ORIGINAL ARTICLE

Challenging the 50-50 rule for the basal-bolus insulin ratio in patients with type 2 diabetes who maintain stable glycaemic control

Roy Harper MD[1] | Eran Bashan PhD[2] | Kevin J. Williams MD[3] |
Sajitha Sritharan[2] | Mark Willis[2] | Deanna J. Marriott PhD[4] | Israel Hodish MD[2,5]

[1]Diabetes Centre, Ulster Hospital, South Eastern Health and Social Care Trust, Belfast, Northern Ireland

[2]Hygieia, Inc., Livonia, Michigan

[3]Cardiovascular Research Center, Lewis Katz School of Medicine at Temple University, Philadelphia, Pennsylvania

[4]School of Nursing, University of Michigan, Ann Arbor, Michigan

[5]Department of Internal Medicine, Division of Metabolism, Endocrinology and Diabetes, University of Michigan Medical Center, Ann Arbor, Michigan

Correspondence
Israel Hodish, MD, Hygieia, Inc., 28803 Eight Mile Road, Suite 102, Livonia, 48108, MI.
Email: ihodish@hygieia.com

Abstract

Background: For patients using basal-bolus insulin therapy, it is widespread clinical practice to aim for a 50-50 ratio between basal and total daily bolus. However, this practice was based on a small study of individuals without diabetes. To assess the rule in real-world practice, we retrospectively analyzed patients on basal-bolus therapy that was adjusted at least weekly by an artificial intelligence-driven titration within the d-Nav® Insulin Management Technology.

Materials and methods: We obtained de-identified data from the Diabetes Centre of Ulster Hospital for patients with four inclusion criteria: type 2 Diabetes (T2D), on d-Nav >6 months, on basal-bolus insulin therapy >80% of the time (based on insulin analogs), and no gap in data >3 months.

Results: We assembled a cohort of 306 patients, followed by the d-Nav service for 3.4 ± 1.8 years (mean ± SD), corresponding to about 180 autonomous insulin dose titrations and about 5000 autonomous individual dose recommendations per patient. After an initial run-in period, mean glycated hemoglobin (HbA1c) values in the cohort were maintained close to 7%. Surprisingly, in just over three-quarters of the cohort, the average basal insulin fraction was <50%; in half of the cohort average basal insulin fraction <41.2%; and in one-quarter the basal insulin fraction was <33.6%. Further, the basal insulin fraction did not remain static over time. In half of the patients, the basal insulin fraction varied by ≥1.9×; and, in 25% of the patients, ≥2.5×.

Conclusion: Our data show that a 50-50 ratio of basal-to-bolus insulin does not generally apply to patients with T2D who successfully maintain stable glycemia.

Therefore, the 50-50 ratio should not serve as an ongoing treatment guide. Moreover, our results emphasize the importance of at least weekly insulin titrations.

1 | BACKGROUND

It is widespread clinical practice to aim for a 50-50 ratio between basal and total daily bolus insulin doses in patients with diabetes who are using basal-bolus insulin therapy, although titration guidelines do not mandate it.[1] However, it appears this practice is based on a classic 1988 study of endogenous insulin levels in individuals without diabetes,[2] which may not be applicable to patients with diabetes. Only one published study has assessed the validity of the 50-50 rule in patients with type 2 diabetes (T2D) treated with basal-bolus insulin therapy, but the frequency of insulin titrations was not stated and, more importantly, glycaemic control was suboptimal during that study,[3] outside of conventional treatment goals.

To assess the validity of the 50-50 rule in real-world practice in patients with T2D under stable control within conventional glycaemic guidelines, we analysed clinical data from patients with T2D who were treated with basal-bolus insulin therapy that was adjusted at least weekly.

Insulin dose adjustments for these patients were performed by an artificial intelligence (AI)-driven titration within the d-Nav Insulin Management Technology (d-Nav). Treatment was optimized and maintained over time, while the basal and bolus insulin requirements of these patients were closely tracked and recorded, thereby providing a unique longitudinal dataset for investigation. The d-Nav titration follows conventional guidelines in insulin titration without mandating the 50-50 rule; therefore, the resulting basal-bolus ratios are driven solely by real-time adaptation to achieve glycaemic control.[1,4]

2 | METHODS

2.1 | The d-Nav insulin management technology

Descriptions and validations of the d-Nav technology as a standard of care in insulin management have been described elsewhere.[4-8] Briefly, patients referred to the d-Nav service are provided with a phone application ('app') or a separate handheld device called d-Nav. Patients use their own glucometer or the d-Nav device to measure glucose before each insulin injection. In turn, the d-Nav app or device provides a recommended dose for the upcoming insulin injection. The AI within the app or device assesses each patient's responses to his or her current insulin doses by analysing glucose patterns. Unlike typical diabetes management, d-Nav titrates insulin therapy at least weekly, rather than during outpatient clinic visits that occur just a few times per year. The AI autonomously adjusts each patient's insulin doses, to find a clinically achievable balance between preventing hyperglycaemia and preventing hypoglycaemia. If insulin requirements drop or hypoglycaemia ensues, the AI within d-Nav makes immediate autonomous adjustments as often as needed, following the safety-first approach of prioritizing the avoidance of hypoglycaemia. The d-Nav
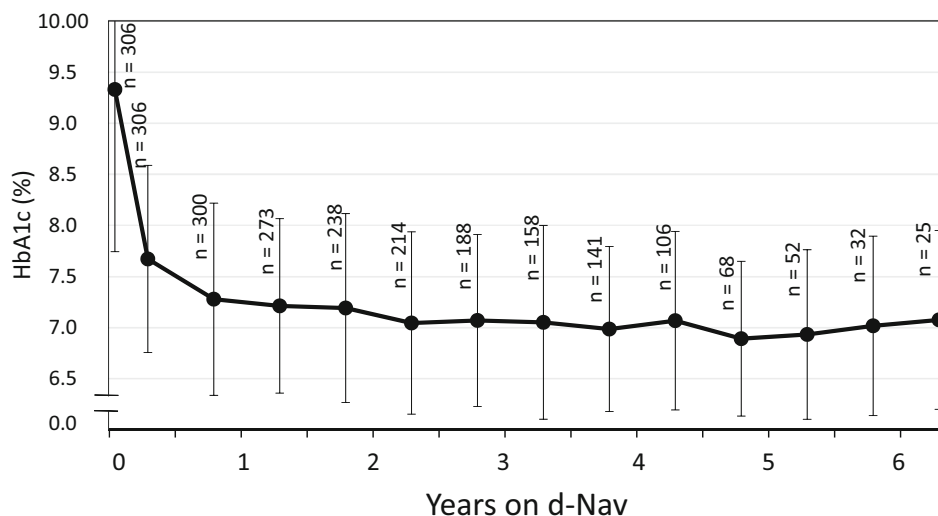

FIGURE 1 Cohort-wide HbA1c values over time in our cohort of 306 patients with type 2 diabetes during long-term management by frequent artificial intelligence-driven insulin titration within the d-Nav service. Displayed are means ± SDs. The x-axis shows years on the d-Nav service, with numbers of patients on the service for each time point. This panel includes data from the initial 6-month run-in period, before glycaemia had stabilized. Because we used rolling enrolment of this cohort, patients who started the service later during the period had a shorter follow-up, indicated by decreasing patient numbers along the x-axis

AI adjusts most types of insulin regimens, including basal-bolus therapy with insulin analogues.[1,4]

Trained healthcare providers periodically follow-up with patients through telephone calls and formal consultations, in-person or virtually, to boost user confidence, correct usage errors and identify uncharacteristic clinical courses.[5,6] These d-Nav specialists do not perform insulin titrations. Additional software is available to provide further insights regarding insulin dynamics.[9] The d-Nav service is linked to the wider healthcare system so that each patient's data are always available for review by the patient's

FIGURE 2 Basal-bolus insulin dosing in our cohort of 306 patients with type 2 diabetes during long-term management by frequent artificial intelligence-driven insulin titration within the d-Nav service. (A) Primary outcome: percentage of the total daily dose of exogenous insulin that was basal insulin ('Basal insulin fraction') for each of the 306 patients in our cohort. Data are arranged from the patient with the lowest to the highest mean value. The graph depicts the mean (heavy black line) and SD (thin vertical grey lines) for each patient. These variables were assessed weekly for each patient while on d-Nav during a period of 3.4 ± 1.8 years (about 180 autonomous insulin dose titrations and about 5000 autonomous individual dose recommendations per patient). The red horizontal line indicates a basal insulin fraction of 50% (meaning a basal-bolus ratio of 50-50). The three vertical dashed lines divide the patients into quartiles. (B) Secondary outcome: fold variation in basal insulin fraction for each patient over time, defined as the patient's highest divided by that patient's lowest basal insulin fraction. Data are arranged from the patient with the lowest to the highest fold variation in basal insulin fraction during long-term follow-up. The three vertical dashed lines divide the patients into quartiles. As noted in the Methods section, parts A and B do not include data from the first 6 months of management by d-Nav, because of the time it takes to achieve stable glycaemia[10]
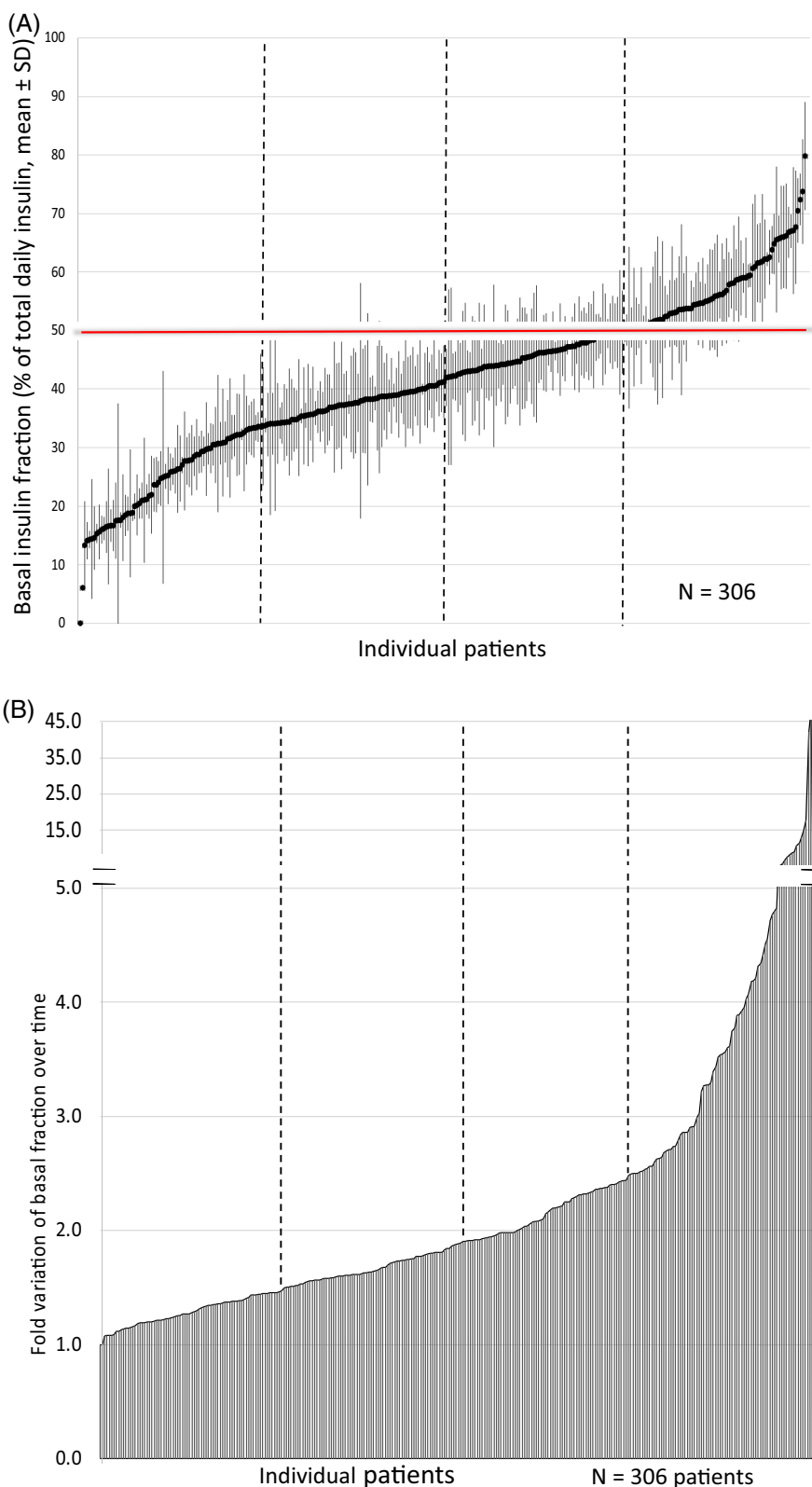
physicians, who handle all other medications for diabetes and any co-morbid conditions.

2.2 | Outcomes

The primary outcome of this study was the average percentage of the total daily dose of insulin that was basal insulin ('basal insulin fraction'), which we calculated for each patient each week. The secondary outcome was the fold variation in the basal insulin fraction in each patient over time, defined here as the ratio of the patient's highest divided by that patient's lowest basal insulin fraction.

A description of the patients and statistical analysis can be found in the supporting information.

3 | RESULTS

We acquired a cohort of 306 patients who were followed for 3.4 ± 1.8 years (mean ± SD), corresponding to about 180 autonomous insulin dose titrations and 5000 individual autonomous dose recommendations per patient. Table S1 shows the demographics and key clinical characteristics during enrolment. The duration of T2D was 19.0 ± 7.4 years, and the time on exogenous insulin injections was 13.3 ± 7.2 years.

Insulin titrations occurred, on average, every 6.8 ± 1.5 days to enable cohort-wide HbA1c maintenance close to 7%, which remained stable over time after the initial run-in period (Figure 1). HbA1c values at the end of the study were 7.3% ± 1.0% (56.3 ± 7.7 mmol/mol).

Surprisingly, in just more than three-quarters of the patients (231/306, 75.5%), the average basal fraction was less than 50% (meaning basal-bolus ratios less than 50-50; Figure 2A). One-half of the cohort (153/306) had a mean basal insulin fraction of less than 41.2% (basal-bolus ratios below 41-59). In one-quarter of the patients, the basal insulin fraction was less than 33.6% (basal-bolus ratios less than 34-66).

Moreover, the basal insulin fraction did not remain static in each patient over time (Figure 2B). In one-half of the patients, the basal insulin fraction varied by a factor of 1.9 or greater, in order to maintain glycaemic control (e.g. when a patient's basal-bolus ratio rises over time from 30-70 to 62-38). In 25% of the patients, the basal insulin fraction varied by a factor of 2.5 or greater.

We found no statistically significant correlations of basal insulin fraction or range of its changes in each patient with any demographic or clinical characteristics. These included each patient's age, duration of diabetes and duration of insulin usage, as well as initial and latest HbA1c levels. We found no statistically significant differences in basal insulin fraction or range of its changes between genders.

Figure S1 provides examples of the dynamics of insulin therapy, including basal insulin fractions, for three representative patients over time.

4 | CONCLUSIONS

In this report, we have shown that the overwhelming majority of patients with T2D who successfully maintain stable glycaemic control during frequently adjusted, AI-driven basal-bolus insulin therapy, require ratios between basal and bolus insulin analogues that are not 50-50. To the best of our knowledge, there are no prior published studies of basal-bolus ratios in patients with T2D under stable control within conventional glycaemic guidelines. We found that the basal-bolus ratio varies considerably among patients, and the ratio for any given patient varies considerably over time. These data complement our previous reports showing that patients' insulin requirements are highly dynamic, highly individual and never achieve static doses.[10,11]

Our current finding of an unequal ratio between exogenous basal and bolus requirements in patients with T2D treated with insulin may be explained by defects in the secretion or action of endogenous basal insulin compared with endogenous prandial insulin, or effects of endogenous glucagon in different patients and at different times (reviewed in[12]). It is plausible that non-insulin antidiabetes medications or the use of insulin analogues play a role as well, although neither of these factors appears probable to explain high variability from patient to patient and over time.

The study's limitations include its observational design, limited ethnic diversity, lack of information on additional antidiabetes medications, possible dietary changes, physical activity and the lack of a negative control group. On the other hand, the 50-50 rule that has been used by providers for years is based on a 1988 study of a few patients without diabetes, about whom we do not have additional background data, nor did this prior study show the mechanisms behind the findings.

In summary, our data show that a 50-50 ratio of basal-to-bolus insulin does not generally apply to patients with T2D who successfully use this therapy to maintain stable glycaemia. Therefore, the 50-50 ratio should not serve as an ongoing treatment guide and, in particular, insulin titration of each regimen component should consider only the pattern of glycaemia and not the ratio between basal and bolus. In view of the variability and dynamics in insulin requirements and basal insulin fraction in each patient over time, our results emphasize the importance of frequent dose titrations when administering insulin to patients with T2D.

DATA AVAILABILITY STATEMENT

ORCID

Kevin J. Williams https://orcid.org/0000-0002-0000-2159

Israel Hodish https://orcid.org/0000-0001-8174-384X

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.