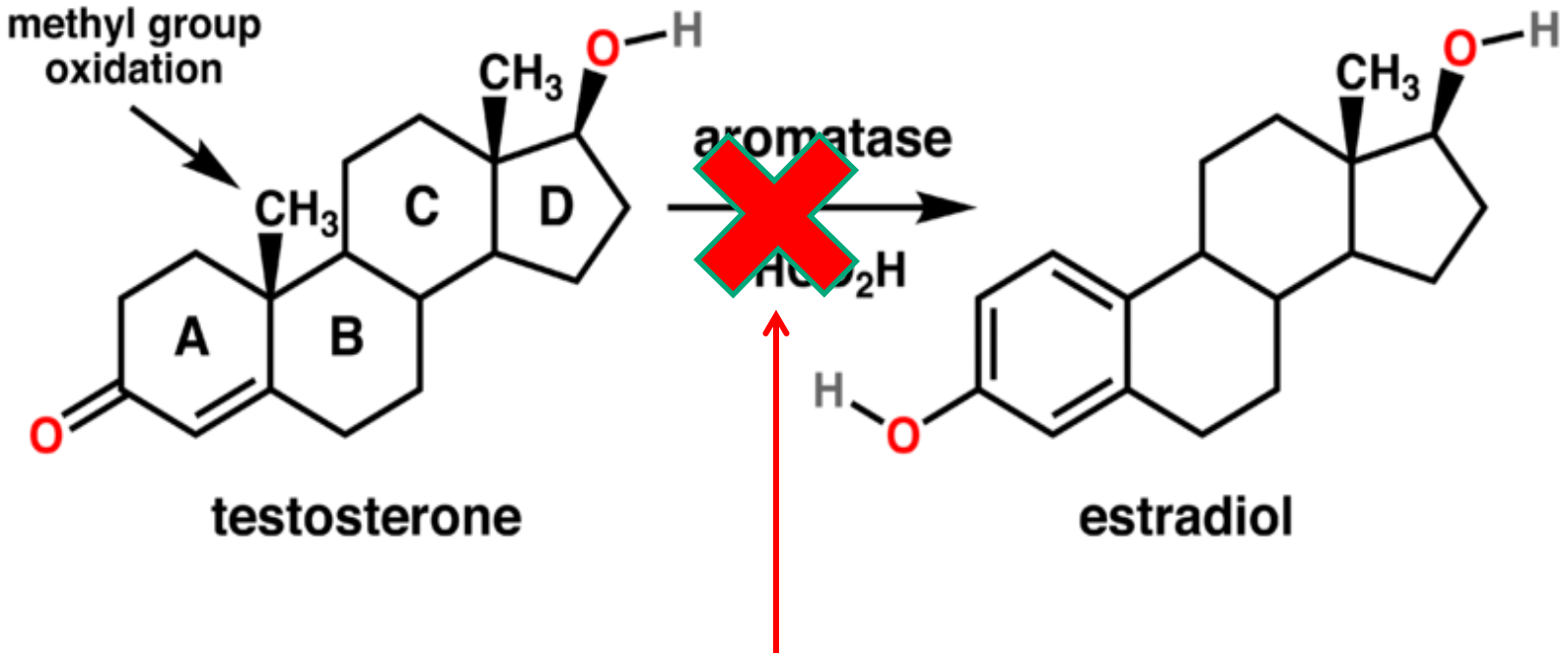
PROGETTO SPECIALE "CARDIO-ONCOLOGIA" 2013-2015
AIOM – ANMCO – AICO – ICOS

Cardiotossicità nel carcinoma mammario da inibitori dell'aromatasi

Stefania Gori, Francesca De Iuliis, Simona Duranti, Jennifer Foglietta, Alessandro Inno,Valentina Sini

Aromatase Inhibitors (AIs)



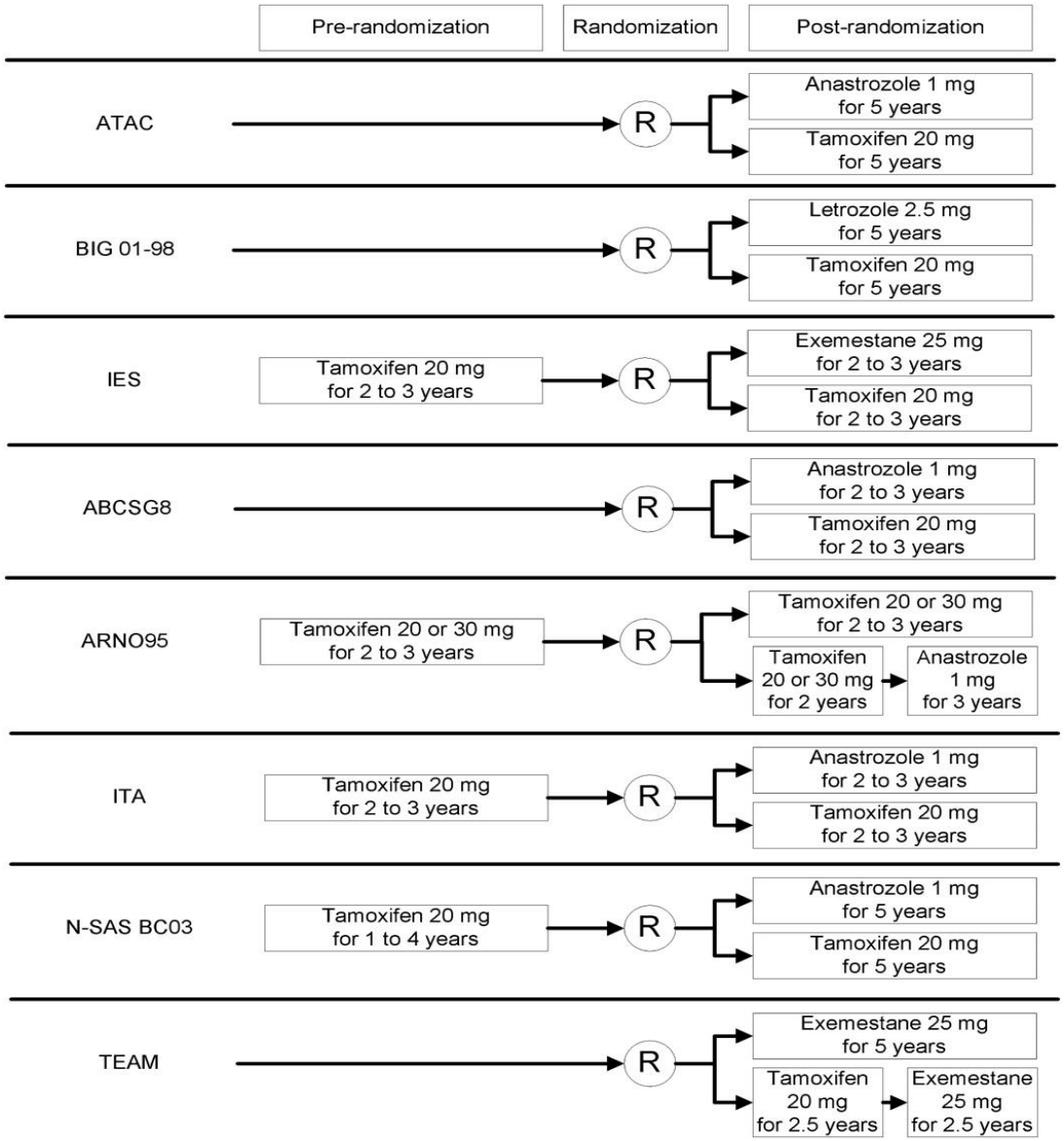
Aromatase Inhibitors (AIs)

Therapeutic Indications

- Third generation AIs, non-steroideal (anastrozole and letrozole) and steroidal AIs (exemestane) are indicated in estrogen (ER) and/or progesterone (PR) positive Breast Cancer, in the adjuvant, neoadjuvant and metastatic setting.
    - Early ER and/or PR positive BC: as monotherapy for 5 years (anastrozole or letrozole) [*up-front strategy**], sequential administration for 3 or 2 years after 2 or 3 years of tamoxifen *[switch strategy***]*, or letrozole after 5 years of tamoxifen *[extended strategy****]*.

* ATAC (anastrozole) and BIG 1.98 trials
** IES, ABCSG-8, ARNO 95, N-SAS BC03, ITA
*** MA-17, ABCSG 6a, NSABP-B33 trials

Major adjuvant studies comparing third-generation aromatase inhibitors and tamoxifen



Amir E, *JNCI* 2011

Tam- and AIs-specific side effects

Tam specific Estrogenic effects	AI specific High estrogen depletion / lack of estrogenic effects	Both Tam and AI Anti-estrogenic effects
Decreased Cholesterol	Hypercholesterolemia	Hot flushes
Increased Bone MD	Osteoporosis	Mood disturbances
Endometrial effects	Menopausal arthritis Carpal-tunnel syndrome	Sexual disfunction
Throembolic effects		Vaginal mucosa
Cerebrovasular effects		Urinary effects

Adjuvant AIs compliance

	Anastrozole[1]	Exemestane[2]	Letrozole[3]
Adverse events leading to withdrawal (% patients)	12%	11%	13%

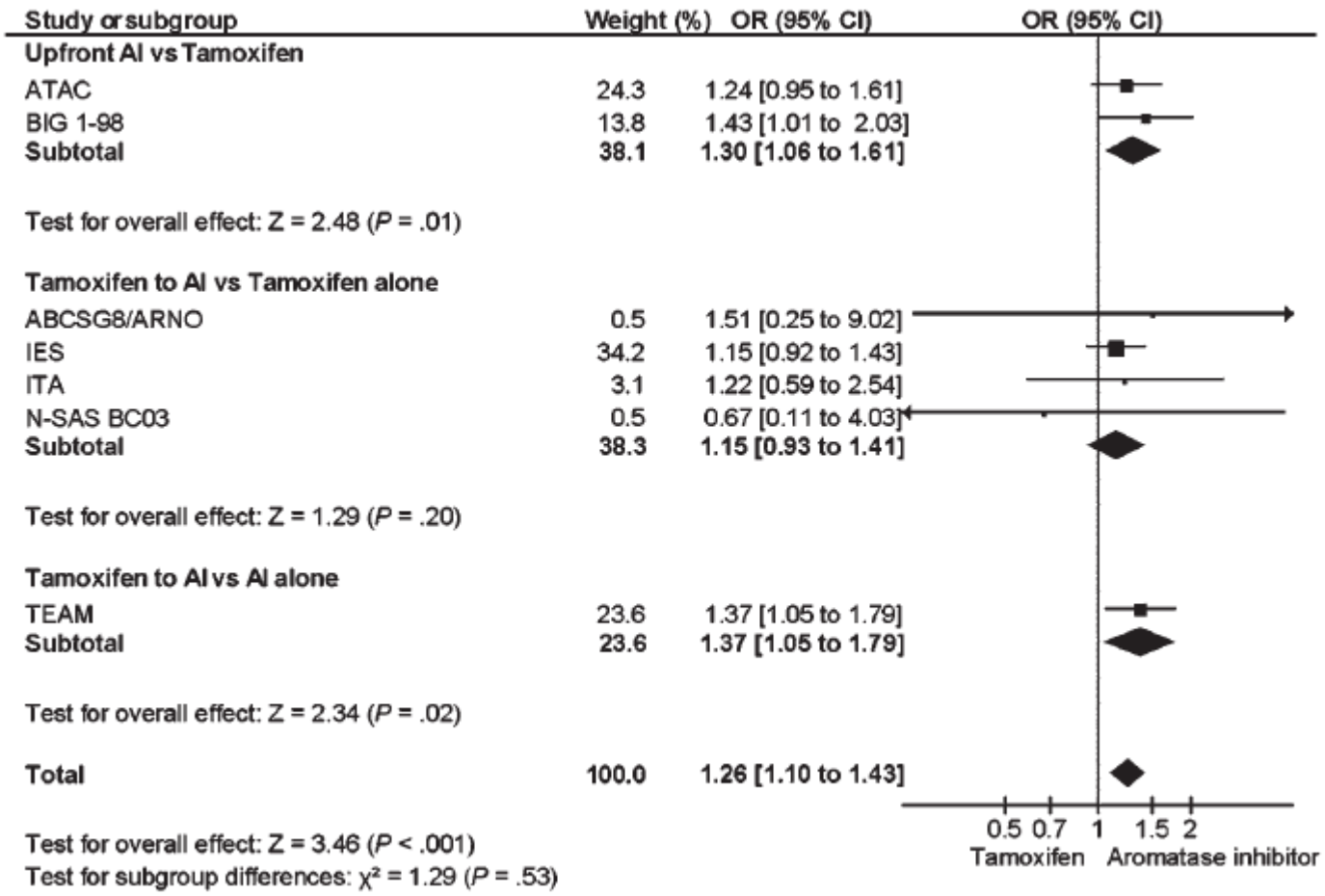
1. ATAC trialists' group. Lancet Oncol 2006;
2. Coombes. NEJM 2004;
3. Coates. J Clin Oncol 2007

Potential cardiovascular effects of AIs

- ***Estrogen deprivation***
  - Lack of favourable effects on cholesterol and lipids
  - Harmful effects on vessel-wall physiology
  - Alterations in glucose metabolism and hemostatic variables
- ***Interference in adrenal steroidogenesis***
  - Changes in aldosterone or cortisol levels -> effect on blood pressure and electrolyte balance
  - Impaired cortisol synthesis
    - Reduced ability of the hypothalamic-pituitary-adrenal axis to exert anti-inflammatory effect on the vascular system

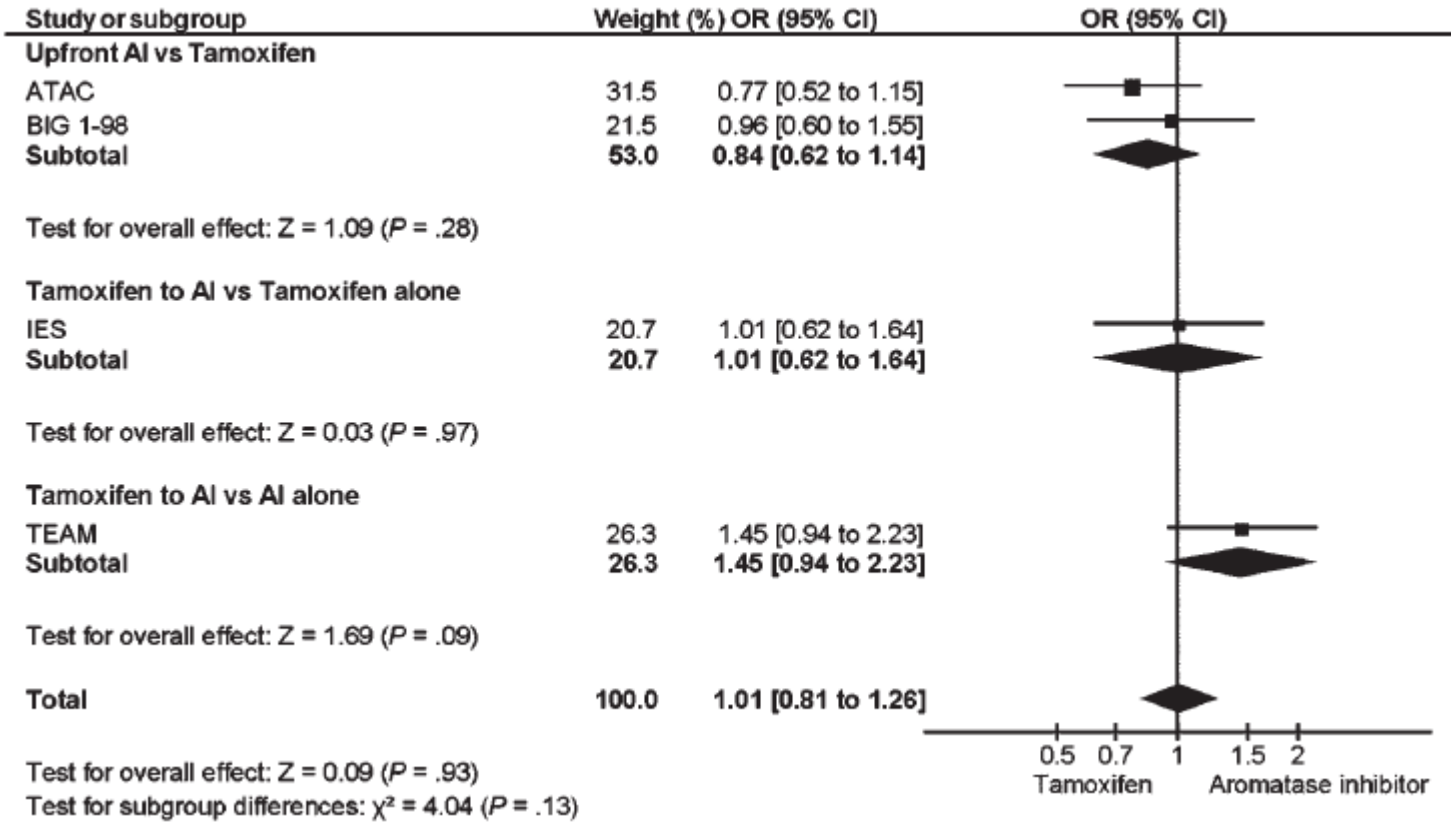
Nabholtz, *Drug Safety* 2006

Cardiovascular events (Tam vs AIs)



Amir E, *JNCI* 2011

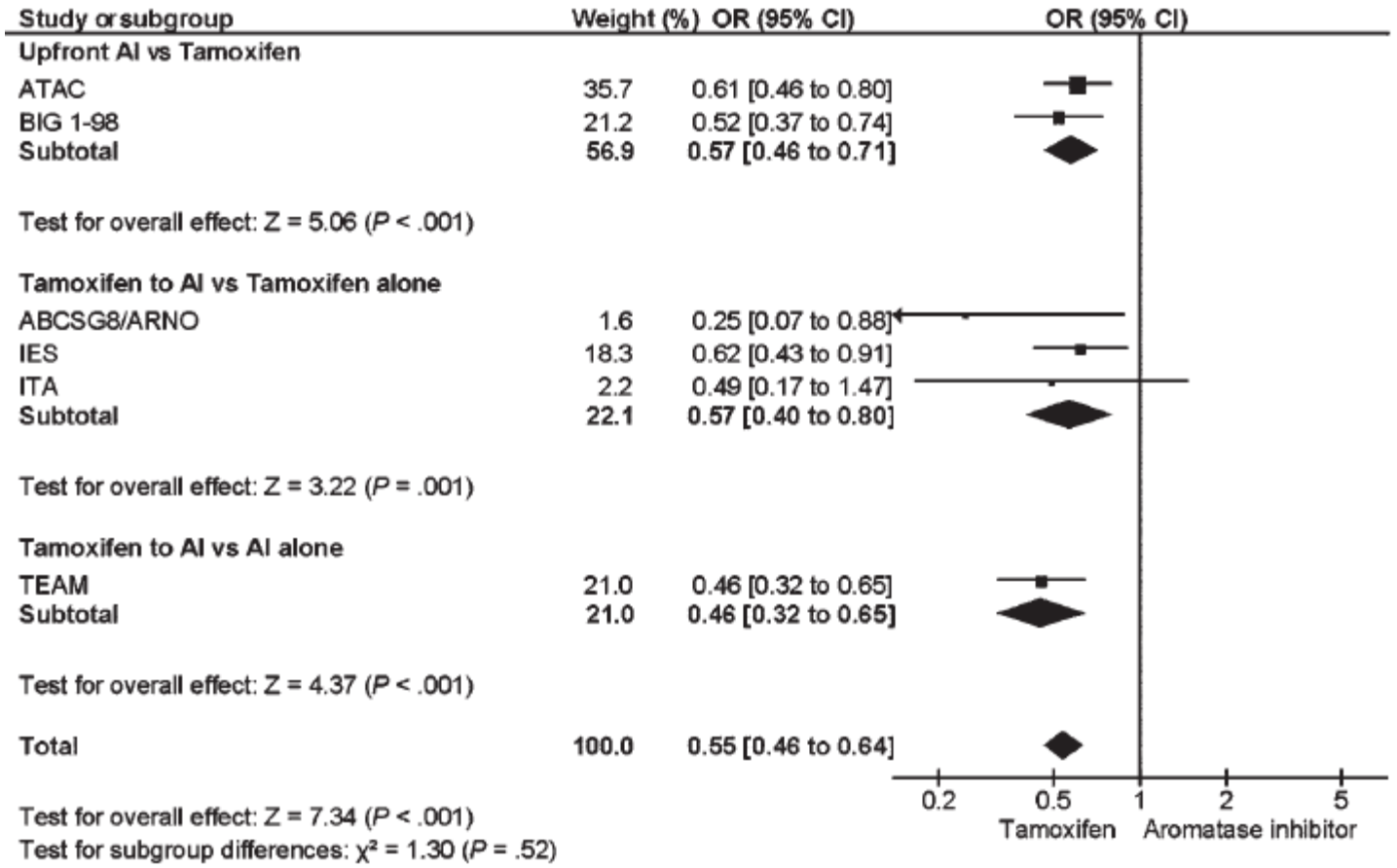
Cerebrovascular Events (Tam vs AIs)



*Cerebrovascular disease was an uncommon adverse event: it occurred in 1.4% of patients in the aromatase inhibitor group and in 1.5% of patients in the tamoxifen group (difference in absolute risk = 20.1%, number needed to harm = 2974)

Amir E, *JNCI* 2011

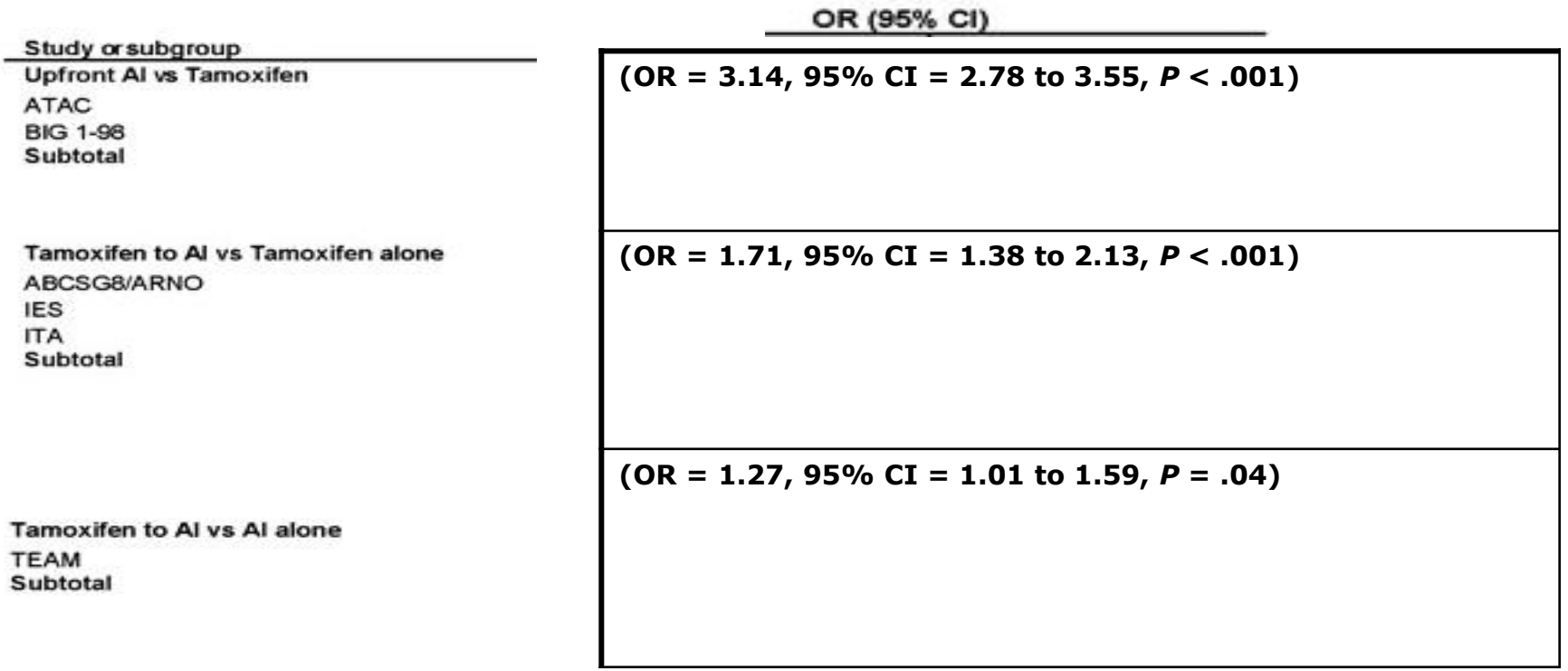
Venous Thrombosis (Tam vs AIs)



*The incidence of thrombosis was 1.6% and 2.8% in the aromatase inhibitor and tamoxifen groups, respectively (difference in absolute risk = 21.3%, number needed to harm = 279)

Amir E, *JNCI* 2011

AIs and lipid metabolism



NB: Hypercholesterolemia was assessed formally by only four studies (ITA, BIG1.98, IES, TEAM) and was not graded consistently among those studies!

Overall AIs vs Tam (OR = 2.36, 95% CI = 2.15 to 2.60, *P < .001)*

Amir E, *JNCI* 2011

AIs and lipid metabolism

Percentage change from baseline in LEAP study (Weeks after baseline: 24)

	Anastrozole	Exemestane	Letrozole
Total cholesterol	+0.37	-3.94	-0.01
Triglycerides	+0.28	+2.15	+5.40
LDL-C:HDL-C	+4.58	+16.97*	+3.39
APO-B:APO-A1	-0.02	+8.98*	-0.77

* Significantly different from anastrozole and letrozole

McCloskey E, *Eur J Cancer* 2007

Considerations on trials variability

- Trials conducted versus TAM (cardioprotective action!)
- Different grade of inhibition of aromatase→ different estrogen concentration → different cardiovascular risk profile
- Different action of AIs on lipidic metabolism (LEAP study)
- Higher risk of cardiotoxicity in women previously treated with anthracyclines and/or trastuzumab and/or RT
- Higher risk of cardiotoxicity in women with comorbidities

Take Home Messages

- Significant increase of cardiac ischemic events during AIs, but NOT of cardiovascular related deaths.
- Increased incidence of hypercholesterolemia, mostly grade low