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| **Table A: Subgroup Analysis of the Number, Annualized Incidence, and Hazard of Carpal Tunnel Syndrome Diagnosis in Both Women’s Health Initiative (WHI) Trials** | | | | | | | | |
|  | **Conjugated Equine Estrogens Trial** | | |  | **Estrogen & Progestin Trial** | | |  |
|  | **CEE,**  **N/Ann. %** | **Placebo,**  **N/Ann. %** | **HR1**  **(95% CI)** | **Interaction**  **p-value2** | **CEE+MPA,**  **N/Ann. %** | **Placebo,**  **N/Ann. %** | **HR1**  **(95% CI)** | **Interaction**  **p-value2** |
| **Age group at screening** |  |  |  | 0.616 |  |  |  | 0.236 |
| 50-59 | 22/2.01 | 22/2.02 | 1.01 (0.56-1.83) |  | 6/0.90 | 14/2.45 | 0.37 (0.14-0.96) |  |
| 60-69 | 104/1.24 | 146/1.71 | 0.73 (0.56-0.93) |  | 109/1.03 | 108/1.08 | 0.95 (0.72-1.23) |  |
| 70-79 | 77/1.49 | 94/1.80 | 0.83 (0.61-1.12) |  | 58/0.99 | 81/1.46 | 0.67 (0.48-0.94) |  |
| **BMI, kg/m2** |  |  |  | 0.832 |  |  |  | 0.448 |
| < 25 | 34/1.04 | 42/1.27 | 0.81 (0.52-1.28) |  | 34/0.65 | 47/0.92 | 0.69 (0.44-1.07) |  |
| 25-< 30 | 60/1.17 | 87/1.61 | 0.72 (0.52-1.00) |  | 64/1.04 | 79/1.34 | 0.77 (0.55-1.07) |  |
| ≥ 30 | 109/1.77 | 132/2.17 | 0.81 (0.63-1.05) |  | 73/1.29 | 76/1.53 | 0.86 (0.62-1.18) |  |
| **Job type** |  |  |  | 0.859 |  |  |  | 0.937 |
| Managerial/Professional | 53/1.33 | 71/1.72 | 0.79 (0.55-1.12) |  | 58/1.12 | 65/1.23 | 0.92 (0.64-1.31) |  |
| Technical/Sales/Admin | 47/1.22 | 73/1.86 | 0.65 (0.45-0.93) |  | 42/1.00 | 50/1.19 | 0.81 (0.54-1.23) |  |
| Service/Labor | 46/1.51 | 57/1.93 | 0.78 (0.53-1.15) |  | 31/1.06 | 39/1.36 | 0.79 (0.49-1.27) |  |
| Homemaker only | 26/1.68 | 30/2.06 | 0.79 (0.47-1.33) |  | 18/1.02 | 25/1.37 | 0.76 (0.41-1.40) |  |
| **Smoking** |  |  |  | 0.453 |  |  |  | 0.574 |
| Never | 95/1.23 | 128/1.64 | 0.74 (0.57-0.97) |  | 83/0.95 | 96/1.17 | 0.80 (0.59-1.07) |  |
| Past | 89/1.61 | 103/1.83 | 0.88 (0.66-1.17) |  | 73/1.05 | 90/1.41 | 0.75 (0.55-1.02) |  |
| Current | 16/1.28 | 27/2.15 | 0.59 (0.32-1.10) |  | 16/1.23 | 14/1.15 | 1.14 (0.56-2.35) |  |
| **Prior HT use** |  |  |  | 0.458 |  |  |  | 0.219 |
| Never | 115/1.47 | 150/1.91 | 0.77 (0.60-0.98) |  | 140/1.06 | 148/1.20 | 0.88 (0.70-1.11) |  |
| Past | 66/1.20 | 92/1.63 | 0.73 (0.53-1.00) |  | 27/0.82 | 45/1.43 | 0.57 (0.35-0.92) |  |
| Current | 22/1.68 | 20/1.45 | 1.12 (0.61-2.06) |  | 6/1.03 | 10/1.90 | 0.55 (0.20-1.53) |  |
| **Diabetes, ever** |  |  |  | 0.673 |  |  |  | 0.830 |
| No | 168/1.27 | 219/1.63 | 0.77 (0.63-0.94) |  | 160/0.99 | 186/1.23 | 0.79 (0.64-0.98) |  |
| Yes | 35/2.53 | 43/2.96 | 0.86 (0.55-1.34) |  | 13/1.36 | 17/1.73 | 0.86 (0.42-1.78) |  |
| **Rheumatoid arthritis** |  |  |  | 0.624 |  |  |  | 0.969 |
| No | 170/1.35 | 226/1.76 | 0.77 (0.63-0.94) |  | 144/0.96 | 173/1.19 | 0.81 (0.65-1.01) |  |
| Yes | 17/1.74 | 16/1.85 | 0.92 (0.46-1.83) |  | 12/1.56 | 13/1.93 | 0.82 (0.37-1.81) |  |
| **Thyroid disease** |  |  |  | 0.762 |  |  |  | 0.498 |
| No | 135/1.26 | 193/1.70 | 0.74 (0.60-0.93) |  | 133/1.01 | 161/1.30 | 0.78 (0.62-0.98) |  |
| Yes | 60/1.59 | 66/1.97 | 0.79 (0.56-1.12) |  | 40/1.04 | 39/1.10 | 0.92 (0.59-1.44) |  |
|  | | | | | | | | |

1The Cox proportional hazards regression model stratified by randomization age strata (50-54, 55-59, 60-69, 70-79) and Dietary Modification Trial randomization arm.

2 Tests for interaction with randomization arm based on product terms between arm and linear age, linear trend for BMI (coded 1-3), and categorical factors for job type, smoking, prior HT use, diabetes, rheumatoid arthritis and thyroid disease in Cox proportional hazards regression models stratified as above.

**Table B. Incidence of Carpal Tunnel Syndrome (CTS) Diagnosis during the Conjugated Equine Estrogens (CEE) Trial Intervention Period by years of follow-up (N=6833). Sample in Center for Medicare & Medicaid Services (CMS) at randomization or later aged in during intervention.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | | | | |
|  | CEE (N=3,380) | Placebo (N=3,453) | HR1 (95% CI) | p-value1 |
|  | No. of events | No. of events |
| **CTS diagnosis2** |  |  |  |  |
| Overall | 203 | 262 | 0.78 (0.65-0.94) | 0.009 |
| ≤ 3 years | 121 | 127 | 0.97 (0.76-1.25) | 0.831 |
| > 3 years | 82 | 135 | 0.61 (0.46-0.80) | 0.001 |
| **CTS procedure3** |  |  |  |  |
| Overall | 52 | 69 | 0.77 (0.54-1.11) | 0.164 |
| ≤ 4 years | 38 | 34 | 1.14 (0.72-1.81) | 0.583 |
| > 4 years | 14 | 35 | 0.42 (0.22-0.77) | 0.006 |
| 1 The Cox proportional hazards regression model stratified by randomization age strata (50-54, 55-59, 60-69, 70-79) and Dietary Modification Trial randomization arm. 2Test for difference of hazard ratios between ≤ vs. > 3 years p-value=0.0126.  3Test for difference of hazard ratios between ≤ vs. > 4 years p-value=0.0108. | | | | |

**Table C. Incidence of Carpal Tunnel Syndrome (CTS) Diagnosis During and After Hormone Trial Intervention Periods Adjusted for Drug Non-adherence: sample in Center for Medicare & Medicaid Services CMS at randomization or later aged in during intervention**

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| --- | --- | --- | --- | --- | --- | --- |
|  | | | | | | |
|  | **Conjugated Equine Estrogens Trial** | | | **Estrogen & Progestin Trial** | | |
|  | CEE | Placebo | p-value1 | CEE+MPA | Placebo | p-value1 |
| **CTS diagnosis** | N=2,725 | N=2,783 |  | N=3,909 | N=3,920 |  |
| HR1 (95% CI) | 0.68 (0.56-0.89) | Ref | 0.0059 | 0.74 (0.56-0.78) | Ref | 0.0356 |
| Events, N (%) | 103 (3.8) | 149 (5.4) |  | 91 (2.3) | 136 (3.5) |  |
| Annualized incidence (%) | 1.23 | 1.70 |  | 0.89 | 1.22 |  |
| **CTS procedure** | N=2,725 | N=2,783 |  | N=3,909 | N=3,920 |  |
| HR1 (95% CI) | 0.61 (0.37-1.00) | Ref | 0.0519 | 0.64 (0.35-1.15) | Ref | 0.1371 |
| Events, N (%) | 28 (1.0) | 39 (1.4) |  | 19 (0.5) | 35 (0.9) |  |
| Annualized incidence (%) | 0.33 | 0.43 |  | 0.18 | 0.31 |  |
|  | | | | | | |

Follow-up time, mean (SD) for CEE trial = 3.3 (2.6) years and for CEE+MPA trial = 2.9 (2.1) years.

Sensitivity analyses: Cox PH models adjusted for non-adherence (follow-up time censored 6 months after becoming non-adherent and weighted by the inverse of the participant’s probability of adherence). Participants who became non-adherent before the start of their CMS coverage are excluded (n=2,716).

1 The Cox proportional hazards regression model stratified by randomization age strata (50-54, 55-59, 60-69, 70-79) and Dietary Modification Trial randomization arm.