment.

To illustrate how to estimate the time horizon to benefit, we will return to the example of intensive glycemic control for type 2 diabetes. Based on the Kaplan-Meier curve for intermediate microvascular endpoints from the UKPDS trial, intensive glycemic control takes approximately 9 years before a noticeable difference can be observed between the two groups (as shown by the vertical dashed line in **Figure 5**). However, it is important to note that the composite microvascular outcome reported in the UKPDS trial consists of intermediate surrogate outcomes that typically do not directly harm patients (i.e. microalbuminuria). Benefits of intensive glycemic control for more meaningful microvascular outcomes (i.e. ESRD) typically take 2 or more decades to manifest.[18,19]

Many patients prescribed intensive glycemic control have life expectancies less than 20 years, and potentially even less than 9 years, which is the earliest we could reasonably expect to observe benefits for intermediate microvascular outcomes. For example, if patients have comorbidities that clearly denote poor prognosis, including advanced cancers, end-stage renal disease, advanced dementia, cirrhosis, and end-stage heart failure and lung disease, then they are unlikely to benefit from intensive glycemic control. In addition to these obvious comorbid conditions that considerably limit life expectancy, there are several highly prevalent but less commonly recognized conditions that also indicate poor prognosis and limited life expectancy. For example, after the first hospitalization for heart failure with either preserved or reduced ejection fraction, patients have a 70% 5-year mortality rate.[20] Likewise, after the first hospitalization for COPD, patients have an 80% 9-year mortality.[21]

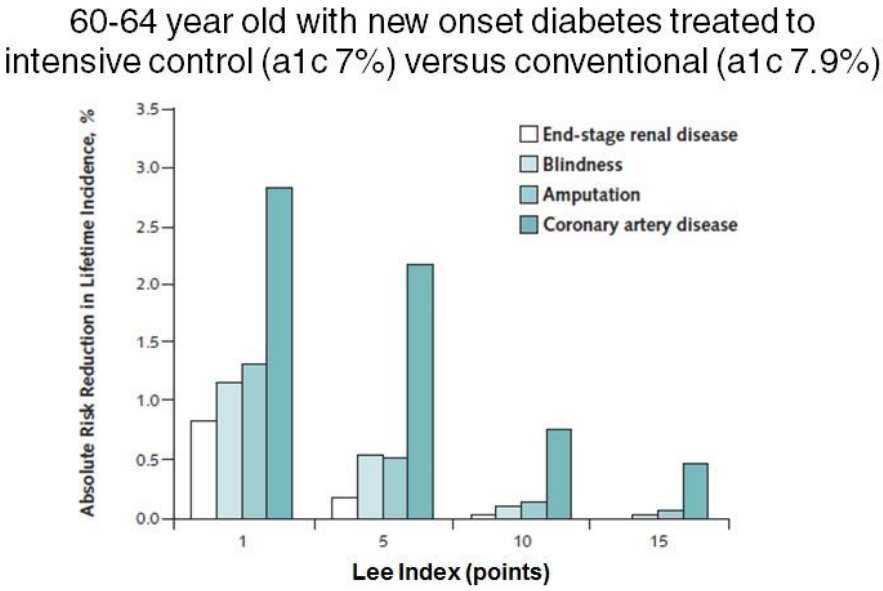
As health care is becoming increasingly complex, clinicians may often have difficulty pointing to a single disease that imposes a poor prognosis, but rather recognize the cumulative burden of multimorbidity and impaired functional status. To help quantify the prognosis related to advanced age, multimorbidity, and poor functional status, Lee and colleagues derived and validated a 4-year and 10-year prognostic index for mortality among community dwelling adults 50 years or older (**Figure 6;** http://eprognosis.ucsf.edu/leeschonberg.php).[22,23] The Lee index has excellent discrimination (C-statistic of 0.83) and calibration (less than a 4% difference between predicted and observed mortality rates across all risk levels).[23] Applying the Lee index to the Health and Retirement Study, a nationally representative longitudinal cohort of community dwelling adults 50 years of age or older, 25% of individuals have scores of ≥ 8 points, which corresponds to greater than 50% 10-year mortality.

Figure 6. Lee Prognostic Index[22]

Risk Factor	Adjusted OR (95% CI)*	Points
Demographics		
Age, y		
60-64	1.9 (1.4-2.5)	1
65-69	2.8 (2.1-3.7)	2
70-74	3.7 (2.8-4.9)	3
75-79	5.4 (4.1-7.1)	4
80-84	8.3 (6.3-11.0)	5
≥85	16.2 (12.2-21.6)	7
Male sex	2.0 (1.8-2.3)	2
Comorbidities and behaviors		
Diabetes mellitus	1.8 (1.5-2.1)	1
Cancer	2.1 (1.7-2.4)	2
Lung disease	2.3 (1.8-2.9)	2
Heart failure	2.3 (1.8-3.1)	2
BMI<25	1.7 (1.4-1.9)	1
Current smoker	2.1 (1.7-2.5)	2
Functional measures		
Bathing	2.0 (1.6-2.4)	2
Managing finances	1.9 (1.6-2.3)	2
Walking several blocks	2.1 (1.8-2.4)	2
Pushing/pulling heavy objects	1.5 (1.3-1.8)	1

Thus, a staggering number of patients are unlikely to live 10 years, let alone 20 years, in order to reap the benefits of intensive glycemic control. This can be reflected in the exceedingly low lifetime absolute benefits for intensive glycemic control that can be expected among patients who have high point scores on the Lee index (**Figure 7**).

Figure 7. Absolute Benefits Decrease with Increasing Lee Index Score (adapted)[24]

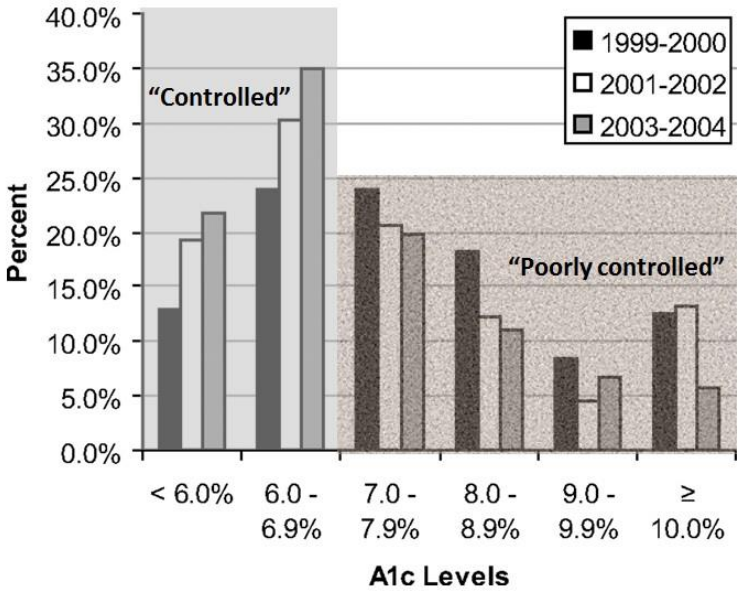


4. Putting it All Together: The Epidemic of Overtreatment in Type 2 Diabetes

Applying the EBM principles of absolute benefits, risks, and time horizon to benefit to intensive glycemic control for diabetes strongly suggests that we are massively overtreating patients with glucose-lowering therapies such that we are treating a large number of patients where the potential harms of therapy exceed the potential benefits.

Glycemic control is improving in the US. Data from three different waves of NHANES, a nationally representative prospective survey of adults, show that HbA_{1c} levels have decreased significantly. As of 2003-2004, over 55% of diabetics have HbA_{1c} levels less than 7%, which by convention is considered "well controlled" (**Figure 8**).[25] However, as discussed in the sections above, achieving 'tight' glycemic control may represent overtreatment if the patients who are achieving HbA_{1c} levels

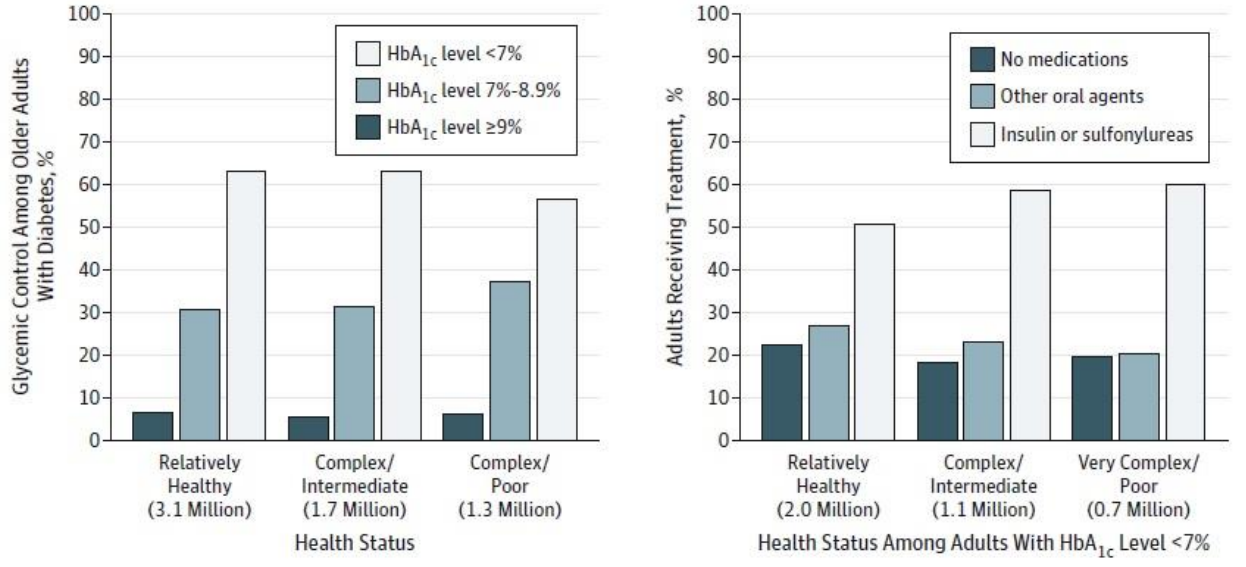
Figure 8. HbA_{1c} Distribution by NHANES Wave (adapted)[25]



less than 7% have less to gain, are exposed to greater harm, and have life expectancies shorter than the time horizon of benefit.

A closer examination of the data indeed shows this very concerning pattern, that many of those who have the least to gain and the most to be harmed are being treated far too intensively. Using NHANES data, Lipska and colleagues found that nearly 60% (1.8 million) of the 3 million older adults with health classified as being "complex/intermediate" (≥3 chronic conditions or ≥2 instrumental activities of daily living impairments) or "complex/poor" (dialysis dependent or ≥2 activities of daily living impairments) have HbA_{1c} levels < 7% (**Figure 9**).[26] Furthermore, among the 1.8 million older adults who have achieved HbA_{1c} levels <7%, nearly 60% have done so with the use of insulin or sulfonylureas, two classes of glucose-lowering therapies with the greatest treatment burden profile.[26] Thus, these mulitimorbid and frail older adults are unlikely to experience the potential benefits of intensive glycemic control, but rather are exposed to the potential harms of therapy including hypoglycemia and decreased quality of life due to the treatment burden itself. Furthermore, in the Veteran Affairs healthcare system, approximately 50% of the 205,857 older veterans prescribed insulin and/or a sulfonylurea who are at high risk for hypoglycemia (≥ 75 years of age; serum creatinine ≥ 2 mg/dL; or dementia) have HbA_{1c} levels < 7%.[27] While the authors were unable to assess the rate of severe hypoglycemia in this high risk cohort, others have shown that hospitalizations for hypoglycemia among older diabetics are now more common in the US than hospitalizations for hyperglycemia (105 vs. 70 admissions per 100,000 person-years),[28] with the patients with the lowest HbA_{1c} levels being at greatest risk.[29] Taken together, we are massively overtreating diabetes without regard for absolute benefits, harms, and incorporating time horizon to benefit.

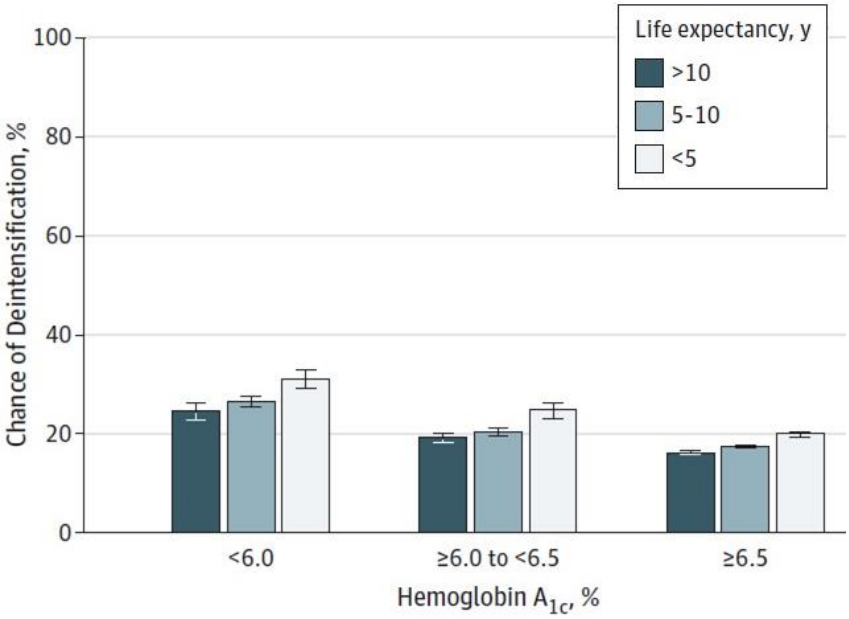
Figure 9. Potential Overtreatment Rates of Diabetes Among Older Adults[26]



One approach to overcoming overtreatment of diabetes is to discontinue glucose-lowering medications if HbA_{1c} levels are inappropriately low (< 7%). However,

medication deintensification is uncommon in clinical practice. Among older veterans who are actively being treated for diabetes, medication deintensification rates are fairly low (<30%), even among patients with extremely tight glycemic control (HbA_{1c} levels <6%) and those with limited life expectancy, as predicted by multimorbidity (Charlson Comorbidity Index) and age (**Figure 10**).[30]

Figure 10. Probability of Medication Deintensification[30]



There are several explanations for the clinical inertia to deintensify glucose-lowering therapies. First, a substantial proportion of clinicians believe that there is value for intensive glycemic control, even among older patients at greater risk for adverse effects. In a national survey of primary care physicians, 39% believed that a hypothetical older diabetic patient at high risk for hypoglycemia (HbA_{1c} of 6.4%, chronic kidney disease, and treated with a sulfonylurea) would benefit by having his HbA_{1c} level below 7%.[31] Similarly, nearly half of providers (45%) worried that the patient would be harmed if his HbA_{1c} level rose above 7.0%.[31] Second, practice guidelines for diabetes are glucose-centric, and do not embrace the principles of EBM. In the American Diabetes Association (ADA) Standards of Medical Care in Diabetes (~93 pages) and the ADA and European Association for the Study of Diabetes position statement (~20 pages), there was not a single mention or discussion of the absolute magnitude of risks and benefit of intensive glycemic control.[32] Furthermore, practice guidelines for diabetes are relatively blind to context. In a review of 28 different practice guidelines for glycemic goals in type 2 diabetes, only 60% considered comorbidities, 40% considered socio-personal context (i.e. financial means, caregiver support, etc.), and 40% considered patient preference.[33] Overall, the synthesis of best available evidence and the incorporation of patient context and preferences in practice guidelines are poor, and may unintentionally lead to uniform glycemic control goals, even when the harms of therapy outweigh its potential benefits.

SUMMARY FOR HOW TO OVERCOME OVERUSE USING AN EBM APPROACH

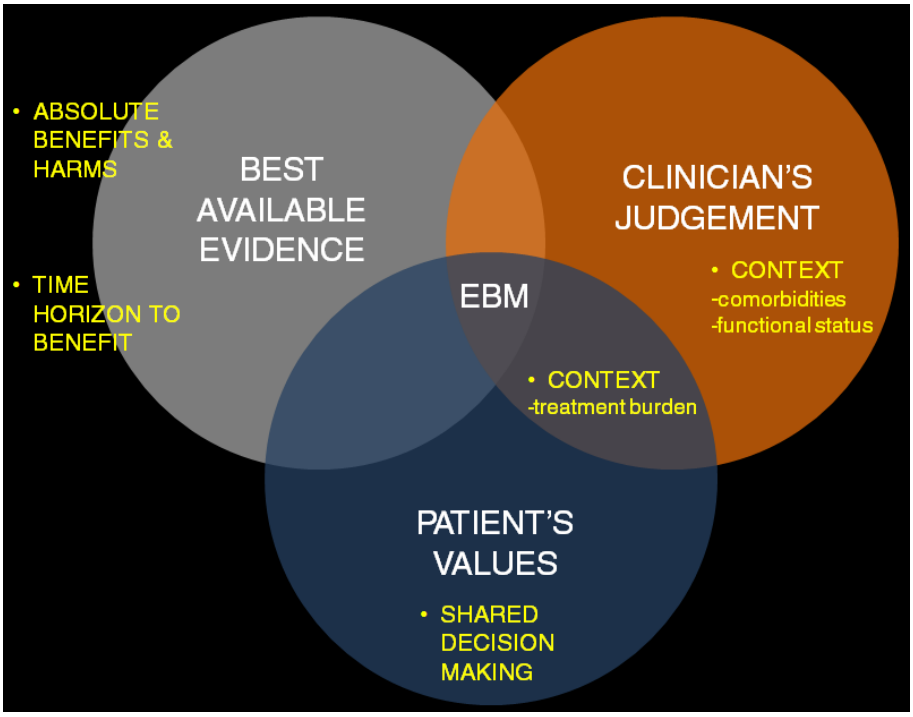


Figure 11. Summary of Using EBM Principles to Overcome Overuse

In summary, **Figure 11** illustrates the EBM framework that can be used for clinical decision making to inform treatment decisions. To promote "right" care and overcome overuse, it is essential to incorporate best available evidence (absolute risks and benefits; time horizon to benefit) with the clinicians' judgement (context of patient's prognosis and treatment burden) and the patient's values (context of treatment burden; shared decision making).

Applying this framework to managing hyperglycemia in type 2 diabetes strongly suggests that no single HbA_{1c} level is appropriate for all patients, and that we should abandon the notion that HbA_{1c} levels < 7% are "well controlled" and > 7% are "poorly controlled." This artificial dichotomy does not adequately portray whether we are optimizing the benefits of treatment, quality of life, and value for patients since most patients with type 2 diabetes in the "poorly controlled" range (i.e. HbA_{1c} >7%) are essentially asymptomatic. Putting these concepts into practice, my approach to treating diabetes is to achieve adequate glycemic control (approximately HbA_{1c} < 9%) to prevent symptomatic disease (polyuria, polydipsia, blurry vision, etc.), and then weigh the risks and benefits of treating the hyperglycemia of diabetes more intensively just like any other risk factor modification. This entails a thorough understanding of the patient's context (age, comorbidities, and functional status) and engaging and partnering with the patient to elicit their perceived treatment burden and their values and preferences for care. The fundamental goal is to help individuals who have diabetes, and not necessarily to prevent diabetes-related complications by any means possible.

As this framework is not unique to intensive glycemic control for diabetes, the **take home message** from this presentation is a call to action to use this EBM approach to inform treatment decisions in practice (clinicians), educate trainees on the effectiveness of treatments (educators), and to inform the broader scientific and clinical community of the value of treatments via publications and guidelines (researchers).

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APPENDIX: ADDITIONAL RESOURCES

Below are additional resources for facilitating the use of an EBM approach for clinical decision making.

Best Available Evidence:
To better understand how to critically appraise the literature to assess the validity and generalizability of the best available evidence, Dr. Anil Makam and Dr. Oanh Nguyen, developed an 11-part lecture series for the UT Southwestern Internal Medicine residency. The slides and audio recordings for many of these lectures can be found on the UT Southwestern Internal Medicine residency website (please note you must be on campus or on the VPN to access): http://imweb.swmed.edu/residency-program/conferences/journal-club.html#14-15-journal-club-articles

Clinician's Judgement:
The Lee index is a prognostic index to predict 4-year and 10-year mortality among community dwelling adults 50 years of age or older that can be used to support the clinician's judgement in estimating life expectancy.
http://eprognosis.ucsf.edu/lee.php

Patient's Values:
Decision aids are a useful tool to help facilitate shared decision making. They are designed for patients to help them think about what is important to them. Currently, to the best of my knowledge, no decision aids exist to help individualize glycemic goals with patients. However, once the decision to treat diabetes is made, Dr. Victor Montori and colleagues at the Mayo Clinic have developed an excellent online Diabetes Medication Choice Decision Aid that can be used to help patients choose which class of glucose-lowering medications best meets their needs.
https://diabetesdecisionaid.mayoclinic.org/