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The LEADER trial in type 2 diabetes: Were the characteristics and outcomes of the participants representative?

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ABSTRACT

Aims: To compare the characteristics and outcomes of people with type 2 diabetes recruited to the LEADER trial to those of participants in the contemporaneous community-based Fremantle Diabetes Study Phase II (FDS2) who fulfilled LEADER entry criteria.
Methods: Baseline characteristics of LEADER and LEADER-eligible FDS2 participants were compared using bivariate methods. Incidence rates of the primary (nonfatal myocardial infarction, nonfatal stroke, cardiovascular disease (CVD) death) and other outcomes in the LEADER placebo group were compared with those in LEADER-eligible FDS2 participants during 3.8 years after entry, the median LEADER follow-up.
Results: Of 1551 FDS2 type 2 participants, 323 (20.8%) were LEADER-eligible. Compared with the LEADER sample, they were an average 6 years older, and were less likely to be male, obese and to have prior CVD. There were 3.9 and 2.9 primary outcomes/100 patient-years in LEADER placebo-treated and FDS2 LEADER-eligible patients, respectively. Incidence rates for first myocardial infarction and stroke were 1.9 and 2.1 events/100 patient-years and 1.1 and 1.0 events/100 patient-years, respectively. FDS2 LEADER-eligible patients had a lower CVD death rate of 0.8 versus 1.6/100 patient-years in the LEADER placebo group, but their non-CVD mortality was greater (2.1 versus 1.0/100 patient-years).
Conclusions: These data suggest recruitment bias in type 2 diabetes CVD outcome trials.

1. Introduction

There are limitations associated with randomized clinical trials designed to assess the efficacy of a new treatment in a sample drawn from an at-risk population. First, only a subset of identified eligible patients may consent to participation, leading to the possibility of selection bias.[1] Second, trial inclusion and exclusion criteria may mean that there are groups within the population with the disease (such as the elderly) who do not participate but who are likely to be treated if the drug is subsequently approved.[2] Although there are techniques for combining the results of clinical trials and prospective epidemiological data that attempt to overcome these potential limitations,[3] such analyses depend on the treatment being widely available in the community. However, observational studies can still be used to assess whether the patient sample recruited to a trial is representative in terms of both baseline characteristics and, in the placebo group, the endpoint(s) of interest.[4]

The Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER; clinicaltrials.gov NCT01179048) found that the glucagon-like peptide-1 (GLP-1) analogue liraglutide lowered the rate of first major cardiovascular event (MACE; death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke) among patients with type 2 diabetes mellitus compared with placebo.[5] The main inclusion criteria comprised age ≥50 years, HbA_{1c} ≥7.0% (≥56 mmol/mol) and a history of cardiovascular disease (CVD) and/or its risk factors or chronic kidney disease (CKD), while patients who had experienced a coronary or cerebrovascular event within the preceding 14 days, and those on incretin-based therapies or rapid-acting insulin, were excluded. A total of 9340 patients were recruited in a range of countries including Australia and randomized to liraglutide or placebo between 2010 and 2012. Consistent with the eligibility criteria, the average age of the patients in the two groups was 64 years, approaching two-thirds were males and their mean duration of diabetes was 13 years. The Fremantle Diabetes Study Phase II (FDS2) is a prospective longitudinal observational study of a representative sample of 1551 people with type 2 diabetes (mean age 66 years, 52% males) recruited from an urban population of 157,000 between 2008 and 2011[6] that was in progress while the LEADER trial was being conducted.

Conflicts of interest: TMED has received grants and personal fees from Novo Nordisk and was a local investigator in the LEADER trial.

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The aim of this study was to demonstrate the applicability of the LEADER trial results to the Australian population with type 2 diabetes by utilising FDS2 data and, in particular, i) to assess the proportion of type 2 diabetes patients from the FDS2 that would have met the LEADER inclusion and exclusion criteria, ii) to compare the key characteristics of the LEADER patients at study entry and those eligible for LEADER in FDS2, iii) to compare the incidence of MACE in FDS2 LEADER-eligible patients with those in the placebo group in LEADER over a similar duration of follow-up, and iv) to compare the key characteristics and outcomes of the two LEADER sub-groups (those with prior CVD and those with no CVD history but risk factors) to those of the equivalent FDS2 sub-groups.

2. Materials and methods

2.1. Patients

We selected all FDS2 participants with type 2 diabetes who would have been eligible to participate in LEADER based on their characteristics at the baseline assessment as well as the full list of LEADER entry criteria.[5] Descriptions of FDS2 recruitment procedures and details of recruited and non-recruited patients have been published.[6] Any patient resident in the study catchment area, a postcode-defined region around the port of Fremantle in Western Australia (WA), during the three-year registration phase who had a clinician-verified diagnosis of diabetes was eligible. Sources of identification and/or diagnostic data included public hospital inpatient/outpatient clinic lists and laboratory databases, notifications by local primary care/specialist physicians and allied health services including diabetes education, dietetics and podiatry, advertisements in pharmacies and local media, and word of mouth. We recruited 36% of the eligible identified patients. Compared with the 3077 eligible people with diabetes who were not recruited to FDS2, the 1732 participants were no different in terms of age (61.7 $\pm$ 17.4 vs 62.2 $\pm$ 13.8 years, $P = 0.23$), sex (52.1% vs 52.1% male, $P = 0.98$), or type of diabetes (89.5% vs 89.8% with clinically diagnosed type 2 diabetes, $P = 0.84$).

2.2. Ethics, consent and permissions

The LEADER trial protocol was reviewed and approved by the institutional review board or ethics committee at each participating centre. All the patients provided written informed consent before participation. The FDS2 was approved by the Human Research Ethics Committee, Southern Metropolitan Area Health Service and all subjects gave written informed consent before participation.

2.3. Clinical methods

At their first visit and then biennially for up to six years, FDS2 subjects had a detailed clinical assessment (comprehensive questionnaires, physical examination and specialized investigations) and provided fasting blood and urine samples for automated biochemical analyses in a single nationally-accredited laboratory.[6] These face-to-face assessments were interspersed with biennial postal questionnaires. Prevalent complications of diabetes were identified using standard definitions[7] based on self-report supplemented by information from the WA Data Linkage System (WADLS)[8] that includes all hospitalizations (public and private) and death registrations from 1970 to end-December 2012. These comprised coronary heart disease (CHD; self-reported history, or prior hospitalization for, myocardial infarction, angina and/or revascularization), cerebrovascular disease (self-reported ischemic stroke, hemorrhagic stroke or transient ischemic attack, or prior hospitalizations for these events), heart failure (prior hospitalization with this diagnosis), peripheral arterial disease (ankle:brachial index (ABI) ≤0.90 on either leg or diabetes-related amputation), peripheral sensory neuropathy (a score of >2/8 on the clinical portion of the Michigan Neuropathy Screening Instrument), retinopathy (any grade detected on fundus photography and/or ophthalmologist assessment), nephropathy (first morning urinary albumin:creatinine ratio >3.0 mg/mmol), and renal impairment (by estimated glomerular filtration rate (eGFR) determined using the CKD Epidemiology Collaboration (CKD-EPI) equation).

The baseline characteristics of FDS2 patients with type 2 diabetes were compared with those in the two LEADER groups (active and placebo), specifically for age, sex, diabetes duration, geographic region of birth (Europe, North America, Asia, Rest of the World), HbA_{1c}, hemoglobin, body mass index (BMI) and body weight, blood pressure, pulse, history of heart failure, CVD history (age > 50 years; prior myocardial infarction, prior stroke or transient ischemic attack, prior revascularization, heart failure, chronic kidney disease), CVD risk factors (age > 60 years; microalbuminuria or proteinuria, hypertension and left ventricular hypertrophy, ankle-brachial index <0.9), and renal function (normal - eGFR >90 mL/min 1.73 m^2, mild impairment - eGFR 60–89 mL/min 1.73 m^2, moderate impairment - eGFR 30–59 mL/min, severe impairment - eGFR <30 mL/min 1.73 m^2).

The following LEADER-equivalent endpoints were ascertained: i) primary (a composite of death from cardiovascular causes, nonfatal myocardial infarction or nonfatal stroke between study entry and 3.8 years of follow-up, the median follow-up time in LEADER[5]), ii) secondary (individual endpoints of death from cardiovascular causes, nonfatal myocardial infarction and nonfatal stroke over the same time), and iii) tertiary (all-cause death, coronary revascularization and heart failure hospitalization over the same time).

2.4. Statistical analysis

Post hoc comparisons between the set of baseline variables listed above for FDS2 and LEADER patient groups were by two-way comparisons of proportions by Fisher's exact test, for normally-distributed variables by Student's *t*-test, and for non-normally-distributed variables by Mann-Whitney *U* test. Since individual LEADER data points were unavailable, comparisons were made using proportions and means $\pm$ SDs from the LEADER placebo and FDS2 groups. Events rates for primary, secondary or tertiary outcome/100 patient years were calculated from FDS2 data and compared with those published for the LEADER placebo group[5] and a crude incidence rate ratio calculated.

3. Results

3.1. Patient characteristics

A consort diagram showing those patients in FDS2 who would have been eligible to participate in LEADER is shown in Fig. 1. This includes those on pre-mixed insulin who were initially excluded from LEADER but subsequently allowed to participate. There were 323 out of 1551 (20.8%) who would have satisfied the final LEADER inclusion and exclusion criteria. The characteristics of FDS2 eligible and ineligible patients as well as those in the LEADER active and placebo groups recruited between September 2010 and April 2012 are summarized in Table 1 with a complete range of variables in Supplementary Table 1.

Compared with the LEADER placebo arm patients, FDS2 LEADER-eligible patients were an average of approximately 6 years older, were less likely to be males, and had a lower body mass index (BMI) and better glycemic control despite fewer being treated with insulin. They were more likely to be hypertensive but fewer were treated with blood pressure lowering medication. They were less likely to have a history of CVD and heart failure at baseline but, consistent with the routine measurement of ABI in FDS2 compared with its infrequent use in usual care,[9] more likely to have peripheral arterial disease. The proportions with chronic kidney disease, defined as an estimated glomerular filtration rate eGFR <60 mL/min/1.73 m^2 by the Modification of Diet in Renal

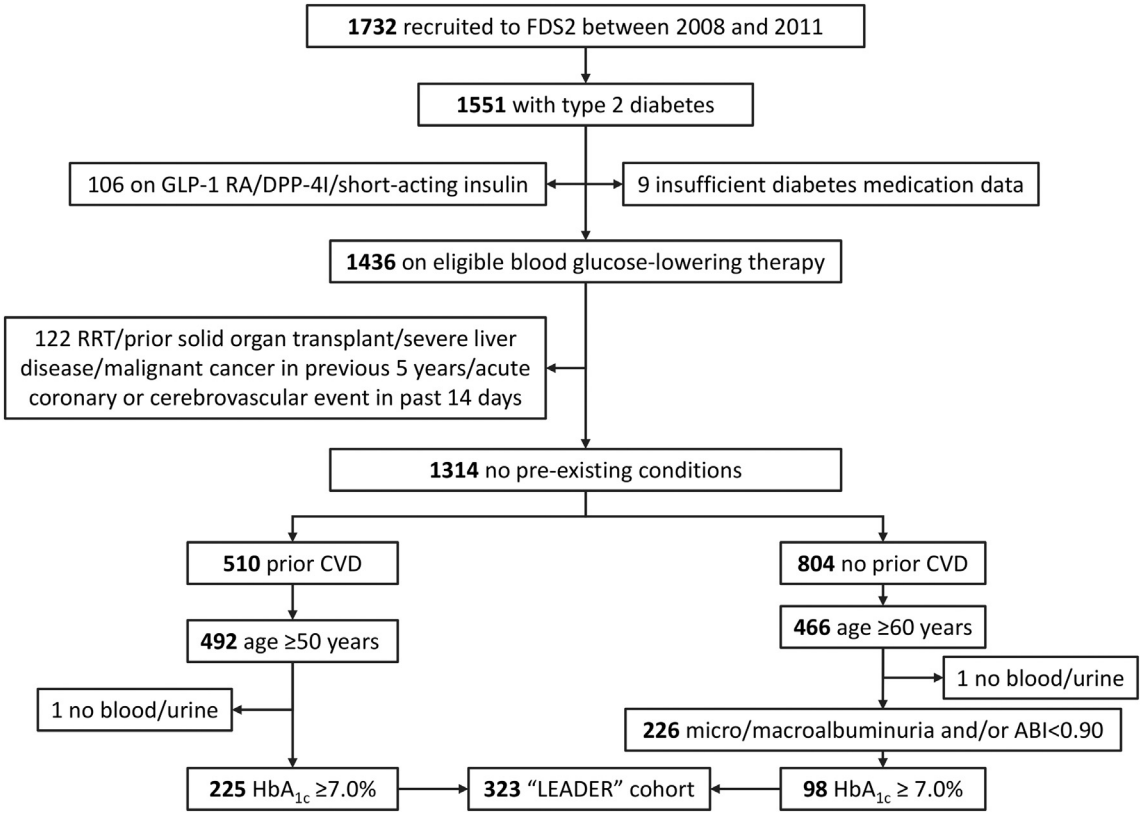

Fig. 1. Consort diagram showing the methods of selection of those patients in FDS2 who would have been eligible to participate in LEADER. Glucagon like peptide-1 receptor agonist = GLP-1 RA, dipeptidyl peptidase-4 inhibitor = DPP-4i, renal replacement therapy = RRT, cardiovascular disease = CVD, ankle:brachial index = ABI.

Disease (MDRD) or Cockcroft-Gault formulae in LEADER[5] and an eGFR <60 mL/min/1.73 m^2 by the CKD-EPI equation in FDS2, were similar but more FDS2 participants had microalbuminuria/proteinuria. The same bivariate comparisons as in Table 1, but restricted to only Australian patients in the LEADER trial, are shown in Table 2. The same patterns seen in Table 1 were present in the Australian placebo-treated LEADER patients compared with LEADER-eligible FDS2 participants.

Comparisons between the two main sub-groups in LEADER (those with a CVD history and those with CVD risk factors) and the same sub-groups in LEADER-eligible FDS2 patients are shown in Table 3. The FDS2 LEADER-eligible patients in the two sub-groups were older, were less likely to be male, had a lower BMI and had better glycemic control than their respective LEADER counterparts. They were less likely to be hypertensive (based on blood pressure and use of antihypertensive therapies), more likely to be hyperlipidemic (based on serum lipids and lipid lowering treatment), less likely to have normal renal function based on eGFR >90 mL/min/1.73 m^2, and more likely to have peripheral arterial disease.

3.2. Cardiovascular disease endpoints

There was a minimum planned follow-up 42 months in LEADER. The actual median time of liraglutide exposure was 3.5 years during a median follow-up of 3.8 years. FDS2 follow-up data comprised events ascertained through WADLS to end-June 2013. For the FDS2 LEADER-eligible cohort, median follow-up to death or end-June 2013, whichever came first, was 3.5 [interquartile range 0.15–5.3] years.

Key outcomes in LEADER and FDS2 are shown in Table 4. Within the limitations of relatively small numbers of events in FDS2, the incidence rates were generally similar. The background primary composite MACE outcome was 34% higher in LEADER with incidence rates of 3.9 and 2.9 events per 100 patient-years for LEADER placebo-treated and FDS2 LEADER-eligible patients, respectively. For individual MACE components, the incidence rates of myocardial infarction (1.9 and 2.1 events per 100 patient-years, respectively) and stroke (1.1 and 1.0 events per 100 patient-years, respectively) were very close, but FDS2 LEADER-eligible patients had a death rate from cardiovascular causes which was 50% that of LEADER placebo-treated patients (0.8 versus 1.6 per 100 patient-years, respectively).

The death rate from non-cardiovascular causes in the FDS2 LEADER-eligible cohort was, by contrast, more than double that in the LEADER placebo-treated patients (2.1 versus 1.0 per 100 patient-years, respectively). Over a quarter (26%) of non-cardiovascular deaths in the FDS2 LEADER-eligible patients were from cancer, most of which (56%) were pulmonary, gastrointestinal or prostatic. The FDS2 LEADER-eligible patients were less likely to undergo revascularization despite being more likely to be admitted for unstable angina. The primary composite MACE outcome incidence for the Australian LEADER placebo-treated participants was 4.6 per 100 patient-years (data on file). This was higher than for both the LEADER placebo-treated participants as a whole (3.9 per 100 patient-years) and the FDS2 LEADER-eligible participants (2.9 events per 100 patient-years).

In the LEADER placebo-treated group, 16.7% of the CVD history sub-group and 7.2% of the CVD risk factor sub-group experienced the primary composite MACE outcome compared with 12.1% and 6.1%, respectively in the equivalent FDS2 LEADER-eligible sub-groups (see Supplementary Table 2).

For the LEADER cohort, an average of 200 patients would have to receive liraglutide for one year for one additional patient not to suffer a component of the primary outcome. The number needed to treat (NNT), assuming the same relative risk reduction and rounding incidence rates to one decimal point, would increase to 250 and 500, respectively, for the FDS2 eligible and ineligible cohorts.

Table 1
Baseline characteristics of LEADER trial groups (liraglutide and placebo) and FDS2 groups (eligible and ineligible for LEADER).

	LEADER			FDS2		
	Liraglutide	Placebo	*P*-value[1]	LEADER-eligible	LEADER-ineligible[a]	*P*-value[2]
Number	4668	4672		323 (20.9)	1224 (79.1)	
Male sex (%)	64.5	64.0	<0.001	51.4	52.1	0.85
Age (years)	64.2 ± 7.2	64.4 ± 7.2	<0.001	70.1 ± 8.7	64.5 ± 12.0	<0.001
Diabetes duration (years)	12.8 ± 8.0	12.9 ± 8.1	0.07	13.8 ± 8.5	9.2 ± 8.3	<0.001
Body mass index (kg/m^2)	32.5 ± 6.3	32.5 ± 6.3	0.016	31.6 ± 6.5	31.2 ± 6.1	0.27
HbA_{1c} (%)	8.7 ± 1.6	8.7 ± 1.5	<0.001	8.2 ± 1.2	7.0 ± 1.4	<0.001
HbA_{1c} (mmol/mol)	72 ± 17	72 ± 16	<0.001	66 ± 13	53 ± 15	<0.001
Metformin (%)	75.8	77.1	0.70	78.0	60.3	<0.001
Sulfonylurea (%)	50.8	50.6	0.18	46.7	26.4	<0.001
Thiazolidinedione (%)	6.3	6.0	0.005	9.9	4.7	0.001
Insulin (%)	43.7	45.6	0.002	36.5	19.0	<0.001
Systolic blood pressure (mm Hg)	135.9 ± 17.8	135.9 ± 17.7	<0.001	151.5 ± 24.1	144.5 ± 21.6	<0.001
Diastolic blood pressure (mm Hg)	77.2 ± 10.3	77.0 ± 10.1	<0.001	80.4 ± 13.4	80.1 ± 12.1	0.74
Beta blockers (%)	56.8	54.1	<0.001	30.7	19.3	<0.001
Calcium channel blockers (%)	32.9	31.7	0.96	31.6	22.8	0.001
ACE inhibitors (%)	51.8	50.3	0.002	41.2	37.4	0.22
Angiotensin receptor blockers (%)	31.9	31.8	0.003	39.9	30.2	0.001
Diuretics (%)	41.8	41.8	0.32	39.0	27.8	<0.001
Statins (%)	72.9	71.4	0.11	75.5	64.4	<0.001
Aspirin (%)	63.8	62.1	<0.001	46.3	35.4	<0.001
Heart failure (%)	17.9[b]	17.8[b]	<0.001	10.5[c]	5.3[c]	0.001
Established CVD and age ≥50 years (%)	82.1	80.6	<0.001	69.7	0	–
Prior myocardial infarction (%)	31.4	30.0	<0.001	12.7[c]	7.3[c]	0.003
Prior stroke/transient ischemic attack (%)	15.6	16.6	<0.001	6.8[c]	4.4[c]	0.08
Prior revascularization (%)	39.3	38.6	<0.001	20.7[c]	10.1[c]	<0.001
Chronic kidney disease (%)	25.4[d]	24.0[d]	0.052	28.8[e]	13.9[e]	<0.001
CVD risk factors and age ≥60 years (%)	17.9	19.4	<0.001	30.3	0	–
Microalbuminuria or proteinuria (%)	10.7	11.9	<0.001	66.1[f]	35.4[f]	<0.001
Ankle brachial index <0.9 (%)	2.4	2.5	<0.001	30.2	18.8	<0.001

[1] *P*-value for comparison between FDS2 LEADER-eligible and LEADER placebo arm.
[2] *P*-value for comparison between FDS2 LEADER-eligible and FDS2 LEADER-ineligible.
[a] Excludes four individuals with undefined eligibility.
[b] New York Heart Association class I, II and III.
[c] Prior hospitalization for/with condition.
[d] eGFR < 60 mL/min/1.73 m^2 by MDRD formula or <60 mL/min/1.73 m^2 by Cockcroft-Gault formula.
[e] eGFR by CKD-EPI equation.
[f] Microalbuminuria or worse (urinary albumin:creatinine ratio ≥ 3.0 mg/mmol).

Table 2
Baseline characteristics of Australian LEADER groups (liraglutide and placebo) and FDS2 groups (eligible and ineligible for LEADER).

	LEADER			FDS2		
	Liraglutide	Placebo	*P*-value[1]	FDS2 LEADER-eligible	FDS2 LEADER-ineligible[a]	*P*-value[2]
N (%)	112	109		323 (20.9)	1224 (79.1)	
Age (years)	67.5	64.9	<0.001	70.1 ± 8.7	64.5 ± 12.0	<0.001
Male sex (%)	81.3	78.9	<0.001	51.4	52.1	0.85
Diabetes duration (years)	16.6	14.4	0.51	13.8 ± 8.5	9.2 ± 8.3	<0.001
Body mass index (kg/m^2)	33.1	34.8	<0.001	31.6 ± 6.5	31.2 ± 6.1	0.27
HbA_{1c} (%)	8.6	8.5	0.059	8.2 ± 1.2	7.0 ± 1.4	<0.001
HbA_{1c} (mmol/mol)	70	69	0.059	66 ± 13	53 ± 15	<0.001
Metformin (%)	83.9	81.7	0.42	78.0	60.3	<0.001
Sulfonylurea (%)	48.2	61.5	0.008	46.7	26.4	<0.001
Thiazolidinedione (%)	3.6	5.5	0.16	9.9	4.7	0.001
Insulin (%)	58.9	55.0	<0.001	36.5[b]	19.0	<0.001
Systolic blood pressure (mm Hg)	136.3	134.2	<0.001	151.5 ± 24.1	144.5 ± 21.6	<0.001
Diastolic blood pressure (mm Hg)	72.2	73.6	<0.001	80.4 ± 13.4	80.1 ± 12.1	0.74
Established CVD and age ≥50 years (%)	86.6	89.0	<0.001	69.7	0	–
Antihypertensive therapy (%)	95.5	91.7	0.026	83.0[c]	69.9[c]	<0.001
Diuretics (%)	32.1	26.6	0.020	39.0	27.8	<0.001
Lipid-modifying drugs (%)	79.5	83.5	0.16	77.1	66.3	<0.001
Platelet aggregation inhibitors (%)	67.0	69.7	<0.001	54.5[d]	38.9[d]	<0.001

[1] *P*-value for comparison between FDS2 eligible and LEADER placebo arm (SDs for LEADER placebo arm taken from whole LEADER placebo arm).
[2] *P*-value for comparison between FDS2 eligible and FDS2 ineligible.
[a] Excludes four individuals with undefined eligibility.
[b] As per revised exclusion criteria, includes intermediate, long-acting and pre-mix insulins.
[c] Excluding diuretics.
[d] Aspirin, dipyridamole, clopidogrel.

Table 3
Baseline characteristics of LEADER and FDS2 LEADER-eligible groups with and without a history of CVD.

	LEADER				FDS2 LEADER-eligible		
	CVD history	CVD risk factors	*P*-value[1]	*P*-value[2]	CVD history	CVD risk factors	*P*-value[3]
N	7592	1748			225	98	
Age (years)	63.9 ± 7.6	65.8 ± 5.2	<0.001	<0.001	70.1 ± 9.1	70.2 ± 7.6	0.98
Male sex (%)	66.5	54.6	<0.001	0.09	53.8	45.9	<0.001
Body mass index (kg/m^2)	32.5 ± 6.3	32.4 ± 6.3	0.06	0.010	31.7 ± 6.3	31.2 ± 6.9	0.52
Diabetes duration (years)	12.8 ± 8.1	12.3 ± 7.5	0.005	>0.99	14.5 ± 8.8	12.3 ± 7.6	0.035
Hypertension (%)[a]	90.7	87.0	<0.001	0.07	75.0	80.6	0.32
Hyperlipidemia (%)[a]	80.8	60.4	<0.001	0.08	90.6	69.4	<0.001
Smoking (%):							
Current	12.2	11.6	0.27	0.18	9.9	7.2	0.53
Previous	48.3	38.2	0.20	0.054	44.4	48.5	0.54
HbA_{1c} (%)	8.7 ± 1.5	8.8 ± 1.6	<0.001	<0.001	8.2 ± 1.3	8.1 ± 1.1	0.35
Glucose-lowering therapy (%):							
Diet-based	5.3	5.7	0.23	0.16	7.1	9.2	<0.001
Oral agents without insulin	51.8	57.5	0.85	0.26	52.4	63.3	<0.001
1 oral agent	20.3	21.6	0.056	0.36	15.1	25.5	
2 oral agents	28.1	31.8	0.15	0.65	32.4	29.6	
≥3 oral agents	3.4	4.1	0.40	0.056	4.4	8.2	
Insulin (±oral agents)	42.9	36.9	0.46	0.06	40.4	27.6	<0.001
Total serum cholesterol (mmol/L)	4.4 ± 1.2	4.6 ± 1.1	0.008	<0.001	4.2 ± 1.1	4.3 ± 1.0	0.49
Serum LDL-cholesterol (mmol/L)	2.3 ± 0.9	2.5 ± 0.9	0.10	<0.001	2.2 ± 0.9[b]	2.3 ± 0.8[b]	0.44
Serum HDL-cholesterol (mmol/L)	1.16 ± 0.31	1.24 ± 0.33	0.026	0.07	1.21 ± 0.33	1.28 ± 0.33	0.09
Serum triglycerides (mmol/L)	2.1 ± 1.6	2.0 ± 1.5	0.004	<0.001	1.9 ± 1.0	1.6 ± 0.8	0.043
eGFR category (ml/min/1.73 m^2; %)							
≥90	34.5[c]	47.4[c]	<0.001	0.039	17.3[d]	36.7[d]	<0.001
60–89	38.8[c]	52.5[c]	0.44	0.038	41.3[d]	63.3[d]	<0.001
30–59	24.4[c]	0[c]	<0.001	–	35.1[d]	0[d]	<0.001
<30	2.3[c]	0[c]	<0.001	–	6.2[d]	0[d]	0.007
Coronary artery disease (%)	69.7	1.0	0.69	–	68.4	0	<0.001
Heart failure (%)	20.6[e]	2.1[e]	0.044	–	15.1[f]	0[f]	<0.001
Peripheral arterial disease (%)	18.4	14.3	0.005	<0.001	25.9	45.9	<0.001
Aspirin use (%)	76.5	41.0	<0.001	0.40	50.4	36.7	0.029

[1] *P*-value for comparison between FDS2 CVD history and LEADER CVD history.
[2] *P*-value for comparison between FDS2 CVD risk factors and LEADER CVD risk factors.
[3] *P*-value for comparison between FDS2 CVD history and FDS2 CVD risk factors.
[a] Defined by American Diabetes Association 2014 guidelines.[5,16]
[b] Calculated using Friedewald formula for serum triglycerides <4.5 mmol/L.
[c] eGFR < 60 mL/min/1.73 m^2 by MDRD formula or <60 mL/min/1.73 m^2 by Cockcroft-Gault formula.
[d] eGFR by CKD-EPI equation.
[e] New York Heart Association class I, II and III.
[f] Prior hospitalization for/with condition.

4. Discussion

The present analyses show that the incidence of MACE events in the FDS2 patients who would have been eligible for recruitment to the LEADER trial was similar to those in the LEADER placebo-treated group during a comparable period of follow-up, especially in the case of the individual MACE endpoints myocardial infarction and stroke. However, cardiovascular mortality in FDS2 patients was half that in the LEADER placebo group, but deaths from non-cardiovascular causes were double, consistent with the older age of the FDS2 LEADER-eligible cohort and their attendant increased competing risk of potentially fatal diseases such as cancer and dementia.

The older age of the FDS2 LEADER-eligible cohort compared with LEADER participants suggests that there is a bias towards recruitment of younger patients in type 2 diabetes CVD outcome trials within the prescribed age range, perhaps because of investigator fear of early death or withdrawal due to disability.[10] Whether this could influence the results of the trial will depend on age-specific efficacy. In the case of LEADER, pre-specified Cox proportional hazard regression analyses performed for subgroups of patients for the primary MACE outcome in active versus placebo-treated participants included comparison of those aged <60 years to those ≥60 years of age (without an upper limit of age in the trial inclusion criteria). There was no significant difference between the respective hazard ratios (HRs) and (95% CIs) of 0.78 (0.62–0.97) and 0.90 (0.79–1.02), with a *P*-value for interaction at 0.20.[5] This suggests that liraglutide reduced the primary endpoint regardless of age even though, because of the inclusion criteria, the <60 years age group in LEADER was enriched for patients with prior CVD relative to those aged ≥60 years. The pre-specified Cox proportional hazard regression analyses for the primary endpoint in those with a CVD history versus those with CVD risk factors showed that the former group was more likely to benefit from liraglutide (HRs and (95% CIs) 0.82 (0.70–0.97) versus 1.20 (0.86–1.67); *P*-value for interaction 0.04).[5]

It is of interest that the FDS2 LEADER-eligible patients were less likely to undergo revascularization than the LEADER placebo-treated patients despite being more likely to be admitted for unstable angina. This may also reflect their greater age since the decision between revascularization and medical management alone can be influenced by the high rate of complications and mortality associated with invasive procedures in the elderly.[11] This could have implications for CVD outcome trials in diabetes in which revascularization was an endpoint. The decision to revascularize could be adversely influenced by factors such as poor glycemic control[12] which may differ between placebo and active groups in trials such as LEADER, with a consequent potential for bias.

Although a detailed comparison of endpoints between LEADER-eligible FDS2 patients and all the Australians who were recruited to LEADER who were allocated placebo was not possible, the latter group had a relatively high primary composite MACE incidence (4.6 per versus 2.9 events per 100 patient-years in FDS2 LEADER-eligible patients). This suggests that, consistent with their higher mean HbA_{1c} as in the LEADER sample as a whole, that they tended to be more complicated clinic-based patients than the community-based FDS2 cohort whose management is across the spectrum from primary to secondary and tertiary care.[6] Nevertheless, the eligibility criteria for LEADER would have

Table 4
Outcomes for LEADER groups (liraglutide n = 4668 and placebo n = 4762) and FDS2 groups (LEADER-eligible n = 323 and LEADER-ineligible n = 1224) listed as number of events and (%) as well as incidence rates per 100 patient-years (py).

	LEADER				IRR (95% CI)[b,c]	FDS2[a]			
	Liraglutide		Placebo			LEADER-eligible		LEADER-ineligible	
	n (%)	IR/100 py	n (%)	IR/100 py		n (%)	IR/100 py	n (%)	IR/100 py
Primary composite outcome	608 (13.0)	3.4	694 (14.9)	3.9	0.74 (0.51–1.05)	33 (10.3)[d]	2.9 (2.0–4.1)	77 (6.3)[d]	1.8 (1.4–2.2)
Expanded composite outcome	948 (20.3)	5.3	1062 (22.7)	6.0	0.88 (0.66–1.14)	57 (17.8)[d]	5.3 (4.0–6.9)	132 (10.8)[d]	3.1 (2.6–3.7)
Death from any cause	381 (8.2)	2.1	447 (9.6)	2.5	1.23 (0.85–1.72)	36 (11.1)	3.1 (2.2–4.2)	104 (8.5)	2.4 (1.9–2.9)
Death from cardiovascular causes	219 (4.7)	1.2	278 (6.0)	1.6	0.49 (0.22–0.95)[g]	9 (2.8)[d]	0.8 (0.4–1.5)	27 (2.2)[d]	0.6 (0.4–0.9)
Death from non-cardiovascular causes	162 (3.5)	0.9	169 (3.6)	1.0	2.16 (1.35–3.33)[g]	24 (7.5)[d]	2.1 (1.3–3.1)	72 (5.9)[d]	1.6 (1.3–2.1)
Myocardial infarction	292 (6.3)	1.6	339 (7.3)	1.9	[f]	24 (7.5)[d]	2.1 (1.3–3.1)	53 (4.3)[d]	1.2 (0.9–1.6)
Fatal	17 (0.4)	0.1	28 (0.6)	0.2	2.18 (0.55–6.22)[g]	4 (1.3)[d]	0.3 (0.1–0.9)	11 (0.9)[d]	0.2 (0.1–0.5)
Non-fatal	281 (6.0)	1.6	317 (6.8)	1.8	[f]	20 (6.2)	1.7 (1.1–2.7)	43 (3.5)	1.0 (0.7–1.3)
Silent	62 (1.3)	0.3	76 (1.6)	0.4	–	–	–	–	–
Stroke	173 (3.7)	1.0	199 (4.3)	1.1	[f]	12 (3.8)[c]	1.0 (0.5–1.8)	15 (1.2)[c]	0.3 (0.2–0.6)
Fatal	16 (0.3)	0.1	25 (0.5)	0.1	1.83 (0.35–5.99)[g]	3 (0.9)[c]	0.3 (0.1–0.8)	2 (0.2)[c]	0.1 (0.0–0.2)
Non-fatal	159 (3.4)	0.9	177 (3.8)	1.0	[f]	9 (2.8)	0.8 (0.4–1.5)	14 (1.1)	0.3 (0.2–0.5)
Transient ischemic attack	48 (1.0)	0.3	60 (1.3)	0.3	[f]	6 (1.9)[e]	0.5 (0.2–1.1)	7 (0.6)[e]	0.2 (0.1–0.3)
Coronary revascularization	405 (8.7)	2.3	441 (9.4)	2.5	0.17 (0.06–0.40)	5 (1.5)	0.4 (0.1–1.0)	14 (1.1)	0.3 (0.2–0.5)
Hospitalization for unstable angina	122 (2.6)	0.7	124 (2.7)	0.7	[f]	16 (5.0)[e]	1.4 (0.8–2.3)	33 (2.7)[e]	0.8 (0.5–1.1)
Hospitalization for heart failure	218 (4.7)	1.2	248 (5.3)	1.4	[f]	23 (7.1)[e]	2.0 (1.3–3.1)	41 (3.3)[e]	0.9 (0.7–1.3)
Microvascular event	355 (7.6)	2.0	416 (8.9)	2.3	–	[d]	[d]	[d]	[d]
Retinopathy	106 (2.3)	0.6	92 (2.0)	0.5	–	[d]	[d]	[d]	[d]
Nephropathy	268 (5.7)	1.5	337 (7.2)	1.9	–	[d]	[d]	[d]	[d]

[a] Four FDS2 patients were missing HbA_{1c} or diabetes treatment details and were excluded from outcome analysis.
[b] Person-years of follow-up to event or death or census for LEADER placebo arm derived from reported number of events and IR when numbers sufficient.
[c] IRR for IR FDS2 LEADER-eligible versus IR for LEADER placebo arm.
[d] Cause of death not ascertainable for 5 FDS2 participants (three eligible - all in prior CVD cohort, two ineligible).
[e] Defined as principal diagnosis code.
[f] Patient-years of follow-up for LEADER Placebo arm derived from n/IR was imprecise.
[g] Patient-years derived from all-cause mortality to improve precision.

tended to restrict patient recruitment sources to specialist clinics regardless of geographical location.

Of relevance to this latter point is evidence from a large US registry database study in which 48% of enrolled patients with type 2 diabetes would have been eligible for recruitment to LEADER[13] compared with only 20.8% of FDS2 participants with type 2 diabetes. This suggests that the US cohort, which came from cardiological and endocrinological clinics as well as primary care, were more likely to have CVD and/or were at greater CVD risk than the FDS2 participants. There is a similar study planned in a UK primary care setting[14] and it will be interesting to see whether the eligibility rate is closer to that in FDS2 than the US registry.

The NNTs to avoid a primary endpoint in the FDS2 cohort, whether eligible or ineligible for LEADER, were greater than in LEADER itself because the event rates were lower. Notwithstanding differences between the Australian healthcare system and the trial setting, the greater NNTs in FDS2 suggest a lower relative cost-effectiveness than in LEADER. Nevertheless, US managed care data indicate that, in patients with type 2 diabetes and established CVD or an elevated CVD risk, liraglutide is a cost-effective and a budget neutral treatment option.[15]

The present study had limitations. The different types of study represented by LEADER and FDS2 meant that between-study standardization of patient characteristics and endpoints was difficult. The smaller LEADER-eligible FDS2 group meant that there were relatively few endpoints in some categories, especially when the sample was subdivided into CVD history and CVD risk factor sub-groups. The strengths of the study are availability of near-complete detailed FDS2 data collected contemporaneously with the LEADER trial collected from a representative community-based sample, and the availability of data from the Australian LEADER participants as well as the trial cohort as a whole.

5. Conclusions

External validation of studies such as LEADER through an observational study such as FDS2 can usefully assess whether the patient sample recruited to a trial is representative in terms of both baseline characteristics and, at least in the placebo group, the endpoint(s) of interest.[4] The present analyses suggest that, although there were differences between the LEADER placebo-treated patients and those eligible for LEADER in FDS2, especially the older age of the latter sample, the event rates were generally similar, especially for myocardial infarction and stroke. This provides some support for the use of liraglutide for management of older patients with type 2 diabetes who have, or are at risk of, CVD based on the findings of LEADER.[5] Similar analyses could be performed in the case of other CVD endpoint trials in type 2 diabetes using newer blood glucose-lowering therapies from the GLP-1 analogue and other classes.

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Appendix A. Supplementary data

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