Update on Cancer-Associated Venous Thromboembolism in Children

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Abstract

Children with cancer have an increased risk for venous thromboembolic events (VTEs) compared to the healthy pediatric population. VTE rates in children with cancer vary among cancer types. Other VTE risk factors include central venous catheters and cancer therapies. VTE diagnosis relies on objective radiological imaging, and management to this date typically involves anticoagulant therapy. Low-molecular-weight heparins (LMWHs) are the most common choice. Evidence for primary VTE prevention is conflicting, and antithrombin replacement, LMWH, or apixaban have been studied. Recently, direct oral anticoagulants such as rivaroxaban or dabigatran were investigated for VTE treatment, showing promise in efficacy and safety. However, bleeding risks in this population need careful consideration, especially periprocedurally or with treatment-related thrombocytopenia. Prediction tools for VTE require adaptation for pediatric cancer patients. Progress in understanding and managing VTE in children with cancer is significant, with ongoing trials and real-world data contributing to improved strategies.

Keywords

- venous thromboembolism
- childhood cancer
- anticoagulants
- primary prevention

Zusammenfassung

Kinder mit malignen Erkrankungen haben im Vergleich zu gesunden Kindern ein erhöhtes Risiko für venöse thromboembolische Ereignisse (VTE). Die VTE-Raten variieren je nach Krebsart. Weitere VTE-Risikofaktoren sind zentrale Venenkatheter und Chemotherapien. Die VTE-Diagnose beruht auf einer objektiven radiologischen Bildgebung, und die Behandlung umfasst in der Regel eine Antikoagulation. Niedermolekulare Heparine (LMWH) sind die häufigste Wahl. Studienergebnisse zur VTE-Prävention sind widersprüchlich. Es wurden bisher Antithrombin-Substitutionen, LMWH oder zuletzt Apixaban untersucht. In jüngster Zeit wurden direkte orale Antikoagulanzien (DOAC) wie Rivaroxaban oder Dabigatran für die VTE-Behandlung untersucht, die vielversprechend in Bezug auf Wirksamkeit und Sicherheit sind. Blutungsrisiken in dieser Patientengruppe müssen jedoch sorgfältig bedacht werden, insbesondere peri-interventionell oder bei behandlungsbedingter Thrombozytopenie. Die Fortschritte für das Verständnis und für die Behandlung von VTE bei Kindern mit malignen Erkrankungen sind beträchtlich, wobei laufende Studien zu verbesserten Strategien beitragen.

Schlüsselwörter

- venöse Thromboembolien
- Pädiatrische maligne Erkrankungen
- Antikoagulation
- Primäre Prävention

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Introduction

Children with cancer have an increased risk for venous thromboembolic events (VTEs) compared to the healthy pediatric population. The incidence of VTE in children with cancer ranges from 4 to 8% compared to around 0.01% (100 per 10,000) in hospitalized children without cancer.[1,2] Reported VTE rates in children with cancer differ by cancer subgroups and are most prevalent in patients with Ewing's sarcoma (12–19%), followed by acute lymphoblastic leukemia (ALL; 3–15%) and lymphoma (5–12%).[3–7] Lower rates are reported in children with acute myeloid leukemia (4–6%) or children with central nervous system tumors (0.5–3%).[3,8] If left untreated, VTE might result in the progression of thrombi, pulmonary embolism, and long-term sequelae such as postthrombotic syndrome, loss of vessel patency, chronic pulmonary hypertension, or neurologic complications, depending on the location of the VTE. Thus, high-risk groups such as children with cancer need focused and tailored treatment, and possibly VTE prevention strategies.

What Is Known?

Risk Factors for VTEs in Children with Cancer

Cancer itself is considered a prothrombotic state.[9] Additionally, most pediatric cancer patients have a central venous catheter (CVC), which is reported to be the most common risk factor for VTE in pediatrics.[3,9–13] Other risk factors include chemotherapeutic treatments such as asparaginase or high-dose steroid treatment specific to ALL protocols, anthracyclines, or platin derivatives.[4,8,14] Asparaginase depletes asparagine and impairs the protein synthesis of multiple proteins. Antithrombin (AT), a coagulation-relevant protein, among others is affected and is decreased with asparaginase treatment. This is known to cause a hypercoagulable state.[15]

In solid tumors, tumor location (i.e., proximity and possible compression of vessels), tumor invasion of vessels, and the presence of metastases or immobilization after surgeries must be considered.[16,17] Other cancer therapeutic strategies such as surgical interventions or radiotherapy can further increase the risk of VTE.[8] Additional VTE risk factors that can affect children with malignancy include intensive care treatment, ongoing inflammation, or hormonal replacement therapy in adolescent girls during chemotherapy.[2,18,19] General risk factors for VTE such as age (pubertal), obesity, history of VTE, or inherited thrombophilia may further increase the risk of VTE in these children.[20]

In pediatric patients, thrombophilia testing is usually reserved for patients with unprovoked TE. In this patient population, almost all TEs are considered provoked as they occur in the setting of provoking risk factors. Therefore, thrombophilia testing is generally not performed in pediatric patients with malignancy. There is no convincing evidence to suggest thrombophilia screening for all pediatric cancer patients.

Evaluation and Diagnosis

Clinical signs of VTE in children with cancer are similar to those in children without cancer. Signs may include swelling, pain, discoloration, change of temperature of an affected limb, malfunctioning CVC, chest pain, shortness of breath, coughing, tachypnea, desaturation, or even shock or cardiac arrest in the case of high-risk pulmonary embolism, as well as headache, emesis, or neurological disturbances.[21–23] Persistent fever or positive blood cultures in disease-related immunocompromised children with a CVC should be further evaluated and a thrombus infection should be considered. Clinically unsuspected (previously asymptomatic) VTEs are often incidentally diagnosed in routine imaging during treatment or cancer follow-up care, and it remains unclear how relevant incidental findings of VTE are for long-term outcomes.[21,24–26] Objective radiological imaging is needed to confirm the presence of VTE. Depending on the location, VTE is most often diagnosed by duplex ultrasonography, magnetic resonance imaging, computed tomography, or ventilation-perfusion scans.[22,23]

Management

General recommendations to manage VTE in children with cancer are based on expert opinion, guidelines for the general pediatric population, or extrapolated from adult cancer patients.[27,28] Consensus exists that all symptomatic VTEs in children with cancer should receive anticoagulant therapy. The most commonly used anticoagulants are low-molecular-weight heparins (LMWHs),[28] which have several advantages compared to other anticoagulants such as vitamin K antagonists (VKAs) or unfractionated heparin (UFH) where food–drug interactions can reduce bioavailability and permanent intravenous access and daily monitoring are needed, respectively.

A recent interventional trial was conducted to compare 6 weeks versus 3 months of anticoagulation duration in children with VTE. Initially, patients with cancer were excluded until the protocol was modified, and thereafter only a limited number of children with malignancy were included.[29] Therefore, the duration of VTE treatment in pediatric cancer patients is recommended at a minimum of 3 months, or longer until the triggering risk factor has resolved (e.g., CVC, treatment with asparaginase).[27]

Primary Prevention

Evidence of primary VTE prevention in children with cancer is scarce and no benefit of primary prevention of VTE in these children with cancer has been proven.

The PAARKA study was an open-label, randomized, controlled, extended phase II trial in pediatric ALL patients which evaluated VTE primary prevention in ALL and lymphoblastic lymphoma patients. Patients were allocated in a ratio of 2:1 (2 patients received no AT replacement to every 1 patient who received AT replacement; ►Table 1).[30] The study was not powered to prove the efficacy or safety of AT replacement, but a trend toward lower incidence of VTEs was observed in the AT replacement arm (►Table 2).[30]

The THROMBOTECT study was an open-label, prospective, and quasi-randomized study that evaluated three strategies to prevent VTE in patients with ALL during induction chemotherapy.[31] Thromboprophylaxis with prophylactic-dosed

Table 1 Characteristics of selected randomized or quasi-randomized studies including children with cancer on anticoagulation treatment or primary prevention for venous thromboembolism

Title	First author, year, journal	Study design	Patient population	*N*	Intervention (*N*) Duration of anticoagulation prophylaxis/treatment
Prevention					
PARKAA	Mitchell, 2002, Thromb Haemost	Randomized controlled	ALL or LBL At the beginning of induction chemotherapy (including ASP) with CVC Age 6 mo to 18 y	Eligible: 109 Randomized: 85	*SOC*: no anticoagulation (60) *AT supplementations* (25) AT once weekly for 4 wk (days 1, 8, 15, 22)
THROMBOTECT	Greiner, 2018, Haematologica	Randomized controlled	ALL At the beginning of induction chemotherapy (including ASP)	Eligible: 1,526 Randomized: 949	*SOC*: UFH flush (randomized 312, treated 372)[a] *LMWH* (enoxaparin prophylactic dosed) (randomized: 317, treated: 216) *AT* (randomized: 320, treated: 341)[a] Prophylaxis was administered during induction chemotherapy (D8 to D33)
PREVAPIX-ALL	O'Brien, 2024, Lancet Haematology	Randomized controlled	ALL At the beginning (D7 to D4) of induction chemotherapy (including ASP) Age 1 to 17 y	Eligible: 537 Randomized: 512	*SOC*: no anticoagulation (256) *DOAC*: apixaban (256, prophylactic dosed) Prophylaxis was administered during induction chemotherapy (D1–4 to D28)
Treatment					
EINSTEIN-Jr	Palumbo, 2022, Blood advances	Randomized controlled, subgroup analysis	Children with venous thromboembolism, 0–17 y *subgroup analysis* on: Hematologic malignancy, solid malignant tumors diagnosed in the last 6 mo	Eligible: 520 Randomized: 500 Subgroup: 56	*SOC*: LMWH or vitamin K antagonists (16) *DOAC*: rivaroxaban (40) Initial treatment with parenteral anticoagulation, switch after at least 5 d Mean treatment duration was 91 d (IQR: 85–91)
DIVERSITY	Halton, 2021, Lancet Haematology	Randomized controlled	Children Age <18 y with diagnosis of acute TE	Eligible: 328 Randomized: 267 Of 267 randomized, 19 (11%) had a history of active or previous cancer	*SOC*: LMWH or vitamin K antagonists (90) *DOAC*: dabigatran (177) Initial treatment with parenteral anticoagulation, switch after at least 5 d Treatment duration of 3 mo, no details on cancer patients

Abbreviations: ALL, acute lymphoblastic leukemia; ASP, asparaginase; AT, antithrombin; CVC, central venous catheter; D, day; IQR, interquartile range; LBL, lymphoblastic lymphoma; LMWH, low-molecular-weight heparin; SOC, standard of care; UFH, unfractionated heparin.
[a]*N* treated was higher than *N* randomized because crossover of the treatment group was allowed after randomization.

LMWH (enoxaparin) and activity-adjusted AT replacement were compared to low-dose UFH line flushes (►**Table 1**).[31] Because of the large crossover between treatment groups, the analysis was displayed in two ways: intention to treat and as treated. In the as-treated analysis, rates of VTE were lower in children treated with LMWH (3.2%) or with AT replacement (2.6%) compared to standard of care with UFH flushes (6.7%). No meaningful difference regarding VTE occurrence was identified between LMWH and AT replacement. None of the secondary outcomes analyzed (major bleeding events, 5-year survival) showed differences between the three groups (►**Table 2**). Some concern was raised by the slightly lower 5-year survival and higher incidence of relapse in the AT replacement group which was observed in the intention-to-treat analysis. Important limitations in this study included the low enrolment because of the inconvenient treatment administration (subcutaneous injection of LMWH). Crossover to other treatment groups after randomization was frequent, especially in the LMWH group where a third of patients opted for another treatment arm, and might have introduced bias to the results. Because of the large crossover especially from the LMWH arm into the other two arms, and the resulting selection bias, we consider only the "as-treated" analysis relevant for this review. Furthermore, only symptomatic VTEs were considered.

A systematic review and network meta-analysis summarized the evidence of primary prophylaxis in pediatric cancer patients studied in six clinical trials, and identified LMWH as the only agent which reduced the cumulative incidence of VTE in the pediatric cancer population (mainly ALL). No higher risk of bleeding was identified. These findings should be interpreted with caution, as the risk of bias was assessed as moderate to high for all included studies, and the heterogeneity across all intervention comparisons was high, limiting the applicability in clinical practice.[32]

Table 2 Results of selected randomized or quasi-randomized studies including children with cancer on anticoagulation treatment or primary prevention for venous thromboembolism

Title	Efficacy outcomes	Safety and other outcomes
Prevention		
PARKAA	*Presence of symptomatic or asymptomatic TE* SOC: $N = 22$, 36.7% (95% CI: 24.4–48.8%) OR: (ref.) AT: $N = 7$, 28% (95% CI: 12.1–49.4%) OR: 0.67 (95% CI of OR: 0.3–2.3)	*Major bleeding:* SOC: $N = 1$, 1.7% (95% CI: 0.04–8.9%) AT: $N = 0$, 0% (95% CI: 0–11%) *Relation of TE to the presence of prothrombotic disorders:* No association was seen between thrombosis and the presence of APLA, FV Leiden, or prothrombin gene
THROMBOTECT	*Thromboembolic events during induction and consolidation chemotherapy (D8–D64)* Overall: $N = 42$, 4.4% (95% CI: 3.2–5.9%) As-treated: UFH: $N = 25$, 6.7% (SE: ± 1.2%, ref.) OR: (ref.) LMWH: $N = 7$, 3.2% (SE: ± 1.2%, $p = 0.47$) OR: 0.47 (95% CI of OR: 0.20–1.09) AT: $N = 9$, 2.6% (SE: ± 0.9%, $p < 0.001$) OR: 0.38 (95% CI of OR: 0.17–0.82)	*Hemorrhage:* No difference between groups in the as-treated analysis. *5-year event-free survival:* No difference between groups in the as-treated analysis; *ALL relapse:* No difference between groups in the as-treated analysis
PREVAPIX-ALL	*Presence of TE during follow-up for median D27 (IQR: 26–28)* SOC: $N = 45$, 18% RR: (ref.) DOAC: $N = 31$, 12% RR = 0.69 (95% CI of OR: 0.45–1.05)	*Major or CRNM bleeding:* SOC: $N = 5$, 2% (ref.) RR: (ref.) DOAC: $N = 13$, 5% RR = 2.60 (95% CI of OR: 0.94–7.17) *Minor bleeding* SOC: $N = 20$, 8% RR: (ref.) DOAC: $N = 37$, 14% RR = 1.85 (95% CI: 1.10–3.10)
Treatment		
EINSTEIN-Jr, subgroup analysis of cancer patients	*Symptomatic recurrent TE:* $N = 0$ *Repeated imaging of TE:* Normalized: SOC: $N = 7$ (46.7%) DOAC: $N = 13$ (35.1%) Improved: SOC: $N = 5$ (33.3%) DOAC: $N = 19$ (51.4%) Unchanged: SOC: $N = 3$ (20%) DOAC: $N = 5$ (13.5%) Deteriorated: SOC: $N = 0$ (0%) DOAC: $N = 0$ (0%)	*Major or CRNM bleeding:* SOC: $N = 0$ DOAC: $N = 1$ (related to Mallory–Weiss tears)

Abbreviations: 95% CI, 95% confidence interval; APLA, antiphospholipid antibody syndrome; AT, antithrombin; CRNM, clinically relevant nonmajor; D, day; DOAC, direct oral anticoagulants; IQR, interquartile range; LMWH, low-molecular-weight heparin; *N*, number; ref., reference; OR, odds ratio; RR, relative risk; SE, standard error; SOC, standard of care; TE, thrombosis or thromboembolism; UFH, unfractionated heparin.

What Is New?

DOAC for VTE Treatment

Several trials investigating direct oral anticoagulants (DOACs) have been and are currently being conducted in children with different underlying disorders for the treatment and prophylaxis of VTE. Rivaroxaban and dabigatran were studied in pediatric VTE clinical trials which have been published. Rivaroxaban and dabigatran have been approved across varying jurisdictions for use in children with VTE.[33–35] The pediatric VTE edoxaban trial (NCT02798471) has been concluded and the results are pending publication, while the pediatric VTE apixaban trial (NCT02464969) is still ongoing.[36,37]

The randomized controlled trial on rivaroxaban versus standard of care (UFH, LMWH, or VKA) in children published a subgroup analysis for childhood cancer-related VTE (►Table 1).[34] Of 500 enrolled participants, 56 had hematologic malignancy or solid tumors. In children with cancer, rivaroxaban showed comparable efficacy and safety to the standard of care group (►Table 2). The other large randomized controlled trial compared dabigatran to standard of care (LMWH, UFH, VKA) in 267 children (DIVERSITY; ►Table 1).[35] This study included 19 (11%) children with an active or previous cancer diagnosis. Overall, the authors observed noninferiority of dabigatran to standard of care with LMWH or UFH; however, no further details in cancer patients were specified.

DOAC for Primary VTE Prevention

PREVAPIX-ALL is a recently published multicenter, randomized controlled trial which studied primary VTE prevention with prophylactic-dose apixaban compared to no systemic anticoagulation in 512 children with ALL or lymphoma during induction chemotherapy (►Table 1).[38] All participants had a CVC *in situ*. No benefit of prophylactic-dose apixaban could be shown, although there was a nonsignificant trend toward less VTE in children on apixaban compared to children with no systemic anticoagulation (►Table 2). VTE was defined as symptomatic and clinically unsuspected VTE. Major bleeding events were infrequent (total $n = 4$) and were evenly distributed in treatment and control groups. However, clinically relevant nonmajor and minor bleeding events, especially epistaxis, occurred more often in the DOAC arm compared to the standard of care arm (►Table 2). The study intervention was administered only for a short time (29 days) and patients were followed up for a mean of 27 days, which probably limited the number of detectable events. Additionally, study attrition in the apixaban arm was high (23%), and low in the nointervention arm (4%). Furthermore, patients with major risk factors for VTE such as extreme hyperleukocytosis or CNS disease were excluded from this study. In subgroup analysis, there was a higher bleeding risk in the apixaban arm in children <10 years, while the bleeding risk was comparable in both arms in children aged 10 years or older. Regarding the occurrence of VTE, there was no difference between the age groups and respective treatment arms.

In obese patients, VTE was prevented in the apixaban arm compared to the standard of care arm (RRR: 91%, $p = 0.007$), while no significant difference in bleeding was observed. Additionally, the measured drug exposure was similar in obese and nonobese children. This preliminary subgroup analysis was presented as an abstract.[39]

What Do We Need to Know?

Bleeding Risk

There are no general recommendations for anticoagulation management in children with cancer for situations of increased bleeding risk such as treatment-related thrombocytopenia, cancer diagnostic interventions such as lumbar punctures or bone marrow aspirates/biopsies, or treatment-related interventions such as lumbar punctures for intrathecal treatment administration. Different centers and studies have local guidelines. As an example, a protocol has been published and implemented in Hamilton, Canada, to guide the LMWH management of children with ALL and VTE: in the first 2 weeks of LMWH treatment, platelets are transfused to maintain a platelet count of >30 G/L. Thereafter, full-dose LMWH is given if platelets are >30 G/L, half-dose LMWH is given if platelets are 20 to 30 G/L, and LMWH is held if platelets are <20 G/L. Additionally, LMWH is held for 24 hours before invasive procedures such as lumbar punctures, and restarted 12 hours after the procedure in the absence of bleeding.[40] The PREVAPIX-ALL study used a platelet cut-off of 20 G/L to hold prophylactic-dose apixaban during thrombocytopenia. A higher risk for minor bleeding episodes and a slight trend toward increased major bleeding was observed in the prophylactic-dose apixaban group compared to no prophylaxis.[38] The EINSTEIN-Jr trial used a platelet cut-off of 50 G/L to hold treatment-dosed rivaroxaban.[34] In adult cancer patients, higher platelet cut-offs (25–50 G/L) are recommended for holding treatment-dosed DOACs.[41] A hallmark of pediatric leukemia treatment is repetitive intrathecal chemotherapeutics administered via lumbar puncture and most treatment protocols for solid tumors include surgery for local treatment. Thus, perioperative and periprocedural guidelines are needed to minimize thrombotic and bleeding risk while on anticoagulation treatment. The current DOAC recommendations are extrapolated from adult trials.[42] However, the pharmacokinetics of DOACs in young children differ from older children and adults and require more frequent dosing. Therefore, the recommended holding times may differ in children, and shorter pause times could be safe. To date, there are not sufficient pediatric data to make any such recommendations. In patients with high thrombotic risk, LMWH or UFH as pre- and postprocedural bridging could be considered.

Primary Prevention

Evidence for the primary prevention of VTE in children with cancer has not shown a convincing benefit of anticoagulation to date, as discussed earlier. This raises the question of whether preventive anticoagulation in the general childhood cancer population is necessary or if it should be considered only in patients with higher risks for VTE according to their VTE risk factors. The PREVAPIX-ALL study showed no difference in VTE in those treated with prophylactic-dose apixaban versus those not treated.[38] The THROMBOTECT study showed a lower VTE prevalence in those with AT replacement compared to those with UFH flushes for CVC patency, and no difference between AT replacement and prophylactic-dosed LMWH.[31] In the general pediatric population, a meta-analysis on the prevention of recurrent CVC-related VTE did not show any benefit of heparin-bonded catheters, UFH, LMWH, VKA, AT replacement, or nitroglycerin.[43] Additionally, the TropicALL trial is currently underway, investigating LMWH versus no anticoagulation for primary VTE prophylaxis in pediatric ALL patients.[44] Another question regarding the dosing of anticoagulants for primary VTE prevention (prophylactic/low dose vs. therapeutic/treatment dose) is yet to be studied.

Secondary Prevention

After completion of the treatment of a primary CVC-related VTE, secondary prophylaxis has been suggested to prevent recurrent VTE, at least while the CVC remains in situ. There is conflicting evidence to use prophylactic or full-dose anticoagulation to prevent recurrent CVC-related VTE. Studies were conducted in the general pediatric population, and cancer patients were included in these studies.[10,45,46] However, there are no specific recommendations available for the pediatric cancer population.

Prediction

Tools for thrombosis prediction exist in adult cancer patients such as the Khorana score.[47] This tool helps predict patients at higher risk for cancer-associated thrombosis. The five predicting variables used by the Khorana score are type of cancer, platelet count, hemoglobin, leucocyte count, and body mass index.[47] This tool cannot be reliably used in the pediatric population as risk factors, such as cancer types in children differ from those types seen in adults. Risk prediction models have been developed and successfully tested for children with ALL. However, they are not yet adapted to the overall pediatric cancer population as they include ALL-specific treatment-related risk factors such as high-dose steroids and asparaginase but no other chemotherapeutics such as platin derivatives. Furthermore, they do not include risk factors specific to solid tumors (e.g., vasal compression or immobilization).[48]

A different approach to predict thrombosis risk could be risk assessment by laboratory assays. A recent study was able to measure the prothrombotic state by global coagulation assays in children with cancer. If validated, these assays could be able to identify and risk stratify children with malignancies for appropriate primary prophylaxis.[49]

Outlook

In the past decade, tremendous progress has been made in the field of pediatric thrombosis with randomized controlled trials investigating the efficacy and safety of DOACs versus standard of care (LMWH, UFH, and VKA). This not only gave insight into the effectiveness and safety of DOACs but also delivered controlled data on the standard of care that has been lacking in pediatric VTE. While pediatric patients with cancer and VTE were included in these trials, the limited number of patients does not always allow separate subgroup analysis.

DOACs with their oral application seem to be a promising solution in this population as compared to the subcutaneous injection of LMWH. Still, LMWH will remain important in the pediatric cancer population in specific situations: for example, if DOACs are not tolerated due to nausea and vomiting, during times of parenteral nutrition, or if enteral absorption is problematic (e.g., mucositis). LMWH is a suitable alternative if drug–drug interactions are expected between DOACs and cancer-treatment-relevant drugs (e.g., DOACs interact with CYP3A and p-glycoprotein inhibitors).[50] This could be the case with treatments for fungal infections such as ketoconazole, itraconazole, voriconazole, and posaconazole, but also if treatment-related thrombocytopenia is expected or if procedures are planned, as there is more periprocedural experience with LMWH in children to this date. Designing new trials for the prevention or treatment of VTE in pediatric cancer patients with DOACs, and gaining experience with DOACs in real-life settings remains important and needs careful attention and planning. It will be important to identify which patients are at risk of VTE so that anticoagulation prophylaxis can be utilized in a targeted manner. Risk prediction tools or laboratory assays could help stratify children with cancer regarding their risk for VTE. These need to be developed and validated.

Real-world data, as gathered in patient registries such as the International Pediatric Thrombosis Network (IPTN), will also contribute to informed decisions and recommendations for the prevention or treatment of VTE in this specific population.[51]

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Conflict of Interest

The authors declare that they have no conflict of interest.

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