Management of Thrombotic Risk Associated with Endocrine and Other Systemic Therapy in Patients with Breast Cancer: Guidance from the SSC of the ISTH

A. INTRODUCTION

Breast cancer represents the most common cancer type and the second leading cause of cancer-related death in females, accounting for 1 in 8 of all new cancer diagnoses, with about 2.3 million women being diagnosed in 2020.[1, 2] Based on the clinical stage and biologic subtype of the cancer, different types of systemic therapies are used, including chemotherapy, hormonal therapies, targeted therapies, immunotherapy and supportive care agents, as well as surgery being used in the vast majority of patients at some point.[3, 4] Endocrine therapies are the key component of the treatment regimens both in the curative and palliative treatment setting for patients with hormone-receptor positive breast cancer, which accounts for 70-80% of cases.[5]

The mainstays of endocrine therapies used to treat patients with hormone-receptor positive breast cancer are selective estrogen receptor modulators (SERM) (i.e., tamoxifen), aromatase inhibitors (AI), as well as selective estrogen receptor down-regulators (SERD) such as fulvestrant and elacestrant.[3, 4] Endocrine therapies are commonly administered for years as adjuvant therapy or in the metastatic setting.[3, 4] Existing data demonstrate that tamoxifen is associated with an increased risk of VTE, while AI are associated with an increase in ATE and related cardiovascular morbidity.[6-8] However, there is limited evidence on the thrombotic risk of other endocrine therapies such as fulvestrant. Cyclin-dependent kinase (CDK) 4/6 inhibitors are used in combination with endocrine therapy in the adjuvant and palliative treatment setting. There is consistent data suggesting an increased risk of VTE in patients with breast cancer treated CDK4/6 inhibitors.[3, 4, 9, 10] Further, other targeted and immunotherapeutic agents are used in certain subgroups of patients with breast cancer including human epidermal growth factor receptor 2 (HER-2) targeted agents, poly ADP ribose polymerase (PARP) inhibitors, and immune checkpoint inhibitors, with heterogeneity in reported thrombotic risks.[11]

Considering the potential adverse thrombotic risks associated with breast cancer therapy, the International Society on Thrombosis and Haemostasis (ISTH) Scientific Standardization Committee (SSC) on Cancer

Associated Thrombosis and Hemostasis developed guidance recommendations regarding the management of thrombotic risk associated with endocrine and other systemic therapies in patients with breast cancer. The guidance statements cover common clinical scenarios related to arterial and venous thrombosis such as the use of endocrine and other systemic therapies in patients with a history of thrombosis, known thrombophilia, or in those with underlying cardiovascular risk factors.

In general, due to the different layers of complexity and management aspects of different specialties, we encourage multi-disciplinary discussions of clinical management of thrombotic risk in patients with breast cancer. We do not anticipate the guidance to differ significantly in low resource settings, since it generally does not recommend treatment but rather focuses on stratification of thrombotic risk with cancer therapy. We recognize that there may be considerations related to the cancer therapy itself in low resources settings, which may restrict a patient to limited cancer treatment options.

B. METHODOLOGY

This guidance document is a joint initiative of the ISTH SSC on Cancer Associated Thrombosis and Hemostasis and the ISTH SSC on Women's Health Issues in Thrombosis and Hemostasis. The guidance panel consisted of hematologists, thrombosis specialists, gynecologists, and surgical and medical oncologists specializing in breast cancer, who were members of the ISTH SSCs or external topic experts. The guidance panel reviewed and graded the available evidence by searching the literature as detailed in the **Supplemental Material**. Recommendations, using the wording "we advise", reflect strong guidance statements supported by high-quality evidence from clinical trials. Suggestions reflect weaker guidance statements based on low-quality evidence or expert opinions. Recommendations and suggestions were discussed, and a consensus was reached after two rounds of voting. Guidance panel members were recused from voting on guidance recommendations if anyone had any direct relevant conflicts.

C. VTE RISK ASSOCIATED WITH BREAST CANCER THERAPIES

The risk of VTE in breast cancer is relatively lower than other solid tumors, with a rate of approximately 9/1000 person-years, compared to pancreatic cancer at 98/1000 person-years, lung cancer at 44/1000 person-years and ovarian cancer at 31/1000 person-years.[12] However, given the high prevalence of breast cancer, breast cancer associated thrombosis is the most common cause of cancer-associated VTE.[12] This represents a significant health concern, particularly when balanced against the generally favorable prognosis in patients with breast cancer, with a high proportion of cancer survivors and patients living with active malignancy.[2]

General pro-thrombotic risk factors apply for patients with breast cancer, with higher risks in those with increased age, higher body mass index (BMI) and concomitant comorbidity. [6] Further, cancer-related factors increase risk of VTE, with a 2-fold increased risk reported with regional disease (axillary nodal metastases), and a 6-fold increased risk in those with metastatic disease compared to local disease.[13]

C.1 Surgery

Approximately 95% of patients with non-metastatic breast cancer will undergo curative resection.[14] A substantial proportion of breast cancer resections are conducted via low invasive procedures, with about 70% of patients undergoing breast conserving surgery in the United States.[15] Given the relatively low risk of VTE and higher risk of hematoma, postoperative pharmacologic thromboprophylaxis remains an area of uncertainty.[16] Several studies, all using American College of Surgeons National Surgical Quality Improvement Program (NSQIP) definitions, reported 30-day symptomatic VTE rates of 0-0.8% following surgical resection [17, 18] and 0.27-1.4% following reconstruction, with longer operation time (such as for free-flap reconstruction) associated with higher risk.[19, 20] Nonetheless, a large UK cohort study reported that surgery was associated with a 2.2-fold increased risk of VTE in the first month after the procedure, after correction for numerous variables such as cancer stage, age and BMI. [6] The use of pharmacologic thromboprophylaxis needs to be balanced against a 2-2.9% rate of hematoma requiring reoperation.[18, 21] Additionally, the rate of bleeding is even higher when considering clinically significant hematomas managed conservatively. Post-operative hematomas can lead to increased infection, breast deformity, poor cosmesis and

delayed adjuvant treatment requiring a thoughtful balance of risk versus benefit for pharmacologic thromboprophylaxis.[22, 23]

The American Society of Breast Surgeons recommends the use of the Caprini Score for individualized VTE risk assessment in the postoperative setting, with a score of >5 points warranting consideration of pharmacologic thromboprophylaxis.[24] Since the Caprini score includes variables such as presence of malignancy (2 points), surgery >45minute (2 points) and age 41 or above (1 point), the majority of breast cancer patients meet the criteria for pharmacologic prophylaxis and this possible overestimation of risk is acknowledged in the guidance. Studies in patients undergoing mastectomy reported over 70%-89% of patients to have a Caprini Score >5 [18, 25], suggesting that using a higher score cutoff for pharmacologic thromboprophylaxis in patients with breast cancer may be appropriate.[26] Guidance of post-operative thromboprophylaxis is beyond the scope of this document and we refer to dedicated surgical guidelines.

C.2 Chemotherapy

Chemotherapy represents a mainstay of treatment for patients with high risk localized breast cancer in the neo- and adjuvant settings, or in those with distant metastatic disease.[3, 4] In a study using Surveillance, Epidemiology, and End Results (SEER) data, patients with breast cancer treated with chemotherapy had an increased odds of VTE (odds ratio [OR] 1.66, 95% CI 1.48–1.86) compared to patients not treated with chemotherapy.[27] Further, in a cohort of 13,202 women with breast cancer (38% local disease; 36% stage unknown; 4% metastatic), the annual VTE incidence was 6% during chemotherapy, 10.8-fold higher than that in those who did not receive chemotherapy.[6] This increased risk persists for 3-12 months after completion of chemotherapy.[6, 28] Indwelling central venous catheters incur an additional 2.5-fold prothrombotic risk.[29, 30] Tools to individually quantify risk in this patient population can identify those who may benefit from anticoagulant thromboprophylaxis. The Khorana Score (KS) is the most validated clinical risk assessment model for prediction of cancer-associated VTE in outpatients receiving chemotherapy.[31] Guidelines recommend consideration of anticoagulant thromboprophylaxis in ambulatory cancer patients with a KS of ≥ 2.[32] However, the KS is heavily weighted by cancer type (2 points for very-high risk and 1-point for high

risk cancers). Based on the categorization of breast cancer as low VTE-risk, patients with breast cancer are not assigned a point in the cancer-type category in the KS.[33] With only four remaining risk variables (maximum of 4 points), only a minor proportion of patients with breast cancer are identified as high risk of VTE by the KS. The lump categorization of most breast cancer patients as low risk for VTE has resulted in mediocre discriminatory ability of available risk assessment tools in breast cancer patients receiving chemotherapy.[33]

C.3 Endocrine Therapy

Approximately 70-80% of breast cancers are hormone receptor positive [34] and are treated with endocrine therapy.[3, 4] In the adjuvant setting, the treatment duration with endocrine therapy ranges between 5-10 years, and decision on duration of treatment is determined based on the risk of recurrence, patient's tolerability to treatment and related adverse events.[3, 4] Endocrine therapy entails treatment with the SERMs (i.e., tamoxifen), AIs such as anastrozole, letrozole or exemestane, or SERDs including fulvestrant or elacestrant. These agents can be used either as monotherapy or in combination with other targeted therapies and can be sequenced over the course of disease.[3, 4]

C.3.1 *Selective estrogen receptor modulators (SERMs)*

Tamoxifen is the only approved SERM for the treatment of hormone receptor positive breast cancer. The event rates and relative risk of VTE in selected clinical trials and cohort studies of tamoxifen is shown in **Supplemental Table 1.** The risk of developing VTE with tamoxifen is increased two to three-fold compared to placebo, especially during the first 2 years of therapy [35, 36], with an estimated attributable excess VTE risk of ~0.3% to 1.9% per year [6, 35]. In a large English population-based cohort study, VTE was more than 5-fold higher in the first 3 months after initiation of tamoxifen compared with the risk before therapy (HR, 5.5; 95% CI, 2.3-12.7), with an absolute rate of 24.1/1000 person-years.[6] Data from the ATLAS trial indicate an ongoing tamoxifen-associated VTE risk even after 5 years of therapy in patients with early breast cancer [37] Mechanistically, the thrombotic risk is partially explained by an increased thrombin generation associated with tamoxifen. [38]

It is presumed that underlying thrombophilia represents an additive risk factor for VTE especially during tamoxifen therapy. However, few and controversial data are available on this issue.[39-41] A prospective, single-center case-control study recruited 150 women receiving tamoxifen, including 50 patients with VTE after initiating tamoxifen treatment and 100 patients without VTE.[42] After adjusting for additional risk factors, significant increased risk was found for the presence of factor V Leiden mutation (VTE cases vs controls: 20% vs. 7%, including one homozygous mutation in each group), and elevated factor VIII activity levels (median: 1.79 vs 1.45 IU/ml; $P < 0.001$), whereas no significant difference was found for the presence of the prothrombin gene G20210A mutation.[42] In the same cohort, BMI $\geq$ 25, varicose veins, and previous VTE were more frequent in the patients with VTE [42]. Accordingly, another case-control study showed a higher prevalence of factor V Leiden mutation in women who were diagnosed with VTE during tamoxifen treatment compared to those without VTE (mutation prevalence: 18.5% in cases vs 4.8% in controls; all heterozygotes), with the presence of the factor V Leiden mutation associated with an OR of 4.73 for VTE (95% CI 2.10 - 10.68).[39] Therefore, it is difficult to precisely estimate the additional prothrombotic risk associated with one or more thrombophilia risk factors.

C.3.2 ***Aromatase inhibitors (AIs)***

Unlike tamoxifen, no increased risk of VTE is observed in patients with breast cancer treated with AIs both when compared to placebo and to Tamoxifen (**Supplemental Table 1)** [6]. Accordingly, a study also showed no impact of AIs on prothrombotic hemostatic parameters while initiation of tamoxifen was associated with greater thrombin generation and reduced sensitivity to the protein C pathway [38]. Thus, the use of AIs should not be considered to have a clinically meaningful increase in VTE risk. Accordingly, if therapeutically acceptable, AIs can be considered as an alternative to tamoxifen in patients with VTE or at high risk of VTE. Supporting the above, thrombin generation was not increased after starting AI treatment (compared to beforehand), but was increased after starting tamoxifen. [38]

C.3.3 ***SERDs***

Fulvestrant is a SERD which is widely used for patients with hormone receptor positive advanced breast cancer. In the pivotal clinical trials, the reported rates of VTE with fulvestrant were low (0.8-1.6%), with no apparent increase in risk as opposed to controls [43-46]. In a combined analysis of two large, randomized trials, a similar risk of VTE was reported for patients with advanced breast cancer treated with fulvestrant compared to anastrozole (3.5% vs 4.5%).[47] Recently, the SERD elacestrant was approved for the treatment of patients with hormone-receptor-positive, HER-2 negative, ESR1-mutated breast cancer who previously progressed on endocrine therapy. In the pivotal randomized EMERALD trial, comparing elacestrant therapy to standard endocrine therapy, the reported rates for VTE and ATE were low, suggesting no increase in thromboembolic risk associated with elacestrant therapy [48, 49]. Studies specifically investigating the risk of VTE associated with oral SERD therapy in clinical practice are needed.

C.4 CDK 4/6 Inhibitors

Palbociclib, ribociclib, and abemaciclib, oral CDK 4/6 inhibitors that lead to cell cycle arrest, are used in combination with AIs or fulvestrant in estrogen receptor positive advanced breast cancer. Abemaciclib and ribociclib are approved in the adjuvant setting to reduce risk of recurrence in high risk patients with localized breast cancer.[50, 51] There is consistent data suggesting an increased risk of VTE in breast cancer patients treated with CDK 4/6 inhibitors, both in the metastatic and the adjuvant settings [9, 10, 52-55]. Of note, the VTE incidence in observational studies is at least 2-fold compared to that in clinical trials [54]. While this risk is higher when CDK 4/6 inhibitors are combined with tamoxifen rather than AIs [50, 56, 57], there is also concern for increased VTE risk regardless of the endocrine backbone.

There appears to be a thrombogenic class effect with a meta-analysis of trials in the metastatic setting reporting an overall risk ratio of 2.62 (1.21-5.65) for VTE with CDK 4/6 inhibitors [58].

In a real-world retrospective cohort study of 424 consecutive metastatic patients receiving CDK 4/6 inhibitors, the rate of VTE during treatment was 9% over a median follow-up of 18.5 months [9]. Similarly, in another multi-center cohort study including 364 patients treated with abemaciclib with a median follow-up of 5.5 months, the rate of VTE was 9.1 / 100 patient years. [54] Furthermore, patients developing VTE during

therapy had a higher risk of death than those who did not (HR 2.09; 95% CI 1.07–4.13). Accumulating observational data support the concept of increased VTE risk with CDK 4/6 inhibitors, with VTE rates of 8.7/100 patient years (PY) for palbociclib, 2.5/100PY for ribociclib and 9.1/100PY for abemaciclib [10]. **Supplemental Table 2** details the rates of VTE in randomized controlled trials of metastatic and early breast cancer patients comparing CDK 4/6 inhibitors plus endocrine therapy to endocrine therapy alone.

C.5 HER2 targeted therapies

Approximately 15-20% of patients with breast cancer have tumors that overexpress HER2 [34]. HER2 targeted treatments such as trastuzamab, pertuzumab, and the antibody–drug conjugates trastuzumab-emtansine or trastuzumab-deruxtecan have not demonstrated an increased risk of VTE, however the apparent low VTE rate despite advanced cancer stages in these large trials does raise the concern of possible underreporting [59-64]. HER-2 targeted tyrosine kinase inhibitors such as lapatinib, neratinib and tucatinib, have also not demonstrated an increased risk of VTE [65-68].

C.6 PARP Inhibitors

Poly (ADP-ribose) polymerase (PARP) inhibitors such as olaparib and talazoparib are used in patients who have pathogenic mutations in DNA repair pathway (e.g., BRCA1 and BRCA2), who are germline BRCA mutation carriers with metastatic disease, and for high-risk BRCA carriers with early-stage disease as adjuvant therapy.[3, 4] The overall risk of VTE was low in the OLYMPIAD and EMBRACA studies, evaluating PARP inhibitors for metastatic breast cancer, and in the OLYMPIA study evaluating olaparib in the adjuvant setting [69, 70]. In a meta-analysis of 32 prospective studies including patients with solid tumors, an increased risk of all-grade thromboembolic events (venous and arterial) was reported for PARP inhibitors (OR: 1.49 [95%CI: 1.14-1.95].[71] However, between-study heterogeneity was substantial and no subgroup analysis within patients with breast cancer was conducted. A 2025 meta-analysis included 9 breast cancer studies with a total of 2329 patients treated with PARP inhibitors and 2119 controls, and did not demonstrate an increased VTE

risk with PARP inhibitors (OR 0.86, 95% CI 0.46-1.59).[72] Accordingly, while real world data is lacking, the clinical trial data on PARP inhibitors in patients with breast cancer, do not indicate an increased VTE risk.

C.7 Immunotherapy

Immune checkpoint inhibitors such as pembrolizumab are used in combination with chemotherapy in advanced, PDL-1 positive triple negative breast cancer, and concurrent pembrolizumab and chemotherapy is used in triple negative breast cancer in the neoadjuvant setting.[73, 74] There is no reported increased risk of VTE with either immunotherapy specifically in breast cancer; however, data are accumulating suggesting a clinically-relevant risk of VTE in patients treated with immune checkpoint inhibitors for other types of solid tumors.[75-77]

GUIDANCE RECOMMENDATIONS

1. We suggest categorization of VTE risk associated with hormonal, targeted and immunotherapeutic breast cancer therapies as detailed in **Supplemental Table 3**.

D. ROLE OF PHARMACOLOGIC THROMBOPROPHYLAXIS DURING SYSTEMIC BREAST CANCER TREATMENT

In general, unstratified pharmacologic thromboprophylaxis in patients with cancer, including breast cancer, is not recommended due to an unfavorable risk-benefit ratio.[78, 79] Individualized risk assessment, to select patients most likely to benefit from primary thromboprophylaxis is recommended.[78, 79] An example of this is patients with active breast cancer who are hospitalized and confined to bed with an acute medical illness, where thromboprophylaxis with a low-molecular weight heparin (LMWH) in the absence of bleeding or other contraindications is recommended for the duration of the hospitalization.[78]

Ambulatory patients with breast cancer represent the majority of clinical encounters for this large patient population. Considerations for pharmacologic thromboprophylaxis differ for ambulatory and

hospitalized cancer patients, with risk assessment part of the key decision making process for the ambulatory cohort.[78] In ambulatory patients with breast cancer starting systemic cancer therapy, primary thromboprophylaxis is considered for selected high risk subgroups, commonly defined by an estimated 6-month risk of VTE of >8-10%.[78] While it is beyond the scope of this guidance, several validated risk assessment models are available to aid providers in quantifying VTE risk in this patient population and thereby selecting patients who may benefit from primary thromboprophylaxis.[80] Risk factors considered in these models are predominately comprised of baseline patient demographics and characteristics, laboratory data, and cancer type, and less commonly cancer therapy.

In addition to available risk assessment models, modification of prothrombotic risk by type of systemic therapy warrants consideration (**Supplemental Table 3**), with tamoxifen and CDK 4/6 inhibitors conferring the highest established increase in VTE risk of the available therapies.[11] This risk is further modified by underlying prothrombotic risk factors including genetic thrombophilia.[39, 42] Therefore, patients with breast cancer initiating systemic therapies known to be associated with an increased thrombotic risk (**Supplemental Table 3**) may be considered for a thrombotic risk assessment. Thrombophilia evaluation should not be routinely performed in every patient but can be considered on a case-by-case basis if clinical suspicion in high (e.g., family history of unprovoked thrombotic events, known family history of thrombophilia).

Currently, insufficient data are available on the risk of VTE recurrence during hormonal or other systemic breast cancer therapies after a first pregnancy- or hormonal contraceptives -associated VTE. Women with these features might be at an increased VTE risk while treated with prothrombotic breast cancer treatment based on previous data in the general population [81]. No dedicated studies on the impact of antiphospholipid antibodies on the risk of VTE in patients with breast cancer undergoing hormonal and other systemic therapies are available, yet the presence of antiphospholipid antibodies might increase the risk of thrombotic events in patients with cancer in general.[82]

In patients with breast cancer, risk of VTE is increased in the first month after surgery.[83] Therefore, a risk stratified approach for the perioperative management of ongoing systemic prothrombotic breast cancer

therapies (**Supplemental Table 3**) should be considered to avoid additive prothrombotic risk. While there is limited evidence to guide when to stop and restart tamoxifen, most physicians at our institutes and on this guidance panel would consider a time-limited tamoxifen hold (usually for several weeks) in non-low-risk patients. The duration of holding tamoxifen is extrapolated from tamoxifen pharmacokinetics. A single-center reported on a risk stratified approach based on individual and procedural risk factors in women taking tamoxifen undergoing surgery; however, the study had several significant limitations such an unusually high VTE rate, and the results were hypothesis-generating at best [84]. General post-surgical risk stratification and thromboprophylaxis is discussed in section C.1 and is beyond the scope of this document.

GUIDANCE RECOMMENDATIONS

2. We advise against routine testing for thrombophilia (i.e., antithrombin, protein C, protein S, factor V Leiden, and prothrombin gene mutation) in patients with no family history of either VTE or a known thrombophilia.
3. We suggest anticoagulant thromboprophylaxis in patients receiving either tamoxifen or CDK 4/6 inhibitors (over no thromboprophylaxis and over withholding these therapies in absence of an acceptable alternative) who have at least one additional prothrombotic risk factor such as:
    a. Known inherited thrombophilia *
    b. Known antiphospholipid antibodies with qualifying laboratory criteria [85]) **
    c. Prior VTE associated with hormone use or unprovoked VTE
    d. Combined therapy with CDK 4/6 inhibitors and tamoxifen
4. In patients on tamoxifen or CDK 4/6 inhibitors undergoing surgery that is associated with a moderate-high thrombotic risk, we suggest holding this therapy from approximately 2 weeks prior to surgery until mobile (usually 24 hours, but extended if large flap-based reconstructive surgery)
5. We advise that patients receiving chemotherapy for breast cancer be stratified for VTE risk using a validated risk assessment model as recommended by VTE guidelines for cancer patients. [32, 86, 87]

* The authors had heterogeneity in agreement regarding whether lower risk thrombophilia (e.g., heterozygous factor V Leiden, heterozygous prothrombin G20210A) should be considered. Risk modifiers include family history of VTE. Heterogeneous data exist on the association of prothrombotic mutations and VTE risk in patients with breast cancer, as discussed above, yet based on similar thrombotic associations of heterozygous factor V Leiden and heterozygous prothrombin G20210A in the general population we consider these two together.

** Heterogeneity in agreement regarding whether only laboratory criteria of antiphospholipid antibodies should be considered.

E. MANAGEMENT OF PATIENTS WITH VTE ON PROTHROMBOTIC THERAPY

E.1 Can prothrombotic therapy be continued?

In general, risk of recurrent VTE on anticoagulation in patients with cancer-associated VTE is increased threefold compared to those with VTE but without cancer [88]. Therefore, management of VTE in patients with breast cancer should consider additional specific risk factors that might confer an increased recurrence risk, including ongoing systemic therapies with an established prothrombotic risk (i.e., tamoxifen and CDK 4/6 inhibitors). There is lack of data on the risk of recurrent VTE and the risk/benefit ratio of continuing tamoxifen or CDK 4/6 inhibitors in patients who develop VTE during active treatment with these agents.

In patients with VTE during tamoxifen therapy, continuation of tamoxifen is generally considered safe for the duration of anticoagulant therapy. This consideration is extrapolated from a post-hoc analysis of women with VTE on anticoagulation, where the risk of recurrent VTE was comparable among those who used estrogen or progesterone containing oral contraception and those who did not.[89] In a recent registry-based study including 479 patients with breast cancer who developed VTE during hormonal therapy, post-VTE continuation of hormonal therapy was associated with an increased risk of VTE within the first 3 months, with no significant differences thereafter. This study has methodological limitations which make these results hypothesis-generating, warranting further research. [90] In addition, when considering safety, recent data show

that concurrent use of tamoxifen and direct oral anticoagulants (DOACs) is not associated with an increased risk of anticoagulation associated major bleeding compared to AIs and DOACs (2.5% vs. 3.3%) [91].

Until further evidence becomes available, each case should be assessed individually for other risk factors for VTE, the risk/benefit of tamoxifen (and CDK 4/6 inhibitors) and possible alternative endocrine therapy options in discussion with the patient and the treating medical oncologist.

GUIDANCE RECOMMENDATIONS

6. In a patient with breast cancer who develops VTE while on tamoxifen or CDK 4/6 inhibitors, we suggest continuation of this cancer therapy together with therapeutic-dose anticoagulant therapy after an individualized risk/benefit assessment and upon multidisciplinary discussion.

E.2 Duration of anticoagulation with ongoing prothrombotic therapy

Guidelines for treatment of cancer-associated VTE across all cancer types recommend at least 6 months of anticoagulation with LMWH or DOACs.[78, 79] Beyond 6 months, although there is limited data, continued anticoagulation is generally offered to high-risk patients including metastatic disease or those receiving ongoing cancer-specific therapies (especially if associated with increased thrombotic risk), with regular re-assessment of the risk-benefit of continuing anticoagulation [32]. There is no data to inform the optimal duration and type of anticoagulant therapy specifically for women with breast cancer and VTE. Although tamoxifen and CDK 4/6 inhibitors are considered as established risk factors for VTE, there is no specific recommendation on the long-term anticoagulation in patient receiving ongoing treatment with these agents [32].

The impact of tamoxifen on risk of VTE appears to attenuate over time, yet some studies suggest an ongoing prothrombotic effect [35]. A cohort study of 13,202 patients with breast cancer, showed the prothrombotic effect of tamoxifen is noticeably reduced 3 months after initiation of therapy [6]. It is therefore

prudent to take into consideration the timing of VTE in relation to initiation of tamoxifen therapy, in addition to individualized assessment of other risk factors when deciding the duration of anticoagulant treatment.

GUIDANCE RECOMMENDATIONS

7. We suggest continuing anticoagulation in patients with VTE for whom tamoxifen or CDK 4/6 inhibitors remain the preferred therapy, provided there are no significant bleeding risk factors.
8. In patients receiving tamoxifen or CDK 4/6 inhibitors with a high bleeding risk in whom time-limited anticoagulation for VTE is preferred, we suggest a multidisciplinary discussion including the oncologist and a thrombosis specialist regarding transitioning to an acceptable therapeutic alternative without increased VTE risk.
9. We advise deciding on optimal anticoagulant type and dose according to VTE guidelines for cancer patients [32].

F. DRUG-DRUG INTERACTION CONSIDERATIONS

LMWH had been the anticoagulant of choice for patients with cancer-associated VTE for decades [92, 93], but in recent years, DOACs are increasingly used in this population based on several randomized controlled trials [94-97]. While pharmacokinetic (PK) interactions with LMWH are typically not a major concern, DOACs often warrant close inspection for potential drug-drug interactions (DDI). All DOACs are involved in P-glycoprotein (gp) pathways, and rivaroxaban and apixaban are also metabolized through cytochrome (CYP) 3A4 system. Concurrent use of DOACs and inhibitors of either one or both pathways can theoretically increase DOAC levels, which might theoretically increase the risk of bleeding complications. On the other hand, inducers of CYP and/or P-gp pathways can theoretically lead to a decrease in DOAC levels and thereby might increase VTE risk. Whether these theoretical concerns derived from in-vitro PK studies adequately correlate with relevant clinical outcomes remains largely unknown.

Tamoxifen is a moderate CYP and P-gp inhibitor, prompting some to advise caution with concurrent use of tamoxifen and DOACs, due to concern over a theoretical increase in bleeding risk with this combination [98-101]. However, a recent large population-based analysis showed that in patients with breast cancer, concurrent AI or tamoxifen use with DOACs was associated with comparable risk of major bleeding events requiring emergency room visits or hospitalizations [91]. Another database analysis including 13,158 patients with cancer treated with DOACs for atrial fibrillation reported a comparable risk of major bleeding in the subgroup of 147 breast cancer patients treated with concurrent tamoxifen and those treated with DOAC alone [102]. These studies reporting on clinical outcomes suggest that tamoxifen can be safely administered with DOACs. This discordance between pharmacokinetic studies and clinical data also highlights that studies with relevant clinical outcomes are needed to understand the relevance of theoretical DDIs with DOACs. There are no major DDI concerns with anticoagulants with other agents commonly used in breast cancer including AI, CDK 4/6 inhibitors, and PARP inhibitors. The safety of CDK 4/6 inhibitors with concurrent DOAC use was further supported by observational data [103].

We summarized potential DDIs of concern between DOACs and systemic therapy commonly used in breast cancer in **Supplemental Table 4**. Strength of evidence was suggested based on available data.

GUIDANCE RECOMMENDATION

10. For patients with breast cancer on tamoxifen, AI, SERD, CDK 4/6 inhibitors, PARP inhibitors or GnRH agonists, we suggest that DOACs can be used concurrently if indicated.

G. ARTERIAL THROMBOEMBOLISM ASSOCIATED WITH SYSTEMIC BREAST CANCER THERAPY

Overall, tamoxifen is not associated with an increased risk of arterial thrombosis (i.e., myocardial infarction or stroke), and a meta-analysis of randomized controlled trials even demonstrated a reduction in adverse arterial cardiovascular events compared to placebo [7, 104]. However, in the large scale randomized ATAC

study, comparing adjuvant therapy with anastrozole to tamoxifen in 9,366 patients with localized breast cancer, the rate of ischemic cardio- vascular disease was non-significantly increased with anastrozole (4.1% vs 3.4%, OR 1.23 [95%CI: 0.95-1.60]), whereas the rate of ischemic cerebrovascular events was lower with anastrozole compared to tamoxifen (2.0% vs 2.8%, OR: 0.70 [0.50-0.97]). [105] Of note, two large meta-analyses that evaluated toxicity differences and included the ATAC study found that cerebrovascular event rates were comparable between tamoxifen and AIs.[106]

There are limited data regarding the association between AIs and ATE, however, in a retrospective cohort study of over 20,000 breast cancer patients, a non-significant increase in the risk of cardiovascular events in patients treated with AIs versus tamoxifen was observed (aHR 1.13, 95% CI: 0.79-1.63).[107] These findings were supported in additional population-based studies [108]. For example, in a large population-based study including 23,525 patients with newly diagnosed breast cancer, treatment with AIs was associated with an increased risk of heart failure (HR: 1.86 [95% CI, 1.14-3.03]) and cardiovascular mortality (HR: 1.50 [95% CI, 1.11-2.04]) compared to tamoxifen, whereas a non-significant increase was observed for risk of myocardial infarction (aHR 1.37, 95% CI: 0.88-2.13) and ischemic stroke (aHR 1.19, 95% CI: 0.82-1.72).[8]

Insufficient data exist to determine a causal increase in ATE risk with CDK 4/6 inhibitors. The evidence on arterial thrombosis with CDK 4/6 inhibitors and additional evidence on tamoxifen is detailed in the **Supplemental Material**.

GUIDANCE RECOMMENDATIONS

11. We suggest that AI therapy be considered as a potential risk factor for cardiovascular disease.
12. We suggest that tamoxifen is not a clinically meaningful risk factor for arterial thromboembolism.

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Management of Thrombotic Risk Associated with Endocrine and Other Systemic Therapy in Patients with Breast Cancer: ISTH SCC guidance document

Supplemental Material

Supplemental Table 1: VTE in selected clinical trials of tamoxifen, AI and fulvestrant therapy in breast cancer

Trial	Country/Cohort years	Stage	Follow-up Duration	Total(N)	Drug	Comparator	Outcome	Event Rates*	Relative Risk/Hazard Ratio	Note
Tamoxifen										
NSABP P-1 [1]	US/1992-1997 Randomized	Breast cancer prevention	Median 47.7 months	13 207 (All) 6610 (Tamoxifen) 6597 (Placebo)	Tamoxifen	Placebo	PE	0.69/1000 PY (tamoxifen) 0.32/1000 PY (Placebo)	RR 2.15 (95% CI 1.08 to 4.51)	PE only increased in women 50 or older
							DVT	1.21/1000 PY (Tamoxifen)	RR 1.44 (95% CI 0.91 to 2.30)	

Trial	Country/Cohort years	Stage	Follow-up Duration	Total(N)	Drug	Comparator	Outcome	Event Rates*	Relative Risk/Hazard Ratio	Note
								0.84/1000 PY (Placebo)		
							Stroke	1.75/1000 PY (Tamoxifen) 1.23/1000 PY (Placebo)	RR 1.42 (95% CI 0.9 to 2.8)	
IBIS-I [2]	UK, Europe, Aus,NZ/1992-2001 Randomized	Breast cancer prevention	Median 95.6mo	7145(All) 3579(Tamoxifen) 3575(Placebo)	Tamoxifen	Placebo	VTE [1]	4.1/1000 PY (Tamoxifen)	RR 1.72, (95% CI 1.27 to 2.36)	Excess of TE during active treatment

Trial	Country/Cohort years	Stage	Follow-up Duration	Total(N)	Drug	Comparator	Outcome	Event Rates*	Relative Risk/Hazard Ratio	Note
								2.4/1000 PY (Placebo)		
Decensi et al, 2005 [3]	Italy/ 1992-1997 Randomized	Breast cancer prevention	5 years	5408 (all) 2700 (Tamoxifen) 2708 (Placebo)	Tamoxifen	Placebo	VTE	4.4/1000 PY (Tamoxifen) 3.1/1000 PY (Placebo)	HR 1.63 (95% CI 1.02–2.63)	Excess in VTE during first 18 months after inclusion
Danish Breast Cancer Cooperative	Denmark/1994-2004 Cohort	stage I or stage II	5 years	16,289	Tamoxifen	Placebo	DVT/PE	1.2% 5-year risk (Tamoxifen)	RR 2.4 (95% CI, 1.6-3.4)	Yrs 1,2 aHRs of 3.5 (95% CI, 1.6-7.5) and 3.4 (95%

Trial	Country/Cohort years	Stage	Follow-up Duration	Total(N)	Drug	Comparator	Outcome	Event Rates*	Relative Risk/Hazard Ratio	Note
Group [4]								0.5% 5-year risk (Placebo)		CI, 1.7-7.0). No increased risk of DVT/PE yrs 5-10 (HR, 1.1; 95% CI, 0.69-1.9),
ATLAS [5]	36 countries, regions/1996–2005 Randomized	Early stage	10 years	6846 3428 (Tam10) 3418(Tam5)	Tamoxifen 10yrs	Tamoxifen 5yrs	PE (hospitalized or died)	41 events (1.2%; Tam 10) 21 events (0.6%; Tam 5)	Event rate 1·87 (95% CI 1·13–3·07, p=0·01	/

Trial	Country/Cohort years	Stage	Follow-up Duration	Total(N)	Drug	Comparator	Outcome	Event Rates*	Relative Risk/Hazard Ratio	Note
English CPRD [6]	UK/1997-2006 Cohort	All stages	5.3 years	13 202(all) 10879 (endo) 3821 (tam)	Tamoxifen	Placebo	VTE (PE, DVT, other thrombosis)	24.1/1000 PY (1st 3mo)	HR 5.5 (95% CI 2.3-12.7)	For women on endocrine therapy, the risk of VTE in the 3 months after beginning therapy was more than double the risk in those who did not
								5.2/1000 PY (subsequent)	HR 1.9 (95% CI 0.9-4.3)	

Trial	Country/Cohort years	Stage	Follow-up Duration	Total(N)	Drug	Comparator	Outcome	Event Rates*	Relative Risk/Hazard Ratio	Note
										receive endocrine therapy (HR, 2.4; 95% CI, 1.7-3.4; AR, 27.7) No increased risk beyond 3mo (HR, 0.9; 95% CI, 0.7-1.1; AR, 7.0).

Trial	Country/Cohort years	Stage	Follow-up Duration	Total(N)	Drug	Comparator	Outcome	Event Rates*	Relative Risk/Hazard Ratio	Note
AI										
Xu et al. 2019 [7]	US (California)/ 1991-2011	First diagnosis of breast cancer	Med 5.4 yrs	12904 4062 (Tam) 3837 (AI) 2922 (ombo)	AI (letrozole, anastrozole, exemestane)	Tamoxifen Combo	DVT, PE	3.3/1000 PY for DVT 2.2/1000 PY for PE)	aHR 0.59 (95% CI 0.43, 0.81)	/
SIADIAP [8]	Spain/2006-2015	Stage I-III	10 years	21 537 3082 (tam) 18,455 (AI)	Tamoxifen	AI (Anastrozole, letrozole, exemestane)	TEE (PE, DVT, phlebitis and thrombophlebitis)	Tamoxifen 49 events (1.59%) 8.16/1000 PY (95%CI 6.10–10.69)	adjusted HR 0.93 (95%CI 0.69–1.26)	No difference in TEE between AI and Tam. 2nd outcome

Trial	Country/Cohort years	Stage	Follow-up Duration	Total(N)	Drug	Comparator	Outcome	Event Rates*	Relative Risk/Hazard Ratio	Note
										(PE+DVT): -100 PE --7 in TAM group, incidence rate 1.17 (95%CI:0.51–2.31); --93 in AI group, incidence rate 1.87 (95%CI:

Trial	Country/Cohort years	Stage	Follow-up Duration	Total(N)	Drug	Comparator	Outcome	Event Rates*	Relative Risk/Hazard Ratio	Note
										1.52–2.28)] - 294 DVTs --42 in TAM group, incidence rate 6.99 (95%CI: 5.10–9.36); --252 in AI group, incidence rate 5.06 (95%CI:

Trial	Country/Cohort years	Stage	Follow-up Duration	Total(N)	Drug	Comparator	Outcome	Event Rates*	Relative Risk/Hazard Ratio	Note
										4.47–5.72)]
								AI 345 events (1.87%) 6.93/1000 PY (95%CI 6.23–7.69)	NA	Increase risk of PE [stabilized IPW HR 2.26 (95%CI 1.02–4.97)]
IBIS II [9]	International/2003-2012 Randomized	Breast cancer prevention	131 months	3864 (All) 1920 (Anastrozole) 1944 (Placebo)	Anastrozole	Placebo	DVT, PE	30 events (1.6%; Anastrozole) 29 (1.5%; Placebo)	NR	/

Trial	Country/Cohort years	Stage	Follow-up Duration	Total(N)	Drug	Comparator	Outcome	Event Rates*	Relative Risk/Hazard Ratio	Note
ATAC [10]	Multinational/ 1996-2000 Randomized	Early breast cancer	Med 33.3mo	9366 3125 (ana) 3116 (Tam) 3215 (Combo)	Anastrozole	Tamoxifen Combo	Any VTE	Anastrozole 64 (2.1%) Tamoxifen 109 (3.5%) Combo 124 (4%)	NR	P -value: <0.001 for any VTE, 0.02 for DVT+PE
							DVT including PE	Anastrozole 32 (1.0%) Tamoxifen 54(1.7%) Combo (2%)		

Trial	Country/Cohort years	Stage	Follow-up Duration	Total(N)	Drug	Comparator	Outcome	Event Rates*	Relative Risk/Hazard Ratio	Note
ABCSG trial 8/ARNO 95 [11]	Germany/1996-2003 Randomized	Locally advanced or minimally invasive breast cancer	Med 28mo	3224 1606 (Tam) 1618 (ana)	Anastrozole	Tamoxifen	Embolism	9 (<1%) Tamoxifen 2 (<1%) (Anastrozole)	OR for Embolism (Ana vs Tam): 0·22 (0·02–1·07), p=0·064	/
							Thrombosis	12 (<1%) Tamoxifen 3 (<1%) Anastrozole	OR for Thrombosis (Ana vs Tam): 0·25 (0·04–0·92), p=0·034	
BIG 1-98 [12]	International/1998-2003	Postmenopausal, early	Med 51mo	4922	Letrozole	Tamoxifen	Thromboembolism	50 (2.0%) Letrozole	NR	/

Trial	Country/Cohort years	Stage	Follow-up Duration	Total(N)	Drug	Comparator	Outcome	Event Rates*	Relative Risk/Hazard Ratio	Note
	Randomized	breast cancer		2,463 (Letrozole) 2459 (tamoxifen)				94 (3.8%) Tamoxifen p <.001		
							Cardiac Events (Ischemic, Heart Failure)	134 (5.5%) Letrozole 122 (5%) Tamoxifen p = 0.48		
TEAM [13]	Europe, Japan, USA/2001-2006 Randomized	Early breast cancer	Med 5.1yrs	9779 4868 (Tam) 4898 (Exe)	Exemestane	Tamoxifen>Exemestane	Thrombosis	99 (2%) Tam->Exe 47(<1%) Exe	NR	/

Trial	Country/Cohort years	Stage	Follow-up Duration	Total(N)	Drug	Comparator	Outcome	Event Rates*	Relative Risk/Hazard Ratio	Note
								p <0·0001		
IES [14]	International/ 1998-2003 Randomized	Postmenopausal, non-metastatic breast cancer	Med 55.7 months	4724 (all) 2320 (Exe) 2338 (Tam)	Exemestane	Tamoxifen	VTE	28 (1.2%) Exemestane 54 (2.3%) Tamoxifen P = 0.004	NR	/
							Cardiovascular events	382 (16.5%) Exe 350 (15%) Tamoxifen p = 0.16		

Trial	Country/Cohort years	Stage	Follow-up Duration	Total(N)	Drug	Comparator	Outcome	Event Rates*	Relative Risk/Hazard Ratio	Note
Fulvestrant										
Al-Mubarak et al. [15]	Metanalysis of 8 randomized trials	Postmenopausal with inoperable locally advanced or metastatic breast cancer		5 studies (Fulvestrant	Fulvestrant	Fulvestrant +AI	VTE	NA	Fulvestrant vs controls: OR 1.20 (95% CI 0.73–1.97) p=0.47	/
				2 (Fulvestrant +AI)				NA	Fulvestrant +AI vs controls: OR: 0.97 (95% CI 0.43–2.18) p=0.95	/

[1] VTE includes DVT, PE, retinal vein thrombosis, superficial thrombophlebitis, non-specific TEE

*Percentages in brackets represent crude percentage of events / patients, if not otherwise specified.

AI, aromatase inhibitor; DVT, deep vein thrombosis; HR, hazard ratio; NA, not applicable; NR, not relevant; OR, odds ratio; PE, pulmonary embolism; PY: patient years; VTE, venous thromboembolism; TEE, thromboembolic events

Supplemental Table 2: Rates of VTE in selected clinical trials comparing CDK 4/6 inhibitors plus endocrine therapy to endocrine therapy alone in patients with breast cancer

Trial	Recruitment dates/design/ inclusion	Patient numbers		Treatment		Median follow up (months)	VTE events (n, %) [% per patient years [1]]		p-value [2]
		CDK 4/6 Inhibitor	Control	CDK 4/6 Inhibitor	Control		CDK 4/6 Inhibitor	Control	
Metastatic breast cancer ER+, Her2-									
PALOMA 1 [16]	Dec 2009-May 2012 Open label 1:1 Postmenopausal, First line treatment for MBC	84	81	Palbociclib 125mg (21 of 28 days) + Letrozole 2.5mg	Letrozole 2.5mg	29.6 (palbociclib arm) 27.9 (letrozole alone arm)	4 (PE), 4.8% [2%]	0, 0% [0%]	-
PALOMA 2 [17]	February 2013 - July 2014 Double blind, 2:1 ratio postmenopausal, first line treatment for MBC	444	222	Palbociclib 125mg (21 of 28 days) + Letrozole	Placebo + Letrozole 2.5mg	23	4 (1=PE), 0.9% [0.47%]	3 (1=PE), 1.4% [0.7%]	p=0.59

Trial	Recruitment dates/design/ inclusion	Patient numbers		Treatment		Median follow up (months)	VTE events (n, %) [% per patient years [1]]		p-value [2]
		CDK 4/6 Inhibitor	Control	CDK 4/6 Inhibitor	Control		CDK 4/6 Inhibitor	Control	
PALOMA 3 [18]	Oct 2013 - Aug 2014 Pre- and postmenopausal, Double blind, 2:1 ratio MBC progressed on ET Postmenopausal, second line treatment for MBC	345	172	Palbociclib 125mg (21 of 28 days) + Fulvestrant 500mg im (days 1, 15 and subsequent 28 day cycles)	Placebo + Fulvestrant 500mg im (days 1, 15 and subsequent 28 day cycles)	8·9	5 (3=PE), 1.4% [1.95%]	0, 0% [0%]	-
PALOMA 4 [19]	March 2015 -Aug 2020 Double-blind, 1:1 Postmenopausal, first line treatment for MBC in mainland China, Hong Kong, Singapore, Taiwan, and Thailand	169	171	Palbociclib 125mg (21 of 28 days) + Letrozole	Placebo + Letrozole 2.5mg	52.8	1=PE, 0.6% [0.13%]	0=PE, 0% [0%]	

Trial	Recruitment dates/design/ inclusion	Patient numbers		Treatment		Median follow up (months)	VTE events (n, %) [% per patient years [1]]		p-value [2]
		CDK 4/6 Inhibitor	Control	CDK 4/6 Inhibitor	Control		CDK 4/6 Inhibitor	Control	
MONARCH 2 [20]	August 2014 - December 2015 Double-blind, 2:1 ratio Pre- or postmenopausal, MBC progressed on ET	446	223	Abemaciclib (150 mg twice daily) + Fulvestrant (500mg)	Placebo (twice daily) + Fulvestrant (500mg)	19.5	9 (4=PE), 2% [1.24%]	1, 0.4% [0.28%]	p=0.11
MONARCH 3 [21]	Nov 2014 - Nov 2015 Double-blind, 2:1 ratio Postmenopausal, first line treatment for MBC	328	165	Abemaciclib + non-steroidal AI [3]	Placebo + non-steroidal AI [3]	26.7	20, 6.1% [2.74%]	1, 0.6% [0.27%]	p=0.0044
MONARCH PLUS [22]	Dec 2016 -Aug 2018 Double-blind, 2:1 Postmenopausal, first line treatment for MBC, in China, Brazil, India, and South Africa.	311	152	Abemaciclib (150 mg twice daily) + non-steroidal AI [3] or Fulvestrant (500mg)	Placebo + non-steroidal AI [3] or Fulvestrant (500mg)	16	8, 2.6% [1.93%]	0, 0% [0%]	P=0.058

Trial	Recruitment dates/design/ inclusion	Patient numbers		Treatment		Median follow up (months)	VTE events (n, %) [% per patient years [1]]		p-value [2]
		CDK 4/6 Inhibitor	Control	CDK 4/6 Inhibitor	Control		CDK 4/6 Inhibitor	Control	
MONALEESA 2 [23]	January 2014 - March 2015 Double-blind, 1:1 ratio Postmenopausal, first line treatment for MBC	334	330	Ribociclib 600mg (21 of 28 days) + Letrozole	Placebo + Letrozole	15.3	2 (PE), 0.6% [0.47%]	0, 0% [0%]	-
MONALEESA 3 [24]	June 2015 - June 2016 Double-blind, 2:1 ratio Postmenopausal, first/second line treatment for MBC	484	242	Ribociclib 600mg (21 of 28 days) + Fulvestrant	Fulvestrant	(inferred) 16.8 ribociclib + Fulvestrant; 13.0 placebo + fulvestrant	1 (PE), 0.2% [0.15%]	1 (PE), 0.4% [0.38%]	p=0.6
MONALEESA 7 [25]	Dec 2014 -Aug 2016 Double-blind, 1:1 ratio Pre- or perimenopausal, first line treatment for	335	337	Ribociclib + ET [4]	Placebo + ET [4]	34.6	9 (PE), 2.7% [0.93%]	3 (PE), 0.9% [0.31%]	p=0.08

Trial	Recruitment dates/design/ inclusion	Patient numbers		Treatment		Median follow up (months)	VTE events (n, %) [% per patient years [1]]		p-value [2]
		CDK 4/6 Inhibitor	Control	CDK 4/6 Inhibitor	Control		CDK 4/6 Inhibitor	Control	
	locally advanced (inoperable) or MBC								
Early breast cancer ER+, Her2-									
PALLAS [26]	Sept 2015 - Nov 2018 Open label, 1:1 ratio Stage II-III, within 12 months of diagnosis	2883	2877	Palbociclib (2 years) + ET [5]	ET [5]	23·7	47, 1.7% [0.83%]	29, 1% [0.51%]	p=0.039
monarchE [27]	July 2017 - Aug 2019 Open-label, 1:1 ratio Node positive, high risk of recurrence	2808	2829	Abemaciclib + ET [5]	ET [5]	42	71 (28=PE), 2.3% [0.72%]	18 (3=PE), 0.5% [0.18%]	p<0.0001

[1] Calculated per arm: (follow up duration in months)/12 x number of patients = patient years; VTE/(patient years) x100=% per patient years

[2] Chi-squared – based on absolute numbers

[3] non-steroidal AI (1 mg anastrozole or 2.5 mg letrozole, daily)

[4] Goserelin (3.6 mg, administered subcutaneously on day 1 of each 28-day cycle) + AI or tamoxifen

[5] ET of choice: tamoxifen or AI (with or without concurrent luteinizing hormone-releasing hormone agonist)

AI, aromatase inhibitor; CDK, cyclin-dependent kinase; ET, endocrine therapy; PE, pulmonary embolism; VTE, venous thromboembolism

Supplemental Table 3: Systemic hormonal, targeted and immunotherapeutic breast cancer therapies and VTE risk

	VTE risk		
	No added risk	**Potential risk** [1]	**Established risk**
Type of systemic breast cancer therapy	AI, SERD, HER2 targeted therapy	Immune checkpoint inhibitors, PARP inhibitors	Tamoxifen, CDK 4/6 inhibitors

Abbreviations: AI, aromatase inhibitor; CDK, cyclin-dependent kinase; PARP, poly ADP ribose polymerase; SERD, selective estrogen receptor down-regulators

[1] Further data are needed.

Supplemental Table 4. Potential drug-drug interactions of oral breast cancer therapies with direct oral anticoagulants

Drugs	PK/PD interactions	Clinical studies	Concerns for drug-drug interaction?	Strength of evidence	Ref
Tamoxifen	Moderate CYP3A4 and P-gp inhibitor	Database analysis showed: 1)Tamoxifen + DOAC are not associated with an increased risk of major hemorrhage compared to AI + DOAC (N=4753) 2) Tamoxifen + DOAC are not associated with increased major bleeding compared to DOAC alone (N=147)	No	Low to moderate (large observational study)	[28, 29]
Aromatase inhibitor (AI)	Weak CYP3A4 inhibitor	Anastrozole + DOAC are not associated with increased major bleeding compared to DOAC alone (N=41)	No	Low to moderate (large observational study)	[29]
CDK inhibitors	None	Palbociclib + DOAC: a 6-month cumulative incidence of major	Likely no	Low (small observational study)	[30]

		bleeding 5% and non-major bleeding of 7% (N=42) [1]			
PARP inhibitors	None	None	No	N/A	N/A
GnRH agonist	None	None	No	N/A	N/A

Abbreviations: CDK, cyclin-dependent kinase; CYP, cytochrome; DOAC, direct oral anticoagulant; GnRH, gonadotropin-releasing hormone; PARP, ploy-ADP ribose polymerase; PD, pharmacodynamics; P-gp, p-glycoprotein; PK, pharmacokinetics.

[1] Comparable to bleeding rates in clinical trials [31, 32]

Literature search terms

We performed a literature search from MEDLINE using the OVID interface from inception through December 31, 2025. The strategy used the following MeSH terms to define the primary population of interest:

("Breast Neoplasms")

AND

("Aromatase Inhibitors" OR "Tamoxifen" OR "Selective Estrogen Receptor Modulators" OR "Fulvestrant" OR "elacestrant" OR "abemaciclib" OR "palbociclib" OR "ribociclib" OR "Poly(ADP-ribose) Polymerase Inhibitors" OR "Immune Checkpoint Inhibitors")

Specific populations within the general population were identified using Mesh terms and one of the following searches:

1. ("Venous Thromboembolism" or "Thrombosis")
2. ("Thrombophilia" OR "factor V Leiden" OR "Hyperprothrombinemia" OR "Protein C Deficiency" OR "Protein S Deficiency" OR "Antithrombin III Deficiency" OR "Antibodies, Antiphospholipid")
3. ("Venous Thromboembolism" or "Thrombosis")
4. ("Factor Xa Inhibitors" OR "Dabigatran") AND ("Drug Interaction")
5. ("Ischemic Stroke" OR "Thromboembolism" OR "Myocardial Infarction")

References of relevant studies were also screened. We restricted studies to those published in English.

Supplemental evidence on arterial thromboembolism and systemic breast cancer therapy

In patients with breast cancer, there are limited data regarding the association between endocrine therapy and other systemic therapies and risk of ATE, with most data focusing on VTE risk.

Tamoxifen

In a post-hoc study of patients with breast cancer treated across seven Eastern Cooperative Oncology Group (ECOG) studies, the association of ATE with adjuvant therapy was analyzed according to menopausal status[33]. In premenopausal patients receiving combination chemotherapy with tamoxifen, the incidence of ATE was significantly higher (1.6%) compared to those receiving chemotherapy alone (0.0%) (p=0.004). In the postmenopausal population, there was no significant difference in the risk of ATE when comparing chemotherapy patients by tamoxifen status (p=0.31). Furthermore, in the cohort of postmenopausal patients who received tamoxifen alone, there was no increase in the incidence of ATE when comparing them to patients on observation alone (1.2% versus 1.7%, p=0.66).

CDK 4/6 inhibitors

Heterogeneous data exist on the association between CDK 4/6 inhibitor therapy and ATE in patients with breast cancer.[34] In a retrospective study including patients treated with palbociclib, ribociclib, or abemaciclib, 9.8% of patients experienced a thrombotic event, with 34% of events being arterial over a median follow-up of 20-months.[35] A systematic review and meta-analysis of randomized controlled trials comparing combination CDK 4/6 inhibitors plus endocrine therapy versus endocrine therapy alone showed that there was no clear increase in ATE risk (OR 1.22, 95% CI: 0.47-3.18). [36] However, the reported rates of ATE in clinical trials evaluating CDK 4/6 inhibitors vary between 0-1%, as opposed to reported rates reaching 4-5% in real-world cohort studies, which may be explained in part by underreporting of ATE in evaluated clinical trials.[37, 38] Further, ATE rates vary according to individual CDK 4/6 inhibitory agents, with the lowest absolute risk reported with ribociclib and the highest risk with abemaciclib.[37] Synoptically, insufficient data exist to determine a causal increase in ATE risk with CDK 4/6 inhibitors.

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