| **Study Reference** | **Medication Dose/Duration** | **Behavioral Components** | **Other Intermediate Outcomes****(Blood Pressure and Heart Range Changes)** |
| --- | --- | --- | --- |
| **Orlistat Trials** |
| Acharya, 2006133Perrio, 2007134 | **Intervention setting:** Primary care**Medication:** Orlistat**Dose:** 76.9% were started at 360 mg QD; 22.7% were started on a dose below 360 mg QD; 0.4% were started on a dose of more than 360 mg QD**Duration:** Median duration of treatment was 150 days**Prescriber:** GP**Incentives:** NR | **Diet prescription:** NR**Exercise prescription:** NR**Behavioral intervention description:** NR**Number of visits:** NR | NR |
| Bakris, 2002126 | **Intervention setting:** NR **Medication:** Orlistat**Dose:** 120 mg TID**Duration:** 52 weeks**Prescriber:** NR**Incentives:** NR | **Diet prescription:** Nutritionally balanced hypocaloric diet (estimated energy requirements minus 600 kcal/day) with no more than 30% calories from fat; met with a dietician periodically to review dietary instructions and food records**Exercise prescription:** Encouraged to participate in moderate physical activity as deemed appropriate by their physician**Behavioral intervention description:** NR**Number of visits:** After screening visit, patients came for BL visit and 11 follow up visits spread over the 52 week duration of the study (13 visits\*)\*calc | Mean (SD), Mean change from BL (SD)   **BL**  **52 wks***Diastolic Blood Pressure, mmHg***IG** 98.4 (3.7) -11.4 (8.3) **CG** 98.3 (3.5) -9.2 (8.4)p 0.002 *Systolic Blood Pressure, mmHg***IG** 154.2 (13.4) -13.3 (15.2) **CG** 150.8 (12.7) -11.0 (15.0)p NS   |
| Broom, 2002132 | **Intervention setting:** "the clinic" unclear if intervention in outpatient clinics or just recruited from there**Medication:** Orlistat**Dose:** 120 mg TID**Duration:** 24 weeks double blind phase, 28 week open-label phase**Prescriber:** NR**Incentives:** NR | **Diet prescription:** Hypocaloric diet containing 30% of calories as fat & a max of 300 mg/day cholesterol. Total energy expenditure was calculated and 600 kcal/day ws subtracted. Achieved by a mild reduction in food intake from each of the 5 major food groups, with dietary advice provided by a dietician**Exercise prescription:** Patients received advice on physical activity**Behavioral intervention description:** NR**Number of visits:** Screening visit, followed by BL assessment, and every four weeks up to week 24. During open-label phase clinic visits were at weeks 30, 36, 44, and 52 (12 visits total\*)\*calc | Mean (SD)  **BL 24 wks***Diastolic Blood Pressure, mmHg***IG** 82.6\* (8.3) 80.6 (NR)**CG** 84.0 (9.1) 83.2 (NR)*Systolic Blood Pressure, mmHg***IG** 136.9 (14.8) 135.8 (NR)**CG** 140.0 (16.4) 138.3 (NR) \*Reported as 86.2 in text. 82.6 likely most accurate. |
| Kelley, 2002127 | **Intervention setting:** 43 centers in US**Medication:** Orlistat**Dose:** 120 mg TID**Duration:** 52 weeks**Prescriber:** NR**Incentives:** NR | **Diet prescription:** Nutritionally balanced, energy deficient diet designed to induce wt loss of 0.25-0.5 kg per week. Contained ~30% of calories as fat, 50% as carbs, and 20% as protein, with a max of 300 mg/day of cholesterol. At BL patients received diet instructions from a registered dietician. Additional dietary instruction was provided at predetermined intervals during the study period. Dietary compliance monitored by use of dietary intake records. At wk 24 the prescribed dietary intake was further reduced by 200 kcal/day (min of 1200 kcal/day). Patients were instructed to take a multivitamin at least 2 h before or after evening dose of study drug**Exercise prescription:** Patients were encouraged to participate in moderate physical activity**Behavioral intervention description:** Lifestyle and behavioral modification literature were available to all patients throughout the study; dietary intake records were used to evaluate compliance**Number of visits:** Subjects were seen every 2-4 weeks for study assessment | Mean (SE)  **BL 52 wks Change***Diastolic Blood Pressure, mmHg***IG** 79.5 (0.5) 77.2 (0.6) -2.3 (0.7)**CG** 80.9 (0.6) 78.0 (0.5) -1.0 (0.5)**p** 0.075 *Systolic Blood Pressure, mmHg***IG** 135.1 (0.9) 134.0 (1.0) -1.2 (1.0)**CG** 134.9(0.9) 134.0 (1.0) -0.9 (1.0)**p** 0.948**IG n analyzed:** 266**CG n analyzed:** 276  |
| Muls, 2001130 | **Intervention setting:** 19 centers in Belgium**Medication:** Orlistat**Dose:** 120 mg TID**Duration:** 24 weeks double blind phase, 24 week open-label extension**Prescriber:** NR**Incentives:** NR | **Diet prescription:** Patients instructed on a nutritionally balanced low-energy diet containing 30% of energy as fat at start of run-in. Energy content calc from estimated total daily energy expenditure minus 600 kcal/day. Lowest energy intake allowed was 1200 kcal/day. Encouraged to take 3 main meals per day. Dietician assessed dietary compliance weeks 4, 12, and 24. Diet maintained through open-label extension**Exercise prescription:** NR**Behavioral intervention description:** NR**Number of visits:** At the start and end of run-in phase, monthly during double blind phase (6 mo), and at weeks 28, 36, and 48 during open-label extension (11 visits\*)\*calc | Mean (SD)  **BL 48 wks***Diastolic Blood Pressure, mmHg***IG** 83.1 (7.4) --**CG** 82.2 (8.3) --*Systolic Blood Pressure, mmHg***IG** 133.6 (13.3) **--****CG**  130.6 (12.1) **--**  |
| Van Gaal, 1998129 | **Intervention setting:** 14 European centers **Medication:** orlistat**Dose:** 30, 60, 120 or 240 mg TID**Duration:** 24 weeks**Prescriber:** NR**Incentives:** NR | **Diet prescription:** Nutritionally balanced, mildly hypocaloric diet designed to result in estimated wt loss of 0.25-0.5 kg/week during run in period. Contained approx 30% calories from fat, 50% as carbohydrates, 20% as protein, and max of 300 mg/day of cholesterol. Number of calories equaled the estimated daily energy expenditure minus 600 kcal per day, with a min of 1200 kcal per day. Diet was adjusted if patient experienced a fall of BMI to 22 kg/m2 or below on 2 consecutive visits. Received dietary advice from a qualified dietician**Exercise prescription:** NR**Behavioral intervention description:** Required to keep diet diary for 4 days during wks 1 & 2 of lead in period, and during wks 3,5,7,9,13,17, and 21 during treatment period**Number of visits:** Measurements (wt, vital signs, AE's) assessed twice during screening, at day 14 of lead in, and at every clinic visit during treatment period (BL, day 15 & 29, and then every 4 wks) (10 visits\*)\*calc | No clinically relevant abnormalities related to treatment were observed during treatment period in laboratory values; no changes in relation to hepatocellular damage, vital signs or ECGs; no evidence to support increased cholelithiasis |
| **Metformin Trials** |  |  |  |
| Trolle, 2007131 | **Intervention setting:** Dept of Gynaecology & Obstetrics, Hostebro Hospital**Medication:** metformin**Dose:** 850 mg BID**Duration:** 6 months (6 mo on med or placebo, followed by 3 mo washout before being switched to alternate treatment for another 6 mo)**Prescriber:** NR**Incentives:** NR | **Diet prescription:** NR**Exercise prescription:** NR**Behavioral intervention description:** NR**Number of visits:** Participants seen prior to inclusion and every 2nd month during treatment periods (6 visits during 12 mo\*)\*calc | Change from BL, median (5-95% percentile)*ITT Analysis*  **6 mo***Systolic Blood Pressure, mmHg* p value**IG** -5.4 (-10.8, -0.1) 0.047**CG** 1 (-3, 5) 0.529Mean differences between changes: -5.0(-11.2, 1.3), p=0.116  |
| **Combination Trials** |
| Gokcel, 2002136 | **Intervention setting:** Outpatient clinic**Medication:** Metformin, Orlistat**Dose:** Orlistat: 120 mg TIDMetformin: 850 mg BID**Duration:** 6 months**Prescriber:** NR**Incentives:** NR | **Diet prescription:** Recommended to follow weight reducing daily diet of 25 kcal/kg of ideal body weight; 50% calories from carbs, 30% from lipids and 20% from proteins; given a list of foods that were permitted and not permitted, as well as guidelines on recommended portions and possible combinations**Exercise prescription:** NR**Behavioral intervention description:** NR**Number of visits:** Before the start of medication and then monthly up to 6 months of treatment (7 visits\*)\*calc | *IG2: orlistat IG3: metformin* Mean (SEM)  **BL 6 mo p value***Diastolic Blood Pressure, mmHg***IG2**  79.77 (1.18) 75.98 (0.84) p < 0.008**IG3** 83.41 (1.30) 77.61 (0.74) p < 0.0001 *Systolic Blood Pressure, mmHg***IG2**  127.21 (1.80) 121.74(1.54) p < 0.0001**IG3**  129.55 (1.98) 123.64 (1.45) p < 0.0001*Heart rate, beats/minute***IG2** 80.25 (1.25) 78.77 (0.93) p < 0.03**IG3**  81.63 (1.37) 79.95 (1.10) p < 0.006% change from BL*Diastolic Blood Pressure, mmHg***IG2** 4.75**IG3** 6.95*Systolic Blood Pressure, mmHg***IG2** 4.30 **IG3** 4.56 *Heart rate, beats/minute***IG2**  2.12 **IG3** 1.84 |