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Clinical Research Article

Long-term Effectiveness and Safety of GH Replacement Therapy in Adults ≥60 Years: Data From NordiNet® IOS and ANSWER

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Abstract

Context: Effectiveness and safety data on GH replacement therapy (GHRT) in older adults with adult GH deficiency (AGHD) are limited.

Objective: To compare GHRT safety and clinical outcomes in older (≥60 years and, for some outcomes, ≥75 years) and middle-aged (35–<60 years) patients with AGHD.

Design/setting: Ten-year follow-up, real-world data from 2 large noninterventional studies—NordiNet® International Outcome Study (IOS) and the American Norditropin® Studies: Web-Enabled Research (ANSWER) Program—were analyzed.

Patients: GH-naïve and non-naïve patients with AGHD.

Intervention: Norditropin® (somatropin).

Main outcome measures: Outcomes included GH exposure, IGF-I standard deviation scores (SDS), body mass index (BMI), glycated hemoglobin (HbA_{1c}), serious and nonserious adverse reactions (SARs and NSARs, respectively), and serious adverse events (SAEs). Adverse reactions were events with possible/probable causal relationship to GHRT.

Results: The effectiveness analysis set comprised 545 middle-aged and 214 older patients (19 aged ≥75 years) from NordiNet® IOS. The full analysis set comprised 1696 middle-aged and 652 older patients (59 aged ≥75 years) from both studies. Mean GH doses were higher in middle-aged vs older patients. For both age groups and sexes, mean IGF-I SDS increased following GHRT, while BMI and HbA_{1c} changes were similar and small.

Incidence rate ratios (IRRs) did not differ statistically between older and middle-aged patients for NSARs [IRR (mean, 95% confidence interval) 1.05 (.60; 1.83)] or SARs [.40 (.12; 1.32)]. SAEs were more frequent in older than middle-aged patients [IRR 1.84 (1.29; 2.62)].

Conclusion: Clinical outcomes of GHRT in AGHD were similar in middle-aged and older patients, with no significantly increased risk of GHRT-related adverse reactions in older patients.

Key Words: adult growth hormone deficiency, elderly, older age, growth hormone replacement therapy, IGF-I SDS, somatropin

Adult growth hormone deficiency (AGHD) is a congenital or acquired condition in which GH levels are reduced. AGHD may persist from childhood or can occur in adulthood due to pituitary adenomas and their related therapies, other hypothalamic-pituitary disorders, or brain trauma [1, 2]. The condition is associated with reduced physical activity, decreased bone mineral density, adverse changes in body composition and metabolism, increased risk of cardiovascular disease, and impaired quality of life (QoL) [3-6]. Decreased production of GH and IGF-I also occur as part of normal aging, but, due to the similar features of aging and growth hormone deficiency (GHD), it is thought that GHD in elderly people could further contribute to fragility [7].

It is well established that GH replacement therapy (GHRT) can improve the metabolic and functional alterations associated with AGHD, leading to better QoL [2, 5, 8, 9]. However, there are limited data on the effectiveness and safety of GHRT in older patients with AGHD, especially those aged

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≥75 years [10-12]. A few studies have suggested that GHRT, even in patients with AGHD aged >60 years, can have beneficial effects on body composition and lipid profile while achieving an IGF-I standard deviation score (SDS) within the preferred range [7, 13]. However, the Endocrine Society's AGHD guidelines indicate that GH dose requirements are lower in older patients because they have an increased susceptibility to GH-related side effects [9]; similarly, the 2019 American Association of Clinical Endocrinologists/American College of Endocrinology GHD clinical practice guidelines suggest that lower GH doses should be considered in elderly patients [2]. Both guidelines state that older patients (aged >60 years) should be started on lower doses of .1 to .2 mg per day of GH and that doses should be increased more slowly than in younger patients.

The decreased production of GH and IGF-I that is characteristic of AGHD also occurs as part of normal aging, resulting in clinical features such as changes in body composition that resemble those of AGHD [14]; however, it is possible to differentiate GHD in elderly patients from the normal physiological reduction of GH secretion using GH stimulation tests [7]. A systematic review published in 2007 of GH as a potential treatment for aging in healthy, non GH-deficient elderly patients concluded that, although GH may alter body composition, it does not improve other clinically relevant outcomes and is associated with high rates of adverse events (AEs) in older patients without AGHD. GH therapy is therefore not recommended in these patients [15]. A more recent systematic review of studies on the use of GHRT in patients ≥60 years with AGHD concluded that treatment decreased total and low-density lipoprotein (LDL) cholesterol levels and significantly improved QoL parameters but that effects on other parameters were equivocal [14]. Six of the 11 included studies reported possible adverse effects, with no clear pattern emerging as to whether these were more prevalent in older vs younger patients.

In light of these concerns about safety in older adults, we compared GHRT safety and clinical outcomes in older adults (aged ≥60 years) vs middle-aged adults (35–<60 years) with AGHD receiving GHRT in a real-world setting. Selected outcomes were also reported for patients aged ≥75 years, who constituted a subgroup of the patients aged ≥60 years. Source data for these analyses were available from 2 large noninterventional, multicenter studies: the NordiNet® International Outcome Study (IOS) and the American Norditropin® Studies: Web-Enabled Research (ANSWER) Program [16, 17]. Access to these 2 large registries has enabled this study to include a uniquely large population of older patients, particularly those aged ≥75 years, in comparison with other studies with similar objectives.

It is important to note that, in our study, the indication for GHRT was strictly AGHD; GH was not used for any antiaging indications in this study. Only patients with AGHD were eligible for the study and exposed to GHRT. Only AGHD-related endpoints and parameters were investigated in this study.

Materials and Methods

Study Design and Assessment of Safety Events

NordiNet® IOS (NCT00960128) and ANSWER (NCT01009905) were observational, noninterventional, multicenter registry studies monitoring the long-term clinical outcomes and safety of GH replacement therapy with Norditropin® (Novo Nordisk A/S, Copenhagen, Denmark) in adults and pediatric populations as prescribed by treating physicians in a real-life clinical setting. The detailed study designs and methodologies have been published previously [16, 17].

NordiNet® IOS was conducted from April 2006 to December 2016, involved 23 countries (469 clinics) across Europe and the Middle East, and included 2524 adults [17]. The ANSWER Program was ongoing between June 2002 and September 2016 in the United States (207 clinics) and included 966 adults [17]. The 2 studies were complementary, with similar aims, and used the same electronic data-management platform. Both were approved by the relevant ethics committees and conducted with written consent from patients, and pseudonymization of all data was performed in accordance with the Declaration of Helsinki, regulatory requirements, and Guideline for Good Pharmacoepidemiology Practices.

In both the Nordinet® and ANSWER Program studies, AEs were assessed by both the investigator and the sponsor. For an AE to be considered a serious adverse reaction (SAR) or a non-serious adverse reaction (NSAR), either the investigator or the sponsor would have to assess the relationship of the AE to GHRT as probable or possible. Serious adverse events that were not considered related to GHRT by either assessor (SAEs) are also described in the current paper.

Events were considered serious if they resulted in death, a life-threatening experience, hospitalization or prolongation of existing hospitalization, or a persistent or significant disability/incapacity or were associated with a congenital anomaly/birth defect or important medical events that, based on appropriate medical judgment, might have jeopardized the patient or required medical or surgical intervention to prevent one of the outcomes listed above.

Endpoints

Clinical and safety outcomes that were reported included GH exposure, IGF-I SDS, body mass index (BMI), waist circumference, glycated hemoglobin (HbA_{1c}), SARs, NSARs, and SAEs. In addition, the levels of non-high-density lipoprotein (HDL) cholesterol (ie, total cholesterol less HDL cholesterol) were available for some patients in the effectiveness analysis set (EAS). Non-HDL cholesterol levels were reported using the following categories suggested by Brunner et al for use in population-based cardiovascular risk stratification: <2.6 mmol/L (<100 mg/dL), 2.6–<3.7 mmol/L (100–<145 mg/dL), 3.7–4.8 mmol/L (145–<185 mg/dL), 4.8–5.7 mmol/L (185–<220 mg/dL), and ≥5.7 mmol/L (≥220 mg/dL) [18].

Patient Populations/Analysis Sets

Safety was assessed in the full analysis set (FAS) from both studies. The FAS included all GH-naïve and non-naïve patients with a diagnosis of GHD who initiated GH replacement after the age of 18 years and who were treated with GH after the age of 20 years.

The EAS, which was used to assess clinical outcomes, comprised patients fulfilling these criteria who additionally were GH-naïve at the baseline visit (at study enrolment, all NordiNet® IOS patients were naïve, but patients in ANSWER could have started GH up to 6 months prior to baseline) and with valid baseline BMI, age, and dosing information. In the current study, the EAS was from NordiNet®

IOS only, to ensure that only GH-naïve patients were included.

Patients were divided into a middle-aged group (aged 35–<60 years) and an older group (aged ≥60 years). Some analyses were also conducted on patients aged ≥75 years—these patients were a subgroup of the patients aged ≥60 years.

Statistical Analyses

Statistical analyses were performed using SAS Version 9.4 M5. Baseline characteristics and some outcome data that have not been statistically compared are presented descriptively. In some cases, group sizes were too small for outcomes to be compared statistically. Statistical comparisons of continuous variables were performed using *t*-tests. Statistical comparisons of incidence rates were performed using Poisson regression. *P*-values <.05 were considered significant.

Clinical outcomes were determined each year for up to 10 years of follow-up. Changes in clinical outcomes were compared statistically between older adults and middle-aged adults at 2 years. The 2-year period was selected because it was considered a long enough period for changes to become apparent and, after 2 years, the number of patients decreased steadily.

SARs, NSARs, and SAEs are presented as incidence rates per 1000 patient-years and as incidence rate ratios (IRRs) for older vs middle-aged adults.

Data Collection and Validation

For both registries, data were verified by the physicians or authorized research staff at study sites before being submitted to a centralized database. Data were validated by automatic validation steps embedded into the data input software; immediate entry errors were flagged based on predetermined value ranges in some data fields. All physicians and authorized research staff were trained to use the web-based application and could make tracked amendments to the database in case of errors.

Results

Patients

These analyses involved 759 patients from the EAS of NordiNet® IOS (545 middle-aged and 214 older patients) and 2348 patients from the FAS of both studies (1696 middle-aged and 652 older patients). Baseline characteristics are presented in Table 1. Nineteen of the 759 patients from the EAS and 59 of the 2348 patients from the FAS were ≥75 years of age.

The mean durations of follow-up per patient were 5.4 years (middle-aged group) and 5.3 years (older group) in the EAS, and 5.2 and 4.7 years, respectively, in the FAS. In both analysis sets, women made up a smaller proportion of the older group compared with the middle-aged group.

All patients included in this analysis had adult-onset AGHD. The most common etiology in both age groups was pituitary adenoma, representing 50.3% (middle-aged group) and 66.8% (older group) of patients in the EAS, and 39.7% and 54.8% of patients, respectively, in the FAS. Other common etiologies included post-procedural hypopituitarism, craniopharyngioma, and isolated/idiopathic GHD.

GH Exposure (FAS)

As expected, mean GH doses were higher at baseline and throughout the study in middle-aged vs older patients (both females and males) (Fig. 1). This difference in dose between the two age groups was numerically larger in females than in males. In the ≥75 years group, among men, mean doses were lower in the ≥75 years group vs the ≥60 years group. In the same age group, among women, mean doses were overall similar to those in the ≥60 years group.

The percentage of women receiving oral estrogen in years 1 and 10 was 10.4% and 21.8% in the middle-aged group, respectively, and 8.5% and 15.8% in the older group, respectively, based on patients with valid GH dosing information for each year. As the recommendation is for doses of GH to be increased in patients receiving concomitant oral estrogen therapy [9], GH exposure was also analyzed for older vs middle-aged women with AGHD not receiving concomitant oral estrogen. In this subgroup of women, as with the total women in the FAS, mean GH doses were higher at baseline and throughout the study in middle-aged vs older patients (Fig. 1). There were three female patients using estrogen patches, all in the middle-aged group.

The cumulative GH dose up until the first adverse drug reaction (ADR) was calculated for each age group. The median cumulative GH dose (mg) was 240.15 for the middle-aged group, 125.32 for the older-age group, and 74.25 for patients aged ≥75 years.

IGF-I SDS (EAS and FAS)

Mean baseline IGF-I SDS was lower for middle-aged patients compared with older patients (Table 1). In the EAS, mean [SD] baseline IGF-I SDS was slightly higher in older (−.63 [1.22]) vs middle-aged women (−.95 [1.39]), but was similar for men (−.94 [1.43] vs −.93 [1.42]) (Table 2). Values in patients ≥75 years are also shown, but the number of patients is too small for comparisons to be made.

In both the EAS and the FAS, mean IGF-I SDS for both age groups and sexes increased from below 0 to positive values ≤1.24 following GHRT (Figs. 2 and 3). In the EAS, there was no statistically significant difference in change in IGF-I SDS at year 2 of follow-up between age groups for either females ($P = .4628$) or males ($P = .3745$).

Patients aged ≥75 years in the EAS (n = 11) had a mean (SD) baseline IGF-I SDS of −.90 (.96) and this increased to a maximum mean of 1.48 following GHRT (maximum of 4 years' follow-up), while those aged ≥75 years in the FAS (n = 23) had a mean baseline IGF-I SDS of −.57 (1.43), which increased to a maximum of 1.16 (maximum of 5 years' follow-up).

At baseline, the proportion of middle-aged patients within the normal IGF-I SDS range (−2 to +2) was similar to the proportion of patients aged ≥60 years (78.1% and 81.5%, respectively). A slightly higher proportion of middle-aged patients were below the normal range (<–2) than patients aged ≥60 years (20.2% and 15.5%, respectively). In both age groups, few patients were above the normal range at baseline. By year 1, the proportion of patients within the normal range had increased in both groups and remained >80% over most of the follow-up years and up to year 10. Moreover, the proportion of patients below the normal range had decreased markedly and remained close to 0 in both groups. There was an increase in the proportion of both

Table 1. Baseline characteristics of middle-aged and older patients in the EAS from NordiNet® IOS and the FAS from NordiNet® IOS and the ANSWER Program

	EAS N = 759			FAS N = 2348		
	35–<60 years (n = 545)	≥60 years (n = 214)	≥75 years (n = 19)	35–<60 years (n = 1696)	≥60 years (n = 652)	≥75 years (n = 59)
Female, n (%)	250 (45.9)	84 (39.3)	6 (31.6)	888 (52.4)	282 (43.3)	20 (33.9)
Age, years (P10, P90)	48.5 (7.0) (38.4; 57.8)	67.2 (4.9) (61.4; 74.7)	76.8 (1.5) (75.1; 78.8)	48.4 (7.1) (37.9; 57.8)	67.1 (5.1) (61.3; 74.6)	77.7 (2.6) (75.4; 81.2)
IGHD, n (%)	153 (28.1)	49 (22.9)	4 (21.1)	658 (38.8)	217 (33.3)	14 (23.7)
MPHD, n (%)	392 (71.9)	165 (77.1)	15 (78.9)	1038 (61.2)	435 (66.7)	45 (76.3)
GH dose, mg/day	.24 (.16)	.20 (.10)	.22 (.13)	.32 (.24) (n = 1601)	.26 (.18) (n = 628)	.24 (.16) (n = 56)
IGF-I SDS	−.94 (1.40) (n = 421)	−.82 (1.36) (n = 168)	−.90 (.96) (n = 11)	−.58 (1.53) (n = 1100)	−.27 (1.54) (n = 410)	−.57 (1.43) (n = 23)
BMI, kg/m^2	29.3 (6.1)	29.0 (4.6)	30.2 (2.3)	30.5 (7.3) (n = 1249)	29.4 (5.4) (n = 496)	28.9 (2.8) (n = 48)
Waist circumference, cm	99.9 (15.0) (n = 302)	101.9 (10.7) (n = 116)	105.9 (9.63) (n = 12)	99.2 (16.5) (n = 569)	102.0 (11.2) (n = 258)	103.1 (8.9) (n = 33)
Bioimpedance, ohm	521.6 (106.7) (n = 160)	527.6 (70.9) (n = 59)	497.6 (58.7) (n = 5)	523.2 (111.2) (n = 304)	521.2 (74.5) (n = 110)	512.7 (67.4) (n = 10)
HbA_{1c}, %	5.36 (.89) (n = 288)	5.61 (.99) (n = 119)	5.55 (.74) (n = 8)	5.36 (.86) (n = 479)	5.51 (.91) (n = 203)	5.4 (.65) (n = 16)
Duration of follow-up, years	5.4 (4.3)	5.3 (3.9)	5.1 (2.5)	5.2 (4.5)	4.7 (3.9)	4.4 (2.8)
Aetiology, n (%)						
Pituitary tumors[a]						
Pituitary adenoma	274 (50.3)	143 (66.8)	16 (84.2)	674 (39.7)	357 (54.8)	44 (74.6)
Prolactin secreting tumor	15 (2.8)	6 (2.8)	0	53 (3.1)	23 (3.5)	1 (1.7)
Acromegaly	11 (2.0)	2 (.9)	0	12 (.7)	5 (.8)	0
Cushing's syndrome	10 (1.8)	0	–	24 (1.4)	4 (.6)	0
TSH-secreting tumor	1 (.2)	0	–	2 (.1)	1 (.2)	0
Cranial tumors[a]						
Post-procedural hypopituitarism	40 (7.3)	28 (13.1)	3 (15.8)	85 (5.0)	49 (7.5)	3 (5.1)
Craniopharyngioma	31 (5.7)	8 (3.7)	0	74 (4.4)	16 (2.5)	2 (3.4)
Irradiation	4 (.7)	0	–	6 (.4)	2 (.3)	0
Meningioma	2 (.4)	3 (1.4)	0	4 (.2)	5 (.8)	0
Astrocytoma	2 (.4)	0	–	4 (.2)	0	–
Germinoma	–	–	–	1 (.1)	0	–
Glioma	–	–	–	1 (.1)	0	–
Vascular						
Sheehan syndrome	13 (2.4)	0	–	43 (2.5)	0	–
Subarachnoid hemorrhage	1 (.2)	1 (.5)	0	2 (.1)	1 (.2)	0
Infiltrative/inflammatory disease						
Granulomatous	2 (.4)	0	–	2 (.1)	1 (.2)	1 (1.7)
Neurofibromatosis	–	–	–	1 (.1)	0	–
Langerhans' cell histiocytosis	–	–	–	1 (.1)	0	–
Isolated/idiopathic GHD	22 (4.0)	2 (.9)	0	298 (17.6)	71 (10.9)	0
Congenital GHD	21 (3.9)	4 (1.9)	0	43 (2.5)	9 (1.4)	0
Acquired GHD (unspecified)	15 (2.8)	5 (2.3)	0	57 (3.4)	17 (2.6)	1 (1.7)
Traumatic brain injury	17 (3.1)	1 (.5)	0	49 (2.9)	6 (.9)	0
Empty sella syndrome	1 (.2)	1 (.5)	0	5 (.3)	5 (.8)	1 (1.7)
Hypothalamic dysfunction[b]	–	–	–	29 (1.7)	5 (.8)	1 (1.7)
Not reported or missing	63 (11.6)	10 (4.7)	0	226 (13.3)	75 (11.5)	5 (8.5)

Data are mean (SD) unless otherwise stated. n values are shown only if data were not available for all patients.
Abbreviations: –, not reported; BMI, body mass index; EAS, effective analysis set; FAS, full analysis set; GHD, growth hormone deficiency; HbA1c, glycated hemoglobin; IGHD, isolated growth hormone deficiency; MPHD, multiple pituitary hormone deficiency; P10, 10th percentile; P90, 90th percentile; SDS, SD score; TSH, thyroid-stimulating hormone.
[a]Stated etiology and/or its respective treatment.
[b]Not elsewhere classified.

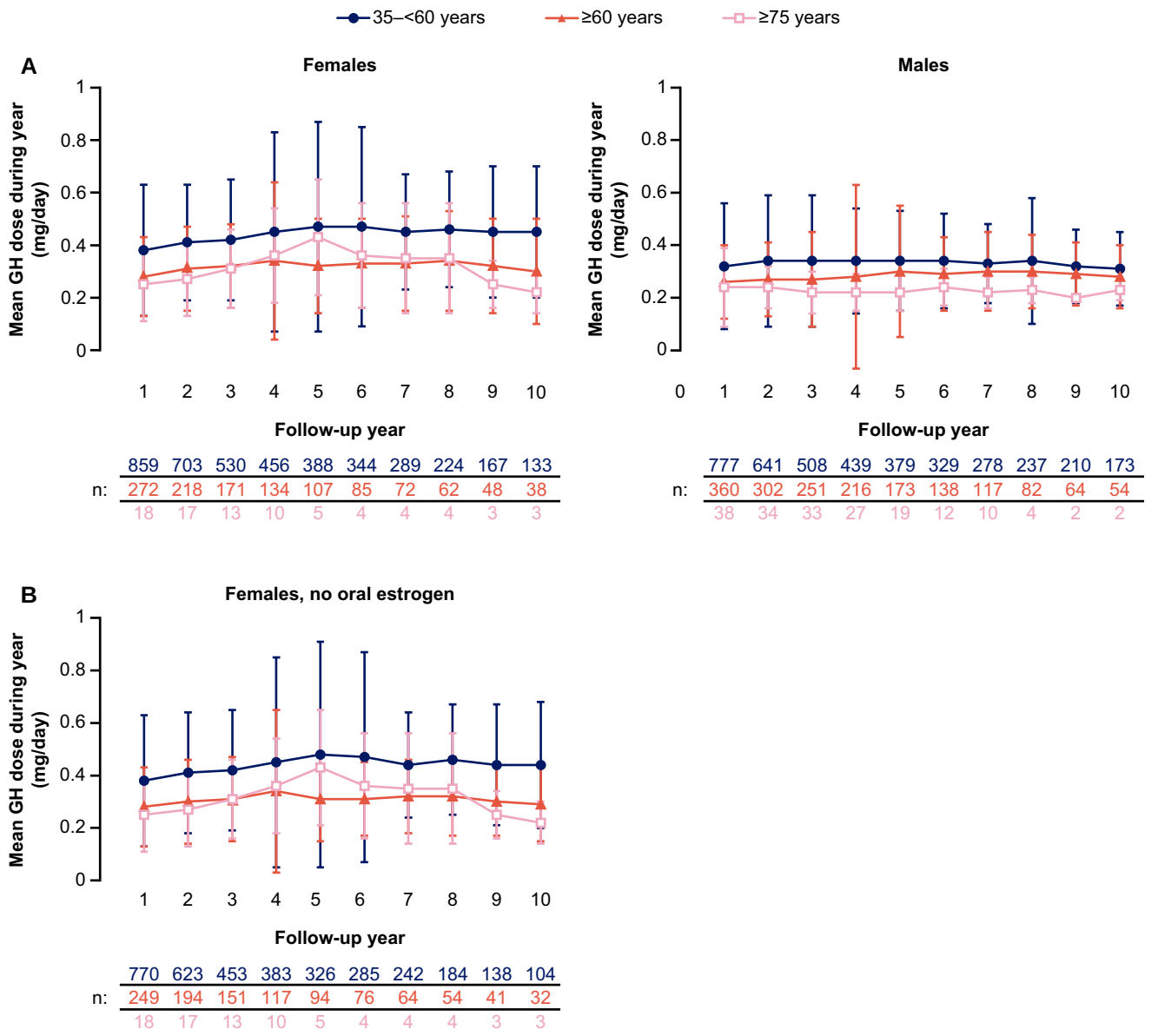

Figure 1. Mean GH exposure for older and middle-aged patients in the FAS for (a) all female and all male patients and (b) female patients who were not receiving concomitant oral estrogen.
Abbreviations: FAS, full analysis set.

middle-aged and older group patients above the normal range by year 1. Maximum proportions of patients with an IGF-I SDS above the normal range during the 10 years of follow-up were 15.9% and 15.6% (middle-aged and older groups, respectively), but percentages varied year on year and were not noticeably greater in either group, or between females and males. The number and proportion of patients in the EAS with IGF-I SDS values below, within, or above the normal range at baseline and, for illustrative purposes, at year 2 are shown in Fig. 4.

BMI (EAS)

Mean (SD) baseline BMI was similar between age groups (middle-aged vs older) for both males (29.6 [5.1] kg/m^2 vs 28.9 [4.3] kg/m^2) and females (28.9 [7.1] kg/m^2 vs 29.0 [5.1] kg/m^2) (Table 2). The change in BMI over up to 10 years was small, and similar across age groups and for both sexes (Supplementary Fig. S1) [19]. At year 2 of follow-up, no significant difference in change in BMI was observed between age groups for either females ($P = .2621$) or males ($P = .6200$).

Similarly, changes in BMI over up to 10 years were small for both male and female patients aged ≥75 years. Patient numbers were too small (ranging between 1 and 8 for males, and 1 and 4 for females) to make comparisons with other age groups.

Waist Circumference and Bioimpedance (EAS)

Changes in waist circumference and bioimpedance at 2-year follow-up in males and females in the middle-aged and older-age groups are shown in Table 3. Differences in the changes were not compared statistically due to large amounts of missing data. For the same reason, mean changes were not determined for patients aged ≥75 years.

Table 2. Baseline characteristics of middle-aged and older female and male patients from the EAS

	Females			Males		
	35–<60 years (n = 250)	≥60 years[a] (n = 84)	≥75 years (n = 6)	35–<60 years (n = 295)	≥60 years[a] (n = 130)	≥75 years (n = 13)
Age, years (P10, P90)	47.2 (7.2) (37.4, 57.5)	66.8 (4.9) (61.3; 74.3)	76.9 (2.3) (75.0; 81.0)	49.6 (6.6) (39.6; 58.2)	67.4 (4.9) (61.7; 75.2)	76.7 (1.0) (75.7; 78.3)
GH dose, mg/day	.23 (.13)	.20 (.11)	.25 (.21)	.24 (.18)	.20 (.10)	.21 (.09)
IGF-I SDS	–.95 (1.39) (n = 194)	–.63 (1.22) (n = 63)	–.55 (1.12) (n = 4)	–.93 (1.42) (n = 277)	–.94 (1.43) (n = 105)	–1.10 (.89) (n = 7)
BMI, kg/m^2	28.9 (7.1)	29.0 (5.1)	29.8 (2.7)	29.6 (5.1)	28.9 (4.3)	30.3 (2.2)
Waist circumference, cm	96.6 (16.6) (n = 147)	98.5 (10.9) (n = 43)	98.5 (7.9) (n = 5)	103.1 (12.5) (n = 155)	103.9 (10.1) (n = 73)	111.1 (7.1) (n = 7)
Bioimpedance, ohm	559.7 (128.1) (n = 72)	592.8 (67.1) (n = 12)	577.0 (NA) (n = 1)	490.4 (72.2) (n = 88)	511.0 (62.3) (n = 47)	477.8 (44.4) (n = 4)
HbA_{1c}, %	5.28 (.74) (n = 126)	5.81 (.97) (n = 44)	5.77 (.58) (n = 3)	5.42 (.99) (n = 162)	5.50 (.99) (n = 75)	5.42 (.85) (n = 5)
Non-HDL cholesterol (mmol/L)	4.35 (1.18) (n = 132)	4.50 (1.38) (n = 45)	3.09 (1.01) (n = 5)	4.56 (1.31) (n = 165)	4.05 (1.11) (n = 78)	4.31 (.65) (n = 5)
Duration of follow-up, years	5.3 (4.3) (n = 247)	5.1 (4.0) (n = 83)	3.6 (2.3)	5.4 (4.2) (n = 291)	5.4 (3.9) (n = 127)	5.9 (2.4)

Data are from NordiNet® IOS only and are mean (SD) unless otherwise stated.
Abbreviations: BMI, body mass index; EAS, effective analysis set; FAS, full analysis set; HbA_{1c}, glycated hemoglobin; HDL, high-density lipoprotein; NA, not applicable; P10, 10th percentile; P90, 90th percentile; SDS, SD score.
[a]This group includes patients aged ≥75 years.

HbA_{1c} (EAS and FAS)

In the EAS, mean baseline HbA_{1c} was slightly higher for older females compared with middle-aged females, whereas it was similar for males in the middle-aged and the older-age groups (Table 2).

In the EAS, change in HbA_{1c} was small and appeared similar for middle-aged vs older ages and for both sexes over up to 10 years (Supplementary Fig. S2) [19]. This pattern was also observed in patients from the FAS (Supplementary Fig. S3) [19].

For patients aged ≥75 years from the FAS, small fluctuations in HbA_{1c} were observed for females (n = 5), while a slight increase in HbA_{1c} was observed in males (n = 11). Numbers in the EAS were too small to draw any conclusions.

Lipid Profile (EAS)

Non-HDL cholesterol levels improved in both age groups and for both sexes over up to 10 years' follow-up, as observed by increases in the percentages of patients in lower non-HDL cholesterol level categories and reductions in the percentages of patients in higher non-HDL cholesterol level categories (Fig. 5). It should be noted that patient numbers were small in some categories from year 5 onwards.

No statistically significant difference in change in non-HDL cholesterol levels from baseline to year 2 of follow-up was observed between age groups for either females ($P = .4619$) or males ($P = .0679$).

AEs (FAS)

Incidence rates of NSARs, SARs, and SAEs, and the IRRs, are summarized in Table 4. No statistically significant differences were observed between older and middle-aged adults in the incidence rates for NSARs [5.66 vs 5.38 per 1000 patient-years; IRR (mean, 95% confidence interval) 1.05 (.60; 1.83)] or SARs [1.00 vs 2.52 per 1000 patient-years; IRR .40 (.12; 1.32)] (Table 4). Similarly, incidence rates of NSARs were not statistically different between patients aged ≥75 years and middle-aged patients. No comparison was made for SARs, as no SARs were reported in the ≥75 years group.

The incidence rate of SAEs (ie, events considered unrelated to GHRT) was higher in the older group vs middle-aged patients [16.64 vs 9.04 per 1000 patient-years; IRR 1.84 (1.29; 2.62)] (Table 4). The IRRs for patients aged ≥75 years (n = 59) vs the middle-aged group were statistically significant for SAEs (Table 4).

To examine the effect of SAEs in the group aged ≥75 years on the overall IRR of the ≥60 years group, the rate of SAEs was analyzed separately for patients aged 60 to <75 years. This analysis showed an incidence rate per 1000 patient-years of 16.03 for patients aged 60 to <75 years, as opposed to 16.64 for all patients aged ≥60 years, including those aged ≥75 years. Thus, the high rate of SAEs seen in the ≥75 years group (n = 59) was not the main driver of the difference between all patients aged ≥60 years (n = 646) vs those aged 35 to <60 years (n = 1684).

A summary of NSARs, SARs, SAEs, and AEs by system organ class is presented in Supplementary Table S1 [19]. The most common NSARs in both groups were musculoskeletal and connective tissue disorders, in 1.3% of middle-aged and 1.5% of older patients. The most common SAR in the 35 to <60-year group was "neoplasms benign, malignant and unspecified" (.77% of patients), nearly half of which were a pituitary adenoma recurrence in patients who had an etiology of pituitary adenoma at baseline. In the older group, no SAR was reported as occurring more than once (ie, in .15% of patients).

An analysis of the incidence rate of ADRs and SAEs in patients with a functional vs nonfunctional tumor etiology at the start of treatment was conducted (Supplementary

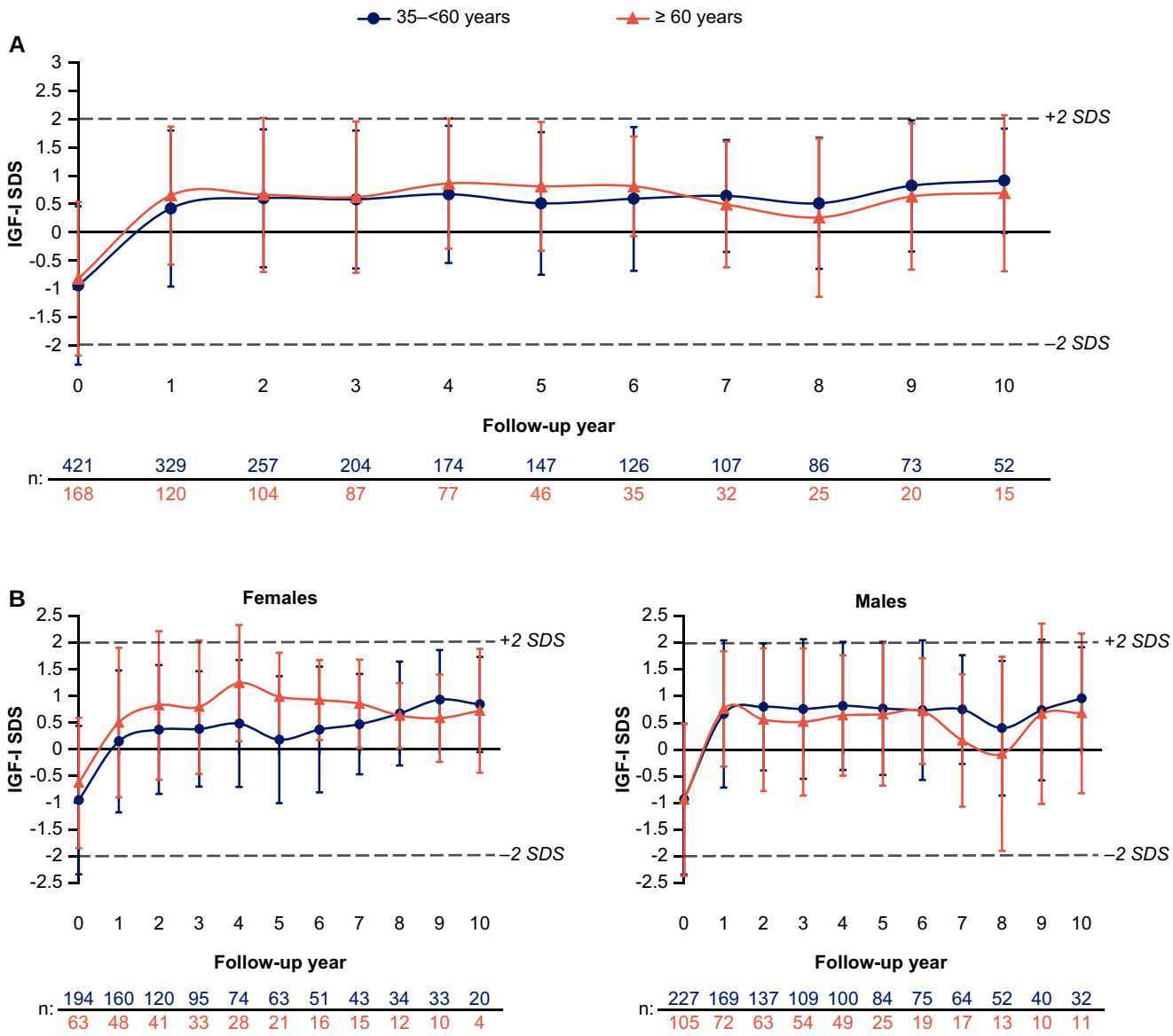

Figure 2. Mean IGF-I SD score for middle-aged and older patients (a) all patients, (b) female and male patients (all EAS). Data are mean (SD). Dotted lines indicate the limits for normal values. Growth hormone treatment started at/after the first visit at year 0.
Abbreviations: EAS, effectiveness analysis set.

Table S2) [19]. The difference in the incidence rate between these 2 patient groups was only significant for SAEs, with a higher rate observed for functional tumors (21.41 vs 12.12 per 1000 patient-years; $P = .0393$). A similar analysis was conducted for patients with a functional tumor etiology in the middle-aged vs older age groups (Supplementary Table S3) [19]. The incidence rate difference between these patient age groups was not significant for either ADRs or SAEs.

For both NSARs and SARs, the percentage of patients reporting any event was generally smaller in the older group vs the middle-aged group. The 2 exceptions were 1 case each of "injury, poisoning, and procedural complications" and vascular disorders, both as NSARs, in the older group vs none in the middle-aged group.

The most common SAEs in both groups were "neoplasms benign, malignant, and unspecified" (1.30% middle-aged, 1.99% older). The next most common SAEs in the middle-aged group were infections and infestations (.71%) and nervous system disorders (.71%). In the older group, these were infections and infestations (1.69%); cardiac disorders (1.38%); nervous system disorders (1.07%); and "injury, poisoning, and procedural complications' (.92%).

Fourteen deaths were recorded in total: 7 deaths were recorded in each of the 2 age groups (.41% middle-aged, 1.07% older). Only 2 deaths, both in the middle-aged group, were considered possibly related to treatment. These 2 cases were due to metastatic colon cancer and anaplastic astrocytoma. The remaining cases were due to malignant neoplasm (n = 3), cerebrovascular accident (n = 2), cardiac failure (n = 1), subdural hematoma (n = 1), suicide (n = 1), and unknown causes (n = 4).

Discussion

We compared safety and clinical outcomes in older (aged ≥60 years) vs middle-aged adults (35–<60 years)

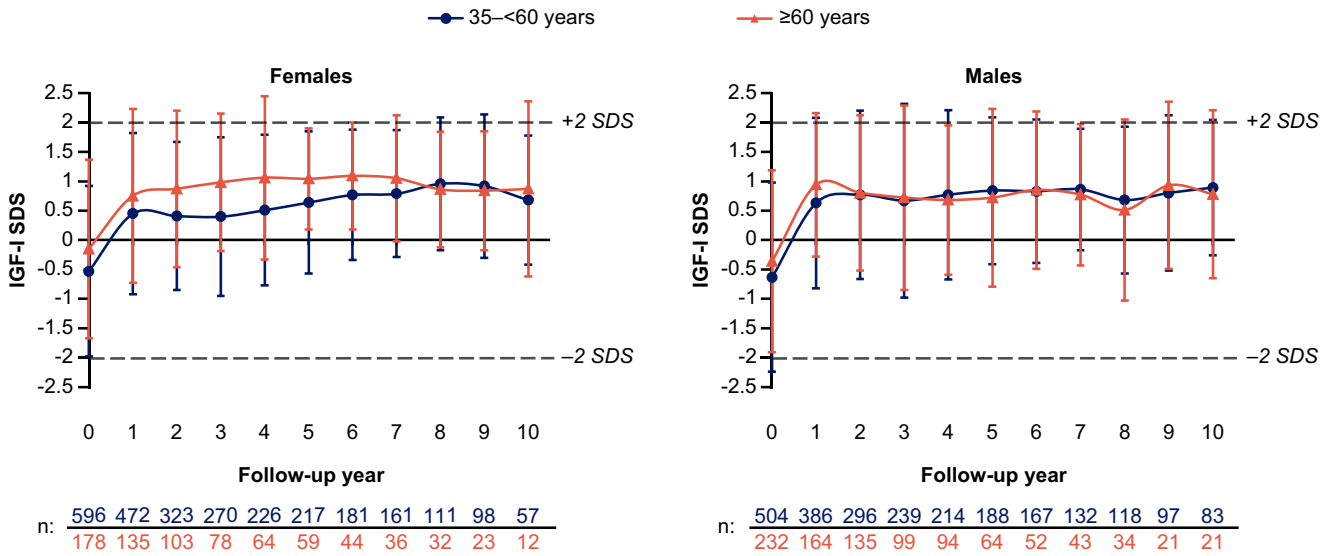

Figure 3. Mean IGF-I SD score for middle-aged and older female and male patients from the FAS. Data are mean (SD).
Abbreviations: FAS, full analysis set.

with AGHD who were treated with GHRT in a real-world setting over periods of up to 10 years. Our study was intended to investigate the safety of GHRT in older patients. The results were reassuring, indicating that older adults with AGHD do not have higher rates of GH-related side effects than middle-aged adults.

Mean doses of GH were lower in older vs middle-aged patients and, in men, were lower in patients ≥75 years vs patients ≥60 years. These data indicate that, overall, guideline recommendations to prescribe lower doses in older patients were followed in real-life practice [2, 9].

The observed lower IGF-I SDS levels in the middle-aged group compared with the older-age group appear prominent in the EAS from NordiNet® IOS and the FAS from NordiNet® IOS and the ANSWER Program. For the middle-aged and older patients from the EAS of this study, this difference appears within the female groups only. One explanation for this could be that the middle-aged group includes premenopausal females, which the older group does not. In terms of effectiveness and safety, mean IGF-I SDS increased in the first year of follow-up and remained within the target range for both sexes in the middle-aged and the older-age groups in the EAS. In the FAS, mean IGF-I SDS remained below the upper limit of +2 in both sexes in all 3 age groups (35–<60 years, ≥60 years, ≥75 years). Over the 10 years of follow-up, up to 15.9% of patients recorded an IGF-I SDS value >+2 in any 1 year, with no apparent difference between age groups. This suggests that older patients respond to GH replacement just as well as younger patients in terms of hepatic production of IGF-I.

Similar results relating to IGF-I SDS were noted in a study from the Pfizer International Metabolic Database (KIMS), which reported outcomes in older (n = 125; >65 years) and younger (n = 2469; <65 years) patients with AGHD treated with GHRT [20]. The authors reported that IGF-I SDS values were largely similar at baseline in the 2 groups and showed a similar increase after 12 months of GH therapy. They reported that a similar percentage of patients had serum IGF-I SDS above +2 in both groups but did not specify the proportions [20].

Reports on the impact of GHRT on glucose metabolism have yielded conflicting results, with earlier studies in particular suggesting an increased risk of developing impaired glucose tolerance or diabetes with long-term GHRT [9]. On the other hand, long-term observational studies have suggested that diabetes incidence does not increase in patients with AGHD receiving GHRT [21-23]; however, it should be noted that these studies did not include older patient groups. Current guidelines suggest that patients with risk factors for developing hyperglycemia can receive GHRT if glucose parameters are monitored [2, 9]. These risk factors include older age, greater BMI, and signs of insulin resistance [24, 25]. In the current study, the observed data suggested that HbA_{1c} levels remained stable for both older and middle-aged patients. This is in line with an earlier report from NordiNet® IOS, which showed that 4 years of GHRT did not adversely affect glucose homeostasis in the majority of adults with GHD [23].

In terms of effectiveness, mean changes in BMI were small and similar between age groups for both sexes. Based on reports from previous studies, large changes in BMI were not expected. An earlier analysis of outcomes from NordiNet® and ANSWER reported that the overall mean (SD) change in BMI from baseline was +.30 (3.30) kg/m^2 for all 857 patients with data and that there was no effect of age at treatment start on change in BMI [17]. Similarly, a study by Höybye et al of baseline characteristics of patients with AGHD in the KIMS database reported that BMI was unchanged after 1 year of GH treatment [26].

Change in non-HDL cholesterol levels from baseline to the second follow-up year was not different between age groups for either females or males, suggesting that GHRT has a similar effect in reducing non-HDL cholesterol in both older and middle-aged AGHD patients. It is reassuring that, over 10 years of treatment with GHRT, the proportion of patients with non-HDL cholesterol values in lower categories increased in both older and middle-aged patients of both sexes. These results are in line with other reports that suggest that the beneficial effects of GHRT on lipid profile are experienced by both older and younger patients with AGHD [20, 27]. For

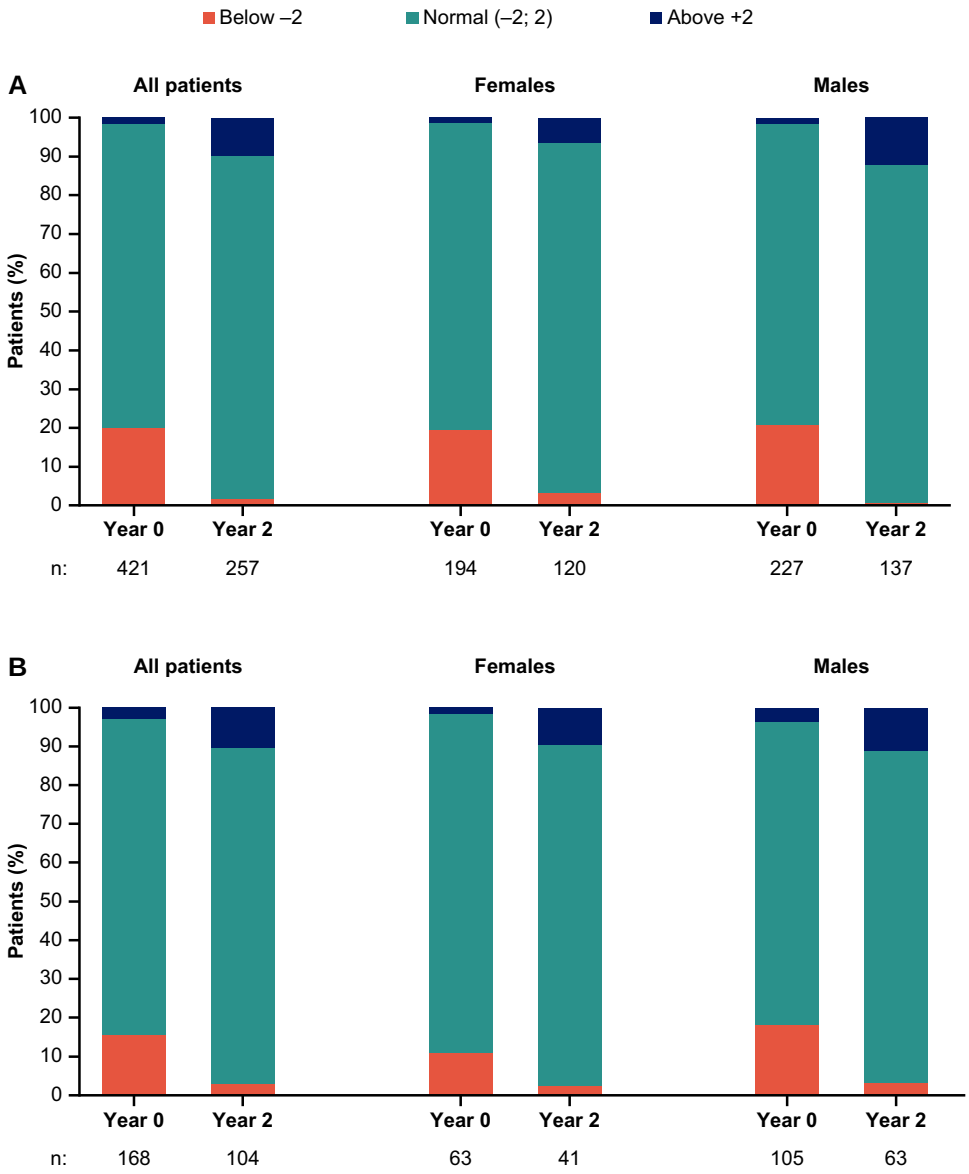

Figure 4. Number and proportion of patients with IGF-I SD score below, within, or above the normal range (–2 to +2) at baseline and year 2 (EAS) for (a) 35 to 60 years group, (b) ≥60 years group.
Abbreviations: EAS, effectiveness analysis set.

Table 3. Changes in waist circumference and bioimpedance at 2-year follow-up: middle-aged and older female and male patients from the EAS

	Females				Males			
	N	35–<60 years	N	≥60 years	N	35–<60 years	N	≥60 years
Waist circumference	66	–.63 (6.60)	14	–1.61 (8.42)	55	–1.69 (5.35)	27	–.26 (6.11)
Bioimpedance, ohm	37	5.6 (118.9)	6	–9.3 (70.8)	40	–27.2 (29.3)	17	–25.8 (31.3)

Data are mean (SD).
Abbreviations: BMI, body mass index; EAS, effective analysis set.

example, the KIMS study cited earlier reports that LDL cholesterol levels fell in both patients aged <65 years (n = 2469) and those aged >65 years (n = 125) after 1 year of GHRT [20]. The Hypopituitary Control and Complications Study also reported a decrease in LDL cholesterol concentrations in male (n = 585) and female (n = 538) patients with adult-onset GHD after 3 years of GHRT, as well as a decrease in LDL/HDL cholesterol ratios in patients with adult-onset

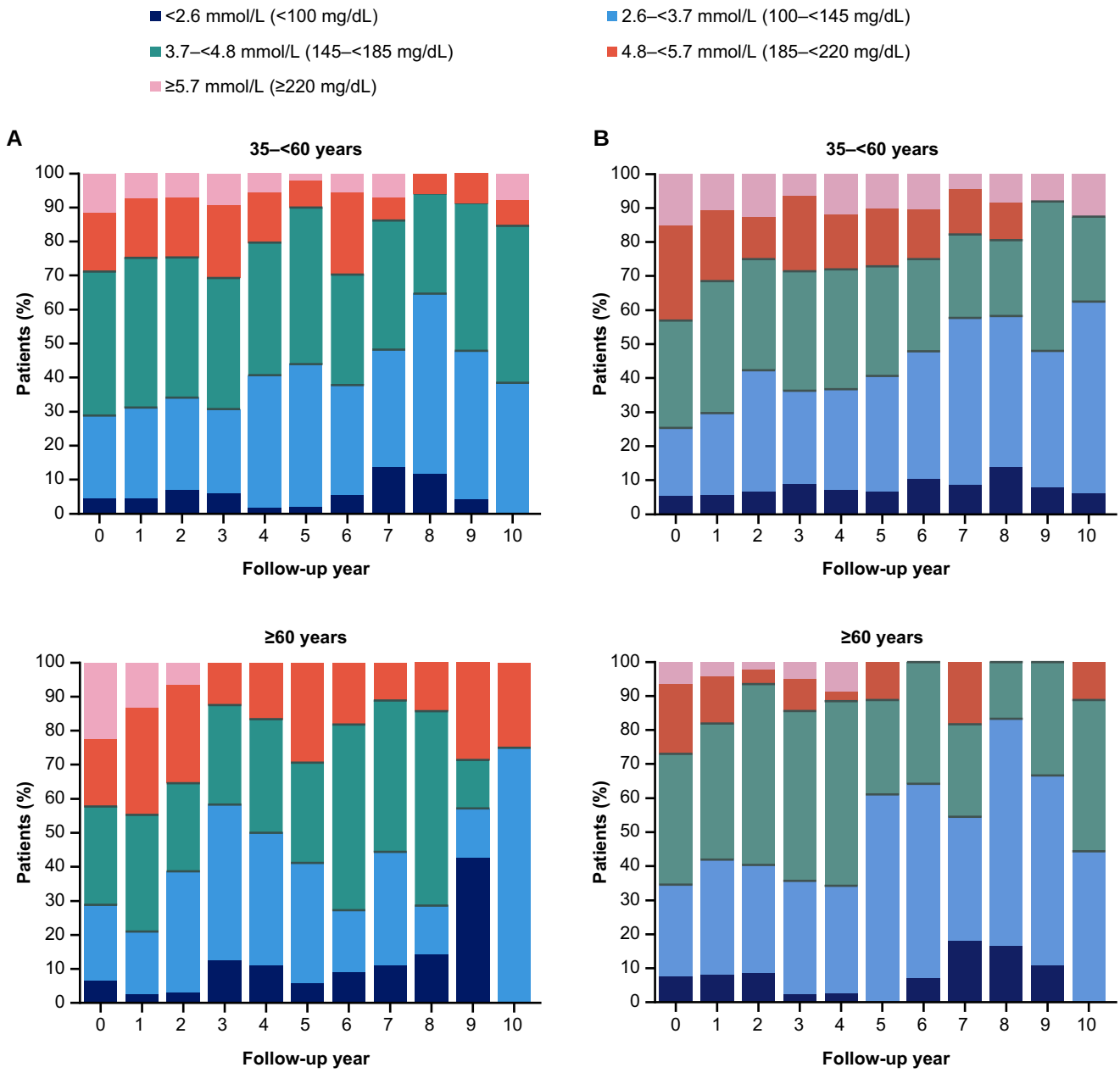

Figure 5. Distribution of non-HDL cholesterol levels in (a) female and (b) male patients in the EAS, by age group.
Abbreviations: EAS, effectiveness analysis set; HDL, high-density lipoprotein.

GHD aged 40 to 60 years (n = 363) and those aged >60 years (n = 160) after 1 year of GHRT [27].

Other studies comparing clinical endpoints in older vs younger patients have generally examined the effectiveness and safety of GHRT over shorter periods or in smaller numbers of patients. A prospective study by Franco et al compared the effects of 2 years of GHRT in younger (n = 24; 27–46 years) vs older (n = 24; 65–75 years) patients with AGHD [13]. No statistically significant difference was observed for IGF-I SDS or change in HbA_{1c}; however, larger reductions in waist circumference ($P < .01$), waist/hip ratio ($P < .05$), and LDL cholesterol ($P < .05$) were observed for older patients compared with the younger group [13]. Similarly, a small study that compared 10 patients with AGHD aged 65 to 71 years with 29 patients aged 26 to 55 years after 7 years of GHRT found improvements in lipid profile in both age groups and in body composition in the younger patients. IGF-I SDS increased to within the normal range, and glucose metabolism was unchanged [7].

There is consistent evidence to support that non-HDL cholesterol levels play a predictive role in determining risk of cardiovascular disease and vascular mortality [18, 28-30]. Using data from the Multinational Cardiovascular Risk Consortium, Brunner et al reported that higher non-HDL cholesterol concentrations were strongly associated with increased long-term risk of atherosclerotic cardiovascular disease [18]. In their report, 30-year cardiovascular disease event rates were roughly 3 to 4 times higher for patients with non-HDL cholesterol levels in the highest category [≥5.7 mmol/L (≥220 mg/dL)] compared with those in the lowest category [<2.6 mmol/L (<100 mg/dL)] (33.7% vs

Table 4. Incidence rates for middle-aged and older patients (≥60 years and ≥75 years) from the FAS

	Patient-years	Patients with events	Rate/1000 patient-years	Comparison vs 35–<60 years: IRR (95% CI)	*P*-value
NSARs					
35–<60 years (n = 1684)	8736	47	5.38	—	—
≥60 years (n = 646)[a]	3006	17	5.66	1.05 (.60, 1.83)	.8596
≥75 years (n = 59)	260	2	7.7	1.43 (.35, 5.89)	.6200
SARs					
35–<60 years (n = 1684)	8736	22	2.52	—	—
≥60 years (n = 646)[a]	3006	3	1.00	.40 (.12, 1.32)	.1327
≥75 years (n = 59)[b]	260	0	0	—	—
SAEs					
35–<60 years (n = 1684)	8736	79	9.04	—	—
≥60 years (n = 646)[a]	3006	50	16.64	1.84 (1.29, 2.62)	.0007
≥75 years (n = 59)	260	6	23.09	2.55 (1.11, 5.86)	.0269

Incidence rates are per 1000 patient-years. SARs and NSARs were defined as an AE or SAE with a suspected causal (possibly or probably) relationship to GHRT, as determined by both the investigator and the sponsor. Other SAEs not considered related to GHRT are also presented.
Abbreviations: AE, adverse event; CI, confidence interval; FAS, full analysis set; GHRT, growth hormone replacement therapy; IRR, incidence rate ratio; NSAR, nonserious adverse reaction; SAE, serious adverse event; SAR, serious adverse reaction.
[a]This group includes patients aged ≥75 years.
[b]No SARs were reported in the ≥75 years group.

7.7%, respectively, for women; and 43.6% vs 12.8%, respectively, for men) [18]. Meanwhile, a 50% reduction of non-HDL cholesterol was associated with reduced risk of cardiovascular disease by 75 years of age for both women and men [18]. The reduction in the percentages of patients with higher levels of non-HDL cholesterol observed in this study may suggest that GHRT could have a similar impact on reducing cardiovascular risk in middle-aged and older female and male patients.

According to the cumulative GH dose results, older patients required a lower cumulative GH dose for an ADR to be reported compared with middle-aged patients, as expected. It should be noted that the total number of patients with ADRs is 88, but, for 4 patients, it was not possible to calculate the cumulative GH dose until they experienced their first ADR. Hence, we only report the cumulative dose for 84 patients and not the total 88.

There was no statistically significant difference in the incidence of NSARs between middle-aged patients and those aged ≥60 years or between middle-aged patients and those aged ≥75 years. Similarly, there was no statistically significant difference in the incidence of SARs between middle-aged patients and those aged ≥60 years, and there were no reported SARs in the ≥75 years group. On the other hand, the incidence of SAEs (considered unrelated to GHRT) was higher in both the older group aged ≥60 years and the subgroup of patients aged ≥75 years vs the middle-aged group. This is to be expected, as older patients tend to have more comorbidities. Analysis of events by system organ class for the middle-aged and ≥60-year group (Supplementary Table S1) [19] showed that the types of SAEs reported in patients aged ≥60 years are those that could be expected in an older population, regardless of whether they are being treated with GHRT [19]. Examples include cardiac disorders and nervous system disorders. Similarly, we would expect the number of deaths as a proportion of the population to be greater in the older group, and this was indeed observed. However, none of the deaths in the older-age group were considered to be related to GH treatment.

The highest rate of SAEs, 23.09 per 1000 patient-years, was observed in the ≥75 years group. By comparing the rate of SAEs for patients aged 60 to <75 years with the rate for all patients aged ≥60 years (16.03 and 16.64 per 1000 patient-years, respectively), we showed that the greater rate of SAEs in the group aged ≥60 years was not driven by the high rate in patients aged ≥75 years. The latter group contained far fewer patients (8.4% of all patients aged ≥60 years) and a much smaller number of patient-years compared with the total older group.

Due to the nature of functional tumors, it is expected that patients with a functional tumor etiology may have a higher number of AEs and ADRs. This was observed for SAEs, where a higher proportion of patients had a significantly higher incidence rate (per 1000 patient-years) compared with patients with a nonfunctional tumor etiology. For patients with a functional tumor etiology, the higher incidence rate of SAEs for older patients compared with middle-aged patients is in line with the proportions observed in the FAS, although the difference was not statistically significant.

Our results confirm and add to those of earlier studies. In the KIMS 12-month follow-up study, treatment with GHRT led to significant improvements in lean body mass and a number of cardiovascular risk factors, as well as QoL, in both the older and younger groups [20]. The total number of AEs reported was similar for younger and older patients with GHD, but the pattern of distribution differed. Younger patients had more AEs related to fluid retention, and older patients had more AEs related to glucose metabolism, cerebrovascular events, and neoplasms [20].

A comprehensive safety analysis from 18 years of the KIMS study has recently been published [31], in which crude rates of all-causality AEs and of GH-related AEs in patients aged ≥45 years were broadly similar to those in patients aged 30 to 44 years (381.8 vs 326.6 per 1000 patient-years). Although the age groups cannot be compared directly with those in our study [the age cut-off for the older group (45 years) was close to the lower limit of our middle-aged group, and consequently

comprises patients from both age groups analyzed in our study], it is of interest that rates of AEs did not differ markedly between different age categories. The authors of the KIMS safety study also stress the need to interpret crude incidence rates cautiously, as other possible confounding factors were not considered.

A notable strength of our current study is the large patient population available from the NordiNet® IOS and ANSWER registries, spanning 24 countries across the world and representing multiple nationalities. Furthermore, the duration of follow-up was comparable between the different age groups included in this study. Another strength is the number of patients aged ≥60 years included in our analyses, as published data in this age group of patients with AGHD are scarce, in particular for older elderly patients. However, even in our study, the numbers of patients aged ≥75 years were low. For future studies of GHRT in AGHD, it is important to include more "older" elderly patients, even those aged ≥80 years.

NordiNet® IOS and ANSWER were subject to the general limitations of large, multicenter, observational studies, in which comorbidities, concomitant medications, and AEs may have been underreported. Although the decision about whether an AE was related to treatment was made initially by site investigators, all reported AEs were reviewed by the sponsor and classified as drug-related adverse reactions if *either* the investigator or the sponsor suspected a possible or probable causal relationship to GHRT. This "double causality" classification minimized the risk of missing adverse reactions.

Further limitations are that, in both studies, the diagnosis of GHD in adult patients over time and between regions, and the management and interpretation of IGF-I assays, may have varied between clinical centers. Prescribing practices may have changed over time due to financial constraints or external influences, and patients did not continue in the registry if prescribed a GH product other than Norditropin®. Persistence and adherence could have potentially affected clinical outcomes but were not assessed in these real-world studies. For example, some of the older patients might have discontinued GH treatment because of comorbidities or because they found it too difficult to continue with the injections. However, our study did not focus on efficacy of treatment per se but rather on how effectiveness and safety outcomes of long-term treatment compared between age groups in the real world.

In conclusion, the results of our study suggest that clinical outcomes with GHRT in patients with AGHD are similar in patients aged ≥60 years compared with those aged 35 to <60 years. In real-life practice, the risk of ADRs (events related to GHRT) was not significantly increased in older patients. Our results therefore support current guidelines that have no clear age limitations in treating adults with GHD with GH.

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Data Availability

Some or all datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

Prior Publication

Some of the data presented here have previously been published in meeting abstract form as follows:

- Weber MW, Gordon MB, Höybye C, Olsen AH, Kelepouris N, Nedjatian N, Biller BMK. Growth hormone (GH) replacement therapy (GHRT) in patients with adult GH deficiency (AGHD) aged ≥60 years: data from NordiNet® IOS and the ANSWER Program. *Endocrine Abstracts*. 2022;81:EP673.
- Biller BMK, Gordon M, Höybye C, Kelepouris N, Nedjatian N, Olsen AH, Weber M. Growth hormone (GH) replacement therapy (GHRT) in patients with adult GH deficiency (AGHD) aged 60 years: data from NordiNet® IOS and the ANSWER Program. *J Endocr Soc*. 2022;6(Suppl 1):A558.

Clinical Trial Registration

NordiNet® IOS (ClinicalTrials.gov, NCT00960128); ANSWER (ClinicalTrials.gov, NCT01009905).

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