Journal of Clinical Epidemiology 113 (2019) 92−100

ORIGINAL ARTICLE

A benefit−harm analysis of adding basal insulin vs. sulfonylurea to metformin to manage type II diabetes mellitus in people with multiple chronic conditions

Wendy L. Bennett[a,b,*], Hélène E. Aschmann[c], Milo A. Puhan[c], Craig W. Robbins[d,e], Elizabeth A. Bayliss[e], Renee Wilson[b], Richard A. Mularski[d,f], Wiley V. Chan[d], Bruce Leff[a], Orla Sheehan[a], Carol Glover[a,g], Katie Maslow[a,g,h], Karen Armacost[a,g], Suzanne Mintz[a,g], Cynthia M. Boyd[a]

[a]*Department of Medicine, The Johns Hopkins University School of Medicine, Baltimore, MD, USA*
[b]*Department of Epidemiology, The Johns Hopkins University School of Public Health, Baltimore, MD, USA*
[c]*Epidemiology, Biostatistics and Prevention Institute, University of Zurich, Zurich, Switzerland*
[d]*Kaiser Permanente Center for Health Research, Portland, OR, USA*
[e]*Kaiser Permanente, Institute for Health Research, Denver, CO, USA*
[f]*Department of Pulmonary and Critical Care Medicine, Oregon Health & Science University, Portland, OR, USA*
[g]*Informing Patient-Centered Care for People with Multiple Chronic Conditions Patient and Caregiver Partners, Baltimore, MD, USA*
[h]*Gerontological Society of America, Washington, DC, USA*

Accepted 30 March 2019; Published online 3 May 2019

Abstract

Objectives: The benefits and harms of diabetes treatments need to be carefully weighed in people with type II diabetes mellitus (DM) and multiple chronic conditions (MCCs). Our objective was to quantitatively assess the benefits and harms of the addition of basal insulin (insulin) vs. sulfonylurea (SU) to metformin in people with DM and MCCs.

Study Design and Setting: Data inputs into the benefit−harms analysis included (1) baseline risks of patient-centered outcomes (death, myocardial infarction, stroke, severe hypoglycemia, diarrhea, nausea) from cohorts and trials; (2) treatment effects for the addition of insulin vs. SU from a network meta-analysis; and (3) patient preference survey for outcome weights. Statistical analysis calculated the probability that adding insulin has greater benefits than harms, when compared with an SU, overall and by prespecified subgroups.

Results: Including the six outcomes, the probability of net benefit for insulin compared with SU was similar, across subgroups by age and diabetes duration (probability range, using conditional logit weights: 0.44−0.56). Adding patient preferences for treatment burden associated with insulin injections shifted the probability to favor SU over insulin (probability range, using conditional logit weights: 0.01−0.12).

Conclusion: In people with DM and MCCs, we demonstrated incomplete evidence to conclude if basal insulin or SU should be added in people with DM and MCCs on metformin alone. The benefit−harm balance was sensitive to treatment preferences, that is., perceived treatment burden, indicating the importance of shared-decision making in caring for people with MCCs who are at high risk for experiencing harms associated with diabetes management.

Keywords: Risk assessment/methods; Multiple chronic conditions; Diabetes/treatment; Diabetes/complications; Patient preferences; Older adults

1. Introduction

People living with type II diabetes mellitus (DM) have high prevalence of multiple chronic conditions (MCCs), and the number of concurrent chronic conditions increases with age [1−4]. In one study, 17% of older women and 27% of older men with DM had at least one of the following conditions in addition to DM: coronary artery disease, stroke, arthritis, and chronic lower respiratory tract disease [5]. In addition, aging with DM is associated with

Research reported in this publication was funded through a Patient-Centered Outcomes Research Institute (PCORI) award (ME-1310-07,619). H.E.A. was also supported by a PhD fellowship of the Béatrice Ederer-Weber Foundation.

* Corresponding author. Division of General Internal Medicine, The Johns Hopkins University School of Medicine, 2024 E. Monument St, Suite 2-616, Baltimore, MD, USA. Tel.: +1 410 502 6081; fax: +1 410 955 0476.

E-mail address: wendy.bennett@jhmi.edu (W.L. Bennett).

https://doi.org/10.1016/j.jclinepi.2019.03.014

What is new?

- Understanding the benefits and harms of diabetes treatments is important in people with type 2 diabetes (DM) and multiple chronic conditions (MCCs) to inform care and treatment guidelines.

What this adds to what was known?

- In a quantitative benefit-harms analysis, the probability for net benefit for adding insulin compared with sulfonylurea to metformin was similar, across subgroups by age and diabetes duration (probability range, using conditional logit weights: 0.44 to 0.56).
- Including treatment burden associated with insulin injections shifted the probability to favor SU over insulin.

What is the implication and what should change now?

- Because patient preferences can greatly shift the balance favoring one treatment over another, shared-decision making is important when caring for people with MCCs who are at high risk for experiencing harms associated with diabetes management.

greater risk of geriatric syndrome, including cognitive, functional, and visual impairments, compared with aging without DM [5].

For patients with DM and MCCs, the implications for treatment include risks associated with polypharmacy as well as greater risk of adverse effects from DM medications, especially hypoglycemia [6−8]. Among older adults aged >70 years and longer DM duration, rates of hypoglycemia and rates of reporting eye complications were both high and similar to the rates of coronary artery disease events [6]. Both the risk of future diabetes complications, such as coronary artery disease events, and the risks of pharmacologic therapy need to be delicately weighed when making treatment decisions for older adults with DM and MCCs.

DM-focused clinical practice guidelines (CPGs), including from the American Diabetes Association, Veterans Administration, and the American College of Physicians, recognize the unique needs and risks associated with having DM, being older and having multiple coexisting conditions [9−11]. However, there is a lack of high-quality evidence informing these recommendations in specific subgroups of patients or patients with MCCs [10,12,13]. CPGs suggest individualized approaches for older adults with DM and coexisting conditions, including "assessment of medical, psychological, functional, and social geriatric domains" to avoid hypoglycemia risk and further guide therapy, but the assessment of the benefit−harm balance is challenging [10].

We aimed to address the need of CPG developers to have quantitative methods that recognize the complexity of patients with MCCs, including their variation in preferences about their care, to make recommendations informed by the best available evidence [14]. The main objective of this article was to synthesize available, high-quality evidence to estimate the benefit−harm balance for the treatment decision of whether to add basal subcutaneous insulin (i.e., "insulin") or a sulfonylurea (SU) oral medication to first-line metformin therapy for people with DM and MCCs. Both basal insulin and SU are considered appropriate second-line therapies in addition to metformin in patients who have not achieved glycemic control [15]. We also sought to (1) assess the benefit−harm balance of this treatment decision in different subgroups, including older age, diabetes duration, and comorbidities and (2) describe the sensitivity of the benefit−harm balance to patients' preferences. This systematic approach to evidence synthesis aims to inform recommendations for CPGs for people with DM and MCCs.

2. Methods

2.1. Approach to the quantitative benefit−harms analysis

We used the Gail/National Cancer Institute approach for assessing benefits and harms in a multidimensional, quantitative benefit-harm analysis [16]. Multidimensional, quantitative benefit−harm analytic approaches can provide transparent information on the usually implicit process of weighing effect estimates for multiple benefit and harm outcomes simultaneously and can provide information on the effect of variations in baseline risk in different populations. This multidimensional approach provides a probability that adding insulin to metformin is more beneficial than adding an SU and gives consideration to multiple data inputs, including multiple patient-centered outcomes, patients' baseline risks for these outcomes, and patient preferences for outcomes.

The inputs for the analysis required several data sources: (1) baseline risks of the outcomes among older people with DM and MCCs; (2) patients' preference weights for diabetes outcomes derived from a survey of patients with DM and MCCs; and (3) estimates of the treatment effects on a wide range of patient-centered outcomes, extracted from existing evidence syntheses. We describe each of these data sources in detail below.

2.2. Data sources

2.2.1. Data source for baseline risks of outcomes relevant to people with DM and MCC

We previously described the steps to inform the analysis we conducted for this article, which involved a multistep

mixed-methods process engaging multiple stakeholders to identify a clinically relevant DM medication management dilemma and high-priority patient-centered outcomes [17]. Patients and caregivers identified high-importance patient-centered outcomes: vision loss, stroke, heart attack, cancer, dialysis, chronic kidney disease, diabetic foot infection, low blood sugars, treatment burden, nausea, diarrhea, depression, and weight gain [17]. We selected the Diabetes and Aging cohort study [6] for information on baseline risks for these outcomes of interest because the cohort reported the most outcomes of interest from our list and followed a population of older patients with type II diabetes from general medical practices [6]. The Diabetes and Aging cohort study reported four of the patient-important outcomes: all-cause mortality, coronary heart disease (which included myocardial infarction [MI] in addition to coronary bypass surgery and angioplasty), cerebrovascular disease (which included stroke), and acute hypoglycemic events. For the outcomes of nausea and diarrhea, we used the SU trial arms of the systematic review that we used for treatment effect estimates to estimate the baseline incidence (see below) [18].

Our multidisciplinary team, including patients and caregivers, prespecified the following subgroup by age, gender, chronic kidney disease, coronary artery disease, recent falls, cognitive impairment, recent episodes of low blood sugar, chronic liver disease, chronic heart failure, advanced disease, and MCCs. The Diabetes and Aging cohort reported outcome incidences for two subgroups: by age (60−69, 70−79, or ≥80 years) and diabetes duration (0−9, ≥10 years) [17]. We did not find current evidence to conduct subgroup analyses for the other prespecified subgroups and focused our analysis on the subgroups by age and diabetes duration.

2.2.2. Preference survey to yield preference weights

To identify preference weights for patient-important outcomes, we used a survey with best−worst scaling, based on balanced incomplete block design [19,20]. In the survey, we provided clinical scenarios to describe the outcomes, except death, and then presented 13 blocks with four outcomes each. Participants were asked to choose which of the outcomes would be the most and least worrisome if the outcome were to happen to them. The survey was pilot tested for face validity and understandability.

We identified a random sample of 451 potential participants who were aged ≥60 years with DM plus two or more additional chronic conditions and were English speaking, using electronic health record data. Participants were mailed the survey and also received reminder phone calls during which they had the option to complete the survey on the telephone. We received 217 completed surveys (response rate 48%), and 207 participants' surveys were deemed sufficiently complete to include in analyses.

2.2.3. Selection of data sources to estimate treatment effects

Our team identified a recently published systematic review and network meta-analysis [21] assessing the comparative effectiveness and risks associated with adding a second-line diabetes medication to metformin. Two studies of 109 included studies reported a direct comparison of metformin + basal insulin vs. metformin + SU [22,23], and one of them contained two of the outcomes of interest [22] aligned with our clinical question. Treatment effect estimates for all the outcomes were based on their network meta-analytic estimates of comparisons of second-line agents (dual treatments with metformin by drug classes). The authors of the systematic review provided the raw data extracted from the randomized controlled trials (RCTs) on all-cause mortality, MI, stroke, severe hypoglycemia, diarrhea, and nausea, as well as many other patient-important outcomes we asked for. There was not enough evidence (even indirect evidence) for the other patient-centered outcomes of interest. Our team determined not to include weight gain in the analysis because the direct estimate from the study by Moon et al. [22] was opposite to the network meta-analytic estimate yielding an imprecise and unstable estimate. We compared the similarity of the trial results from the network meta-analysis to treatment effects from observational studies with this comparison [24,25]. The observational study estimates were also included in a sensitivity analysis, described below.

2.3. Statistical analysis

2.3.1. Estimation of treatment effects for basal insulin vs. SU added to metformin for patient-important outcomes

Using data from the network meta-analysis by Palmer et al. [18], we calculated the treatment effects for insulin + metformin vs. SU + metformin in patients with MCCs who required additional treatment to improve glycemic control. We calculated the logRR for the outcomes of all-cause mortality, MI, stroke, hypoglycemia, nausea, and diarrhea using the network ''meta'' command of STATA version 13.1 (StataCorp. 2013. *Stata Statistical Software: Release 13*. College Station, TX, StataCorp LP.), which assumed random effects. Because few events occurred (0−1 in most trial arms) for mortality, stroke, and MI, we adjusted the estimates with the prior assumption that with 95% probability, the relative risk (RR) of metformin + insulin vs. metformin + SU lies between 0.50 and 2.0 to reduce bias associated with sparse data [26,27].

2.3.2. Calculation of preference weights from the patient survey

We used three analyses of the preference survey to set weights [1]: Best minus worst scores, which count how many times an outcome was selected as best (least

worrisome) or worst (most worrisome), averaged across respondents [2], conditional logit regression of choosing a pair of outcomes as most worrisome and least worrisome [3], and surface under the cumulative ranking curve (SUCRA) scores, estimating the mean difference of the scores using a network meta-analysis model [28].

We scaled best-minus−worst scores, which originally were on a scale of −4 to 4, to a scale of 0 to 1, to have weights on a scale of 0 to 1, with 1 corresponding to death. We assumed the same relative weight of loss of vision and death when we converted conditional logit parameters (on the log scale) to weights setting the reference (the least worrisome outcome) to a weight of 0. SUCRA scores have a natural scale of 0 to 1, and we did not need to rescale them.

2.3.3. Benefit−harm analysis to assess the probability that basal insulin has a more favorable benefit−harm balance compared with SU when added to metformin

We used the Gail/National Cancer Institute approach for quantitative benefit−harm analysis [16]. The first step was to calculate the expected number of events for each outcome over 5 years in a population of 10,000 based on the baseline incidence and the treatment effect estimates. We set the incidence rate in the simulated Metformin + SU population using baseline risks described previously. We considered all-cause mortality as a competing risk. In 100,000 repetitions of the analysis, we considered uncertainty of the estimates in baseline incidence and relative effects by sampling values from normal distributions according to the confidence interval (CI) of the respective estimate. We assessed the robustness of our results to the selection of baseline risks for each of the outcomes in the subgroups by applying corrections for incident stroke and MI using the rates from the Look AHEAD RCT in which participants were younger and had a relatively shorter diabetes duration [29].

The final step was to calculate the probability that insulin is associated with a more favorable benefit−harm balance compared with SU, as the proportion of the 100,000 repetitions where the index was negative, that is, where there were less-weighted events (corresponding to number of deaths) in the insulin group than in the SU arm.

2.4. Sensitivity analyses

We conducted several sensitivity analyses. In our first sensitivity analysis, we added treatment burden as an additional outcome into the analysis. For treatment burden, we considered the average importance that the respondents in our survey assigned to the additional treatment burden of an injection. In our second sensitivity analysis, we used the relative treatment effect estimates for outcomes from a retrospective cohort study conducted in the Veterans Health Administration (VHA), Medicare, and National Death Index databases [25,30] as prior knowledge in the network meta-analyses by adding a corresponding study to the network.

3. Results

Table 1 shows the estimates for the treatment effects of the addition of insulin vs. SU to metformin for the patient-important outcomes of mortality, MI, stroke, hypoglycemia, diarrhea, and nausea based on indirect and direct comparisons in the RCTs included in the network meta-analysis by Palmer et al. [18] corrected for sparse data bias. Although patients in focus groups identified other outcomes (blindness, loss of vision, chronic kidney disease, end-stage renal disease, acute renal failure, depression, and liver injury) as important, there are no data available to address these outcomes across the two treatments. After adjustment for sparse data, the addition of insulin compared with SU was associated with greater risk for mortality (RR: 1.10, 95% CI: 0.56, 2.14) and a lower risk for MI (RR: 0.94, 95% CI: 0.48, 1.84). The risk of hypoglycemia, nausea, and diarrhea was lower with the addition of basal insulin compared with SU. Only the relative risk estimate for nausea was statistically significant.

Table 2 shows the preference weights using different analytic approaches for the patient preferences survey (best minus worst score, SUCRA, conditional logit, and equal weights). Death was assigned as having the greatest relative importance (value = 1) in all modeling approaches, all scaled between [0, 1]. All outcomes were considered important to some extent, as each outcome was selected as one of the most worrisome outcomes by some patients. By definition, ‘‘equal weights’’ showed all outcomes equally weighted as 1. For the other analytic approaches, on average, loss of vision was considered to be the most worrisome outcome (range of preference weights: 0.79−0.97), followed by stroke (range of preference weights: 0.71−0.91), MI (range of preference weights: 0.68−0.72), and cancer (range of preference weights: 0.66−0.71).

Table 3 shows the expected number of events for each outcome (death, MI, stroke, severe hypoglycemia, diarrhea, and nausea). The incidence rates for nausea and diarrhea were similar in all age groups. Because we did not have age-specific information on nausea and diarrhea, people aged >69 years had relatively fewer events of nausea and diarrhea compared with people aged <69 years due to the higher competing risk of death. Although not reaching statistical significance, the overall difference in numbers of events due to adding insulin instead of SU was largest for the outcomes of diarrhea and nausea, but the precision was also lowest for these outcomes (i.e., for age 60−69 years, insulin had 1,860 [per 10,000] diarrhea events vs. 2,705 [per 10,000] in SU arm). Increasing age was associated with the greatest increase in event rates for the outcomes of MI, death and stroke, greater than duration of diabetes and treatment with SU or basal insulin.

Table 4 shows the benefit−harm balance and compares the results using different approaches to derive weights from the survey on patients’ preferences. When we used equal weights not accounting for patient preferences (i.e., all outcomes

Table 1. Treatment effects (relative risks) for metformin + basal insulin vs. metformin + sulfonylurea for patient-important outcomes with available data[a,b] and description of network meta-analysis (number of trials, events, sample size, and trial duration) per outcome [18]

Outcome	RCTs in network meta-analysis (18), *n*	Total events, *n*	Total sample size, *N*	Median trial duration (min/max), mo	RR (95% CI)
Mortality	41	128	34,822	7.4 (5.5, 26)	1.10 (0.56, 2.14)[b]
Myocardial infarction	31	87	26,456	6 (5.5, 26)	0.94 (0.48, 1.84)[b]
Stroke	27	79	26,017	12 (5.5, 26)	1.02 (0.52, 2.01)[b]
Hypoglycemia	73	4,619	45,710	6 (5.5, 26)	0.61 (0.37, 1.01)
Diarrhea	65	3,212	43,515	6 (5.5, 26)	0.67 (0.39, 1.16)
Nausea	46	2,445	30,921	6 (5.5, 26)	0.20 (0.08, 0.50)

Abbreviation: CI, confidence interval; RR, relative risk.

[a] We did not identify direct or indirect evidence for the following outcomes: blindness, loss of vision, chronic kidney disease, end-stage renal disease, acute renal failure, depression, and liver injury.

[b] Adjusted for sparse data bias with a prior relative risk of 1 (0.5, 2).

received the same weight [Table 2]), the benefit–harm analysis strongly favored the addition of insulin to metformin over SU, across age and by diabetes duration strata (probability range: 0.86–0.97). Although SUCRA assigned less weight to death compared with other approaches, results from SUCRA and conditional logit weights showed similar probabilities for the benefit of insulin vs. SU, closer to a coin toss (probability range: 0.44–0.61). In the best minus worst score approach, the outcomes of nausea, diarrhea, and hypoglycemia received greater weight than with SUCRA and conditional logit weights, and more of these events occurred with SU (Table 3). The best minus worst scaling showed the greatest probability for adding insulin over SU in the youngest age group (age 60–69 years) and those with a shorter diabetes duration (< 10 years), with a probability of 0.82 (probability range 0.82–0.93), and the probability decreased with increasing age and diabetes duration (Table 3).

Fig. 1A demonstrates the impact of the variation in individual preferences on the benefit–harm balance, using the weights from individual best minus worst scores. We identified a wide range of individual variation in patients' preferences, which resulted in a spread of probability estimates. For example, we found a range in probabilities from insulin being clearly favored to SU being slightly favored, with the ranges similar by duration of diabetes.

In Fig. 1B, we assessed the sensitivity of the benefit–harm balance to perceived treatment burden associated with insulin injections. By most respondents in the survey, insulin injections were considered burdensome; therefore, the benefit–harm balance shifted in favor of SU over insulin. Appendix Table 1 shows the sensitivity of the benefit–harm balance to adding the outcome of perceived treatment burden, across subgroups by age and diabetes duration. The addition of SU was favored in all age groups and all durations of diabetes when treatment burden was considered.

Appendix Table 1 shows a sensitivity analysis, which included results from an observational study in the VHA

Table 2. Preference weights derived from the patient preference survey with different analytic approaches scaled to an interval of (0,1) (conditional logit parameters on log scale, surface under the cumulative ranking curve [SUCRA] scores, best minus worst scores) and equal weights

Outcome	Conditional logit (logOR)	SUCRA	Best minus worst score	Equal weights
Death	1	1	1	1
Loss of vision	0.79	0.97	0.79	1
Stroke	0.71	0.91	0.74	1
Myocardial infarction	0.68	0.82	0.72	1
Cancer	0.66	0.71	0.69	1
Chronic kidney disease	0.58	0.70	0.63	1
End-stage renal disease (dialysis)	0.50	0.59	0.59	1
Diabetic foot infection	0.37	0.49	0.48	1
Dangerously low blood sugars	0.35	0.45	0.48	1
Episodes of low blood sugars	0.16	0.21	0.33	1
Nausea or diarrhea	0.08	0.11	0.28	1
Treatment burden	0.07	0.26	0.29	1
Depression	0.05	0.21	0.25	1
Weight gain	0	0.06	0.23	1

Table 3. Number of expected events (95% CI based on CI of the relative effect estimate and baseline incidence) per 10,000 people over 5 y with type II diabetes for each clinical outcome, by subgroups of age and diabetes duration

		Outcomes					
Age	Treatment arm[a]	Death	Myocardial infarction	Stroke	Severe hypoglycemia	Diarrhea	Nausea
Diabetes duration ≥ 10 y							
60–69	SU	1,530 (1,458, 1,602)	673 (617, 729)	384 (344, 424)	433 (390, 476)	2,705 (0, 5,375)	1,105 (169, 2,038)
	Insulin	1,739 (890, 3,004)	659 (320, 1,201)	409 (196, 751)	272 (158, 438)	1,860 (0, 4,401)	246 (27, 674)
70–79	SU	2,806 (2,711, 2,901)	773 (713, 834)	602 (550, 654)	652 (597, 706)	2,502 (0, 4,970)	1,022 (156, 1,884)
	Insulin	3,125 (1,689, 5,074)	749 (362, 1,366)	632 (305, 1,152)	408 (235, 656)	1,702 (0, 4,054)	225 (25, 619)
80+	SU	4,854 (4,700, 5,006)	835 (745, 923)	662 (585, 739)	686 (610, 762)	2,145 (0, 4,262)	876 (134, 1,615)
	Insulin	5,227 (3,115, 7,606)	795 (371, 1,473)	684 (318, 1,268)	423 (231, 698)	1,436 (0, 3,467)	190 (21, 527)
Diabetes duration < 10 y							
60–69	SU	934 (895, 974)	396 (367, 424)	254 (232, 276)	143 (128, 159)	2,797 (0, 5,557)	1,143 (175, 2,106)
	Insulin	1,071 (536, 1,901)	390 (188, 717)	272 (131, 502)	90 (52, 145)	1,932 (0, 4,566)	256 (29, 700)
70–79	SU	1,922 (1,860, 1,985)	502 (467, 538)	432 (399, 466)	224 (202, 246)	2,644 (0, 5,253)	1,080 (165, 1,991)
	Insulin	2,171 (1,130, 3,681)	491 (237, 902)	458 (221, 838)	140 (81, 226)	1,812 (0, 4,294)	240 (27, 657)
80+	SU	4,090 (3,968, 4,211)	567 (503, 631)	664 (601, 727)	238 (203, 274)	2,283 (0, 4,536)	933 (143, 1,720)
	Insulin	4,460 (2,559, 6,772)	544 (255, 1,014)	690 (328, 1,267)	147 (81, 243)	1,538 (0, 3,689)	203 (23, 563)

[a] Treatment arms are sulfonylurea (SU) vs. basal insulin (insulin).

population, along with the network meta-analysis results, for the treatment effects of metformin + insulin vs. metformin + SU. The addition of the observational study's results changed the benefit–harm probabilities for all outcomes, compared with Table 3, which showed the main results. Except for the equal weights approach, the addition of insulin to metformin was associated with lower probability of benefit compared with the addition of SU to metformin, even in the best–worst scale and the equal weight approaches.

4. Discussion

The benefit–harm analysis shows insufficient evidence that basal insulin had a better benefit–harm balance when added to metformin, compared with adding SU to metformin, among patients with type II diabetes and MCCs, across subgroups by age and diabetes duration. We showed that the benefit–harm balance is sensitive to patients' preferences, using varying approaches to the preference weights, as well as in the sensitivity analysis assuming treatment burden for

Table 4. Probability[a,b] of benefit for the addition of basal insulin to metformin compared with addition of sulfonylurea—based on the outcomes, all-cause mortality, stroke, myocardial infarction, severe hypoglycemia, nausea, and diarrhea

	Weights			
Age	Conditional logit	SUCRA	BWS score	Equal weights
Diabetes duration ≥10 y				
60–69	0.53 (0.53, 0.61)	0.57 (0.57, 0.66)	0.74 (0.74, 0.88)	0.96 (0.96, 0.99)
70–79	0.48 (0.48, 0.53)	0.51 (0.51, 0.58)	0.64 (0.64, 0.77)	0.92 (0.92, 0.98)
80+	0.46 (0.45, 0.49)	0.48 (0.47, 0.52)	0.56 (0.56, 0.67)	0.88 (0.88, 0.98)
Diabetes duration < 10 y				
60–69	0.56 (0.56, 0.68)	0.61 (0.61, 0.74)	0.82 (0.82, 0.93)	0.97 (0.97, 0.99)
70–79	0.49 (0.49, 0.55)	0.51 (0.51, 0.6)	0.67 (0.67, 0.82)	0.94 (0.94, 0.98)
80+	0.44 (0.44, 0.48)	0.45 (0.45, 0.5)	0.55 (0.55, 0.67)	0.86 (0.86, 0.97)

Abbreviation: BWS, best–worst scaling.

[a] Probability ranges from 0 to 1 where 0.5 is the same as a coin toss; probability > 0.5 favors addition of insulin, probability <0.5 favors the addition of SU.

[b] Probability ranges based on possible estimates based on an analysis using different baseline incidences for myocardial infarction, stroke, nausea, and diarrhea.

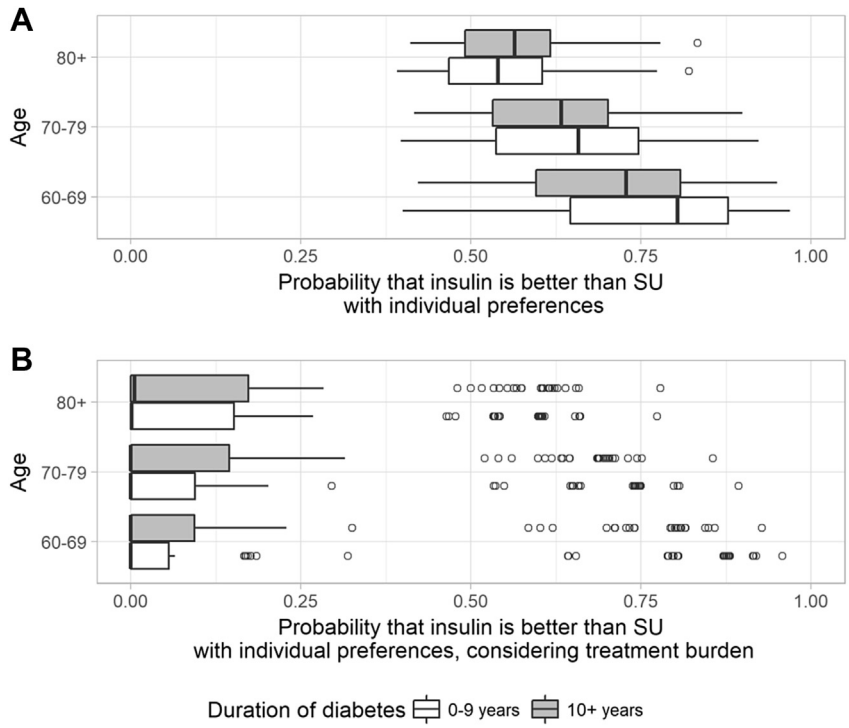

Fig. 1. Probability[a,b] of benefit for addition of basal insulin to metformin compared with addition of sulfonylurea (SU), given individual preference weights, using the best minus worst scores. (A) Without treatment burden considered. (B) Considering treatment burden of injecting insulin. [a]Probability ranges from 0 to 1 where 0.5 is the same as a coin toss; probability >0.5 favors addition of insulin, probability <0.5 favors the addition of SU. [b]Probability ranges based on possible estimates based on an analysis using different baseline incidences for myocardial infarction, stroke, nausea, and diarrhea.

insulin injections. Considering the available evidence, for patients concerned about treatment burden with insulin, the benefit−harm balance favors SU for patients, irrespective of age and duration of diabetes. Further studies comparing the addition of basal insulin vs. SU to metformin monotherapy may change the benefit−harm balance, as we could not include many patient-important outcomes, because there was no evidence available (e.g., blindness and chronic kidney disease), and the relative effects for mortality, MI, and stroke are based on sparse data.

To our knowledge, these results are the first benefit−harm analysis to assess medication choices in type II diabetes. The strength of the quantitative benefit−harm analytic approach is that it includes and synthesizes the highest quality data for the particular question and enables us to look at different benefit to harm balance across subgroups and adds transparency, making the relative importance assigned to different outcomes explicit. Statistical uncertainty, that is, imprecision in estimates can be taken into account, and nonstatistical uncertainty arising from lacking evidence can be explored in sensitivity analyses. Transparent, quantitative approaches similar to the one we used can be useful for guideline developers to communicate the underlying assumptions and justify their recommendations, as well as grading the overall evidence. The challenge with the method is in applying it in the clinic to inform a personalized treatment decision for a given patient when the benefit−harm balance varies according to the baseline risk or the patient's preference. Ultimately, this analytic approach could be scaled into point-of-care tools to integrate patient-level and published data to help patients and clinicians make more informed decisions.

Even before we had the capacity to run models for each individual weighing each outcome, our results are informative. For example, evidence consistently shows that patients perceive high treatment burden with insulin as a major barrier to initiation and adherence [31−33]. We did not detect any meaningful differences in outcome preferences across age groups in our survey nor did we identify any other useful predictor variable; therefore, we applied the preferences of all 207 respondents to each subgroup. Larger scale patient preference surveys or machine learning algorithms to describe the underlying structure of the preference data may help to explain the high variation in preferences we observed. Although differences in preferences across subgroups are not established, importantly, surveys to inform on the relative importance of outcomes should be performed in the target population, as healthy individuals, clinicians, and guideline developers can have different preferences [34,35]. However, we were unable to assess differences by preferences across all subgroups of interest because of the dearth of published data. Pooling large cohorts together in a diabetes data consortium (e.g., Chronic Kidney Disease Prognosis Consortium) could enable well-

powered analyses of subgroups. As noted in the section Methods, the VA study provided a ''real-world'' treatment example among veterans started on metformin, comparing those who had insulin vs. SU added on. The addition of the treatment effects from an observational ''real world'' study from the VA changed the results for all outcomes showing that the addition of insulin to metformin was associated with lower probability of benefit compared with the addition of SU to metformin. Likely the results changed because the VA study reported significantly greater risk of hypoglycemia in the insulin (compared with SU) group, which was the opposite for the trials, and insulin increased mortality to a greater extent in the VA study compared with the trial results.

Strengths of our analytic approach include stakeholder engagement in identifying the research question and outcomes, the transparency of the data sources, and their limitations. In addition, we had access to explicit preference weights derived from a patient survey, as guideline developers usually balance benefits and harms for patients across multiple outcomes, as a gestalt and without access to patient input about preferred outcomes.

We identified several important limitations of the approach and our findings. First, we limited our analysis to one comparison of second-line agents, as a proof in concept approach. Further research could expand this approach, looking across multiple different treatment options. Second, we lacked evidence for most of the outcomes that patients deemed of high importance, indicating a need for further study on these outcomes. Third, the available evidence for the outcomes we could analyze (other than nausea) did not demonstrate a statistically significant difference between treatments. Fourth, we sought the most recent, highest quality evidence for this analysis, and the results could (and should) change as more evidence is generated, and we anticipate being able to update these findings with new published evidence. Fifth, although we presented several ways to analyze a best−worst scaling preference survey and generate average weights for the patient population, we are unable to determine which approach is most appropriate in our population. Further research could explore which analysis in fact represents average weights best. However, in cases where the variation in preferences is large, analyses with average weights may be of limited value.

In conclusion, we demonstrated the lack of evidence, including patient preferences, supporting the addition of basal insulin vs. SU to metformin. When perceived or actual treatment burden associated with insulin injections is high, SU is clearly favored. We also showed the sensitivity of the benefit−harm approach to treatment decisions in people with DM and MCCs, indicating the importance of shared decision-making in caring for people with MCCs who are at high risk for experiencing harms associated with diabetes management. Insufficient evidence exists for many patient-important outcomes, including blindness and renal outcomes, to confidently judge the benefit−harm balance of adding basal insulin vs. SU to metformin in people with MCCs.

CRediT authorship contribution statement

Wendy L. Bennett: Conceptualization, Investigation, Methodology, Writing - review & editing, Writing - original draft. **Hélène E. Aschmann:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing - review & editing, Writing - original draft. **Milo A. Puhan:** Conceptualization, Investigation, Methodology, Formal analysis, Writing - review & editing. **Craig W. Robbins:** Conceptualization, Investigation, Writing - review & editing. **Elizabeth A. Bayliss:** Conceptualization, Investigation, Writing - review & editing. **Renee Wilson:** Conceptualization, Project administration, Software, Writing - review & editing. **Richard A. Mularski:** Conceptualization, Writing - review & editing. **Wiley V. Chan:** Conceptualization, Writing - review & editing. **Bruce Leff:** Conceptualization, Writing - review & editing. **Orla Sheehan:** Conceptualization, Writing - review & editing. **Carol Glover:** Conceptualization, Writing - review & editing. **Katie Maslow:** Conceptualization, Writing - review & editing. **Karen Armacost:** Conceptualization, Writing - review & editing. **Suzanne Mintz:** Conceptualization, Writing - review & editing. **Cynthia M. Boyd:** Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Writing - review & editing.

Acknowledgments

The authors would like acknowledge Dr Suetonia Palmer and Prof. Giovanni F. M. Strippoli for sharing their extracted data from the systematic review and network meta-analysis ''Comparison of Clinical Outcomes and Adverse Events Associated With Glucose-Lowering Drugs in Patients With Type 2 Diabetes—A Meta-analysis'' (JAMA, 2016) and for providing additional extracted data on further patient-centered outcomes that were not included in the publication. The authors would like to thank Professor Leonhard Held of the University of Zurich for his advice on how to account for sparse data in the network meta-analytic estimates.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jclinepi.2019.03.014.

References

[1] Garin N, Koyanagi A, Chatterji S, Tyrovolas S, Olaya B, Leonardi M, et al. Global multimorbidity patterns: a cross-sectional, population-based, multi-country study. J Gerontol A Biol Sci Med Sci 2016; 71(2):205−14.

[2] Abad-Diez JM, Calderon-Larranaga A, Poncel-Falco A, Poblador-Plou B, Calderon-Meza JM, Sicras-Mainar A, et al. Age and gender differences in the prevalence and patterns of multimorbidity in the older population. BMC Geriatr 2014;14:75.
[3] Barnett K, Mercer SW, Norbury M, Watt G, Wyke S, Guthrie B. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. Lancet 2012;380(9836):37−43.
[4] Goodman RA, Ling SM, Briss PA, Parrish RG, Salive ME, Finke BS. Multimorbidity patterns in the United States: implications for research and clinical practice. J Gerontol A Biol Sci Med Sci 2016;71(2):215−20.
[5] Weiss CO, Boyd CM, Yu Q, Wolff JL, Leff B. Patterns of prevalent major chronic disease among older adults in the United States. JAMA 2007;298:1160−2.
[6] Huang ES, Laiteerapong N, Liu JY, John PM, Moffet HH, Karter AJ. Rates of complications and mortality in older patients with diabetes mellitus: the diabetes and aging study. JAMA Intern Med 2014;174(2):251−8.
[7] Prinz N, Stingl J, Dapp A, Denkinger MD, Fasching P, Jehle PM, et al. High rate of hypoglycemia in 6770 type 2 diabetes patients with comorbid dementia: a multicenter cohort study on 215,932 patients from the German/Austrian diabetes registry. Diabetes Res Clin Pract 2016;112:73−81.
[8] Walker J, Halbesma N, Lone N, McAllister D, Weir CJ, Wild SH. Socioeconomic status, comorbidity and mortality in patients with type 2 diabetes mellitus in Scotland 2004-2011: a cohort study. J Epidemiol Community Health 2016;70:596−601.
[9] Qaseem A, Wilt TJ, Kansagara D, Horwitch C, Barry MJ, Forciea MA. Hemoglobin A1c targets for glycemic control with pharmacologic therapy for nonpregnant adults with type 2 diabetes mellitus: a guidance statement update from the American College of Physicians. Ann Intern Med 2018;168:569−76.
[10] Older adults: standards of medical care in diabetes-2018. Diabetes care 2018;41:S119−25.
[11] Conlin PR, Colburn J, Aron D, Pries RM, Tschanz MP, Pogach L. Synopsis of the 2017 U.S. Department of Veterans affairs/U.S. Department of defense clinical practice guideline: management of type 2 diabetes mellitus. Ann Intern Med 2017;167:655−63.
[12] Lipska KJ, Krumholz H, Soones T, Lee SJ. Polypharmacy in the aging patient: a review of glycemic control in older adults with type 2 diabetes. JAMA 2016;315:1034−45.
[13] Sardar MR, Badri M, Prince CT, Seltzer J, Kowey PR. Underrepresentation of women, elderly patients, and racial minorities in the randomized trials used for cardiovascular guidelines. JAMA Intern Med 2014;174(11):1868−70.
[14] Puhan MA, Yu T, Stegeman I, Varadhan R, Singh S, Boyd CM. Benefit-harm analysis and charts for individualized and preference-sensitive prevention: example of low dose aspirin for primary prevention of cardiovascular disease and cancer. BMC Med 2015;13:250.
[15] 8. Pharmacologic approaches to glycemic treatment: standards of medical care in diabetes-2018. Diabetes care 2018;41:S73−85.
[16] Gail MH, Costantino JP, Bryant J, Croyle R, Freedman L, Helzlsouer K, et al. Weighing the risks and benefits of tamoxifen treatment for preventing breast cancer. J Natl Cancer Inst 1999;91:1829−46.
[17] Bennett WL, Robbins CW, Bayliss EA, Wilson R, Tabano H, Mularski RA, et al. Engaging stakeholders to inform clinical practice guidelines that address multiple chronic conditions. J Gen Intern Med 2017;32:883−90.
[18] Palmer SC, Mavridis D, Nicolucci A, Johnson DW, Tonelli M, Craig JC, et al. Comparison of clinical outcomes and adverse events associated with glucose-lowering drugs in patients with type 2 diabetes: a meta-analysis. JAMA 2016;316:313−24.
[19] Aschmann HE, Puhan MA, Armacost K, Bayliss EA, Bennett WL, Chan WV, et al. Applying best-worst scaling to identify health-outcome preferences among patients with diabetes or hypertension and multiple chronic conditions. Cochrane Database Syst Rev 2017;9(suppl 1):1041.
[20] Louviere JJ, Flynn TN, Marley AA. Best-worst scaling: theory, methods and applications. Cambridge, UK: Cambridge University Press; 2015.
[21] Bolen S, Tseng E, Hutfless S, Segal JB, Suarez-Cuervo C, Berger Z, et al. AHRQ comparative effectiveness reviews. In: Diabetes medications for adults with type 2 diabetes: an update. Rockville, MD: Agency for Healthcare Research and Quality (US); 2016.
[22] Moon JS, Ha KS, Yoon JS, Lee HW, Lee HC, Won KC. The effect of glargine versus glimepiride on pancreatic beta-cell function in patients with type 2 diabetes uncontrolled on metformin monotherapy: open-label, randomized, controlled study. Acta Diabetol 2014;51(2):277−85.
[23] Onuchin SG, Elsukova OS, Solov'ev OV, Onuchina EL. [Capabilities of hypoglycemic therapy in women with decompensated type 2 diabetes mellitus]. Ter Arkh 2010;82(8):34−41.
[24] Roumie CL, Greevy RA, Grijalva CG, Hung AM, Liu X, Murff HJ, et al. Association between intensification of metformin treatment with insulin vs sulfonylureas and cardiovascular events and all-cause mortality among patients with diabetes. JAMA 2014;311:2288−96.
[25] Roumie CL, Greevy RA, Grijalva CG, Hung AM, Liu X, Griffin MR. Diabetes treatment intensification and associated changes in HbA1c and body mass index: a cohort study. BMC Endocr Disord 2016;16(1):32.
[26] Greenland S, Mansournia MA, Altman DG. Sparse data bias: a problem hiding in plain sight. BMJ 2016;352:i1981.
[27] Greenland S. Bayesian perspectives for epidemiological research: I. Foundations and basic methods. Int J Epidemiol 2006;35:765−75.
[28] Salanti G, Ades AE, Ioannidis JP. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. J Clin Epidemiol 2011;64:163−71.
[29] Wing RR, Bolin P, Brancati FL, Bray GA, Clark JM, Coday M, et al. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. N Engl J Med 2013;369:145−54.
[30] Min JY, Griffin MR, Hung AM, Grijalva CG, Greevy RA, Liu X, et al. Comparative effectiveness of insulin versus combination sulfonylurea and insulin: a cohort study of veterans with type 2 diabetes. J Gen Intern Med 2016;31:638−46.
[31] Ng CJ, Lai PS, Lee YK, Azmi SA, Teo CH. Barriers and facilitators to starting insulin in patients with type 2 diabetes: a systematic review. Int J Clin Pract 2015;69:1050−70.
[32] Hayes RP, Fitzgerald JT, Jacober SJ. Primary care physician beliefs about insulin initiation in patients with type 2 diabetes. Int J Clin Pract 2008;62:860−8.
[33] Hayes RP, Bowman L, Monahan PO, Marrero DG, McHorney CA. Understanding diabetes medications from the perspective of patients with type 2 diabetes: prerequisite to medication concordance. Diabetes Educ 2006;32(3):404−14.
[34] Montori VM, Brito JP, Murad MH. The optimal practice of evidence-based medicine: incorporating patient preferences in practice guidelines. JAMA 2013;310:2503−4.
[35] MacLean S, Mulla S, Akl EA, Jankowski M, Vandvik PO, Ebrahim S, et al. Patient values and preferences in decision making for antithrombotic therapy: a systematic review: antithrombotic therapy and prevention of thrombosis, 9th ed.: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2012;141:e1S−23S.