Dapagliflozin in renal impairment: Association of British Clinical Diabetologists (ABCD) Nationwide Dapagliflozin Audit

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On behalf of the ABCD nationwide dapagliflozin audit contributors

ADA, San Diego

11, June, 2017

Sandwell and West Birmingham Hospitals NHS

Where EVERYONE Matters

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Disclosures

- Dr Bob Ryder has received speaker fees, consultancy fees and/or educational sponsorships from AstraZeneca, GI Dynamics, Janssen, Novo Nordisk, Sanofi-Aventis and Takeda

PHOTOGRAPHY PROHIBITED

Please do not take photos during this presentation

ABCD nationwide audits

- Assess safety and efficacy of new diabetes therapies as they come into real clinical use from phase 3 clinical trials
- Secure on-line
- Anonymised

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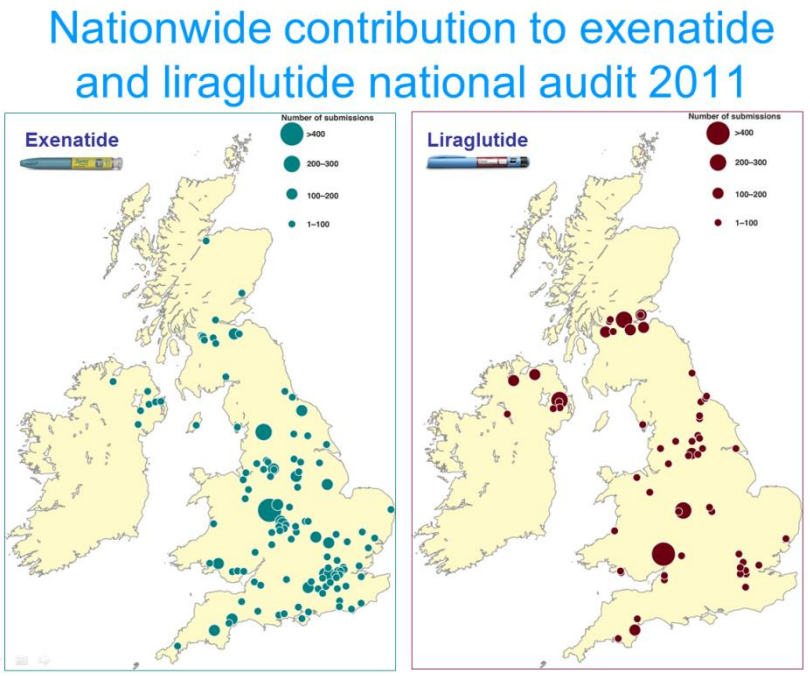
ABCD nationwide exenatide and liraglutide audits



- Real-life data
  - >13000 patients from
  - >150 centres
  - >500 contributors
- There have been (by 2015)
  - 12 published papers
  - 23 abstracts
  - 13 oral presentations

http://www.diabetologists-abcd.org.uk/GLP1_Audits/PresentationsPostersAbstractsExenatide.htm
http://www.diabetologists-abcd.org.uk/GLP1_Audits/PresentationsPostersAbstractsLiraglutide.htm

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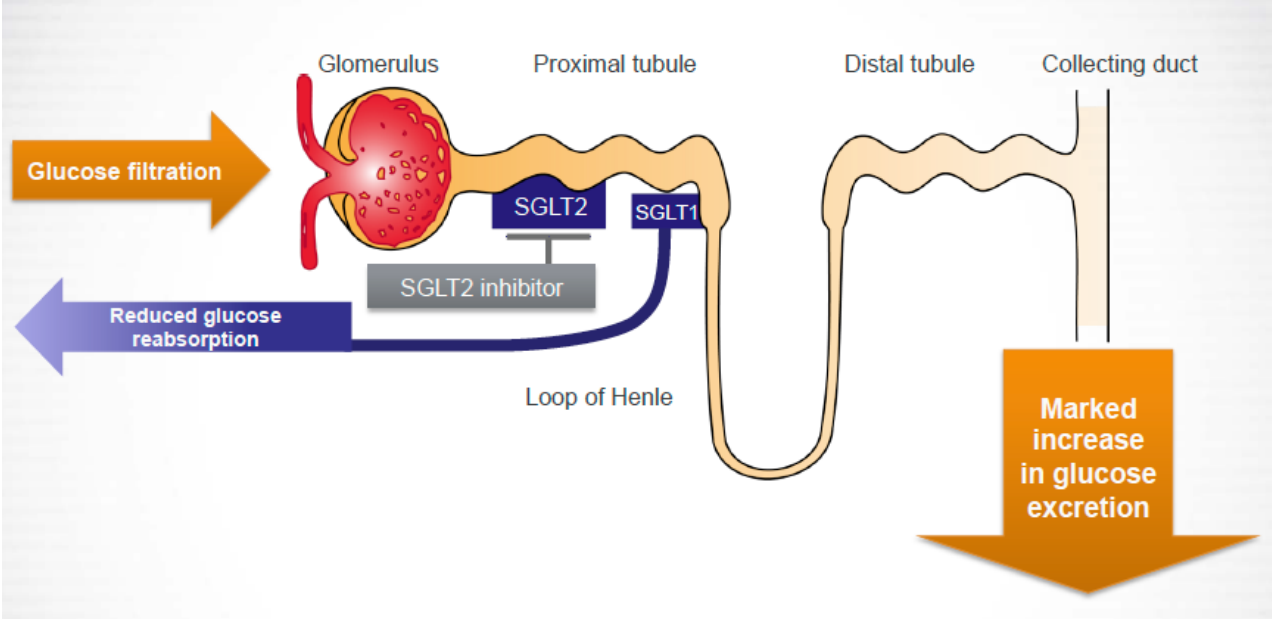
SGLT2 inhibitors – a chance to learn in the same way about a new class



- Canagliflozin
- Dapagliflozin
- Empagliflozin

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Bailey CJ (2011) *Trends Pharmacol Sci* **32**: 63–71

ABCD nationwide dapagliflozin audit

- Launched October 2014
- Findings so far …..

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Year 1 Audit Overview – October 2015

Data Input	Oct 2014 – Oct 2015	vs Combined Clinical Trials – Dapagliflozin
Centres	44	
Contributors	129	
Number of Patients	943	
Age (years)	56.7±10.4	
Sex [Males(%)]	55.9%	
Duration of diabetes (years)*	11.4 (6–16)	
Baseline HbA_{1c} (mmol/mol)	80.2±16.1	
Baseline HbA_{1c}(%)	9.5±1.5	8.0
BMI (kg/m²)	37.0±13.3	32.2
Baseline weight (kg)	103.3±22.7	
Duration of follow up (months)*	6.4 (0–12.3)	

Reported as mean±SD or median (IQR)*

Data presented at ABCD autumn meeting, November 2015

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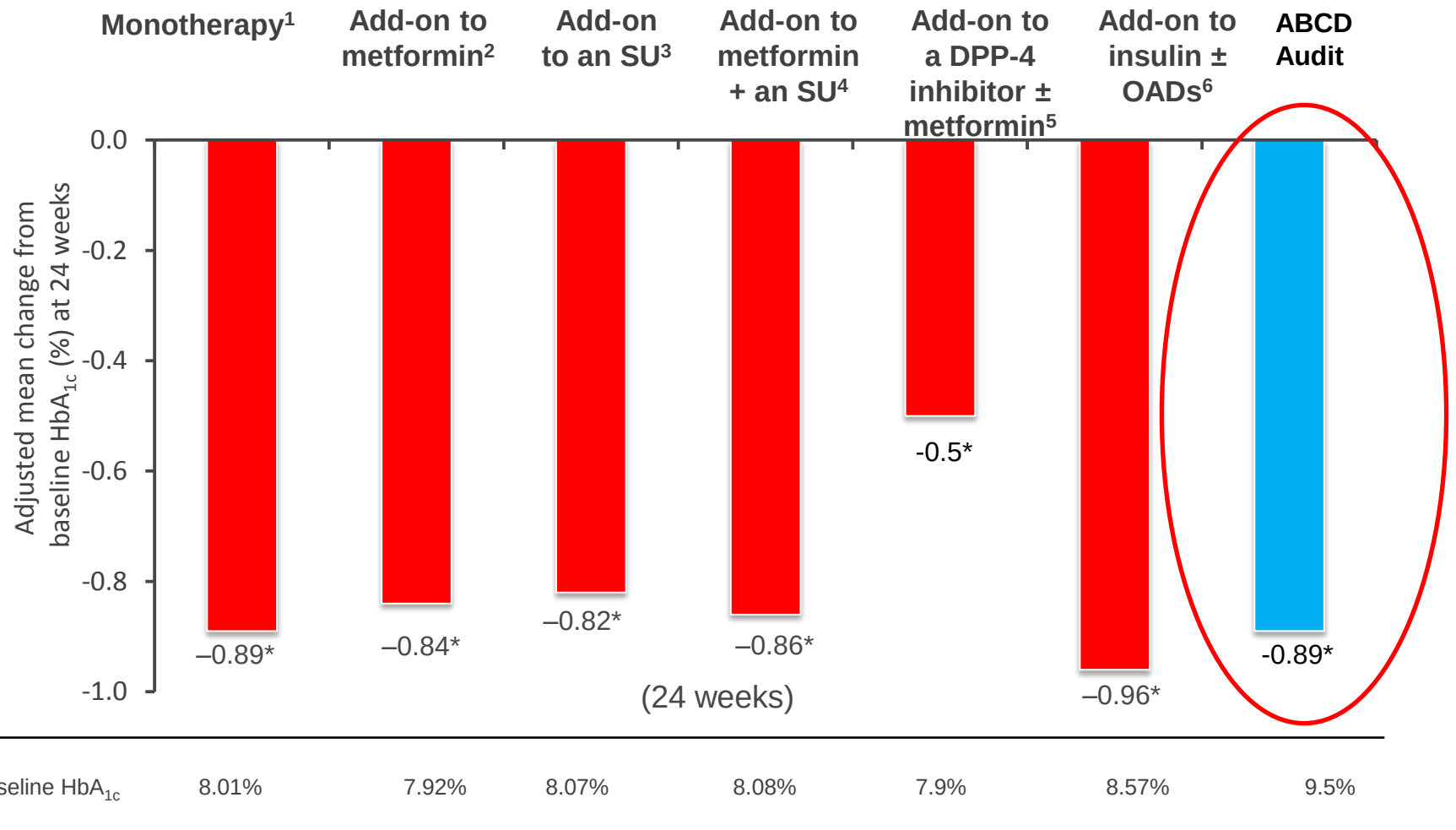
Reductions in HbA_{1c}: RCT data vs. ABCD audit



1. Ferrannini E et al (2010) *Diabetes Care* **33**: 2217–24; 2. Bailey CJ et al (2010) *Lancet* **375**: 2223–33; 3. Strojek K et al (2011) *Diabetes Obes M* 928–38; 4. Matthaei S et al (2015) *Diabetes Care* **38**: 365–72; 5. Jabbour SA et al (2014) *Diabetes Care* **37**: 740–50; 6. Wilding JPH et al (2012) *Ann Ir Med* **156**: 405–15

Data presented at ABCD autumn meeting, November 2015

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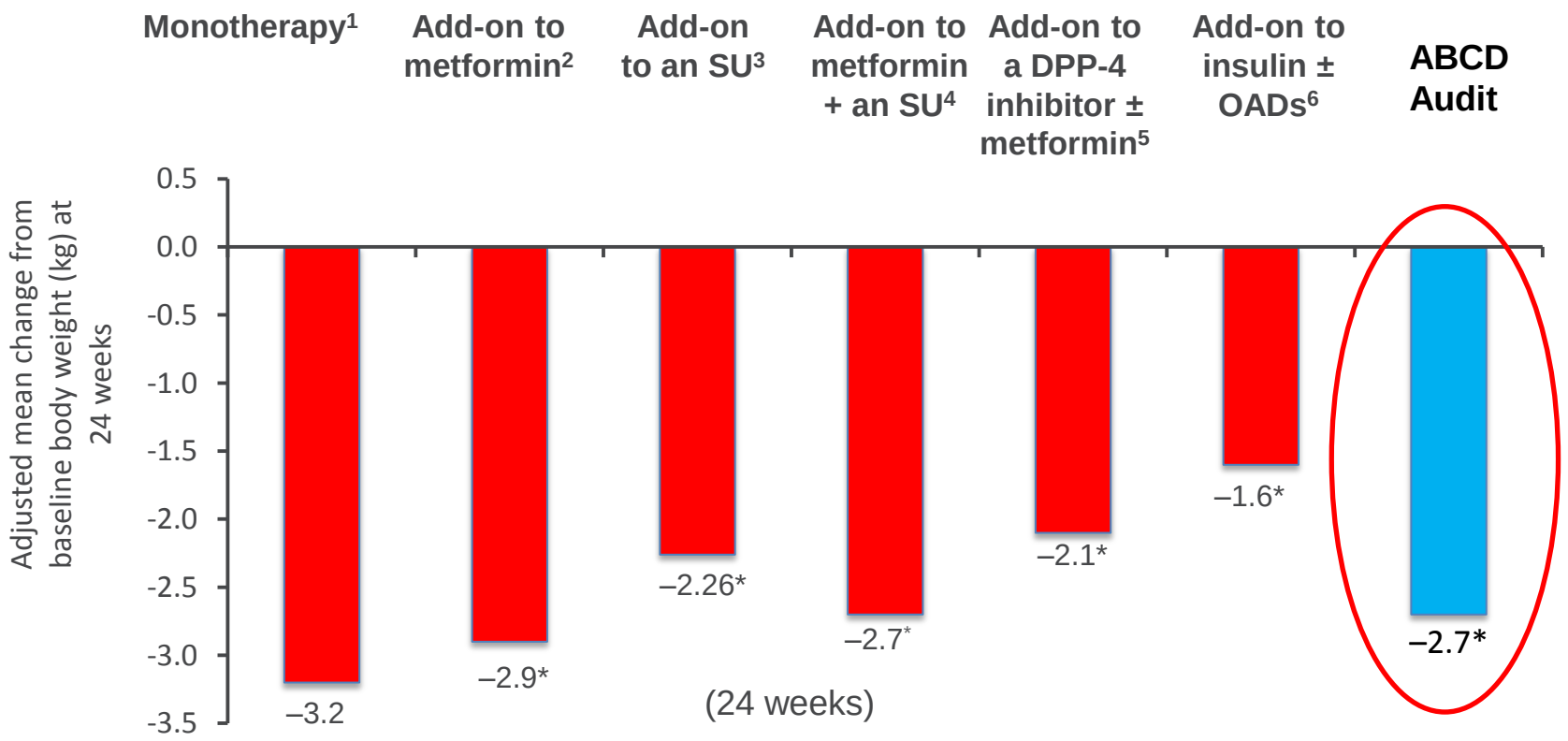
Weight loss: : RCT data vs. ABCD audit



Baseline weight (kg)	94.2	86.3	80. 6	88.6	91.0	94.5	94.5

1. Ferrannini E et al (2010) *Diabetes Care* **33**: 2217–24; 2. Bailey CJ et al (2010) *Lancet* **375**: 2223–33; 3. Strojek K et al (2011) *Diabetes Obes Metab* **13**: 928–38; 4. Matthaei S et al (2015) *Diabetes Care* **38**: 365–72; 5. Jabbour SA et al (2014) *Diabetes Care* **37**: 740–50; 6. Wilding JPH et al (2012) *Ann Intern Med* **156**: 405–15;

Data presented at ABCD autumn meeting, November 2015

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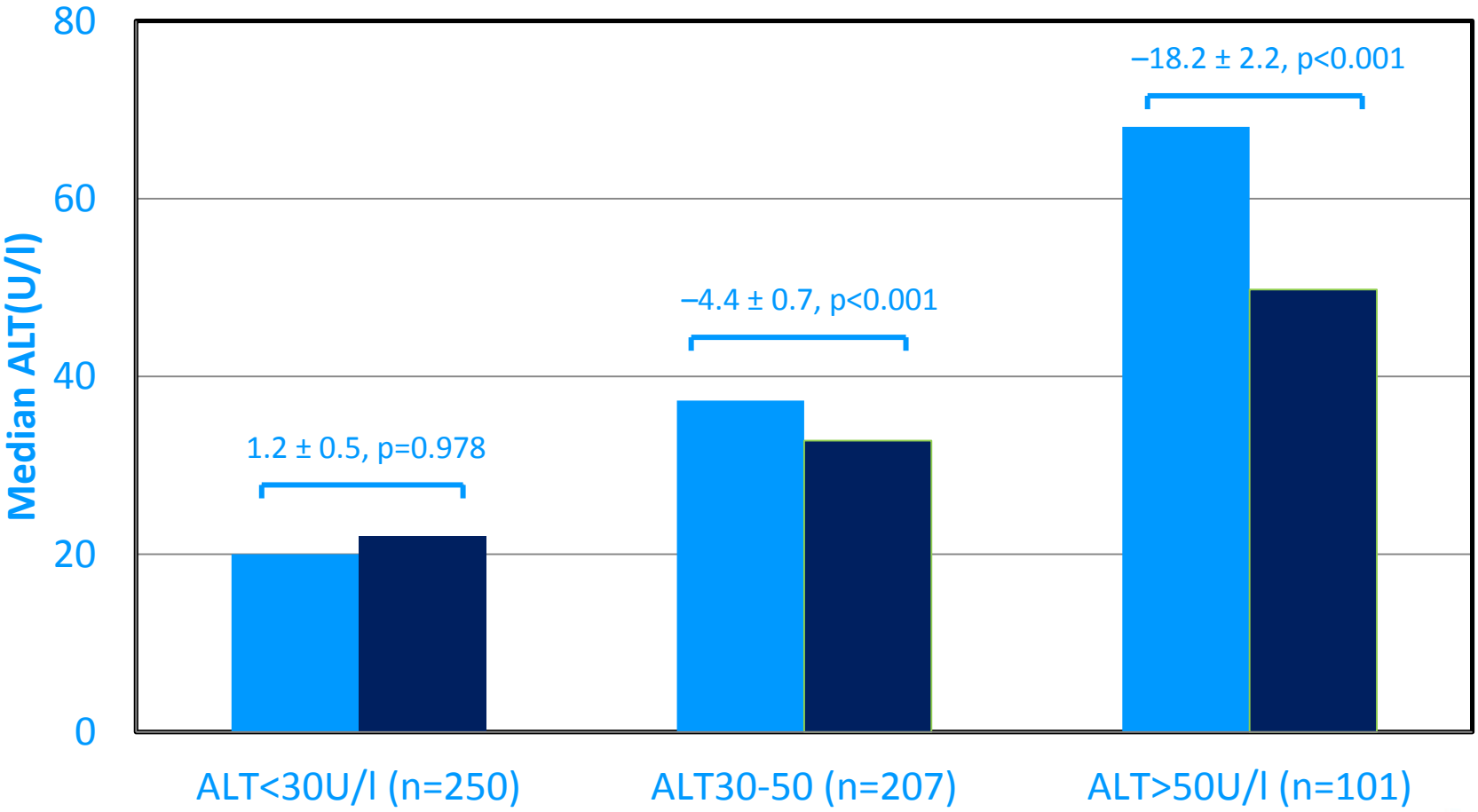
ALT response to dapagliflozin



Data presented at DUK annual professional conference, Glasgow, March 2016

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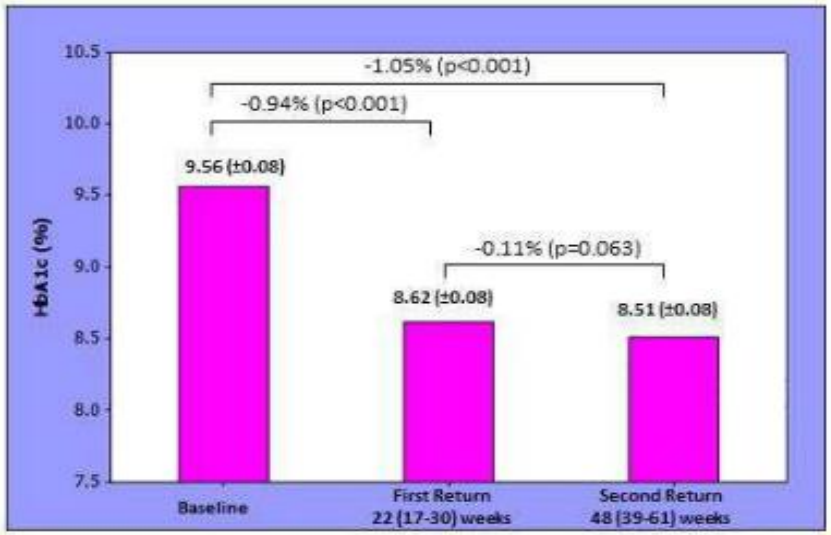
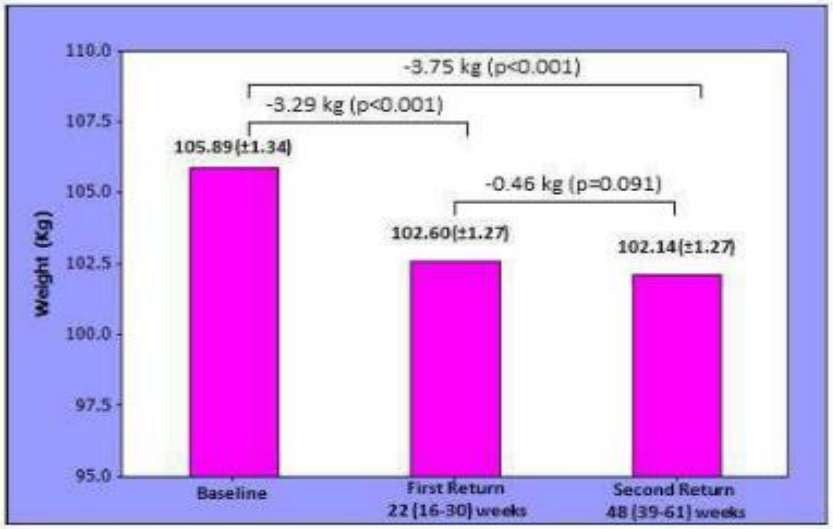
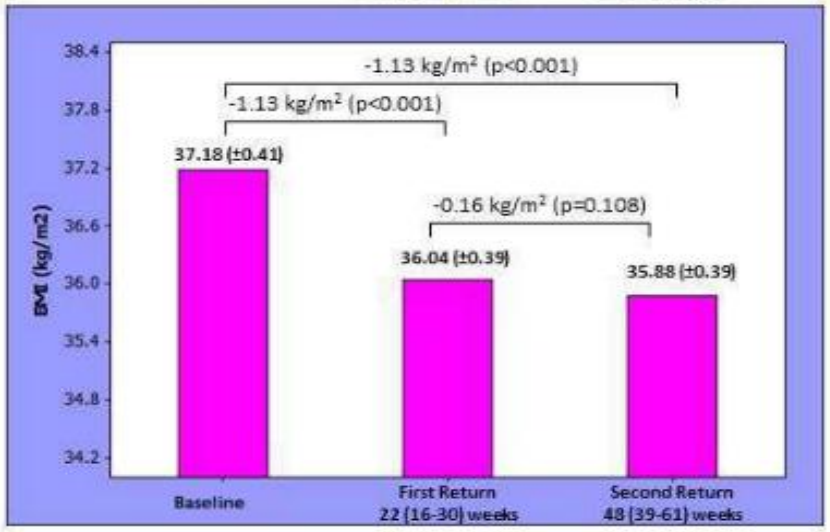
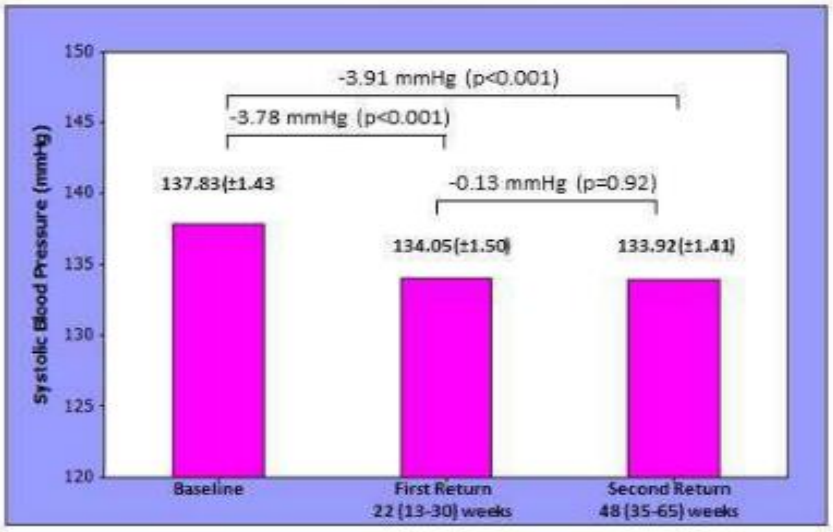
Dapagliflozin – improvements sustained









Data presented at ADA meeting, New Orleans, June 2016

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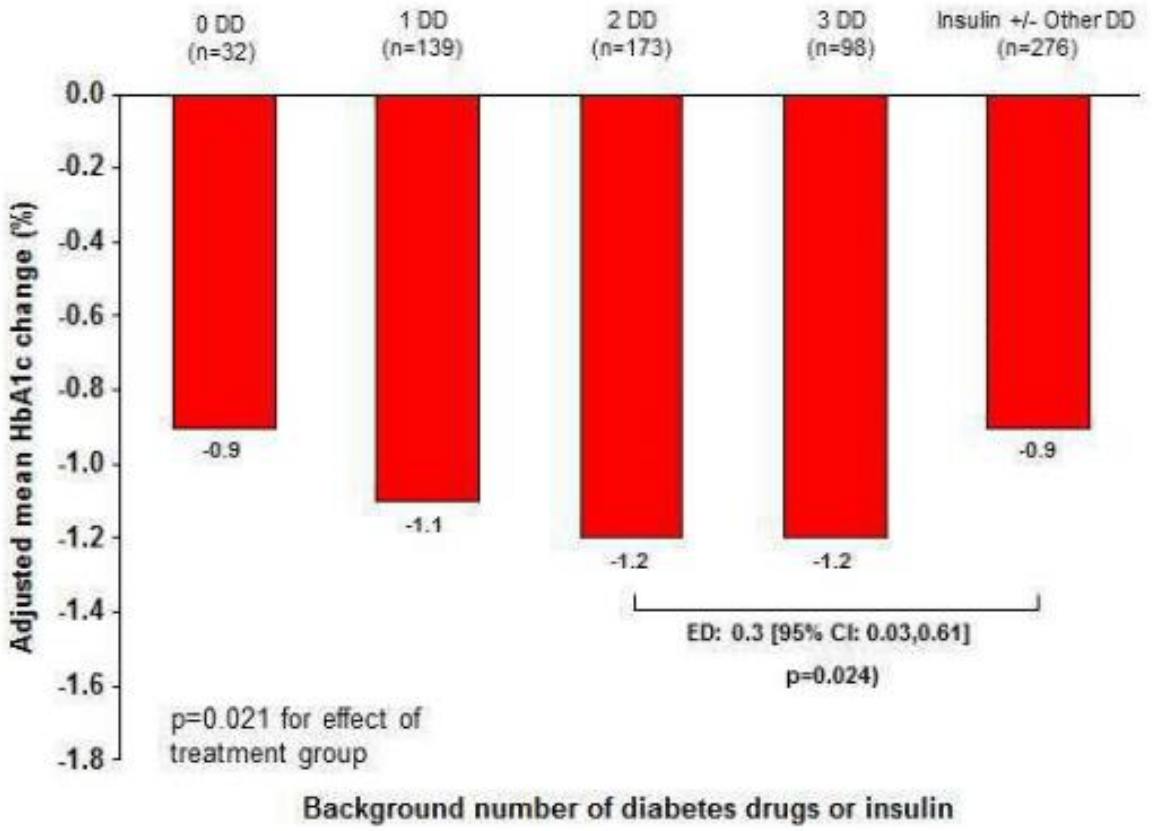
Figure 1: Change in HbA1c stratified by background diabetes therapy



Data are adjusted mean and estimated difference (ED) were analysed by ANCOVA with baseline HbA1c and eGFR as covariates.
DD; diabetes drugs

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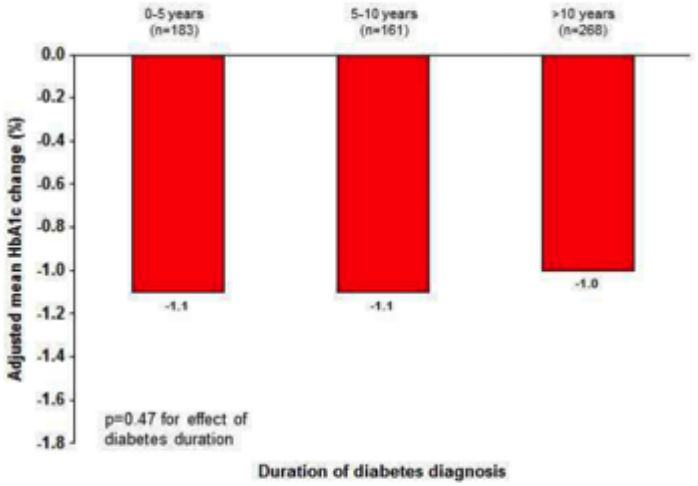
Figure 2: Change in HbA1c stratified by duration of diabetes



Data are adjusted mean analysed by ANCOVA with baseline HbA1c and eGFR as covariates.

Data presented at ADA meeting, New Orleans, June 2016

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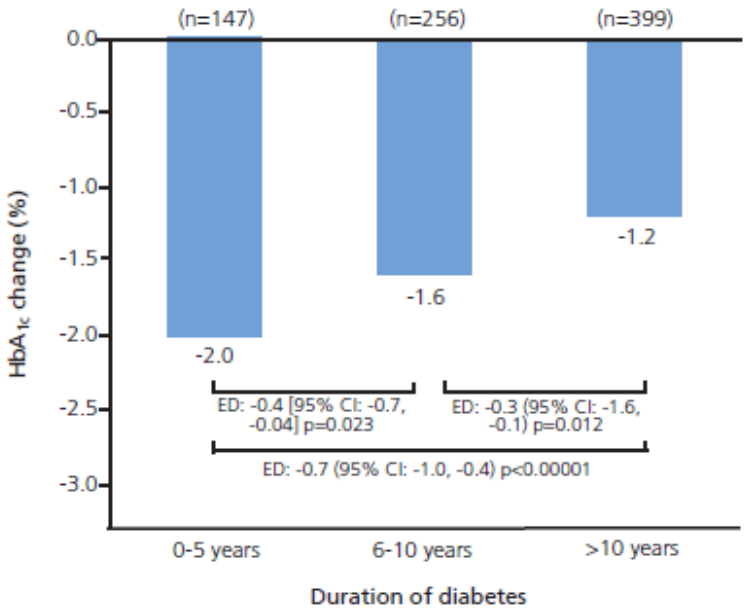
Figure 2. Mean HbA_{1c} changes after 26 weeks of liraglutide treatment, stratified according to duration of diabetes



Columns show adjusted mean changes analysed by ANCOVA with baseline HbA_{1c} as a covariate. ED: estimated difference; CI: confidence interval

Thong KY et al. Br J Diabetes Vasc Dis 2015; 15(4): 169–172

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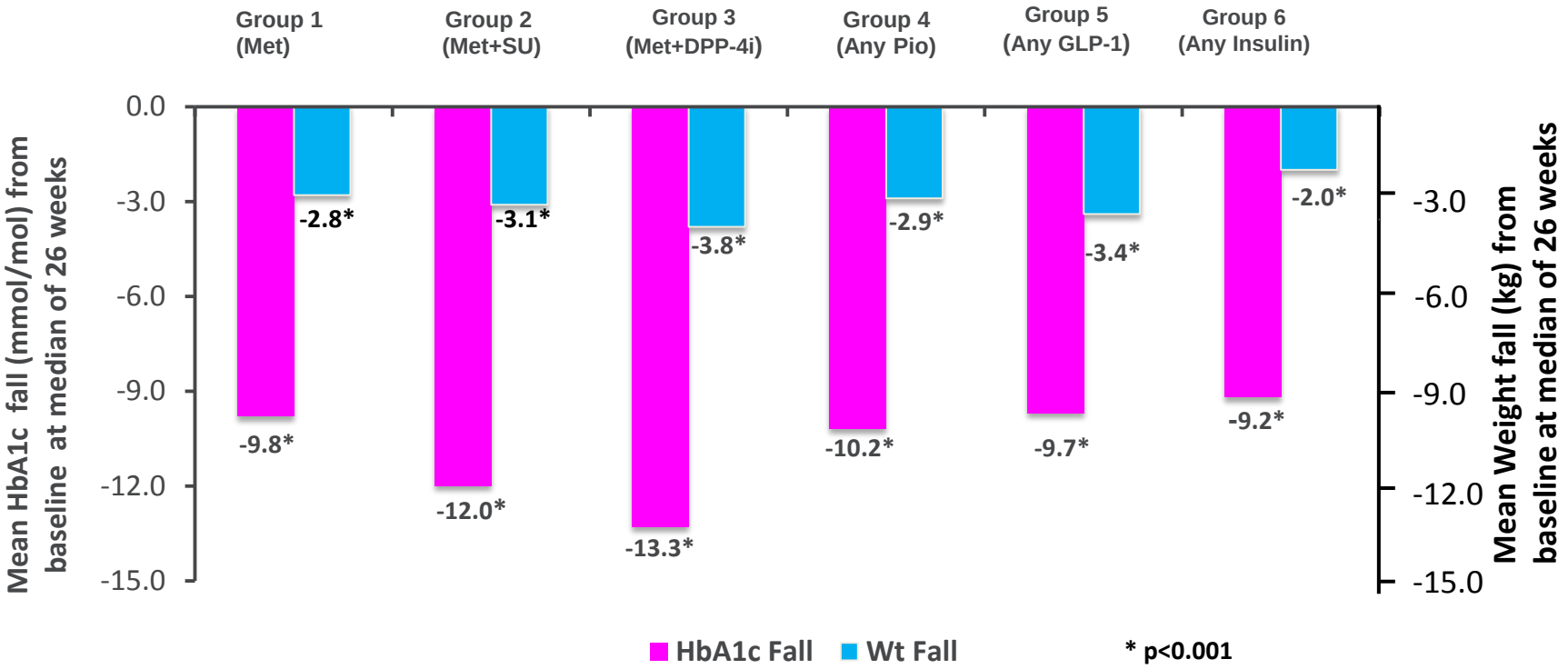
Effect of dapagliflozin on HbA1c and weight after its addition to various combinations of other diabetes medications: ABCD nationwide dapagliflozin audit*



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* EASD 2016 Poster Presentation: M. Yadagiri, P. Sen Gupta, R.E.J. Ryder et al on behalf of all ABCD nationwide dapagliflozin audit contributors

52nd EASD Annual Meeting 12 -16 September 2016

Dapagliflozin in Renal Impairment – FDA

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use FARXIGA safely and effectively. See full prescribing information for FARXIGA.

FARXIGA (dapagliflozin) tablets, for oral use
Initial U.S. Approval: 2014

----------INDICATIONS AND USAGE----------

FARXIGA is a sodium-glucose cotransporter 2 (SGLT2) inhibitor indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. (1)

Limitation of use:

- Not for treatment of type 1 diabetes mellitus or diabetic ketoacidosis. (1.1)

----------DOSAGE AND ADMINISTRATION----------

- The recommended starting dose is 5 mg once daily, taken in the morning, with or without food. (2.1)
- Dose can be increased to 10 mg once daily in patients tolerating FARXIGA who require additional glycemic control. (2.1)
- Assess renal function before initiating FARXIGA. Do not initiate FARXIGA if eGFR is below 60 mL/min/1.73 m^2. (2.2)
- Discontinue FARXIGA if eGFR falls persistently below 60 mL/min/1.73 m^2. (2.2)
- *Hypoglycemia:* In patients taking insulin or an insulin secretagogue with FARXIGA, consider a lower dose of insulin or the insulin secretagogue to reduce the risk of hypoglycemia. (5.3)
- *Genital mycotic infections:* Monitor and treat if indicated. (5.4)
- *Increased LDL-C:* Monitor and treat per standard of care. (5.5)
- *Bladder Cancer:* An imbalance in bladder cancers was observed in clinical trials. FARXIGA should not be used in patients with active bladder cancer and should be used with caution in patients with a prior history of bladder cancer. (5.6)
- *Macrovascular outcomes:* There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with FARXIGA or any other antidiabetic drug. (5.7)

----------ADVERSE REACTIONS----------

- The most common adverse reactions associated with FARXIGA (5% or greater incidence) were female genital mycotic infections, nasopharyngitis, and urinary tract infections. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Bristol-Myers Squibb at 1-800-721-5072 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

----------USE IN SPECIFIC POPULATIONS----------

- *Pregnancy:* There are no adequate and well-controlled studies in pregnant women. Use during pregnancy only if the potential benefit justifies the potential risk to the fetus. (8.1)

https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/202293s003lbl.pdf

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Dapagliflozin in Renal Impairment – FDA

2.2 Patients with Renal Impairment

Assessment of renal function is recommended prior to initiation of FARXIGA therapy and periodically thereafter.

FARXIGA should not be initiated in patients with an eGFR less than 60 mL/min/1.73 m^2.

No dose adjustment is needed in patients with mild renal impairment (eGFR of 60 mL/min/1.73 m^2 or greater).

FARXIGA should be discontinued when eGFR is persistently less than 60 mL/min/1.73 m^2 [see *Warnings and Precautions (5.2)* and *Use in Specific Populations (8.6)*].

https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/202293s003lbl.pdf

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Aims

- To evaluate the efficacy of dapagliflozin real clinical use in
  - mild renal impairment (eGFR 60-90 ml/min)
  - moderate renal impairment (eGFR 30-59ml/min)

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In view of FDA guidance, how is it possible to get data on dapagliflozin in patients with eGRF 30-59?

- Because clinician's, at least in the UK, do not necessarily prescribe according to medication license …..

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The ABCD audit

- Collected anonymised data of real patients treated with dapagliflozin in the UK
  - patient age, gender, diabetes duration, ethnicity
  - diabetes medications;
  - HbA1c, weight, eGFR
  - lipids;
  - blood pressure;
  - adverse events and dapagliflozin discontinuation

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ABCD nationwide dapagliflozin audit

Data Input	Oct 2014 – Jan 2017
Centres	59
Contributors	156
Number of patients	2027

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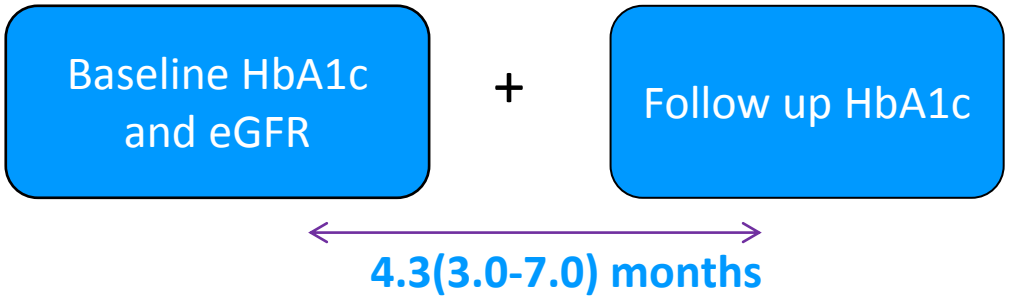
Methods

- Data from ABCD Dapagliflozin Audit (2014-2017)
- Selection criteria :



- Patients categorised into 3 groups depending on baseline eGFR:
  - Group 1 : eGFR > 90 ml/min
  - Group 2 : eGFR 60-90 ml/min
  - Group 3 : eGFR 30-59ml/min

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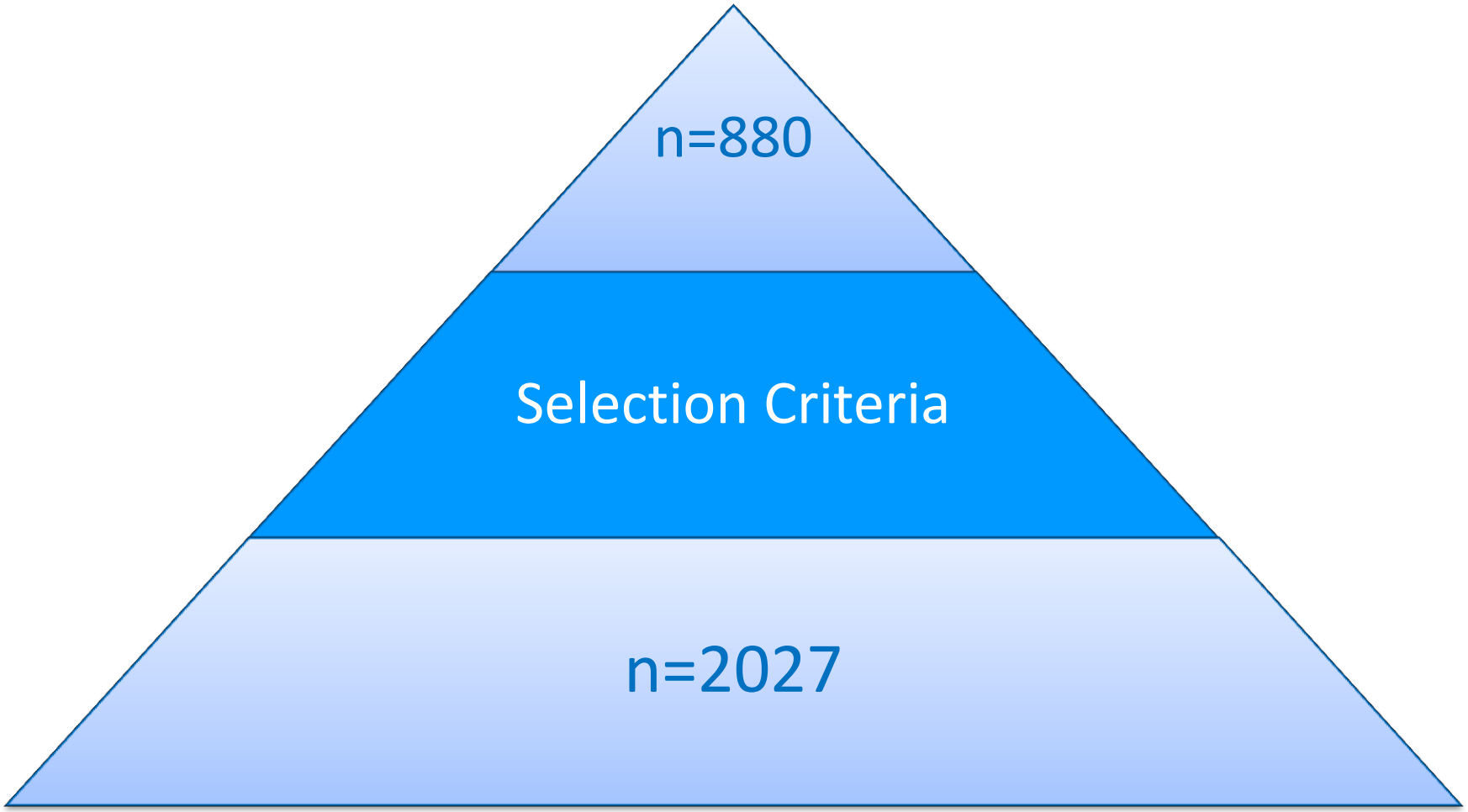
Methods



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Audit Characteristics(n=880)

Age(years)◆	57.2±10.0
Duration of Diabetes(years)*	7.0(1.9-13.0)
Sex[Males(%)]	58.4
Baseline ALT(U/l)◆	40.1±21.5
Baseline HbA1c(mmol)◆	80.4±15.3
Baseline HbA1c(%)◆	9.5±1.5
BMI(Kg/m²)◆	35.8±7.4
Weight(Kg)◆	102.6±22.3

Vs Combined Clinical Trials-Dapagliflozin
8.0
32.2

Reported as (Mean±SD)◆ or Median(IQR)*

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Vs Combined Clinical Trials-Dapagliflozin
8.0
32.2

Reported as (Mean±SD)◆ or Median(IQR)*

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Baseline Characteristics

N (%)	Gr 1 (>90ml/min) n= 185 (21%)	Gr 2 (60-90ml/min) n= 651 (74%)	Gr 3 (30-59ml/min) n=43 (5%)
Males(%)	58.7	59.0	65.1
Age(yrs)◆	52.4±10.2	58.3±9.4	64.4±9.6
T2DM duration(years)*	11.0(7.0-15.0)	8.2(3.9-12.3)	15.0(11.0-20.0)
HbA1c(mmol)◆	82.6±16.2	80.3±17.5	78.1±16.0
HbA1c(%)◆	9.7±1.4	9.5±1.5	9.3±1.4
Weight(Kg)◆	106.8±22.1	101.2±22.4	105.9±18.3
BMI(Kg/m^2)◆	37.2±7.8	35.3±7.3	37.1±6.1
ALT(U/l)◆	33.7±18.1	42.9±22.4	30.3±13.6
SBP(mm Hg)◆	136.4±16.9	135.0±15.6	137.6±17.6

Reported as (Mean±SD)◆ or Median(IQR)*

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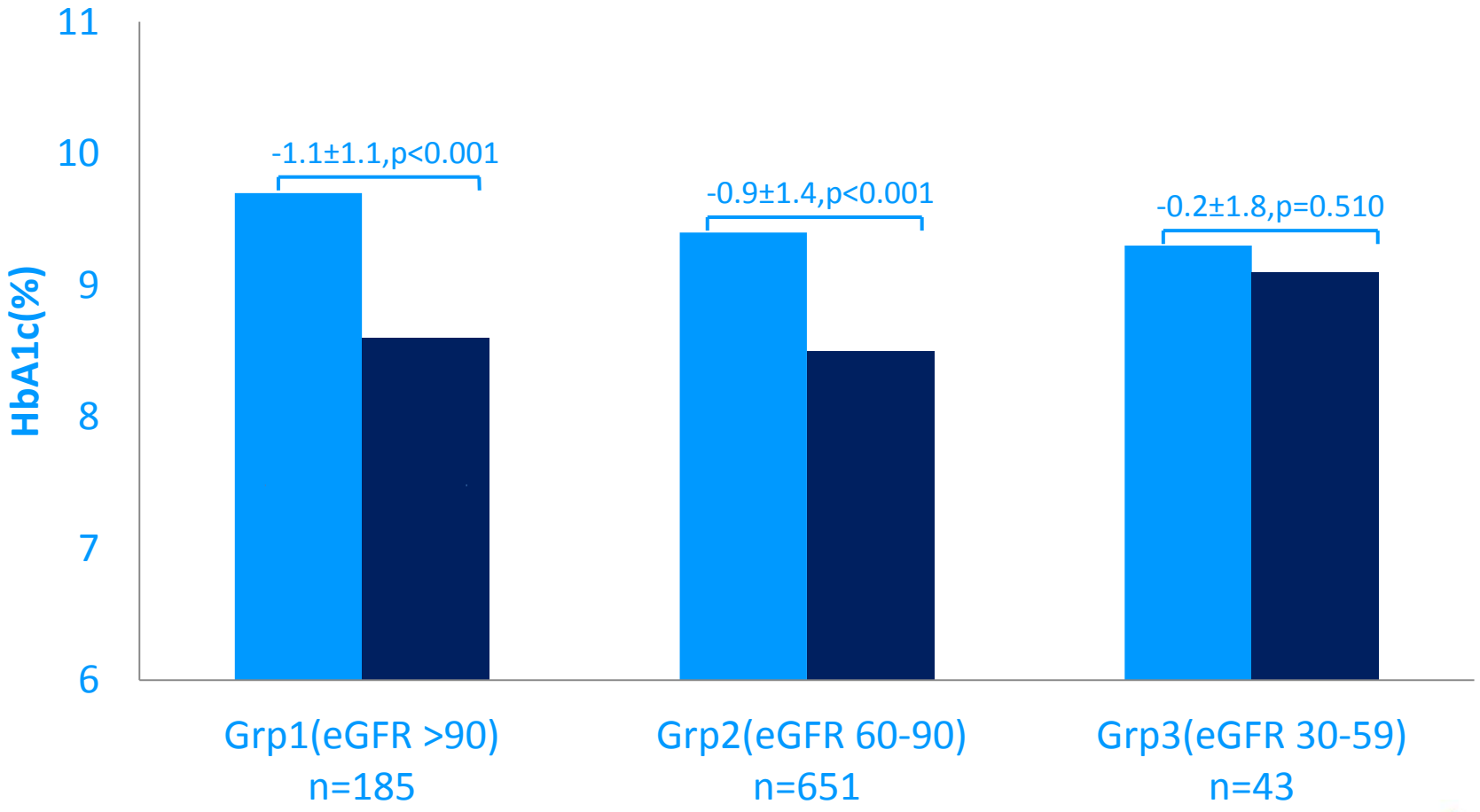
Results – HbA1c (%)



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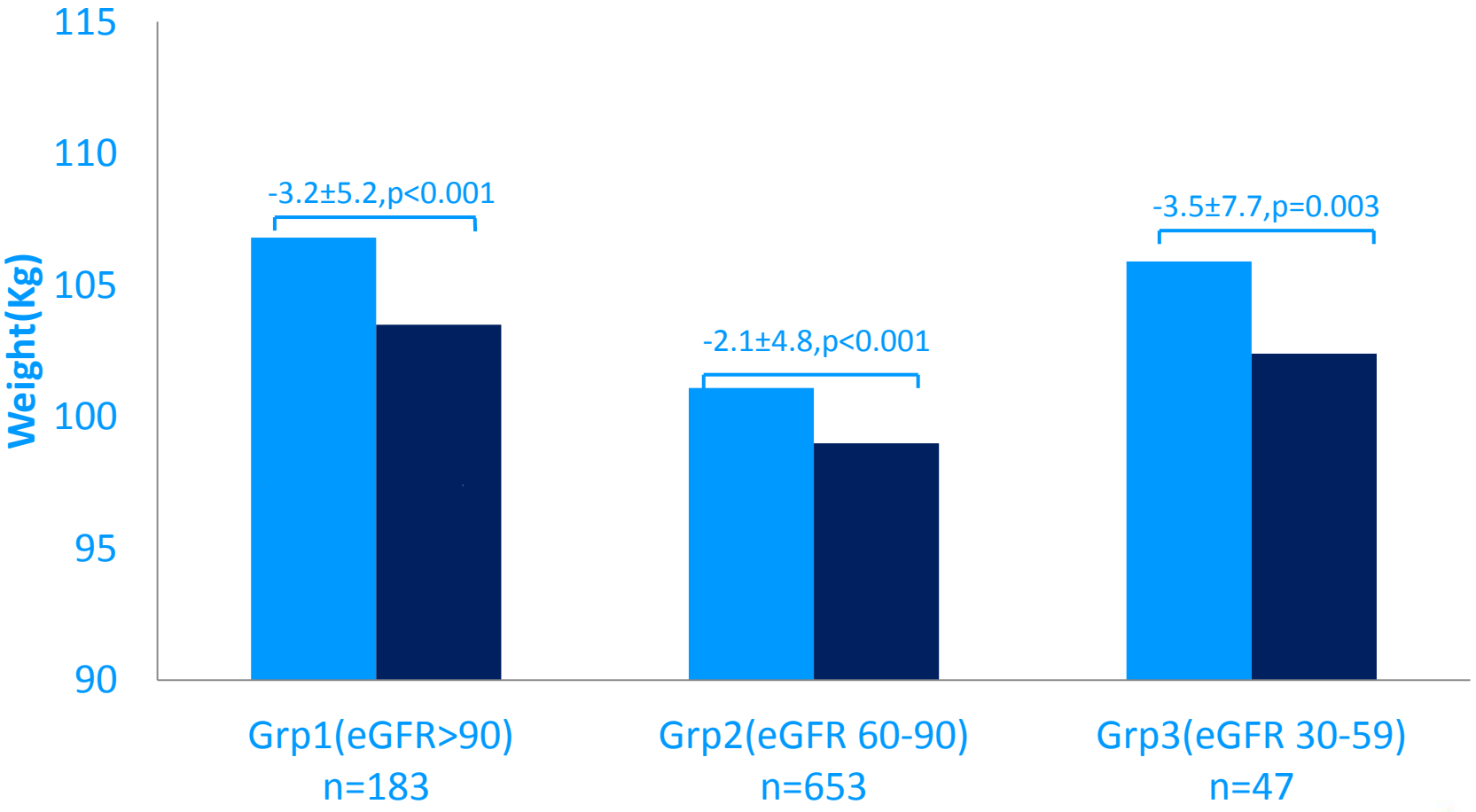
Results - Weight



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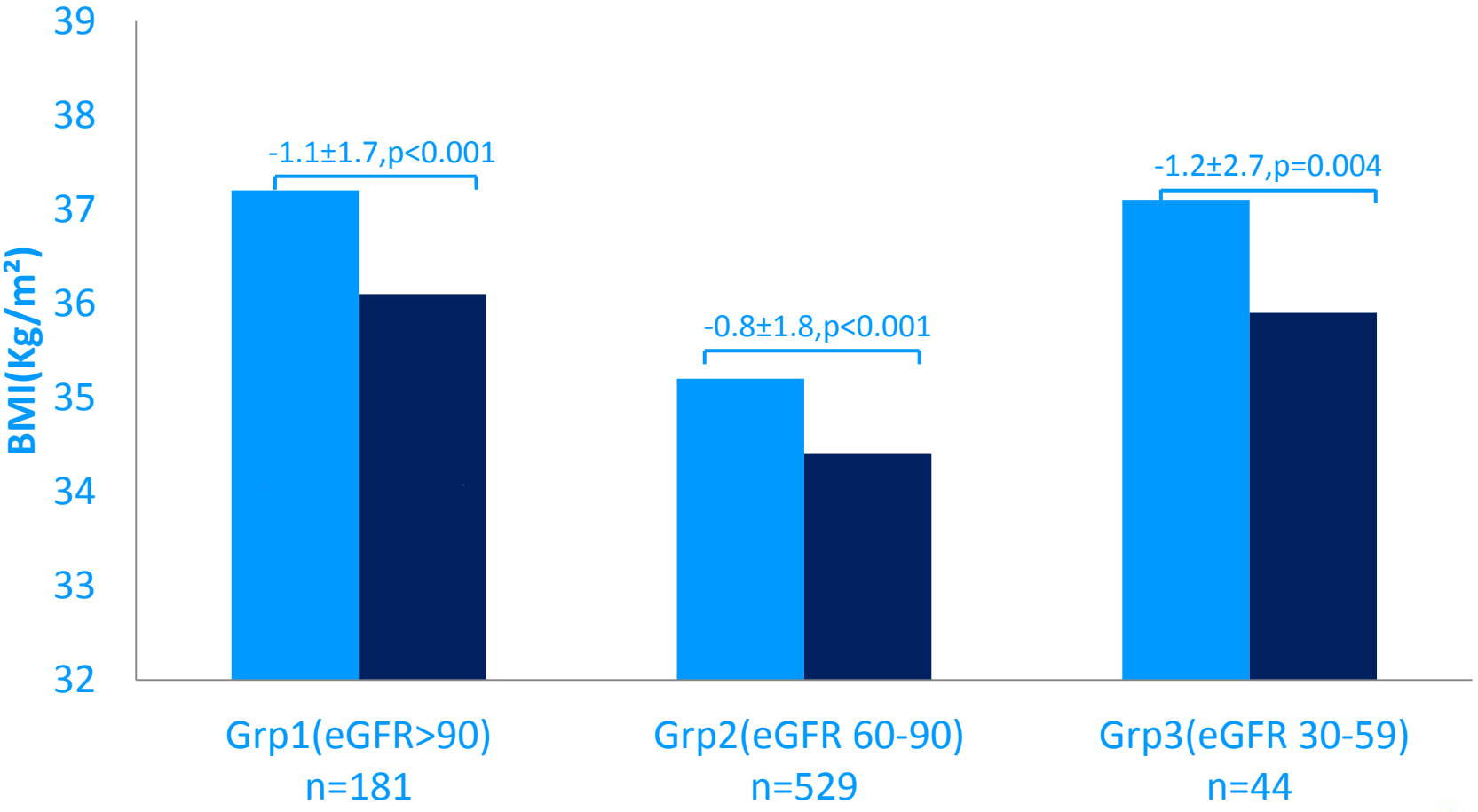
Results - BMI



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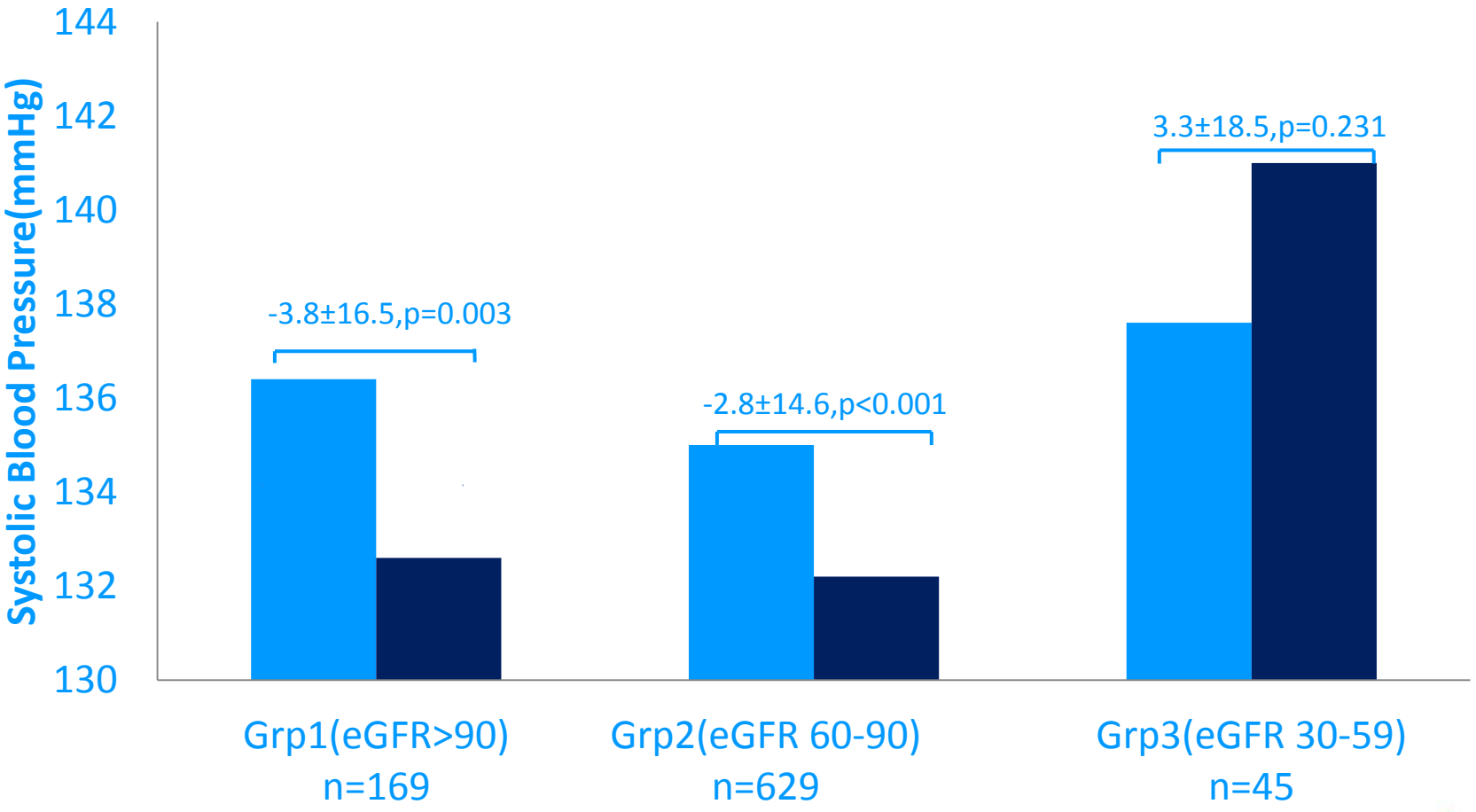
Results – Systolic BP



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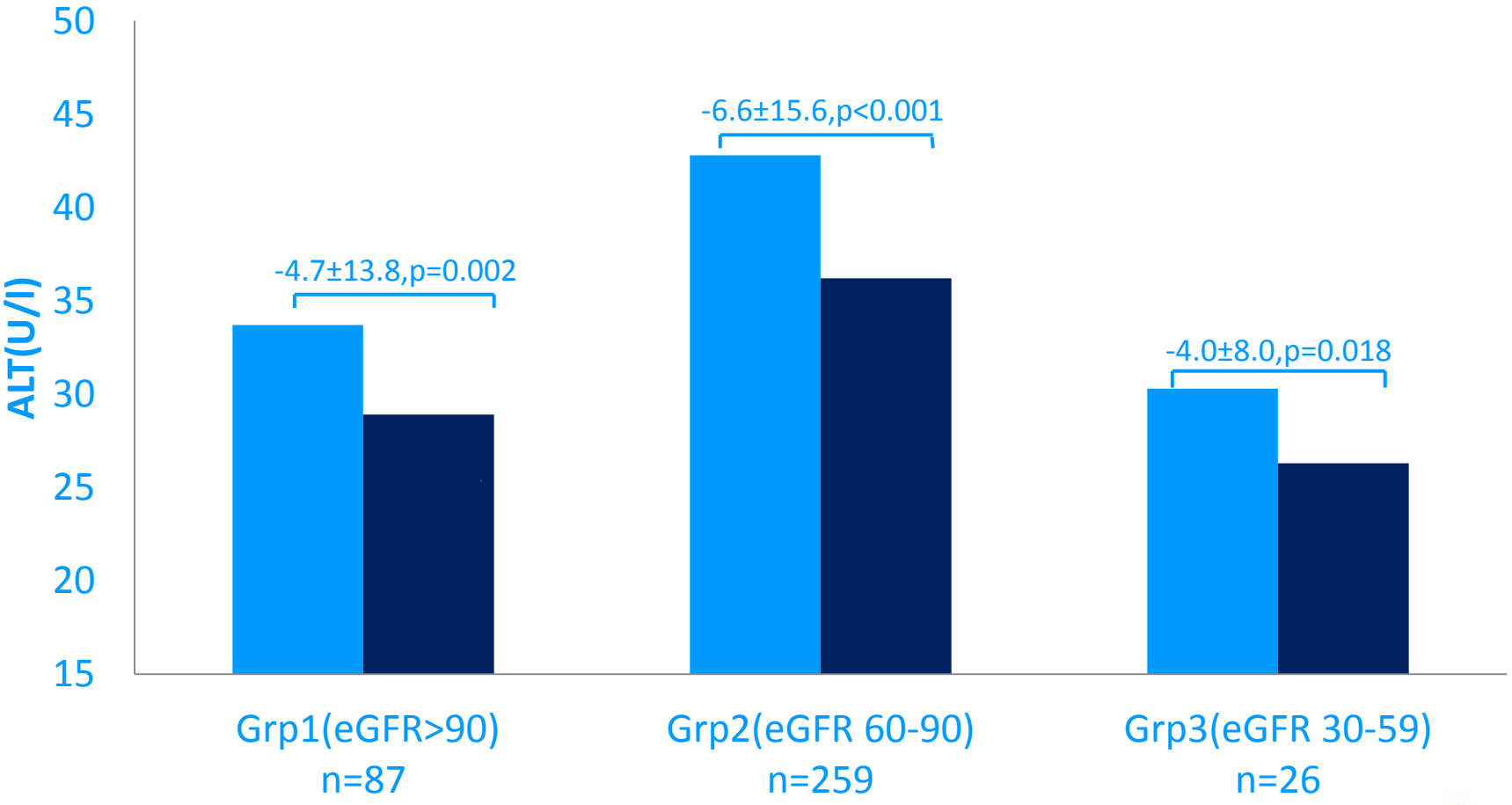
Results - Alanine Aminotransferase



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Conclusion

- Dapagliflozin reduces HbA1c,weight, BMI, systolic BP and ALT by statistically and clinically significant amounts in normal and mild renal impairment
- In moderate renal impairment, there is a reduction in weight and ALT but has no significant impact on HbA1c or systolic BP

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ABCD nationwide dapagliflozin audit contributors

The following are those whom we know about.

ABCD nationwide dapagliflozin audit – initial setup, maintenance and nationwide analysis: *Ryder REJ, Adamson K, Bailey CJ, Walton C, Thong KY, Sen Gupta P, Cull ML, Yadagiri M. Statistician: Blann A*

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Somewhat similar results from a clinical trial

clinical trial

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Long-term study of patients with type 2 diabetes and moderate renal impairment shows that dapagliflozin reduces weight and blood pressure but does not improve glycemic control

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In patients with diabetes, glycemic improvement by sodium-glucose cotransporter-2 inhibition depends on the kidney's ability to filter glucose. Dapagliflozin, a sodium-glucose cotransporter-2 inhibitor, reduces hyperglycemia in patients with diabetes and normal or mildly impaired renal function. In this randomized, double-blind, placebo-controlled study we assessed daily treatment with dapagliflozin in 252 patients with inadequately controlled type 2 diabetes and moderate renal impairment. The primary endpoint, the mean change in HbA1c, was not statistically different from placebo after 24 weeks (−0.41% and −0.44% for 5- and 10-mg doses, respectively, and −0.32% for placebo). The mean weight change from baseline was −1.54 and −1.89 kg for

Current medications for treating type 2 diabetes mellitus (T2DM) target the pancreas, liver, intestines, muscle, or adipose tissue and act by increasing insulin secretion or action, or by improving insulin sensitivity.[1] The sodium-glucose cotransporter-2 (SGLT2), located in the renal proximal tubule, reabsorbs the majority of filtered glucose.[2,3] Inhibition of renal glucose reabsorption via inhibition of SGLT2, an insulin-independent process, represents a novel approach to treating T2DM.

Several clinical trials with dapagliflozin, a potent and selective SGLT2 inhibitor, showed that it reduces hyperglycemia and improves glycemic control in patients with T2DM. These trials examined dapagliflozin as monotherapy[4] or in

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