The Best of the Past Year from JCEM, Diabetes Care, and Endo Practice

Mahnaz Mellati, MD.
10/14/2017
Disclosures

- I have no relevant financial interests.

- I will discuss non-FDA approved medications or routes of use for medications, that have been used in clinical trials.
Learning Objectives

- Understand the results of recently published clinical trials.
- Explain how discussed articles affect our practice.
- Discuss the safety of novel diabetes medications.
Outline

- 3 adrenal articles
- 3 DM articles
Who is Tired???
Primary Hyperaldosteronism (PA)

- Most common cause of secondary HTN. Treatable and potentially curable.
- Screening test: ARR - calculated w/ plasma aldo and renin activity.
- Factors affecting ARR: plasma K, renal insufficiency, aldo blockers, etc.
- Estrogen -> promoter region of angiotensinogen -> plasma AngII
- Effect of oral contraceptive on ARR has been debated for sometime.

Young WFJr., Cardiol Rev 1999; 7(4)
McKenna TJ, JCEM 1991; 73(5)
20 healthy, normotensive, premenopausal women, 15 OC users and 19 OC nonusers, mean age 25 ± 1 yr, ingesting a controlled sodium diet

BP and other criteria measured during follicular phase

30 mcg of ethynil estradiol

BP and other criteria measured during follicular phase
One Side of the Story: Oral Contraceptives Increase ARR

Kang AK., AJP 2001; 280(3)
91 healthy, normotensive, women, 18-35 /or, ingesting a controlled sodium diet

BP and other criteria measured during follicular and luteal phases

21 days of OCP administered, w/ 20-30 mcg of EE or EV + DNG

BP and other criteria measured during 18-21d and 21-26d

Weigratz I., Contraception, 2003;67(5)
# One Side of the Story: Oral Contraceptives Don’t Affect ARR

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Control cycle</th>
<th>Cycle 1</th>
<th>Cycle 3</th>
<th>Cycle 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aldosterone</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30EE/DNG</td>
<td>172.3 ± 118.2</td>
<td>122.3 ± 87.4</td>
<td>171.8 ± 119.6</td>
<td>215.3 ± 141.4*</td>
</tr>
<tr>
<td>20EE/DNG</td>
<td>232.0 ± 165.1</td>
<td>164.1 ± 138.7*</td>
<td>120.6 ± 67.1**</td>
<td>161.8 ± 82.6</td>
</tr>
<tr>
<td>EE/EV/DNG</td>
<td>209.8 ± 135.9</td>
<td>185.1 ± 127.3</td>
<td>140.5 ± 97.6</td>
<td>180.6 ± 141.9</td>
</tr>
<tr>
<td>EE/LNG</td>
<td>209.6 ± 95.6</td>
<td>159.0 ± 68.9</td>
<td>144.0 ± 85.5</td>
<td>161.6 ± 57.1</td>
</tr>
</tbody>
</table>

*Weigratz I., Contraception, 2003;67(5)*
Do OCPs Affect ARR?
Effect of Combined Hormonal Replacement Therapy on the Aldosterone/Renin Ratio in Postmenopausal Women


JCEM 2017, 102(7): 2339-2334
Participants

- Inclusion Criteria:
  - consenting
  - healthy
  - postmenopausal
  - no renal, liver, CVD
  - no HTN
  - not on meds x2m

- Instructions:
  - maintain usual Na intake
  - No meds to be taken (e.g. analgenics, coryza meds, etc) during the study

20 participants recruited in 2 yrs, 5 withdrew for personal reasons

Conjugated Estrogen 0.625 mg + Medroxyprogesterone 2.5 mg daily
Sampling

- Baseline -> 2w -> 6w post HRT
- Collected samples: Plasma aldosterone, DRC, PRA, cortisol, Na, K, Cr, Serum E2, progesterone, LH, FSH, Spot urine Na, K, Cr, cortisol, aldosterone.
- Timing of sample collection: 9-10am, after having pt seated for 5-15 min.
Results

(e)

Aldosterone (pmol/L)

Baseline 2 week 6 weeks

# $P<0.05$, * $P<0.01$, + $P<0.001$
Results

(c)

DRC (mU/L)

Baseline  2 week  6 weeks

# P<0.05, * P<0.01, + P<0.001
Results

# P<0.05, * P<0.01, + P<0.001
After starting HRT, ARR significantly increased when calculated as PAC/DRC, but did not change when ARR was calculated using PRA.

After 6w of HRT, PAC/DRC gave + result in 3 women.
Using DRC as opposed to PRA to calculate ARR, can lead to false + results in those taking HRT.
Limitations

- Small sample size
- Only normotensive subjects studied
- Only postmenopausal women studied
Subacute Hypercortisolism (SH)

- Pts w/ SH are at increased risk for metabolic and CVD.
- Commonly used test for screening SH, 1 mg DST, has a specificity of 70-80% (high rate of false +).
- SH is an ACTH independent condition => ↓ACTH, but ACTH is pulsatile and difficult to measure correctly.

Tauchmanova L., JCEM 2000; 87911)
Di Dalmazi G., Eur J Endocrinol 2012; 166(4)
Nieman LK., JCEM 2008; 93(5)
DHEA is also ACTH driven, but with short half life (25 min) and circadian pattern of secretion.

DHEAS, has a long half life (10-16 h) => possibly better indicator of ACTH level.

DHEAS use has been proposed as a marker of cure, after Cushing surgery.

• **R5.** A diagnosis of subclinical Cushing syndrome (SCS) is made if the serum cortisol level is more than 5.0 μg/dL after a 1-mg dexamethasone suppression test, in a patient with an adrenal adenoma and absence of typical physical stigmas of hypercortisolism. A low or suppressed level of adrenocorticotropic hormone (ACTH) or a low dehydroepiandrosterone sulfate concentration supports the diagnosis (**Grade D; BEL 4**). A second abnormal test result of HPA axis function, such as a 2-day low-dose dexamethasone suppression test, may also be needed to establish the diagnosis of SCS (**Grade B; BEL 2**).
**R 3.2.** We recommend that all patients with adrenal incidentalomas undergo a 1mg overnight dexamethasone suppression test to exclude cortisol excess ($\ominus\ominus\ominus\ominus$).

**R 3.4.** We suggest that post-dexamethasone serum cortisol levels between 51 and 138nmol/L (1.9–5.0µg/dL) should be considered as evidence of ‘possible autonomous cortisol secretion’ and cortisol levels post dexamethasone >138nmol/L (>5.0µg/dL) should be taken as evidence of ‘autonomous cortisol secretion’. Additional biochemical tests to confirm cortisol secretory autonomy and assess the degree of cortisol secretion might be required. However, for the clinical management, the presence of potentially cortisol-related comorbidities and age of the patient are of major importance.
Diagnosis — Subclinical Cushing's syndrome should be ruled out by performing the 1 mg overnight dexamethasone suppression test (DST). An abnormal 1 mg overnight dexamethasone suppression is consistent with ACTH-independent cortisol production, a finding that should be confirmed with 24-hour urinary free cortisol, serum ACTH concentration, dehydroepiandrosterone sulfate (DHEAS), and a high-dose (8 mg) overnight DST. Clinically significant glucocorticoid secretory autonomy is confirmed by a post-overnight DST 8 AM serum cortisol concentration >5 mcg/dL (>138 nmol/L).
Low DHEAS: A Sensitive and Specific Test for the Detection of Subclinical Hypercortisolism in Adrenal Incidentalomas

M. Conall Dennedy, Anand K. Annamalai, Olivia Prankerd-Smith, Natalie Freeman, Kuhan Vengopal, Johann Graggaber, Olympia Koulouri, Andrew S. Powlson, Ashley Shaw, David J. Halsall, Mark Gurnell

JCEM 2017, 102(3): 786-792
Patients & Methods


- Excluded 17 pts: concomitant drugs influencing GC metabolism/secetration, major psych illness, overt EtOH use, overt CS features, previous pituitary sx.
**Patients & Methods**

- **Initial labs:** plasma metanephrines, ARR, **24-hour urine collection for UFC (x2)**, **1mg DST**, serum DHEAS, electrolytes, liver blood tests, fasting plasma glucose, fasting lipids, and complete blood count.

- If 1mg DST $\geq 1.8$ mcg/dL and/or $+ 24$hr UFC => repeat 24-hour UFC, midnight serum cortisol, **48-hour low-dose (0.5 mg qd) dexamethasone suppression test (LDDST)**, and plasma ACTH (measured on 2 occasions between 8 AM and 9 AM)
SH Defined as:

- ≥2 of the following:
  1. Failure to suppress serum cortisol to <1.8 mcg/dL following dexamethasone
  2. Sleeping midnight serum cortisol >1.8 mcg/dL
  3. Awake midnight serum cortisol >7.5 mcg/dL
  4. Raised UFC

All patients with SH had a 9 AM ACTH level <10 pg/mL
DHEAS Ratio = measured DHEAS / LL of DHEAS ref range

DHEAS lower than measurable = LL of ref range

<table>
<thead>
<tr>
<th>Age, y</th>
<th>Sex</th>
<th>Lower Limit</th>
<th>Upper Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>µmol/L</td>
<td>µg/dL</td>
</tr>
<tr>
<td>18–29</td>
<td>Female</td>
<td>1.5</td>
<td>56</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>2.2</td>
<td>82</td>
</tr>
<tr>
<td>30–39</td>
<td>Female</td>
<td>1.6</td>
<td>59</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>2.1</td>
<td>78</td>
</tr>
<tr>
<td>40–49</td>
<td>Female</td>
<td>0.7</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>1.5</td>
<td>56</td>
</tr>
<tr>
<td>&gt;50</td>
<td>Female</td>
<td>0.4</td>
<td>15</td>
</tr>
<tr>
<td>50–60</td>
<td>Male</td>
<td>1.1</td>
<td>41</td>
</tr>
<tr>
<td>&gt;60</td>
<td>Male</td>
<td>0.4</td>
<td>15</td>
</tr>
</tbody>
</table>
Figure 1: Etiology and Age Distribution and Nodule Side for AI

A

SH: Subclinical hypercortisolism; NFA: Non-functioning adenoma; APA: Aldosterone Producing Adenoma; ACC: Adrenocortical Carcinoma
Results

A

\[ p < 0.0001 \]

DHEAS Ratio

NFA | SH

1.12
Results

![Graph showing cortisol levels](image)

- **p < 0.0001**

Axes:
- **Cortisol (nmol/L)**
- **Cortisol (mcg/dL)**

Legend:
- **NFA**
- **SH**

Range:
- 0 to 700 nmol/L
- 0 to 25.4 mcg/dL
Results

A

24 Urinary Cortisol Ratio

NFA

SH
A DHEAS ratio of ≤1.12, yields a sensitivity of >99% and specificity of 91% - better than 1mg DST, for diagnosing SH in pts w/ adrenal incidentaloma.
Conclusion

- A single DHEAS measurement can be used as a screening tool for SH in pts w/ adrenal incidentaloma.
Limitations

- Retrospective
- Single center
- Single platform for DHEAS measurement
- In scenarios of suppressed DHEAS (preexisting ACTH suppression, e.g.: opioid use, pituitary/hypothalamic dz)
Don't judge me for the choices I make when you don't know the options I had to choose from.
Resetting the Abnormal Circadian Cortisol Rhythm in Adrenal Incidentaloma Patients With Mild Autonomously Autonomous Cortisol Secretion

Miguel Debono, Robert F. Harrison, Rita Chadarevian, Carole Gueroult, Jean-Louis Abitbol, and John Newell-Price

JCEM 2017, 102(9): 3461-3469
Study Design & Pts

- phase 1 & 2a, prospective, open-label, controlled, single-center study
Study Design & Pts

Inclusion criteria:
- 45- to 80-year-old M & postmenopausal F
- Stable antih-HTN & DM x4 w prior to screening

Exclusion criteria:
- Overt Cushing syndrome
- H/o malignancy, EtOH dependence/abuse
- Primary adrenocortical insufficiency
- Severe uncontrolled DM, HTN, liver/renal/CVD, infection
- Night-shift workers
- Depression or psychosis,
-Tx w/ GC x3m
- Concomitant treatment with any other drug known to affect the HPA axis, cortisol-binding globulin, or the CYP450 3A4 cytochrome system
- Adrenocortical tumors >4 cm
Study Design

**CASE**

Patients with adrenal incidentalomas and autonomous cortisol secretion (AI/ACS)

$n = 6$

**CONTROL**

Patients with adrenal incidentalomas and no autonomous cortisol secretion (AI/NoACS)

$n = 6$

**CONTROL**

Healthy subjects with no adrenal incidentaloma (HC)

$n = 6$
Metyrapone

Cholesterol

- Pregnenolone
  - 17 alpha
  - 3 beta
  - 17 OH
  - 21 OH
  - 11 beta
  - 18 OH

- Progesterone
  - 17 alpha
  - 3 beta

- Deoxycorticosterone
  - 11 beta

- Corticosterone
  - 11 beta

- Deoxycortisol
  - 11 beta

- Cortisol
  - 21 OH

- DHEA
  - 17,20

- Androstenedione
  - 17,20

- Testosterone

- Dihydrotestosterone

- Estrone

- Estradiol
Results

Phase 1: Baseline Analysis
Hourly serum cortisol (18:00h – 18:00h), Hourly salivary cortisol (18:00h – 23:00h; 08:00h -18:00h); Hourly IL-6 (18:00h – 18:00h)

Interim Analysis: Data analysis to identify dose and time of administration of metyrapone

Phase 2: Intervention Study (AI/ACS – 6 subjects)
Hourly serum cortisol (18:00h – 18:00h), Hourly salivary cortisol (18:00h – 23:00h; 08:00h -18:00h); Hourly IL-6 (18:00h – 18:00h)

Interim Analysis: Data analysis to identify dose and time of administration of metyrapone

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Hourly serum cortisol (18:00h – 18:00h), Hourly salivary cortisol (18:00h – 23:00h; 08:00h -18:00h); Hourly IL-6 (18:00h – 18:00h)
Results
Results

Salivary Cortisone (nmol/L) vs. Clock Time

- AI/ACS
- No ACS (AI/NoACS & HC)
- AI/ACS post Metypapone 500mg at 18:00 and 250mg at 22:00
Results

- **AI/ACS**
- **No ACS (AI/NoACS & HC)**
- **AI/ACS post Metyrapone**
  - 500mg at 1800 and
  - 250mg at 2200
Results

- Adverse events: 6 reported, in 4 pts
  - 4 mild headaches (one possibly related)
  - 1 episode of hypertension
  - 1 episode of mild dizziness with a serum cortisol level of 22 nmol/L at 11
Pts w/ SH have elevated evening/nocturnal cortisol exposure and higher IL-6 levels.

Serum cortisol after 1 mg DST of ≤ 1.12 mcg/dL in patients with AI is associated with a normal physiological cortisol rhythm as healthy controls.

Administration of metyrapone specifically in the evening allows the cortisol rhythm to be “reset,” with an immediate improvement in IL-6 levels.
Conclusion

- The abnormal cortisol rhythm in SH pts maybe able to be “reset” with the use of 11β-hydroxylase inhibitor, metyrapone.
Limitations

- Phase I & II a -> How far from clinical practice?
Nobody knows, the blood sugars I've seen... nobody knows, my worst lows.
Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes

Bruce Neal, M.B., Ch.B., Ph.D., for the CANVAS Program Collaborative Group

NEJM 2017; 377:644-657
Results

A) Glycated Hemoglobin

B) Body Weight

No. of Patients
Placebo 4231 3987 3854 3539 2891 1561 1014 878 899 783 805 726 695 245
Canagliflozin 5644 5329 5211 4864 4228 2778 2206 1965 2042 1797 1889 1690 1661 556

No. of Patients
Placebo 4245 4024 3931 3692 2977 1623 1036 935 920 834 826 761 714 252
Canagliflozin 5651 5344 5277 5044 4331 2877 2247 2041 2086 1902 1928 1775 1669 567
Results
Results

A. Death from Cardiovascular Causes, Nonfatal Myocardial Infarction, or Nonfatal Stroke

- Hazard ratio, 0.86 (95% CI, 0.75–0.97)
- P<0.001 for noninferiority
- P=0.02 for superiority

B. Death from Cardiovascular Causes

- Hazard ratio, 0.87 (95% CI, 0.72–1.06)

C. Nonfatal Stroke

- Hazard ratio, 0.90 (95% CI, 0.71–1.15)

D. Nonfatal Myocardial Infarction

- Hazard ratio, 0.85 (95% CI, 0.69–1.05)
# Results

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Canagliflozin (N=5795)</th>
<th>Placebo (N=4347)</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke</td>
<td>26.9</td>
<td>31.5</td>
<td>0.86 (0.75–0.97)</td>
</tr>
<tr>
<td>Death from cardiovascular causes</td>
<td>11.6</td>
<td>12.8</td>
<td>0.87 (0.72–1.06)</td>
</tr>
<tr>
<td>Nonfatal myocardial infarction</td>
<td>9.7</td>
<td>11.6</td>
<td>0.85 (0.69–1.05)</td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td>7.1</td>
<td>8.4</td>
<td>0.90 (0.71–1.15)</td>
</tr>
<tr>
<td>Fatal or nonfatal myocardial infarction</td>
<td>11.2</td>
<td>12.6</td>
<td>0.89 (0.73–1.09)</td>
</tr>
<tr>
<td>Fatal or nonfatal stroke</td>
<td>7.9</td>
<td>9.6</td>
<td>0.87 (0.69–1.09)</td>
</tr>
<tr>
<td>Hospitalization for any cause</td>
<td>118.7</td>
<td>131.1</td>
<td>0.94 (0.88–1.00)</td>
</tr>
<tr>
<td>Hospitalization for heart failure</td>
<td>5.5</td>
<td>8.7</td>
<td>0.67 (0.52–0.87)</td>
</tr>
<tr>
<td>Death from cardiovascular causes or hospitalization for heart failure</td>
<td>16.3</td>
<td>20.8</td>
<td>0.78 (0.67–0.91)</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>17.3</td>
<td>19.5</td>
<td>0.87 (0.74–1.01)</td>
</tr>
<tr>
<td>Progression of albuminuria</td>
<td>89.4</td>
<td>128.7</td>
<td>0.73 (0.67–0.79)</td>
</tr>
<tr>
<td>40% reduction in eGFR, renal-replacement therapy, or renal death</td>
<td>5.5</td>
<td>9.0</td>
<td>0.60 (0.47–0.77)</td>
</tr>
</tbody>
</table>
Results

A Hospitalization for Heart Failure

Hazard ratio, 0.67 (95% CI, 0.52–0.87)

Patients with an Event (%)

No. at Risk
Placebo: 4347, 4267, 4198, 4123, 3011, 1667, 1274, 1256, 1236, 1210, 1180, 1158, 829, 233
Canagliflozin: 5795, 5732, 5653, 5564, 4437, 3059, 2643, 2610, 2572, 2540, 2498, 2451, 1782, 490

Weeks since Randomization

B Death from Any Cause

Hazard ratio, 0.87 (95% CI, 0.74–1.01)

Patients with an Event (%)

No. at Risk
Placebo: 4347, 4316, 4279, 4236, 3119, 1759, 1356, 1344, 1328, 1310, 1292, 1280, 924, 258
Canagliflozin: 5795, 5768, 5723, 5679, 4576, 3182, 2761, 2736, 2710, 2687, 2651, 2615, 1904, 532

Weeks since Randomization

C Progression of Albuminuria

Hazard ratio, 0.73 (95% CI, 0.67–0.79)

Patients with an Event (%)

No. at Risk
Placebo: 3819, 3473, 3096, 2700, 1690, 877, 724, 652, 626, 565, 548, 485, 303, 67
Canagliflozin: 5196, 4791, 4475, 4027, 2968, 1951, 1730, 1593, 1528, 1408, 1354, 1213, 775, 185

Weeks since Randomization

D Composite of 40% Reduction in eGFR, Requirement for Renal-Replacement Therapy, or Death from Renal Causes

Hazard ratio, 0.60 (95% CI, 0.47–0.77)

Patients with an Event (%)

No. at Risk
Placebo: 4347, 4287, 4227, 4151, 3029, 1674, 1274, 1253, 1229, 1202, 1173, 1148, 819, 229
Canagliflozin: 5795, 5737, 5664, 5578, 4454, 3071, 2654, 2623, 2576, 2542, 2495, 2450, 1781, 493

Weeks since Randomization
## Results

### Table 2. Adverse Events.

<table>
<thead>
<tr>
<th>Event</th>
<th>Canagliflozin</th>
<th>Placebo</th>
<th>P Value††</th>
</tr>
</thead>
<tbody>
<tr>
<td>All serious adverse events</td>
<td>104.3</td>
<td>120.0</td>
<td>0.04</td>
</tr>
<tr>
<td>Adverse events leading to discontinuation</td>
<td>35.5</td>
<td>32.8</td>
<td>0.07</td>
</tr>
<tr>
<td>Serious and nonserious adverse events of interest recorded in the CANVAS Program</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute pancreatitis (adjudicated)</td>
<td>0.5</td>
<td>0.4</td>
<td>0.63</td>
</tr>
<tr>
<td>Cancer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal cell</td>
<td>0.6</td>
<td>0.2</td>
<td>0.17</td>
</tr>
<tr>
<td>Bladder</td>
<td>1.0</td>
<td>1.1</td>
<td>0.74</td>
</tr>
<tr>
<td>Breast</td>
<td>3.1</td>
<td>2.6</td>
<td>0.65</td>
</tr>
<tr>
<td>Photosensitivity</td>
<td>1.0</td>
<td>0.3</td>
<td>0.07</td>
</tr>
<tr>
<td>Diabetic ketoacidosis (adjudicated)</td>
<td>0.6</td>
<td>0.3</td>
<td>0.14</td>
</tr>
<tr>
<td>Amputation</td>
<td>6.3</td>
<td>3.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fracture (adjudicated)††</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>15.4</td>
<td>11.9</td>
<td>0.02</td>
</tr>
<tr>
<td>Low-trauma</td>
<td>11.6</td>
<td>9.2</td>
<td>0.06</td>
</tr>
<tr>
<td>Venous thromboembolic events</td>
<td>1.7</td>
<td>1.7</td>
<td>0.63</td>
</tr>
<tr>
<td>Infection of male genitalia§</td>
<td>34.9</td>
<td>10.8</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
## Results

<table>
<thead>
<tr>
<th>Event</th>
<th>Canagliflozin</th>
<th>Placebo</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious and nonserious adverse events of interest collected in CANVAS alone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Osmotic diuresis</td>
<td>34.5</td>
<td>13.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Volume depletion</td>
<td>26.0</td>
<td>18.5</td>
<td>0.009</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>50.0</td>
<td>46.4</td>
<td>0.20</td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>3.0</td>
<td>4.1</td>
<td>0.33</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>6.9</td>
<td>4.4</td>
<td>0.10</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>40.0</td>
<td>37.0</td>
<td>0.38</td>
</tr>
<tr>
<td>Mycotic genital infection in women</td>
<td>68.8</td>
<td>17.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Severe hypersensitivity or cutaneous reaction</td>
<td>8.5</td>
<td>6.1</td>
<td>0.17</td>
</tr>
<tr>
<td>Hepatic injury</td>
<td>7.4</td>
<td>9.1</td>
<td>0.35</td>
</tr>
<tr>
<td>Renal-related (including acute kidney injury)</td>
<td>19.7</td>
<td>17.4</td>
<td>0.32</td>
</tr>
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</table>
Fast-Acting Insulin Aspart Improves Glycemic Control in Basal-Bolus Treatment for Type 1 Diabetes: Results of a 26-Week Multicenter, Active-Controlled, Treat-to-Target, Randomized, Parallel-Group Trial (onset 1)

David Russell-Jones, Bruce W. Bode, Christophe De Block, Edward Franek, Simon R. Heller, Chantal Mathieu, Athena Philis-Tsimikas, Ludger Rose, Vincent C. Woo, Anne Birk Østerskov, Tina Graungaard and Richard M. Bergenstal

Diabetes Care 2017; 40(7):943-950
1143 adults w/ T1DM

- Mealtime Faster Aspart  
  n= 381

- IAsp  
  n= 380

- Postmeal Faster Aspart  
  n= 382
Results
Results
## Results

<table>
<thead>
<tr>
<th>Treatment-emergent hypoglycemia</th>
<th>Faster aspart mealtime</th>
<th>Faster aspart postmeal</th>
<th>IAsp mealtime</th>
<th>Rate ratio (95% CI)</th>
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<tr>
<td></td>
<td>N (%)</td>
<td>E</td>
<td>R</td>
<td>N (%)</td>
</tr>
<tr>
<td>Severe</td>
<td>26 (6.7)</td>
<td>46</td>
<td>0.25</td>
<td>30 (8.0)</td>
</tr>
<tr>
<td>Severe or BG confirmed</td>
<td>358 (92.7)</td>
<td>10,993</td>
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<tr>
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<tr>
<td>Within 1 h after a meal</td>
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<tr>
<td>Within 2 h after a meal</td>
<td>258 (66.8)</td>
<td>1,391</td>
<td>7.464</td>
<td>231 (61.3)</td>
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Faster Aspart Versus Insulin Aspart as Part of a Basal-Bolus Regimen in Inadequately Controlled Type 2 Diabetes: The onset 2 Trial

Keith Bowering, Christopher Case, John Harvey, Michael Reeves, Michael Sampson, Robert Strzinek, Ditte-Marie Bretler, Rikke Beck Bang and Bruce W. Bode

Diabetes Care 2017; 40(7):951-957
Patients

689 adults w/ T2DM

- Faster Aspart
  - n = 345

- IA Sp
  - n = 344
Results

![Graph showing mean HbA1c over time](chart.png)

- **Faster aspart**
- **Insulin aspart**

Mean HbA1c (%) vs. Time since randomization (weeks). The graph illustrates a decrease in mean HbA1c with time for both treatments. Baseline is indicated at week 0.
Results

The graph shows the PPG increment (mmol/L) over time for different treatment groups.

- **Faster aspart**
- **Insulin aspart**

Median bolus dose: 0.16 U/kg
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Faster aspart (or so called: Fiasp by Novo) is superior to insulin aspart in pts w/T1DM, and is non-inferior to insulin aspart in those w/T2DM.
Pending FDA approval, but the questions about coverage, price and who will really benefit from this novel agent (cost-effectiveness) remains to be answered by each one of us!
Thank you!

Discussion