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Association of Hospitalizations with Randomized Glycemia-Lowering Treatment in the GRADE Study

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Abstract

Objective: To compare rates of and risk factors for hospitalizations among GRADE participants taking metformin and randomly assigned to insulin glargine U-100, glimepiride, liraglutide, or sitagliptin.

Research Design and Methods: Intention-to-treat (ITT) (N=5,047) and on-assigned-treatment (AT) (N=4,830) datasets were used. Baseline differences between those with vs. without hospitalizations were compared. Kaplan-Meier analysis and log-rank tests were used to determine the incidence of time-to-first hospitalization and treatment group differences, respectively. Time-to-event analyses were used to examine factors affecting subsequent hospitalization risk.

Results: During GRADE, 1,636 participants (32.4%) had at least one hospitalization and 751 (14.9%) were hospitalized more than once. Hospitalized participants were older, less likely to be Hispanic, and more likely to be White, have a history of hypertension and higher baseline BMI. There were no treatment group differences in the incidence of time-to-first hospitalization in the ITT dataset ($p=0.148$). A difference was observed in the AT dataset ($p=0.021$) with a reduced hazard rate (HR) for those taking liraglutide vs. glimepiride (HR 0.78, 95% CI [0.66, 0.92]; $p=0.022$). Factors increasing the risk for subsequent hospitalizations were meeting the secondary outcome (HbA1c $>7.5\%$, confirmed), each prior hospitalization, and change from assigned treatment (29%, 41% and 56% increase in risk, respectively). Assignment to liraglutide vs. glimepiride reduced risk by 13%.

Conclusions: Hospitalizations were common in the GRADE study, and rates were nearly identical across treatment groups. The small, but significant reduction in risk for subsequent hospitalizations among participants assigned to liraglutide vs. glimepiride may influence treatment decisions in populations similar to GRADE.

Twitter Summary:

About 1/3 of participants in the @GRADE_Study were hospitalized at least once during the study, and the hospitalization risk was similar across all 4 medication groups. This further supports the comparable safety of these medications when used with metformin.

Keywords

diabetes treatment; hospitalizations; serious adverse events

The latest statistics from the Centers for Disease Control indicate that 11.6% of the U.S. population or 38.4 million people in the United States have diagnosed diabetes, with most having type 2 diabetes mellitus (1). Much of the diabetes-related disease burden lies in the development of both macrovascular (coronary heart disease, heart failure, stroke and peripheral arterial disease) and microvascular (nephropathy, retinopathy and peripheral neuropathy) complications (2). Individuals with diabetes require acute medical care, including emergency department care and inpatient hospitalizations, more often than people without diabetes. It has been reported that in the United States, between 2010 and 2019, there were 304 million hospitalizations, and a quarter of these (78 million) were associated with diabetes (3). In 2018, close to 1 of every 3 hospitalizations was of a person with diabetes, of which 95% had type 2 diabetes (4). Adverse hospital outcomes including higher rates of inpatient complications, longer length of stay, higher in-hospital mortality, and higher hospitalization costs have all been associated with diabetes (3, 4).

The Glycemia Reduction Approaches in Diabetes, a Comparative Effectiveness (GRADE) Study was a randomized clinical trial in people with type 2 diabetes of less than 10 years duration, treated with maximally tolerated doses of metformin as monotherapy, and with baseline HbA1c values between 6.8 and 8.5% (51–69 mmol/mol) (5). The study compared the efficacy of adding, by random assignment, one of four common diabetes treatments (insulin glargine U-100, glimepiride, liraglutide, or sitagliptin) to metformin to achieve and maintain recommended glycemic levels. Treatment group differences were observed for the primary metabolic outcome (HbA1c $\geq 7.0\%$ [53 mmol/mol], confirmed), met by 77% of participants assigned to sitagliptin, 72% of those assigned to glimepiride, 68.2% of those assigned to liraglutide, and 67% of those assigned to glargine ($p < 0.001$) (6). Statistically significant treatment group differences were also observed for the secondary metabolic outcome (HbA1c $> 7.5\%$ [> 58 mmol/mol], confirmed), which was met by 55%, 50%, 46%, and 39% of those assigned to sitagliptin, glimepiride, liraglutide, and glargine respectively ($p < 0.001$) (6). In this secondary analysis of the GRADE study, we examined the associations of treatment assignment with the risk for incident and recurrent inpatient hospitalizations, and whether the risk factors and reasons for hospitalizations, as reported, differed by treatment group.

Research Design and Methods

Participants

The GRADE study design and key results have been published (6–10). Briefly, 5,047 adults with type 2 diabetes for less than 10 years, treated with maximally tolerated metformin (minimum 1,000 mg, maximum 2,000 mg per day), and with baseline HbA1c levels between 6.8 and 8.5% (51 and 69 mmol/mol) were randomly assigned to either insulin glargine U-100 (hereafter, glargine), the sulfonylurea glimepiride, the glucagon-like peptide-1 (GLP-1) receptor agonist liraglutide, or the dipeptidyl peptidase-4 (DPP-4)

inhibitor sitagliptin and followed for a mean of five years. Individuals with known contraindications to any of the GRADE medications, those with an active cancer diagnosis or any cancer treatment in the prior five years, those with cardiovascular events (MI, stroke, cardiac or peripheral revascularization, and unstable angina) within the last six months, and those with heart failure NYHA 3 or greater were not eligible for the study. Individuals with a prior history of pancreatitis were also excluded. The complete list of exclusion criteria may be found in the full protocol, available at <https://clinicaltrials.gov/study/NCT01794143>. The primary outcome of the GRADE study was the time to treatment failure defined as a confirmed HbA1c $\geq 7.0\%$ (≥ 53 mmol/mol) while on maximally tolerated metformin and the randomly assigned treatment (6). Rescue insulin was added to the assigned treatment after reaching the secondary outcome of confirmed HbA1c $> 7.5\%$ (> 58 mmol/mol) (11).

The occurrence of serious and non-serious adverse events was ascertained at each scheduled quarterly visit and as reported by participants between quarterly visits. All hospitalizations (defined as inpatient hospital admission of ≥ 24 hours) were categorized as serious adverse events (SAEs). Staff completed a SAE report form for all adverse events which resulted in hospitalization, or which extended an existing hospitalization using information provided by the participant or their proxy, (e.g., spouse, or child), and from review of available medical records. Completed SAE reports were submitted for central review by an Adverse Event Specialist who assigned a system organ class (SOC) designation and high-level group term (HLGT) using MedDRA[®] (Medical Dictionary for Regulatory Activities) (12).

Datasets

Hospitalizations reported between the baseline visit and final study visit were included in these analyses. SAEs that did not include inpatient admission (e.g., emergency department care, short-stay observation unit care, deaths occurring outside the hospital inpatient unit) were excluded. All cases where multiple reportable SAE events that occurred during a single hospital admission (e.g., hospital admission for an elective surgery complicated by a post-operative stroke) were reviewed to ensure that hospitalizations were correctly counted. Because more than one SAE could occur during a single hospitalization, the number of SOC and HLGT events reported exceeded the total number of hospitalizations. The intention-to-treat (ITT) dataset included all participants (N=5,047) and all available study data. The on-assigned-treatment (AT) dataset (N=4,830) included randomized participants who took at least one dose of assigned medication and attended at least one post-randomization visit, and included data from all available visits up to the point of treatment modification. Treatment modification was defined as the addition of rescue insulin following confirmation of the secondary metabolic outcome as required by the protocol, the permanent discontinuation of metformin and/or the randomized medication, and/or the addition of any glucose-lowering medication other than metformin and the randomized medication. Temporary discontinuation of metformin or the randomized treatment, the use of non-randomized medication while hospitalized (e.g., use of insulin), or dose adjustments of metformin or randomized treatment within the FDA-approved dose guidelines were not counted as treatment modifications. Data from any visits occurring after treatment modification were not included in the AT dataset. The ITT analyses were the primary analyses; the AT analyses were considered to be sensitivity analyses.

Subgroup Variables

The following baseline subgroups were pre-specified: age (< 45, 45–59, ≥ 60 years), sex (female, male), self-reported race (Black, White, other) and ethnicity (non-Hispanic, Hispanic), BMI tertiles (18.2–30.7, 30.8–36.2, 36.3–74.3 kg/m²), baseline HbA1c (6.8–7.2, 7.3–7.7, 7.8–8.5% or 50.8–55.2, 56.3–60.7, 61.8–69.4 mmol/mol), and diabetes duration tertiles (0–2.3, 2.4–5.2, 5.3–10.9 years).

Statistical Analyses

Key baseline characteristics of participants with no hospitalizations vs. participants with one or more hospitalizations were compared using the ITT dataset. Categorical variables were summarized as counts, and row percentages were compared using chi-squared tests. Continuous variables were summarized as mean ± standard deviation and were compared using two-sample t-tests.

For the ITT and AT datasets, Kaplan-Meier (KM) curves were used to display the cumulative incidence of first hospitalization by treatment group, and log-rank tests were used to test treatment group homogeneity.

If a test was significant, six pairwise tests for treatment group differences were conducted using a Cox proportional hazards (PH) model, and the p-values were adjusted for multiple comparisons using the Holm method. As a secondary analysis, the cumulative incidence of all hospitalizations was compared across treatment groups using the Wald test from a proportional rate model of Lin et al. (13) with a single term for treatment group and a robust estimate of the variance-covariance matrix.

Treatment homogeneity in incidence of first hospitalizations across each of the pre-specified baseline subgroups was tested using a PH model with a robust variance estimate and terms for treatment group, the subgroup variable, and the interaction of treatment-by-subgroup. The interaction p-values from the seven models were then adjusted for multiple comparisons using the Benjamini-Hochberg false discovery rate method. As a secondary analysis, this was repeated for incidence of all hospitalizations using the proportional rate model.

The extent to which the risk of hospitalization was affected by prior hospitalizations, randomized treatment group assignment, current HbA1c, treatment modification, and reaching the primary and secondary GRADE outcomes was assessed using a multi-type recurrent events (MTRE) model (14). Effects were tested both individually and jointly. In the joint multivariate model, HbA1c and primary outcome were omitted because they are correlated with the secondary outcome.

Finally, tables of MedDRA System Organ Class (SOC) for the ITT and AT subset show the number of events and crude rate per 1,000 person-years (PY) overall and by treatment group. For rows with at least 50 events, the table gives the p-value for heterogeneity of rates across treatment groups based on a generalized linear model with a Poisson quasi-likelihood, and total time at risk as the offset. SOCs were listed in order of frequency, and those with a significant heterogeneity p-value or more than 200 events are expanded into HLGT.

Results

Rates and causes of hospitalizations

Of the 5,047 participants enrolled in GRADE, 1,636 (32.4%) were hospitalized at least once during the study (Figure 1). For the ITT analysis, the rate of hospitalization was 137.5 per 1,000-person years (PY). The mean number of hospitalizations among those with any hospitalizations was the same (1.9) for each treatment group. Among the 1,636 hospitalized participants, 885 (54.1%) were hospitalized just once, 751 (45.9%) were hospitalized more than once, and 240 (14.7%) had four or more hospitalizations (Figure 1). In the AT analysis, the hospitalization rate was 107.3 per 1,000-PY, and the average number of hospitalizations was 1.5 (glimepiride, liraglutide, and sitagliptin) and 1.6 (glargine).

The most common reasons for hospitalizations in the ITT group based on the MedDRA[®] SOC groupings were Cardiac Disorders (N=596, 23.8 per 1,000-PY), Surgical and Medical Procedures (N=596, 23.8 per 1,000-PY), and Infections and Infestations (N=579, 23.1 per 1,000-PY) (Table S1). Treatment group differences by SOC category were observed only for Cardiac Disorders (p=0.003), which were nearly half as likely in liraglutide-assigned participants compared to the other treatment groups, and for Metabolism and Nutrition disorders (N=89, p=0.007) which were less common among glargine participants. Using the more granular MedDRA[®] HLGT definitions, treatment group differences favoring liraglutide were observed for hospitalizations related to heart failure (N=15, 2.4 per 1,000 PY for liraglutide; N=24, 3.8 per 1,000 PY; N=42, 6.7 per 1,000 PY; N=50, 7.9 per 1,000 PY for glargine, glimepiride, and sitagliptin, respectively, p=0.016) and coronary artery disorders (N=40, 6.4 per 1,000 PY for liraglutide; N=85, 13.6 per 1,000 PY for glargine; N=83, 13.3 per 1,000 PY for glimepiride; and N=78, 12.4 for sitagliptin, p=0.014).

Characteristics of those who were hospitalized during GRADE

GRADE participants who were hospitalized were older, more likely to be White, less likely to be Hispanic, more likely to be male, and more likely to have a history of hypertension and had a higher baseline BMI compared to those who were never hospitalized (Table 1). However, they did not differ by baseline HbA1c or duration of diabetes.

Treatment group differences in hospitalizations-Time to event analyses

The cumulative incidence of first hospitalization did not differ among the four treatment groups in the ITT analysis (Figure 2a, log-rank test p=0.148). Among the subgroups of age, sex, race, ethnicity, HbA1c, BMI, and diabetes duration, there was no treatment heterogeneity for time-to-first hospitalization in the unadjusted or adjusted analyses. In the AT analysis, the cumulative incidence of first hospitalization was lowest for participants assigned to liraglutide (Figure 2b, log-rank test p=0.021); after Holm adjustment of the six pairwise comparisons, liraglutide was significantly lower than glimepiride (HR liraglutide/glimepiride 0.78, 95% CI [0.66, 0.92]; p=0.022). As with the ITT analysis, there was no significant treatment heterogeneity in the unadjusted or adjusted analyses.

The cumulative incidence of all hospitalizations was similar across treatment groups in ITT analyses. In the unadjusted subgroup analysis, nominally significant treatment heterogeneity

for diabetes duration was observed ($p=0.024$) which became non-significant after adjusting for multiple comparisons ($p=0.191$). The cumulative incidence of all hospitalizations in the AT analysis differed by treatment group ($p=0.026$) and was lowest among liraglutide participants, but was significantly lower only in comparison to glimepiride (HR liraglutide/glimepiride 0.79, 95% CI [0.66, 0.95]; $p<0.05$) after Holm adjustment for all six pairwise comparisons. No significant treatment heterogeneity was observed for any of the subgroups in unadjusted or adjusted analyses in the AT dataset (data not shown).

Multi-type recurrent event model of all hospitalizations, ITT analysis

Factors associated with an increased risk of subsequent hospitalizations during GRADE included having reached the primary or secondary metabolic outcome, having had treatment modification, or having a previous hospitalization. The associated risk was highest with prior treatment modification (HR 1.73, $p<0.001$), while each prior hospitalization increased the risk for future hospitalization by 44% (HR 1.44, $p<0.001$) (Table 2, Univariate Models). In a multivariate model, treatment group, having reached the secondary metabolic outcome, having treatment modification, and the number of prior hospitalizations all impacted the risk for future hospitalizations ($p=0.032$ for treatment group, $p<0.001$ for all other predictors) (Table 2, Multivariate model). For treatment group, the difference in risk was only significant for liraglutide versus glimepiride (HR 0.87, $p=0.025$). Significant increased risk for subsequent hospitalizations was observed for prior treatment modification (HR 1.56, $p<0.0001$), and each prior hospitalization increased the risk for subsequent hospitalizations exponentially. A single hospitalization multiplied the HR by 1.41, increasing to 1.99 (1.41^2) after two hospitalizations and to 2.8 (1.41^3) after three hospitalizations (Table 2, Multivariate model).

Conclusions

In this secondary analysis examining the frequency, risk factors, and causes for hospitalizations during the GRADE study, we found that nearly one-third of participants were hospitalized at least once over a mean five-year follow-up with nearly half of those having two or more hospitalizations. The impact of treatment group on the time-to-first hospitalization and on the risk of subsequent hospitalizations appeared to be minimal except for a small, but statistically significant difference in the cumulative incidence of time-to-first hospitalization favoring the GLP1-receptor agonist (GLP1-RA) liraglutide versus the sulfonylurea glimepiride limited to the AT analysis, and a small (13%) lower risk for future hospitalizations also favoring liraglutide over glimepiride. The difference may reflect the lower rates of hospitalizations related to cardiac disorders among participants assigned to liraglutide. Otherwise, no treatment heterogeneity was observed for the time-to-first hospitalization or the risk for subsequent hospitalizations for any subgroup variables after adjustment for multiple comparisons.

Reasons for hospitalizations were similar across treatment groups with the exception of fewer hospitalizations for cardiac disorders, specifically for heart failure in participants assigned to liraglutide. This is consistent with what has been previously reported (8, 10) and with the known cardiovascular benefits of the GLP1-RA class of medications. Assignment

to liraglutide (versus glimepiride, but not versus glargine or sitagliptin) decreased the risk for subsequent hospitalizations in a multivariable, multi-type recurrent event model, but was less important than reaching the secondary outcome, treatment modification, or prior hospitalization. The latter two factors were associated with the greatest risk of future hospitalization. The increased risk of hospitalization with treatment modification includes participants who had their treatment modified according to the protocol, requiring the addition of basal and/or prandial insulin after reaching the secondary metabolic outcome, those with intolerance to the study medication, and those with a comorbid condition or health event which necessitated a change in treatment (e.g., participants with known cardiovascular disease may have been switched to a GLP-1 RA if not assigned or to a SGLT2 inhibitor when recommendations for these medications in some populations were released, or discontinuation of GLP1-RA or DPP-4 after admission for pancreatitis). We certainly would not interpret the association of treatment modification with risk for hospitalization as a reason to avoid treatment modification; rather, treatment modification was likely a surrogate for a concomitant health concern warranting escalation (or de-escalation) of the prescribed diabetes treatment regimen. We suspect that the increased risk of future hospitalizations reflected participants with an increased burden of disease requiring more frequent hospital admissions. Baseline characteristics associated with an increased risk of hospitalization(s) included older age, male sex, White race, non-Hispanic ethnicity, history of hypertension, and higher BMI. In GRADE, younger participants were more racially diverse, included a greater proportion of people of Hispanic ethnicity, were less likely to have CVD, and were taking fewer medications to treat co-morbid conditions. Older participants were more likely to be male than female. These associations should be interpreted in the context of the composition of participants who met inclusion criteria for this trial.(7)

The main strength of this study is the opportunity to examine hospitalizations prospectively in a randomized treatment cohort, allowing for head-to-head comparisons of four commonly used treatment regimens on an important and costly outcome. Additional strengths are the large racially, ethnically, and geographically diverse cohort, application of a standardized approach to diabetes treatment, and frequent and comprehensive follow-up over a mean of five years. Adverse events, including SAEs and hospitalizations, were systematically assessed and classified by central reviewers experienced with MedDRA classifications and masked to treatment assignment. The analyses used robust models to examine differences over time for adverse events and hospitalizations. The principal weakness of this study is the lack of generalizability owing to the careful selection of participants for trial entry (relatively short duration of diabetes, exclusion of people with poor glycemic control (HbA1c > 8.5% [> 69 mmol/mol]), inclusion of those treated only with metformin, willingness to accept random treatment assignment, among others) and likely enhanced adherence to treatment via provision of an expert care team, free study medications and monitoring supplies when indicated. Moreover, our findings are only applicable to the treatments used in GRADE; newer, increasingly more commonly used medications for type 2 diabetes were not studied (e.g. SGLT2 inhibitors, weekly GLP-1RA, dual incretin agonists).

In summary, nearly one-third of the GRADE cohort experienced one or more hospitalizations while in the GRADE study. The similar rates of initial and subsequent

hospitalizations across the four GRADE treatment groups should provide reassurance regarding the comparative safety of the four medications when used in combination with metformin, although we cannot overlook the small, but significantly lower risk observed with liraglutide versus glimepiride. This may be an important variable in the complex treatment decision process when treating patients similar to those enrolled in GRADE. Deteriorating glycemic control increased the risk for hospitalizations and highlights the substantial medical burden of type 2 diabetes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data Availability:

The Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study (GRADE) is funded by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). This manuscript is based on follow-up data and outcome assessments from the 5,047 participants enrolled into the study. This database will be available in the NIDDK Central Repository in 2025.

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Article Highlights

- Why did we undertake this study?
 - To better understand how medications used in the GRADE study affected hospitalization rates over five years.
- What is the specific question(s) we wanted to answer?
 - How often were GRADE participants hospitalized? What factors affected the risk of hospitalization one or more times?
- What did we find?
 - Nearly one-third of GRADE participants were hospitalized at least once. Factors increasing the risk for subsequent hospitalization included the number of prior hospitalizations, change from assigned treatment, and HbA1c over 7.5%. Assignment to liraglutide vs glimepiride was associated with a reduction in the risk for subsequent hospitalizations.
- What are the implications of our findings?
- These results are largely reassuring for the use of GRADE medications from the standpoint of hospitalization risk.

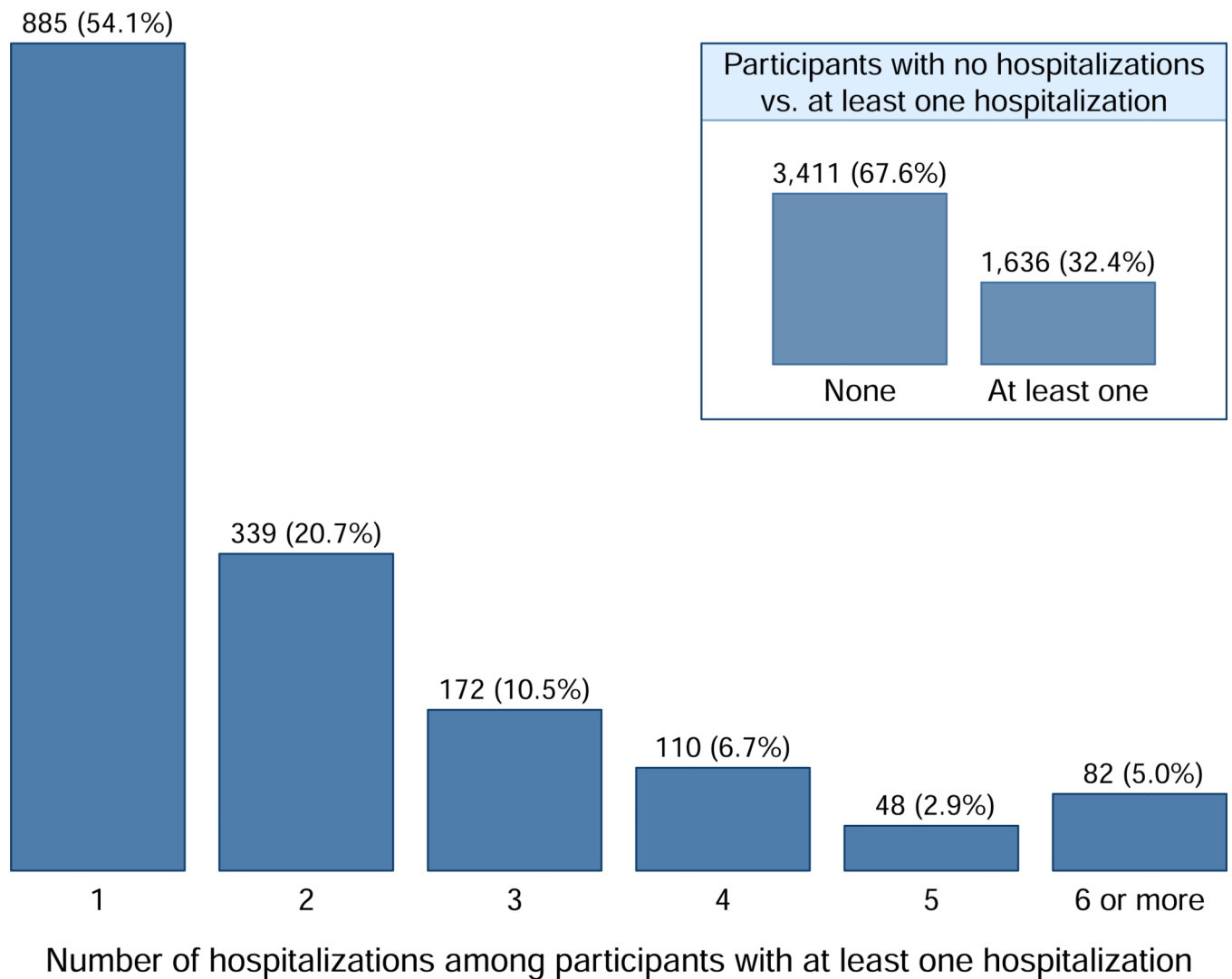


Figure 1.

Bar graph showing frequency of hospitalizations among GRADE participants with one or more hospitalizations (N=1,636). The number of participants with 1, 2, 3, etc. hospitalizations are given with associated percentages out of the 1,636 who were hospitalized at least once (e.g., among the 1,636 participants hospitalized at least once, 54.1% were hospitalized only once). The inset graph shows the numbers and percentages of participants with no hospitalization vs. one or more hospitalizations out of the 5,047 participants in the ITT dataset.

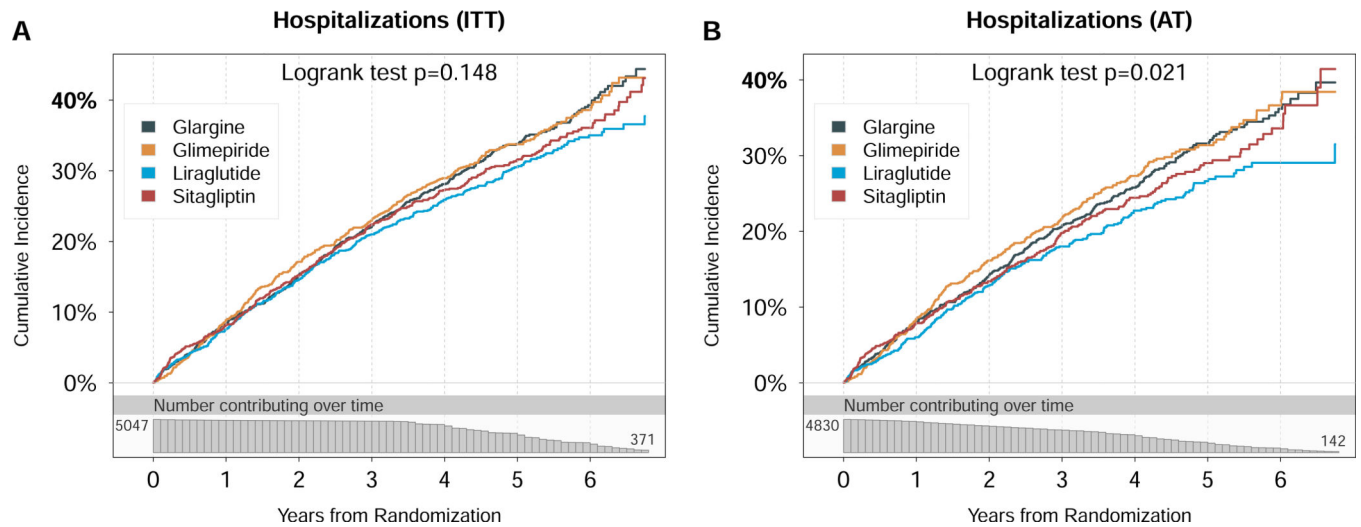


Figure 2.

Cumulative incidence curves for time-to-first hospitalization for the ITT (panel A) and AT (panel B) cohorts, for the four treatment groups (glargine=dark grey, glimepiride=orange, liraglutide=light blue, sitagliptin=red). The log-rank test p-value is shown at the top and the distribution of the number contributing over time at the bottom of the graphs.

Table 1. Baseline characteristics of participants grouped by no hospitalizations (“None”) and at least one hospitalization (“One or More”) during the GRADE study.

	Hospitalizations		p-value
	None	One or More	
Number of Participants	3,411	1,636	
Age at baseline visit (years)	55.9 ± 9.9	59.7 ± 9.7	<0.001
Age subgroups (years)			<0.001
<45 years	493 (14.5%)	126 (7.7%)	
45–59 years	1,685 (49.4%)	640 (39.1%)	
60+ years	1,233 (36.1%)	870 (53.2%)	
Female sex	1,303 (38.2%)	534 (32.6%)	<0.001
Race			0.020
Black	678 (19.9%)	322 (19.7%)	
White	2,206 (64.7%)	1,108 (67.7%)	
All others	527 (15.5%)	206 (12.6%)	
Ethnicity			<0.001
Non-Hispanic	2,684 (79.3%)	1,393 (86.0%)	
Hispanic	702 (20.7%)	227 (14.0%)	
Systolic blood pressure (mmHg)	127.8 ± 14.4	129.4 ± 15.3	<0.001
Diastolic blood pressure (mmHg)	77.4 ± 9.7	77.1 ± 10.1	0.268
History of hypertension	2,505 (73.4%)	1,374 (84.0%)	<0.001
BMI (kg/m ²)	34.0 ± 6.7	35.0 ± 6.9	<0.001
Duration of diabetes (years)	4.2 ± 2.7	4.3 ± 2.7	0.452
HbA1c (%)	7.5 ± 0.5	7.5 ± 0.5	0.295
HbA1c (mmol/mol)	58.4 ± 5.2	58.2 ± 5.3	0.295

For categorical variables, the table reports counts and percentages, and p values for treatment group homogeneity based on a chi-squared test. For continuous variables, the table reports mean ± standard deviation, and p values for treatment group homogeneity on a t-test.

Table 2.

Univariate and multivariate multi-type recurrent event (MTRE) model results of all hospitalizations in GRADE participants for the ITT group.

Univariate and multivariate multi-type recurrent event models for future hospitalizations as a function of primary outcome, secondary outcome, treatment modification, most recent HbA1c, and number of prior hospitalizations, modeled as time-dependent covariates. All models include treatment group (glargine, glimepiride, liraglutide, and sitagliptin) as a covariate. Treatment modification is defined as the permanent discontinuation of metformin and/or of the randomized medication or the addition of any glucose lowering medication other than metformin and the randomized medication.

	Risk of a Future Hospitalization	
	Estimate (95% CI)	P Value
Univariate Models		
Treatment group		0.1558
Number of prior hospitalizations	1.44 (1.36, 1.52)	<0.0001
Treatment modification	1.73 (1.56, 1.92)	<0.0001
HbA1c related		
Most recent HbA1c	1.03 (0.98, 1.09)	0.2345
Primary outcome (HbA1c $\geq$ 7% confirmed)	1.14 (1.03, 1.27)	0.0145
Secondary outcome (HbA1c>7.5% confirmed)	1.19 (1.06, 1.33)	0.0031
Multivariate Model		
Treatment group ¹	<i>see footnote</i>	0.0323
Number of prior hospitalizations	1.41 (1.34, 1.49)	<0.0001
Treatment modification	1.56 (1.37, 1.78)	<0.0001
Secondary outcome (HbA1c>7.5% confirmed)	1.29 (1.13, 1.47)	0.0002

¹ Hazard Ratios vs glimepiride: Glargine HR=1.01 (p=0.933), Liraglutide HR=0.87 (p=0.025), Sitagliptin HR=0.92 (p=0.192)