The Impact of Frailty on the Effectiveness and Safety of Intensive Glucose Control and Blood Pressure–Lowering Therapy for People With Type 2 Diabetes: Results From the ADVANCE Trial

Tu N. Nguyen,[1] Katie Harris,[2] Mark Woodward,[2–4] John Chalmers,[2] Mark Cooper,[5] Pavel Hamet,[6] Stephen Harrap,[7] Simon Heller,[8] Stephen MacMahon,[2,3] Giuseppe Mancia,[9] Michel Marre,[10] Neil Poulter,[11] Anthony Rogers,[2] Bryan Williams,[12] Sophia Zoungas,[2,13] Clara K. Chow,[1,14,15] and Richard I. Lindley,[1,15]

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OBJECTIVE

To develop a frailty index (FI) and explore the relationship of frailty to subsequent adverse outcomes on the effectiveness and safety of more intensive control of both blood glucose and blood pressure (BP), among participants with type 2 diabetes in the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial.

RESEARCH DESIGN AND METHODS

Cox proportional hazard models were used to estimate the effectiveness and safety of intensive glucose control and BP intervention according to frailty (defined as FI >0.21) status. The primary outcomes were macro- and microvascular events. The secondary outcomes were all-cause mortality, cardiovascular mortality, severe hypoglycemia, and discontinuation of BP treatment due to hypotension/dizziness.

RESULTS

There were 11,140 participants (mean age, 65.8 years; 42.5% women, 25.7% frail). Frailty was an independent predictor of all primary outcomes and secondary outcomes. The effect of intensive glucose treatment on primary outcomes showed some evidence of attenuation in the frail: hazard ratios for combined major macro- and microvascular events 1.03 (95% CI 0.90–1.19) in the frail versus 0.84 (95% CI 0.74–0.94) in the nonfrail (P = 0.02). A similar trend was observed with BP intervention. Severe hypoglycemia rates (per 1,000 person-years) were higher in the frail: 8.39 (6.15–10.63) vs. 4.80 (3.84–5.76) in nonfrail ($P < 0.001$). There was no significant difference in discontinuation of BP treatment between frailty groups.

CONCLUSIONS

It was possible to retrospectively estimate frailty in a trial population, and this FI identified those at higher risk of poor outcomes. Participants with frailty had some attenuation of benefit from intensive glucose-lowering and BP-lowering treatments.

[1]Westmead Applied Research Centre, Faculty of Medicine and Health, University of Sydney, Sydney, New South Wales, Australia
[2]The George Institute for Global Health, University of New South Wales, Sydney, New South Wales, Australia
[3]The George Institute for Global Health, Department of Epidemiology and Biostatistics, Imperial College, London, U.K
[4]Department of Epidemiology, Johns Hopkins University, Baltimore, MD
[5]Department of Diabetes, Monash University, Melbourne, Victoria, Australia
[6]Centre de Recherche du Centre Hospitalier de l'Université de Montréal, Montreal, Quebec, Canada
[7]Department of Physiology, Royal Melbourne Hospital, University of Melbourne, Victoria, Australia
[8]Academic Unit of Diabetes, Oncology & Metabolism, University of Sheffield, Sheffield, U.K.
[9]Istituto Auxologico Italiano, University of Milan-Bicocca, Milan, Italy
[10]Department of Endocrinology, Hôpital Bichat-Claude Bernard, University of Paris, Paris, France
[11]Imperial Clinical Trials Unit, Imperial College London, London, U.K.
[12]National Institute for Health Research, University College London, Hospitals Biomedical Research Centre, London, U.K.
[13]School of Public Health and Preventive Medicine, Monash University, Melbourne, Victoria, Australia
[14]Department of Cardiology, Westmead Hospital, Sydney, New South Wales, Australia
[15]The George Institute for Global Health, Sydney, New South Wales, Australia

Corresponding authors: Tu Nguyen, ngoc.tu.nguyen@sydney.edu.au, and Richard Lindley, richard.lindley@sydney.edu.au

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Frailty, defined as a state of vulnerability that carries an increased risk of poor outcomes in older adults, is common (1). Frailty is a complex process that involves multiple system impairments and has been shown to cause altered responses to some medical therapies (2). Aging and frailty are associated with many physiological changes that can alter drug absorption, distribution, metabolism, and excretion (2,3). Experimental studies have shown that compared with the nonfrail, frail older people have increased body fat, reduced lean body mass, and lower levels of serum albumin (1,3). In addition, decreased liver metabolism and reduced renal clearance have also been observed in the frail (2). Some studies showed that responses to therapies were altered in frail people, such as influenza and pneumococcal vaccines (4–6) and antithrombotic medications (7,8).

The identification of frailty as a part of routine clinical assessments and wider population screening in older people has been recommended because it may help identify a group at higher risk of adverse effects in whom treatment adjustment should be considered (9). The concept of frailty is generally accepted, but there is still a lack of consensus for the ideal measure (10). Among current tools for identifying or quantifying frailty, the Frailty Index based on a comprehensive geriatric assessment (FI-CGA) is commonly used (11), which conceptualizes frailty as an accumulation of deficits throughout the lifetime.

Diabetes is common in older people (12), many of whom have multiple morbidities, including hypertension and frailty. In people with diabetes, the prevalence of frailty can be as high as 50% (13). Yet, there is a dearth of information about the impact of frailty on the effects of common treatments for diabetes that could help guide management decisions. The presence of frailty in those with diabetes may alter responses to treatment and the frequency of adverse outcomes (3). However, given that routine frailty assessment for those older people with diabetes is the exception rather than the norm, there is limited evidence about whether treatment decisions should be modified if these conditions coexist.

Our aims were to examine *1*) the development of a Frailty Index in people with type 2 diabetes in the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial, *2*) the relationship of frailty at baseline to subsequent adverse outcomes among participants, and *3*) the impact of frailty on the effectiveness and safety of more intensive control of both blood glucose and blood pressure (BP) intervention among participants. We hypothesized that the Frailty Index would identify high-risk frail older people, that the effectiveness of glucose-lowering agents and antihypertensive drugs would differ between frail and nonfrail participants, and that there would be an increased risk of adverse events among the frail compared with the nonfrail.

RESEARCH DESIGN AND METHODS

This was a secondary post hoc analysis of the baseline and follow-up data of the ADVANCE trial (14,15). In brief, the ADVANCE trial was a 2-by-2 factorial design, randomized controlled trial of 11,140 participants in 215 collaborating centers in 20 countries from Asia, Australasia, Europe, and North America. Detailed methods have been published previously (14,15). The trial included two randomized interventions: *1*) a double-blind assessment of the efficacy of perindopril/indapamide versus placebo and *2*) an open-label evaluation of an intensive glucose-lowering regimen using modified-release gliclazide versus standard care.

ADVANCE was designed to assess the effects on vascular disease using a fixed combination of perindopril/indapamide versus placebo in patients with type 2 diabetes. Further, the intensive glucose-lowering arm of ADVANCE was designed to assess the effects of lowering the glycated hemoglobin value to a target of $\leq$6.5%. Inclusion criteria included a diagnosis of type 2 diabetes at $\geq$30 years of age, an age of at least 55 years at the time of study entry, and a history of major macro- or microvascular disease or at least one other risk factor for vascular disease. Exclusion criteria included a definite indication for, or contraindication to, any of the study treatments or a definite indication for long-term insulin therapy at the time of study entry. The ADVANCE study received ethics approval from the Ethics Committee of each study center. All participants provided written informed consent (ClinicalTrials.gov registration no. NCT00145925).

Frailty Index

In this study, we used the data from the ADVANCE trial to create a Frailty Index measure based on a deficit accumulation approach described by Rockwood and colleagues (16) that we then applied to all participants. According to Rockwood and colleagues (16), the variables chosen to construct a Frailty Index need to be *1*) health-related, *2*) age-associated, and *3*) neither overly common nor overly uncommon (16,17). An index with 30–40 variables is sufficiently accurate for predicting adverse outcomes (16). This index is constructed as the proportion of deficits present in an individual of the total number of age-related health variables considered, with a value from 0 to 1. The Frailty Index can hence be applied to almost any set of health-related variables, provided there are a sufficient number, across a diverse range of attributes (11). From the baseline data of the ADVANCE Trial, 34 variables were identified as suitable based on common cardiovascular risk factors (BP, cholesterol, and adiposity), history of previous diseases, and quality of life markers and used to construct a Frailty Index for ADVANCE trial participants (Supplementary Table 1). All variables included in the Frailty Index were scored such that 0 signified the absence of a deficit, and the presence of a deficit was given a score of 1 or 0.5. The Frailty Index was constructed in an individual by summing the scores of all variables and calculating the proportion of deficits present of the total number of variables considered. The Frailty Index values range from 0 to 1, and the cut point to identify frailty was a Frailty Index $>$0.21, as applied in previous studies (17,18).

Outcome Variables

The primary study outcomes were macrovascular events (defined as death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke), microvascular events (defined as new or worsening nephropathy or retinopathy), and combined macro- and microvascular events. The secondary outcomes were all-cause mortality, mortality due to cardiovascular diseases (CVDs mortality), severe

hypoglycemia (for the glucose treatment intervention), and discontinuation of BP treatment due to hypotension/dizziness (for the BP treatment intervention) (15,19).

Statistical Analysis

Data were summarized, with continuous variables presented as mean (SD), and categorical variables as frequencies and percentages.

Frailty and Study Outcomes

Crude incidence rates (per 1,000 person-years) of outcomes by frailty were modeled using Poisson regression with a log offset for person-years, including frailty as a covariate.

To examine the impact of our Frailty Index on adverse outcomes, two sets of models were fitted. First, we constructed Cox proportional hazard models with frailty as the only predictor variable. Second, we constructed models that included intensive glucose treatment, age, and sex, in addition to frailty, because there is strong evidence of and impact of sex and age on frailty (20,21).

Intensive Glucose Control, BP Intervention, and Study Outcomes in Frail and Nonfrail Participants

Separate analyses were undertaken for the two randomized interventions in ADVANCE: *1*) the BP-lowering treatment results were obtained from the database locked at the end of the follow-up for the BP-lowering part of the study (mean follow-up, 4.3 years) (19); and *2*) at the end of 5 years of follow-up of the intensive glucose control strategy (15).

Crude incidence rates (per 1,000 person-years) of outcomes by glucose intervention and BP-lowering treatment were calculated in the same manner as previously described.

To examine the impact of frailty on the effectiveness and safety of intensive glucose treatment, we fit Cox proportional hazard models including an interaction term between glucose treatment and frailty status. Similarly, we examined the impact of frailty on the effectiveness and safety of the BP-lowering intervention with an interaction between BP- lowering treatment and frailty. Results are presented as hazard ratios (HRs) and 95% CIs for the frail and nonfrail. Interaction terms between frailty status and treatments were included to model the homogeneity of treatment effects in the frail and the nonfrail, and *P* values for interaction are presented to guide any statistically significant differences between the frail and nonfrail.

Subgroup Analysis by Age

We examined the impact of frailty on outcomes (combined major macro- and microvascular disease, all-cause mortality, and severe hypoglycemia) by age-group ($<$65 years and $\geq$65 years) in the Cox models. We also examined the effect of intensive glucose treatment and BP-lowering treatment in the frail and nonfrail by age-group.

All *P* values were two-sided, and those $<$0.05 were considered to indicate statistical significance, with no adjustment for multiple statistical testing (15,22). Analyses of the data were performed using SPSS for Windows 24.0 (IBM Corp, Armonk, NY) and R Studio 3.6.3 (R Core Team, 2020).

RESULTS

There were 11,140 ADVANCE participants. Their mean age was 65.8 years, and 42.5% were women. The baseline characteristics of participants by frailty status are presented in Table 1.

The Frailty Index values were approximately normally distributed, with a mean of 0.17 and SD of 0.08, with values ranging from 0 to 0.53, and median of 0.16 (Supplementary Fig. 1). Using the cut point of 0.21, the prevalence of frailty was 25.7% in the study participants (25.1% in men and 26.5% in women, *P* = 0.089).

The Relationship of Baseline Frailty to Subsequent Adverse Outcomes

The unadjusted rates (95% CI) per 1,000 person-years for outcomes in ADVANCE study participants by frailty status are presented in Table 2. Frail participants had a higher incidence of macro- and microvascular events (combined or alone), all-cause mortality, CVDs mortality, and severe hypoglycemia. In Cox models adjusted for intensive glucose treatment, age, and sex, frailty was independently associated with increased adverse outcomes (macro- and microvascular events, combined or alone, all-cause mortality, CVDs mortality, and severe hypoglycemia) (Fig. 1 and Supplementary Fig. 2).

The Impact of Frailty on the Effectiveness and Safety of Intensive Glucose Control

When examined by frailty status, intensive glucose control was more effective in nonfrail participants compared with the frail. For the combined macro- and microvascular events, the HRs were 0.90 (95% CI 0.83–0.98) in all participants and 0.84 (95% CI 0.75–0.94) in the nonfrail versus 1.03 (95% CI 0.90–1.19) in the frail (*P* for interaction = 0.020). Similar patterns were observed for major macrovascular events (HR 0.85 [95% CI 0.73–1.00] in the nonfrail vs. HR 1.10 [95% CI 0.93–1.32] in the frail, *P* for interaction = 0.033), major microvascular events (HR 0.83 [95% CI 0.72–0.96] in the nonfrail vs. HR 0.95 [95% CI 0.78–1.16] in the frail, *P* for interaction = 0.298), and all-cause mortality (HR 0.83 [95% CI 0.71–0.98] in the nonfrail vs. HR 1.11 [95% CI 0.92–1.34] in the frail, *P* for interaction = 0.021) (Fig. 2).

Severe hypoglycemia was more common in frail participants. In the intervention arm, the unadjusted rates (95% CI) per 1,000 person-years were 5.67 (4.83–6.66) overall and 8.39 (6.15–10.63) in the frail versus 4.80 (3.84–5.76) in the nonfrail. The difference between rates in the frail and nonfrail was statistically significant (*P* = 0.001). In the standard control arm, the unadjusted rates (95% CI) per 1,000 person-years were 3.05 (2.46–3.80) overall and 3.85 (2.37–5.33) in the frail versus 2.78 (2.05–3.52) in the nonfrail (*P* = 0.172). The unadjusted HR of more intensive glucose control on severe hypoglycemia was 1.86 (95% CI 1.42–2.44). This impact was greater in frail participants (HR 2.18, 95% CI 1.37–3.48) compared with the nonfrail (HR 1.73, 95% CI 1.24–2.40), albeit not statistically significant (*P* = 0.419) (Fig. 2).

The unadjusted rates (95% CI) per 1,000 person-years for outcomes in ADVANCE study participants by glucose intervention are presented in Supplementary Table 2.

The Impact of Frailty on the Effectiveness and Safety of the BP-Lowering Intervention

For the effectiveness of BP lowering in nonfrail participants compared with the frail for combined macro- and microvascular events, the HRs were 0.91 (95% CI 0.83–1.00) in all participants, 0.86 (95% CI 0.77–0.97) in the nonfrail, and 0.97

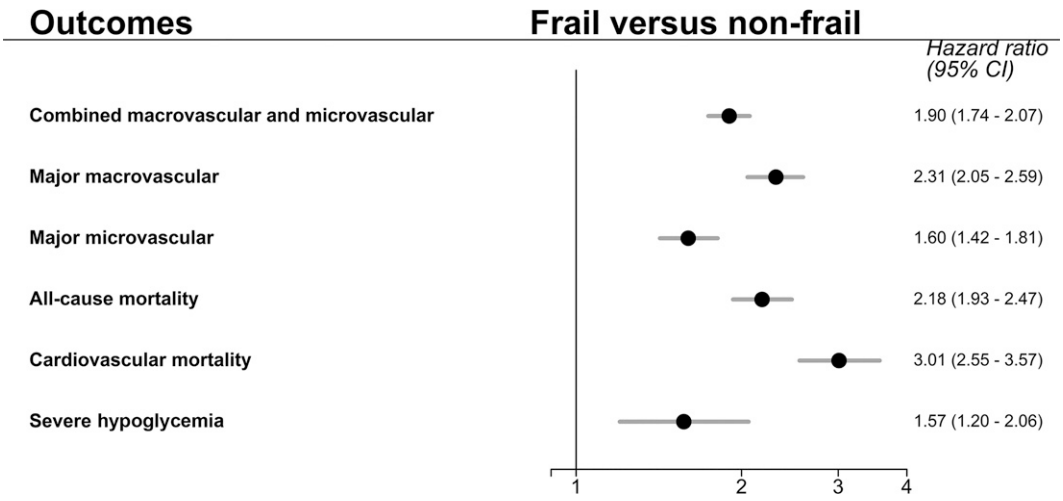

Figure 1—Adjusted HRs of frailty (frail vs. nonfrail) on the study outcomes (all treatment groups combined). Adjusted for intensive glucose treatment, age, and sex.

(95% CI 0.83–1.13) in the frail (P = 0.262). The HRs for all cause-mortality were 0.86 (95% CI 0.75–0.98) in all participants, 0.79 (0.66–0.94) in the nonfrail, and 0.95 (0.78–1.16) in the frail (P = 0.165) (Fig. 2).

Discontinuation of BP treatment due to hypotension/dizziness occurred in 1.24% (69 of 5,569) of participants in the treatment arm and in 0.39% (22 of 5,571) of participants in the placebo arm. There was no significant difference in discontinuation of BP treatment due to hypotension/dizziness between the frail and the nonfrail: 0.96% in the frail versus 1.34% in the nonfrail in the intervention arm, and 0.14% in the frail versus 0.48% in the nonfrail in the control arm.

Subgroup by Age

There was no subgroup effect of age on the association between frailty and severe hypoglycemia or between frailty and death. There was, however, significant interaction between age and frailty with combined major macro- and microvascular events, such that the effect of being frail versus nonfrail was greater in those ≥65 years (HR 2.16, 95% CI 1.93–2.41) than those <65 years (HR 1.61, 95% CI 1.39–1.87; P = 0.01) (Supplementary Table 4). The effect of intensive glucose control was greater in the <65 age-group than in older participants, most notably in those with frailty (Supplementary Table 5).

CONCLUSIONS

In this study of individuals with type 2 diabetes who participated in the ADVANCE trial, the prevalence of frailty was 25.7% using an accumulated deficit score derived from the trial baseline data (ADVANCE

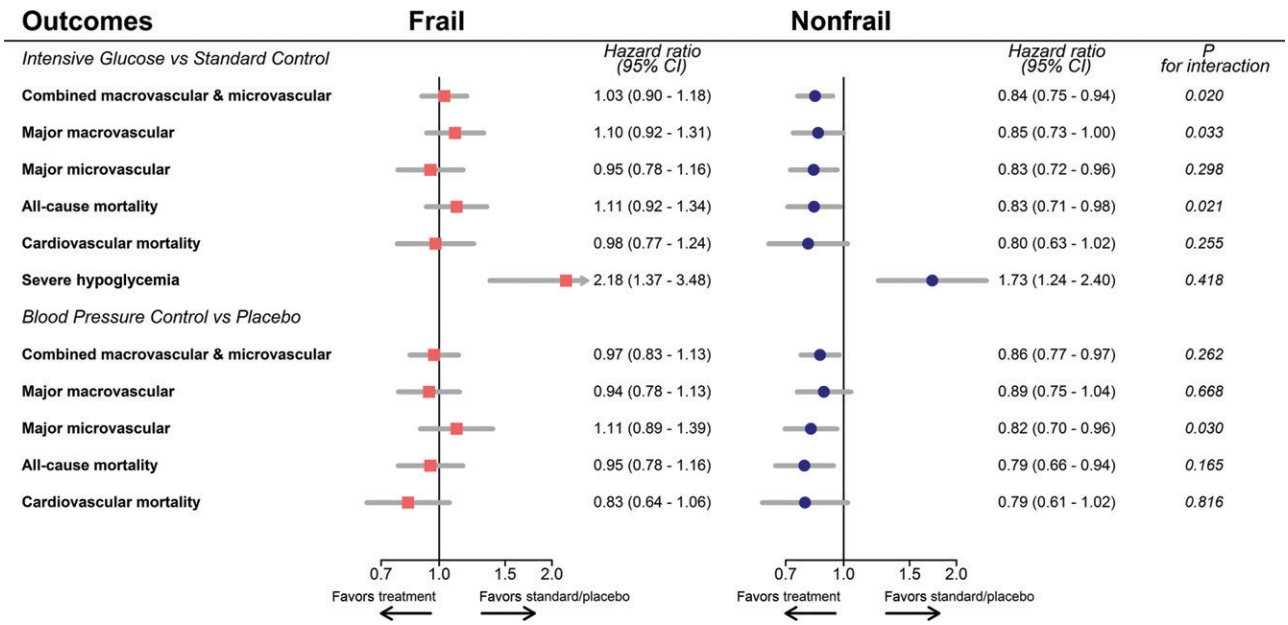

Figure 2—Unadjusted HRs of intensive glucose treatment vs. standard control and blood pressure intervention vs. placebo on the study outcomes in frail and nonfrail participants.

Table 1—Baseline characteristics of the study participants by frailty status

	All (*N* = 11,140)	Frail (*n* = 2,865)	Nonfrail (*n* = 8,275)
Age, years, *n* (%)	65.78 (6.39)	66.27 (6.79)	65.60 (6.24)
<65 years	4,527 (40.6)	1,170 (40.8)	3,357 (40.6)
≥65 years	6,613 (59.4)	1,695 (59.2)	4,918 (59.4)
Female sex, *n* (%)	4,733 (42.5)	1,256 (43.8)	3,477 (42.0)
Systolic BP (mmHg)	145.02 (21.54)	153.47 (23.72)	142.09 (19.91)
Diastolic BP (mmHg)	80.65 (10.93)	84.21 (11.92)	79.41 (10.29)
Mini-Mental State Examination score	28.51 (1.90)	28.10 (2.27)	28.65 (1.72)
BMI (missing 25)			
Underweight, *n* (%)	54 (0.5)	7 (0.2)	47 (0.6)
Normal weight, *n* (%)	2,987 (26.9)	390 (13.6)	2,597 (31.5)
Overweight, *n* (%)	8,074 (72.6)	2,462 (86.1)	5,612 (68.0)
Waist circumference (cm)	98.52 (13.12)	104.40 (13.05)	96.49 (12.51)
Current smoking, *n* (%)	1,550 (13.9)	359 (12.5)	1,191 (14.4)
Current drinking of alcohol once a week or more, *n* (%)	3,396 (30.5)	1,036 (36.2)	2,360 (28.5)
Diabetes duration (years)	7.94 (6.36)	8.32 (6.64)	7.80 (6.25)
Age at first diagnosis of diabetes (years)	57.84 (8.72)	57.95 (8.94)	57.80 (8.64)
HbA_{1c}, %	7.52 (1.56)	7.85 (1.70)	7.40 (1.48)
Coronary artery bypass grafting, *n* (%)	951 (8.5)	567 (19.8)	384 (4.6)
Q wave on electrocardiogram, *n* (%)	1,037 (9.3)	616 (21.5)	421 (5.1)
Blindness due to diabetes, *n* (%)	107 (1.0)	49 (1.7)	58 (0.7)
Other eye problems, *n* (%)	730 (6.6)	302 (10.5)	428 (5.2)
Chronic leg ulceration, *n* (%) (missing 1)	179 (1.6)	100 (3.5)	79 (1.0)
Amputation secondary to vascular disease, *n* (%)	65 (0.6)	41 (1.4)	24 (0.3)
Sedentary, *n* (%)	1,777 (16.0)	871 (30.4)	906 (10.9)
History of comorbidities, *n* (%)			
Myocardial Infarction	1,334 (12.0)	819 (28.6)	515 (6.2)
Ischemic heart disease (missing 14)	2,694 (24.2)	1,413 (49.4)	1,281 (15.5)
Currently treated hypertension	7,655 (68.7)	2,582 (90.1)	5,073 (61.3)
Atrial fibrillation (missing 13)	847 (7.6)	460 (16.1)	387 (4.7)
Stroke/transient ischemic attack	1,439 (12.9)	630 (22.0)	809 (9.8)
Heart failure	356 (3.2)	267 (9.3)	89 (1.1)
Chronic kidney disease (missing 47)	2,327 (21.0)	755 (26.5)	1,572 (19.1)
Suspected dementia (missing 1)	132 (1.2)	76 (2.7)	56 (0.7)
Peripheral revascularization	216 (1.9)	135 (4.7)	81 (1.0)
Hospitalization due to unstable angina	1,214 (10.9)	713 (24.9)	501 (6.1)
Polypharmacy	4,031 (36.2)	1,932 (67.4)	2,099 (25.4)
EuroQol-5D, *n* (%)			
Mobility			
Have some problem	2,818 (25.3)	1,522 (53.1)	1,296 (15.7)
Unable to walk	12 (0.1)	12 (0.4)	0 (0.0)
Self-care			
Have some problem	632 (5.7)	465 (16.2)	167 (2.0)
Unable to wash/dress	17 (0.2)	16 (0.6)	1 (0.0)
Usual care			
Have some problem	1,729 (15.5)	1,037 (36.2)	692 (8.4)
Unable to do	78 (0.7)	66 (2.3)	12 (0.1)
Pain/discomfort			
Some pain/discomfort	5,200 (46.7)	1,891 (66.0)	3,309 (40.0)
Extreme pain/discomfort	257 (2.3)	165 (5.5)	92 (1.1)
Anxiety/depression			
Anxiety/depression to some extent	2,983 (26.8)	1,203 (42.0)	1,780 (21.5)
Extreme anxiety/depression	130 (1.2)	88 (3.1)	42 (0.5)
Poor self-related health	4,059 (36.4)	1,862 (65.0)	2,197 (26.5)
Randomized treatments, *n* (%)			
BP-lowering treatment	4,117 (49.8)	1,452 (50.7)	5,569 (50.0)
Intensive glucose treatment	4,161 (50.3)	1,410 (49.2)	5,571 (50.0)

Continuous data are presented as mean (SD), and categorical data are shown as indicated.

Table 2—Unadjusted rates (95% CI) per 1,000 person-years for outcomes in ADVANCE study participants by frailty status

Events	All (N = 11,140)	Frail (n = 2,865)	Nonfrail (n = 8,275)
Primary study outcomes			
Combined macro- and microvascular events	42.78 (41.00–44.64)	66.83 (62.36–71.61)	35.09 (33.25–37.04)
Microvascular events	22.10 (20.85–23.43)	30.58 (27.67–33.79)	19.33 (17.99–20.77)
Macrovascular events	22.16 (20.91–23.48)	39.12 (35.83–42.72)	16.62 (15.39–17.95)
Secondary study outcomes			
All-cause mortality	19.27 (18.13–20.48)	33.14 (30.19–36.37)	14.63 (13.5–15.87)
Cardiovascular mortality	10.15 (9.33–11.04)	20.73 (18.43–23.32)	6.62 (5.87–7.46)
Severe hypoglycemia	4.36 (3.83–4.96)	6.07 (4.87–7.55)	3.80 (3.24–4.45)

All P values <0.001.

Trial Frailty Index). This index had predictive value for most of the trial outcomes. We found some evidence that treatment benefits were commonly attenuated in the frail compared with the nonfrail participants. We also observed an increased absolute risk of severe hypoglycemia in the frail. Thus, the balance of risk and benefit became less favorable with increasing frailty.

The Literature of Frailty Prevalence and the Possible Mechanism of the Link Between Frailty and Diabetes

Construction of the Frailty Index in This Study

In studies conducted in community-dwelling people, the overall weighted prevalence of frailty was ~10% (23). In people with diabetes, this is increased three- or four-fold (13,23). In patients with diabetes, there are many potential causes for frailty, such as deterioration in muscle and nerve function, declining cardiopulmonary reserve, reduction of executive function, and weight loss secondary to restrictive diets (13). Studies have shown that muscle strength in patients with diabetes is lower and declines at a higher speed compared with those without diabetes (24,25). Reduced insulin signaling can lead to decreased protein synthesis and increased protein degradation, which will ultimately result in reduced muscle mass (26). Diabetic neuropathy is also responsible for deficits in muscle strength, and denervation leads to muscle atrophy through the impairment of motor nerve conduction (26).

The Impact of Frailty on Responses to Therapies and Implications

Our findings suggest that frail participants with type 2 diabetes may not obtain the same benefits with more intensive glucose control and BP lowering as the nonfrail. In addition, the most serious adverse effect of treatment, severe hypoglycemia, as observed by Zoungas et al. (27), was greater in intensive glucose control than in standard control. Our study further explored this effect in the frail and nonfrail, which demonstrated that the impact was greater in frail participants compared with the nonfrail, albeit not statistically significant.

Most of the evidence base for the management of cardiometabolic diseases is from those individuals who were robust enough to participate in previous clinical trials (28,29). The evidence gap for older people may mask important differences in response to standard treatments, responses that might be particularly relevant in the presence of frailty. Many older people are receiving a large number of medications, mostly in the absence of robust evidence (28). Clinicians commonly have to assume that the risks and benefits of drugs (mainly tested in younger populations) also apply to their older and frailer patients. However, we know that the chances of adverse side effects increase with age and frailty. In an aging population, we should have more reliable evidence to know whether our usual treatments are still effective in the large numbers of older and frailer patients (28).

Our findings suggest that the routine assessment of frailty should be part of all randomized controlled trials including older people. As such evidence accumulates, routine clinical assessment of frailty will become more important in personalizing treatment for older people.

Our results suggest that frailty detection may provide two main benefits for patients with diabetes. First, it may help clinicians choose an appropriate diabetes treatment plan tailored to the frailty status. As shown in the *Results*, among frail participants, those who were <65 were more likely to experience severe hypoglycemia due to intensive glucose treatment. It may reflect that physicians focused on age rather than frailty. Intensive glucose treatment may usually be assumed safer in patients <65, and hence, this population may be more likely to receive strong glucose control agents or stronger doses, irrespective of their frailty status. According to a recent systematic review and meta-analysis of frailty in people with diabetes, the evidence on the effect of frailty in patients with diabetes aged <65 years is still limited (30).

A study by Heller et al. (31), where two different glucose-lowering treatment strategies were compared, found that similar proportions of older, vulnerable patients aged ≥65 years with type 2 diabetes achieved or maintained glycemic treatment goals without clinically significant hypoglycemia. Incidences of total and documented symptomatic hypoglycemic events were significantly lower in patients treated with the glucose-dependent strategy versus the glucose-independent strategy (10.2% vs 53.8%, 5.1% vs 36.6%, respectively; $P <$ 0.001 for each), indicating that a glucose-dependent strategy may be preferable in the treatment of frail patients with diabetes (31).

Indeed, the International Diabetes Federation (IDF) Guideline is the first guideline to provide specific recommendations for frail patients with diabetes (32). Frail patients are prone to decreased appetite and to adverse drug reactions, which may lead to hypoglycemia. According to the IDF guideline, review of the treatment targets for blood glucose is needed, and the target HbA_{1c} often relaxed up to 8.5% among frail

older patients with diabetes (32). In addition, agents that might cause nausea or gastrointestinal disturbance or excess weight loss, such as metformin or glucagon-like peptide-1 receptor agonist (also known as GLP1 inhibitors), are not recommended by IDF guideline for such patients, and lifestyle changes should also not include dietary changes that can lead to weight loss (32). It is noteworthy that while GLP1 inhibitors are discouraged in the frail, GLP1 inhibitors have been shown to benefit patients with established atherosclerotic CVDs, and one might expect a significant overlap of CVD and frail patient populations (33).

Second, the early detection of frailty can help facilitate interventions to delay or reverse frailty, such as physical exercise or nutrition interventions, and regular medication review to prevent potential adverse events (34,35). This should be considered together with other guidelines and studies that recommend that clinicians should adjust HbA_{1c} and BP goals based on patient's comorbidities and life expectancy, accounting for their likelihood of benefiting from the treatment (36).

The evidence on the safety of intensive BP treatment in old and frail people is controversial. According to the Systolic Blood Pressure Intervention Trial (SPRINT), the benefits of intensive BP control on CVD outcomes and all-cause mortality were consistent in participants both with and without frailty (defined by a Frailty Index), with similar serious adverse events in the frail and the nonfrail (37). In the HYpertension in the Very Elderly Trial (HYVET) study—a double-blind, placebo-controlled study of the same antihypertensives used in ADVANCE, in people with hypertension aged ≥80—there was no evidence of an interaction between effect of treatment for hypertension and frailty as measured by a Frailty Index but these trials had very different BP targets (120 mmHg in SPRINT and 150 mmHg in HYVET) (38). In contrast, observational studies, including the PART-AGE study (Predictive Value of Blood Pressure and Arterial Stiness in Institutionalised Very Aged Population) found that all-cause mortality risk increased in older people living in nursing homes with a systolic BP of <130 mmHg and older people taking two or more antihypertensive medications (39). A recent large prospective observational study of 415,980 older people in the U.K. found there was excess mortality in adults >75 years with systolic BP <130 mmHg irrespective of baseline frailty (40). Although there maybe confounding present in these observational studies.

Strengths of this Study

We have constructed a Frailty Index retrospectively from previously collected trial data, and this index had prognostic value with internal validity. The large sample size has enabled precise estimates of benefits for those with frailty and participants were recruited from 20 countries in 4 continents.

Limitations

The limitations of this study include the post hoc secondary analysis design and a limited number of baseline variables available to construct a Frailty Index. Our Frailty Index will not be directly comparable to others, because by necessity, we were limited by available baseline trial data, but seemed to provide useful predictive information. ADVANCE used an intervention whereby intensive glycemic control was forced by increasing the initiation of insulin therapy compared with a standard control (in particular in combination with sulfonylurea therapy), and as expected, the risk of severe hypoglycemia increased significantly. Thus, our results may only be valid to the aforementioned intervention, rather than the current state of the art.

Conclusion

We have shown that it was possible to retrospectively estimate frailty in a trial population and that this Frailty Index identified those at higher risk of poor outcomes. In addition, we have shown that those with frailty had some attenuation of benefit from BP lowering and intensive glucose lowering. We recommend that frailty be prospectively measured at baseline in all future trials that include older people.

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References

1. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. Lancet 2013;381:752–762

2. Hilmer SN, Wu H, Zhang M. Biology of frailty: implications for clinical pharmacology and drug therapy in frail older people. Mech Ageing Dev 2019;181:22–28

3. Hubbard RE, O'Mahony MS, Woodhouse KW. Medication prescribing in frail older people. Eur J Clin Pharmacol 2013;69:319–326

4. Yao X, Hamilton RG, Weng NP, et al. Frailty is associated with impairment of vaccine-induced antibody response and increase in post-vaccination influenza infection in community-dwelling older adults. Vaccine 2011;29:5015–5021

5. Ridda I, Macintyre CR, Lindley R, et al. Immunological responses to pneumococcal vaccine in frail older people. Vaccine 2009;27:1628–1636

6. Jefferson T, Rivetti D, Rivetti A, Rudin M, Di Pietrantonj C, Demicheli V. Efficacy and effectiveness of influenza vaccines in elderly people: a systematic review. Lancet 2005;366:1165–1174

7. Nguyen TN, Pepperell D, Morel-Kopp MC, Cumming RG, Ward C, Hilmer SN. Effect of frailty and age on platelet aggregation and response to aspirin in older patients with atrial fibrillation: a pilot study. Cardiol Ther 2016;5:51–62

8. Nguyen TN, Morel-Kopp M-C, Pepperell D, Cumming RG, Hilmer SN, Ward CM. The impact of frailty on coagulation and responses to warfarin in acute older hospitalised patients with atrial fibrillation: a pilot study. Aging Clin Exp Res 2017;29:1129–1138

9. Turner G; British Geriatrics Society; Age UK; Royal College of General Practioners. Best practice guidelines for the management of frailty: a British Geriatrics Society, Age UK and Royal

College of General Practitioners report. Age Ageing 2014;43:744–747
10. Martin FC, Brighton P. Frailty: different tools for different purposes? Age Ageing 2008;37:129–131
11. Rockwood K, Mitnitski A. Frailty defined by deficit accumulation and geriatric medicine defined by frailty. Clin Geriatr Med 2011;27:17–26
12. Kirkman MS, Briscoe VJ, Clark N, et al. Diabetes in older adults. Diabetes Care 2012;35:2650–2664
13. Perkisas S, Vandewoude M. Where frailty meets diabetes. Diabetes Metab Res Rev 2016;32(Suppl. 1):261–267
14. ADVANCE Management Committee. Study rationale and design of ADVANCE: action in diabetes and vascular disease–preterax and diamicron MR controlled evaluation. Diabetologia 2001;44:1118–1120
15. Patel A, MacMahon S, Chalmers J, et al.; ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med 2008;358:2560–2572
16. Searle SD, Mitnitski A, Gahbauer EA, Gill TM, Rockwood K. A standard procedure for creating a frailty index. BMC Geriatr 2008;8:24
17. Blodgett J, Theou O, Kirkland S, Andreou P, Rockwood K. Frailty in NHANES: comparing the frailty index and phenotype. Arch Gerontol Geriatr 2015;60:464–470
18. Clegg A, Bates C, Young J, et al. Development and validation of an electronic frailty index using routine primary care electronic health record data. Age Ageing 2016;45:353–360
19. Patel A, MacMahon S, Chalmers J, et al.; ADVANCE Collaborative Group. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. Lancet 2007;370:829–840
20. Gordon EH, Peel NM, Samanta M, Theou O, Howlett SE, Hubbard RE. Sex differences in frailty: a systematic review and meta-analysis. Exp Gerontol 2017;89:30–40
21. Hubbard RE. Sex differences in frailty. Interdiscip Top Gerontol Geriatr 2015;41:41–53
22. Schulz KF, Grimes DA. Multiplicity in randomised trials I: endpoints and treatments. Lancet 2005;365:1591–1595
23. Yanase T, Yanagita I, Muta K, Nawata H. Frailty in elderly diabetes patients. Endocr J 2018;65:1–11
24. Leenders M, Verdijk LB, van der Hoeven L, et al. Patients with type 2 diabetes show a greater decline in muscle mass, muscle strength, and functional capacity with aging. J Am Med Dir Assoc 2013;14:585–592
25. Kalyani RR, Tra Y, Yeh HC, Egan JM, Ferrucci L, Brancati FL. Quadriceps strength, quadriceps power, and gait speed in older U.S. adults with diabetes mellitus: results from the National Health and Nutrition Examination Survey, 1999-2002. J Am Geriatr Soc 2013;61:769–775
26. Umegaki H. Sarcopenia and frailty in older patients with diabetes mellitus. Geriatr Gerontol Int 2016;16:293–299
27. Zoungas S, Patel A, Chalmers J, et al.; ADVANCE Collaborative Group. Severe hypoglycemia and risks of vascular events and death. N Engl J Med 2010;363:1410–1418
28. Lindley RI. Drug trials for older people. J Gerontol A Biol Sci Med Sci 2012;67:152–157
29. Hempenius L, Slaets JP, Boelens MA, et al. Inclusion of frail elderly patients in clinical trials: solutions to the problems. J Geriatr Oncol 2013;4:26–31
30. Hanlon P, Fauré I, Corcoran N, et al. Frailty measurement, prevalence, incidence, and clinical implications in people with diabetes: a systematic review and study-level meta-analysis. Lancet Healthy Longev 2020;1:e106–e116
31. Heller SR, Pratley RE, Sinclair A, et al. Glycaemic outcomes of an Individualized treatMent aPproach for oldER vulnerable patlents: a randomized, controlled stUdy in type 2 diabetes Mellitus (IMPERIUM). Diabetes Obes Metab 2018;20:148–156
32. Han Cho N, Colagiuri S, Distiller L, et al. International Diabetes Federation Global Guideline for Managing Older People with Type 2 Diabetes. Brussels, International Diabetes Federation, 2013
33. Sheahan KH, Wahlberg EA, Gilbert MP. An overview of GLP-1 agonists and recent cardiovascular outcomes trials. Postgrad Med J 2020;96:156–161
34. Dent E, Morley JE, Cruz-Jentoft AJ, et al. Physical frailty: ICFSR International Clinical Practice Guidelines for Identification and Management. J Nutr Health Aging 2019;23:771–787
35. Dent E, Lien C, Lim WS, et al. The Asia-Pacific Clinical Practice Guidelines for the Management of Frailty. J Am Med Dir Assoc 2017;18:564–575
36. Moreno G, Mangione CM, Kimbro L; American Geriatrics Society Expert Panel on Care of Older Adults with Diabetes Mellitus. Guidelines abstracted from the American Geriatrics Society Guidelines for Improving the Care of Older Adults with Diabetes Mellitus: 2013 update. J Am Geriatr Soc 2013;61:2020–2026
37. Williamson JD, Supiano MA, Applegate WB, et al.; SPRINT Research Group. Intensive vs standard blood pressure control and cardiovascular disease outcomes in adults aged ≥75 years: a randomized clinical trial. JAMA 2016;315:2673–2682
38. Warwick J, Falaschetti E, Rockwood K, et al. No evidence that frailty modifies the positive impact of antihypertensive treatment in very elderly people: an investigation of the impact of frailty upon treatment effect in the HYpertension in the Very Elderly Trial (HYVET) study, a double-blind, placebo-controlled study of antihypertensives in people with hypertension aged 80 and over. BMC Med 2015;13:78
39. Benetos A, Labat C, Rossignol P, et al. Treatment with multiple blood pressure medications, achieved blood pressure, and mortality in older nursing home residents: the PARTAGE Study. JAMA Intern Med 2015;175:989–995
40. Masoli JAH, Delgado J, Pilling L, Strain D, Melzer D. Blood pressure in frail older adults: associations with cardiovascular outcomes and all-cause mortality. Age Ageing 2020;49:807–813