## P-15

### Incident diabetes with antihypertensive drugs: updated network and bayesian meta-analyses of clinical trial data

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New-onset diabetes (NOD) associated with antihypertensive medications is controversial. A 2007 network meta-analysis included 22 clinical trials reported through 15 SEP 06. Since then, data from 14 more trials (e.g., TRANSCEND, PRoFESS, ONTARGET, NAVIGATOR) have been published and one retracted (Kyoto), resulting in a total of 17,235 subjects with NOD (from a total of 217,820 at risk). Meta-analyses were performed using the network technique of Lumley (Stat Med. 2002;21:2313-24) and the traditional Bayesian method (WINBUGS Version 1.4.1, non-informative priors, 99,000 iterations, 1000 burn). For each therapy, the number of new cases of incident diabetes/number at risk (number of trials) were: Placebo: 4879/52,700 (18); Diuretic: 1422/28,786 (15); Beta-blocker: 3043/43,084 (16); Calcium channel blocker (CCB): 3204/47,928 (18); Angiotensin converting-enzyme (ACE)-inhibitor: 2564/40,534 (13); Angiotensin receptor blocker (ARB): 4099/44,459 (16). These numbers reflect ''double-counting'' for the 6 trials that included more than 2 arms (AASK, ALLHAT, COPE, MRC-E, ONTARGET, STOP-Hypertension 2). The incoherence value ($\omega$) for the network meta-analysis was 0.048. The results were:

| Drug Class | Network Meta-analysis | Bayesian Meta-analysis |
|---|---|---|
| | Odds Ratio (95% CI) | Posterior Probability (2.5-97.5% CrI) |
| Diuretic | 1.00 (referent) | 1.00 (referent) |
| Beta-blocker | 0.93 (0.82 - 1.06) | 0.93 (0.82 - 1.06) |
| CCB | 0.78 (0.70 - 0.88) | 0.78 (0.70 - 0.88) |
| Placebo | 0.75 (0.86 - 1.16) | 0.75 (0.87 - 1.16) |
| ACE-inhibitor | 0.65 (0.59 - 0.72) | 0.66 (0.58 - 0.72) |
| ARB | 0.64 (0.59 - 0.69) | 0.64 (0.58 - 0.69) |

CI = confidence interval. CrI = credible interval.

The rank order, from lowest to highest risk for NOD, for antihypertensive drugs was: ARB, ACE, placebo, CCB, beta-blockers and diuretics. Compared to placebo, both the ARB and ACE-inhibitor had a significantly lower risk of NOD (both $P < 0.0001$), whereas a diuretic or beta-blocker was significantly higher (both $P < 0.001$). These data corroborate earlier conclusions that significant differences exist across pharmacological classes of antihypertensive agents with regard to risk for NOD.

**Keywords:** Incident diabetes; antihypertensive drugs; network meta-analysis

## P-16

### Combination therapy with nebivolol/amlodipine is superior to metoprolol/amlodipine in the control of cuff and 24-hr ambulatory blood pressure

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The control of blood pressure continues to be difficult to achieve even though there are numerous combinations of anti-hypertensive drugs from which to chose from. With the rise in obesity as a comorbid disease state it would seem prudent to utilize metabolically neutral drugs in the antihypertensive armamentarium. Since many patients are placed on the calcium-channel blocker amlodipine as initial therapy, we decided to evaluate if the addition of the beta-blocker, nebivolol or metoprolol would have greater BP control as add on therapy. Both Beta Blockers are cardioselective but only nebivolol has vasodilatory properties exerted through the nitric oxide pathway. We selected 43 hypertensive patients to undergo a 2-4 week washout period and if they had a SDBP >95 mmHg at two consecutive visits, they underwent 24-hr ABPM. They then were given amlodipine 10mg daily for the full 12 weeks, since this was a prospective, randomized, open label study with blinded endpoints (PROBE), patients were randomized 1:1 fashion to nebivolol 10mg or metoprolol 50mg for 4 weeks and after 24-hr ABPM they were up-titrated to nebivolol 20mg or metoprolol 100mg once daily.

**Results:** ABPM N M D

Placebo: 144/85 mmHg 144/85 mmHg 0
4weeks A: 129/77 mmHg 131/79 mmHg 2/2
8weeks: 119/69 mmHg 125/74 mmHg 6/5
12weeks: 117/68 mmHg 123/73 mmHg 6/5

**Results:** Cuff Measures

N M D
Placebo: 146/97 mmHg 151/99 mmHg 0
4weeks A: 131/88 mmHg 138/90 mmHg 7/3
8weeks: 130/81 mmHg 130/87 mmHg 0/6
12weeks: 126/79 mmHg 131/86 mmHg 5/7

As can bee seen from the results, the addition of nebivolol to the amlodipine had a greater reduction of BP at both 8 weeks (10/8 mmHg)and 12 weeks (12/9mmHg) as compared to metoprolol at weeks 8 (6/5 mmHg) and 12 weeks (8/6 mmHg). These were statistically significant. When compared to the Baseline ABPM the amlodipine/nebivolol treated patients had a reduction of 27/17 mmHg and the amlodipine/metoprolol treated patients had a reduction of 21/12 mmHg at study end

**Conclusion:** The add on of nebivolol to amlodipine mono therapy has an additive effect in the control of both the cuff and 24-hour ambulatory blood pressure.

**Keywords:** beta-blocker; calcium-channel blocker; 24-hr ambulatory blood pressure monitoring

## P-17

### Dose-response relationships of potassium sparing diuretics to systolic blood pressure and serum potassium from randomized trials

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Potassium sparing diuretics (PSDs) may be valuable for the management of hypertension, but more knowledge is needed regarding how different PSDs and different doses affect blood pressure and serum potassium. We conducted systematic reviews and meta-analyses to address this deficiency. From an initial search yielding 3,584 articles, 56 randomized comparisons were identified. Overall placebo-adjusted changes in office systolic blood pressure (SBP) were for triamterene -1.9 (not statistically significant), amiloride (AMIL) -9.5, spironolactone (SPIR) -13.3, and eplerenone (EPLER) -9.2. Doubling the dose of AMIL did not significantly reduce SBP: -0.8 (-4.1, +2.5), P=0.571. However, doubling the doses of SPIR and EPLER reduced SBP (95% CI) by -3.7 (-5.7, -1.6) and -2.5 (-4.0, -1.0), respectively, with SPIR and EPLER having similar dose-response effects. Nonetheless, after dose adjustment, SPIR decreased SBP more than EPLER by -5.4 (-8.1, -2.7). However, increasing doses of EPLER led to continuing declines in SBP, allowing compensation for its lesser potency. Dose equivalency between SPIR and EPLER was found to be 1 to 3.5 (1.9, 11.9) (e.g., SPIR 50 mg = EPLER 175 mg). For serum potassium, AMIL and SPIR had similar dose-response effects, but, for the lowest effective doses, AMIL carried a higher serum potassium than SPIR. In conclusion, different PSDs and different doses exhibit marked heterogeneity in their effects on SBP and serum potassium. For reduction in SBP, SPIR and EPLER are equivalent at a dose ratio of 1 to 3.5. These findings allow a patient-specific approach in the management of hypertension.

**Keywords:** potassium sparing diuretics; aldosterone antagonists; randomized trials