The meta-analysis has been an invaluable tool in the evaluation of adjuvant therapy for breast cancer and has supported the use of tamoxifen, anthracyclines, and taxanes via the compilation of results from small trials that individually yielded less than dramatic results. Indeed, recent results of the Early Breast Cancer Trialists’ Collaborative Group (EBCTCG) meta-analysis demonstrated the enduring benefit in 15-year recurrence-free and overall survival for 5 years of adjuvant tamoxifen for women of any age with early-stage steroid receptor–positive breast cancer (1). It also confirmed an age-related increase in the risks of thromboembolic events and endometrial cancer without an excess in non-breast cancer–related deaths.

In recent years, the use of tamoxifen in postmenopausal women has been eclipsed by enthusiasm about aromatase inhibitors. Multiple studies have documented a greater reduction in breast cancer recurrence and a seemingly more favorable toxicity profile with aromatase inhibitors compared with tamoxifen, which has led to their widespread use over tamoxifen, despite the fact that an overall survival benefit with this approach has not been observed. These results have led to guidelines by entities such as the American Society of Clinical Oncology (2) and the National Comprehensive Cancer Network (3) stating that aromatase inhibitors should be considered in place of or in sequence with tamoxifen for most postmenopausal women with early-stage hormone receptor–positive breast cancer.

The emergence of data from large trials of adjuvant aromatase inhibitors has enabled several meta-analyses to be performed, one of which is reported by Amir et al. (4) in this issue of the Journal. The authors hypothesized that the relative toxicity of aromatase inhibitors compared with tamoxifen could explain the discordant observation of their improved benefit in disease-free survival without enhanced overall survival benefit. Their meta-analysis was restricted to seven randomized controlled trials that enrolled 30023 patients and compared 5 years of aromatase inhibitor, 5 years of tamoxifen, or a switch from one to the other as primary endocrine therapy. In addition to conventional breast cancer endpoints, they focused on six prespecified serious adverse events—cardiovascular disease, cerebrovascular disease, bone fracture, thromboembolic events, endometrial carcinoma, and other non-breast cancers. In large part, the analysis confirmed what we already know: Compared with tamoxifen, the use of aromatase inhibitors was associated with a statistically significant increase in bone fractures and decrease in endometrial cancer and thromboembolic events and no difference in the risks of second cancers. What we learned, however, was that there was no difference in the risk of cerebrovascular disease with tamoxifen compared with aromatase inhibitors, and the risk of cardiovascular disease was statistically significantly higher with aromatase inhibitors compared with tamoxifen, although the magnitude of the difference was small—an absolute difference in risk of 0.8% and a number needed to harm of 132. It is notable that use of up-front aromatase inhibitors was also associated with a non-statistically significantly higher odds of death without breast cancer recurrence compared with the use of tamoxifen alone or switching from tamoxifen to aromatase inhibitors (odds ratio = 1.11, 95% confidence interval = 0.98 to 1.26, P = .09). Of particular interest was the finding that those treated with a switching strategy had a statistically significant reduction in the odds of death without breast cancer recurrence compared with those treated with 5 years of tamoxifen or 5 years of an aromatase inhibitor alone (odds ratio = 0.87, 95% 95% confidence interval = 0.77 to 0.99, P = .03). In absolute terms, the difference is exceedingly small—a 0.2% difference in absolute risk of death without breast cancer recurrence. From these findings, Amir et al. (4) concluded that the switching strategy allows patients to reap the positive benefits of the aromatase inhibitors while limiting potential toxicity.

The analysis by Amir et al. (4) should be considered in the context of another recent meta-analysis from the EBCTCG of breast cancer outcomes in adjuvant trials of aromatase inhibitors vs tamoxifen in postmenopausal women (5). These two meta-analyses differ in several ways. First, the EBCTCG compared two cohorts—cohort 1, which received 5 years of tamoxifen vs 5 years of an aromatase inhibitor and cohort 2, which received 5 years of tamoxifen vs the switch from tamoxifen to an aromatase inhibitor—whereas the meta-analysis by Amir et al. (4) compared a switching strategy to 5 years of tamoxifen or to 5 years of an aromatase inhibitor. Second, the meta-analysis by Amir et al. (4) placed a particular emphasis on non-breast cancer–related endpoints and toxicity, whereas the EBCTCG meta-analysis did not. The EBCTCG analysis was based on primary data available before 2006, whereas the Amir et al. (4) analysis relied on data presented up to 2010. Thus, the meta-analysis by Amir et al. (4) included the Tamoxifen Exemestane Adjuvant Multinational (TEAM) trial of 9766 patients (6) and the National Surgical Adjuvant Study Breast Cancer 03 (N-SAS BC03) study of 696 patients (7), whereas the EBCTCG study did not. Ultimately, with 5 years of follow-up, the EBCTCG meta-analysis showed that cohort 1 aromatase inhibitor recipients had a 2.9% absolute decrease in recurrence, a 1.1% decrease in breast cancer mortality, a 0.2% increase in death without recurrence, and a 0.8% decrease in death from any cause, with only the first result achieving statistical significance. At 3 years
from treatment divergence (5 years after starting hormonal treat-
ment), the cohort 2 switch recipients showed a statistically signifi-
cant improvement in recurrence (absolute benefit of 3.1%), breast
cancer mortality (absolute benefit of 0.7%), and death from any
cause (absolute benefit of 1.1%), and a non-statistically significant
reduction in death without breast cancer recurrence (absolute ben-
efit of 0.4%) (5).

Of note, neither meta-analysis included extended adjuvant
approaches beyond 5 years, and both excluded data from the
switching arms of the Breast International Group 01-98 trial (BIG
1-98). The exclusion of such critical data could have altered the
results of either meta-analysis, although the BIG 1-98 trial did not
show a difference in breast cancer recurrence, breast cancer deaths,
or non-breast cancer deaths for letrozole monotherapy, switching
from letrozole to tamoxifen, or switching from tamoxifen to letro-
zole (8). It could be argued that omitting the switching strategy
arms of BIG 1-98 from both meta-analyses and the lack of data
from TEAM in the EBCTCG meta-analysis are critical gaps be-
because the most important question in current clinical practice
for many is not the comparison of a switching strategy with 5 years
of tamoxifen, but rather a comparison of a switching strategy
with 5 years of aromatase inhibitor, a question that can only be
answered by these trials.

Other studies of aromatase inhibitor use also enhance our
understanding of the side effects and efficacy of these agents. For
example, the National Cancer Institute of Canada MAP.3 che-
moprevention study of exemestane vs placebo showed a reduction
in invasive breast cancer and no excess cardiovascular events with
median follow-up of 3 years (9), and the National Cancer
Institute of Canada MA-27 adjuvant therapy study showed no
material differences between two different aromatase inhibitors,
letrozole and exemestane, in benefit or toxicity (10). Finally,
compliance is a critical determinant of outcomes for all patients,
and several studies have raised concerns about long-term adher-
ence and compliance with both aromatase inhibitors and tamox-
ifen. Differential compliance could certainly contribute to small
differences in outcome, but it was not evaluated in this meta-
analysis (11).

What we lack today is a predictive model that integrates car-
diovascular and bone risks with the risk of breast cancer recur-
rence to facilitate a personalized selection of therapy. The BIG
1-98 investigators have taken the first step by deriving a com-
posite risk model that includes estrogen and progesterone receptor
expression, Ki-67, HER2 expression, tumor size, and lymph node
status to stratify patients into a high-risk group (which benefited
more from letrozole monotherapy), an intermediate-risk group
(which did equally well with letrozole or switching strategies),
and a low-risk group (which benefited from any endocrine
approach) (12). The ability to incorporate cardiovascular and
bone health into such a model that is intuitive and easy to use—
perhaps an enhanced version of the Adjuvant! Online format—
would be of great use to doctors and patients. We hope that,
with time, more sophisticated prognostic and predictive testing
for breast cancer and non-breast cancer–related endpoints will
become the norm.

Finally, the provocative findings from both the Amir et al. (4)
and EBCTCG meta-analyses are far from mature given that the
length of follow-up of trials of adjuvant aromatase inhibitors is still
relatively short. Notably, survival benefits with adjuvant tamoxifen
were not truly evident until after 5 years of follow-up. Thus, it is
conceivable that a late survival advantage with aromatase inhibitors
over tamoxifen may also emerge over time. Moreover, although it
appears that the risk of fracture reverts to baseline after cessation
of aromatase inhibitors, it is uncertain whether cardiovascular risk
will also evolve over time.

It is also important to emphasize that the absolute differences
in the endpoints examined—whether toxicity or efficacy—albeit
statistically significant, were small. Ongoing uncertainty about
the optimal endocrine approach for postmenopausal women with
early-stage breast cancer was reflected in the recommendations
of the 2011 St Gallen consensus panel, whose members were
equally divided about whether all postmenopausal patients
should receive an aromatase inhibitor at some point in their

treatment or not (13). The panelists felt that certain patients
could be treated with tamoxifen alone, whereas others (eg, lymph
node–positive patients) would be best served by receiving an
up-front aromatase inhibitor. A practical approach while we
await further maturation of adjuvant endocrine data would be to
choose initial endocrine therapy for the individual patient with
careful attention to the risk of breast cancer recurrence, the
risk of toxicity, and comorbidities. Ultimately, results of the meta-
analysis by Amir et al. (4) as well as those from the EBCTCG
meta-analysis suggest that switching strategies are also rational
and effective, leading us to conclude that we should not “ditch
the switch.”

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