Screening for Occult Cancer in Patients with Venous Thromboembolism: Past, Present, and Future

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Abstract

A strong link between cancer and thrombosis has been well recognized. The occurrence of venous thromboembolism (VTE) can be the first clinical sign of an undiagnosed (i.e., occult) cancer. Cancer is more often diagnosed after unprovoked compared with provoked VTE events, with a reported risk in recent studies of around 5%. Extensive, imaging-based screening strategies to detect occult cancer after unprovoked VTE do not appear to have a clear clinical benefit compared with a more limited cancer screening. To identify patients with unprovoked VTE at high risk of occult cancer, risk factors have been explored and prediction models developed. Relevant risk factors for occult cancer include male sex, age, anemia, chronic lung disease, and thrombocytosis. Studies with preselection of patients based on risk assessment and evaluation of limited versus extensive screening strategies are currently ongoing. Also, novel and promising approaches for early detection of cancer in patients with unprovoked VTE by means of liquid biopsies, which include analysis of circulating tumor cells, cell-free tumor DNA, proteomics, or platelet mRNA sequencing, are currently under investigation. In this review, we provide an overview of the risk of cancer diagnosis after VTE, discuss the studies which investigated different screening strategies for occult cancer, summarize risk factors and risk scoring models for identification of patients at high risk of cancer diagnosis after VTE, and highlight ongoing research to optimize screening and identification of patients at risk of occult cancer, which will shape the future clinical practice.

Keywords

► cancer
► venous thromboembolism
► thrombosis

Introduction

A two-way interrelation between cancer and thrombosis has been well established. Cancer is one of the strongest risk factors for venous thromboembolism (VTE) and, as such, its presence significantly increases the risk of VTE. Conversely, the occurrence of VTE may be the first manifestation of an occult (i.e., undiagnosed) cancer. The incidence of cancer in patients with VTE is up to sixfold higher when compared with a population of similar age without VTE.[1–3]

In clinical practice, suspicion of an underlying cancer is frequently raised in patients with VTE, especially when the event is unprovoked, that is, in the absence of a trigger or identifiable VTE risk factor.[4] The 1-year incidence of a cancer diagnosis following unprovoked VTE has been reported to be

5 to 10%, with most of the cancers being diagnosed in the first 6 months after VTE.[5,6] Although the probability of a cancer diagnosis seems to be elevated in the first year, it has been suggested that it may remain high even for a longer period.[7]

Compared with unprovoked VTE, the risk of occult cancer after provoked VTE is lower, with an incidence around 1% within 12 to 24 months. The risk of a cancer diagnosis is equally low after surgery-related VTE and nonsurgical VTE risk factors such as estrogen use.[6,8–10] While cancer screening in this group is often not pursued due to a high expected number needed to screen, it might be beneficial in patients who develop recurrent VTE, especially when recurrences occur during antithrombotic treatment, which could reflect cancer-induced hypercoagulability. However, studies investigating the incidence of cancer after unprovoked recurrent VTE are scarce. One older cohort study reported that 17% of patients with recurrent VTE developed cancer during an observation period of 2 years versus only 4.5% of patients with no VTE recurrence.[10] Recently, Rézig et al published a prospective study of 197 patients who had recurrent unprovoked VTE that occurred within 2 years.[1] The 1-year risk of a cancer diagnosis was 36% (95% confidence interval [CI]: 20–59) in patients with VTE recurrence during anticoagulant treatment versus 5.5% (95% CI: 2.9–10) among patients with VTE recurrence after stopping anticoagulation.

Over the last decade, progress has been made to better understand the incidence of cancer after VTE and identify risk factors for occult cancer detection. In parallel, the evidence of screening for cancer after unprovoked VTE has changed following publication of several randomized controlled trials, which aimed to identify screening strategies that provide the best diagnostic yield for occult cancer detection. Therefore, in this review, we critically appraise (1) imaging-based screening strategies in patients with unprovoked VTE; (2) risk factors associated to occult cancer; (3) novel approaches of screening for occult cancer under investigation; and (4) future ways to optimize screening in high-risk VTE populations.

Screening Process

Screening is defined by the World Health Organization as "the presumptive identification of unrecognized disease in an apparently healthy, asymptomatic population by means of tests, examinations, or other procedures that can be applied rapidly and easily to the target population." As patients with VTE are far from healthy and asymptomatic, the term "active case finding" or "early diagnosis" rather than "screening" would probably better fit the search for cancer in this group. For the sake of consistency, we will use the terminology "screening" that was applied in virtually all literature on this topic.

In the general population, screening for cancer of the colon, cervix, and breast reduces disease-specific mortality,[11–16] although in some settings the screening process continues to be fragmented and sometimes inefficient.[15,17–21] Clinicians must balance between over- and underscreening and avoid improper use of screening. Some concepts that apply to cancer screening in the general population are also relevant in the setting of VTE.

To optimize the screening process, the PROSPR Consortium (Population-based Research Optimizing Screening through Personalized Regimens) introduced a conceptual framework that essentially can be applied to any screening strategy.[22] The model focuses on the following steps in the process: risk assessment, detection, diagnosis, and treatment (►Fig. 1). When translating the first step of this model to the setting of VTE, it is important that clinicians offer cancer screening only to patients in whom the benefits are likely to outweigh the risks associated with interventional diagnostic procedures, the negative consequences of overdiagnosis, and the emotional burden of false-positive findings. In other words, risk assessment is important to ensure that the baseline risk (i.e., prevalence of pretest probability) is high enough to justify cancer screening. For the detection phase, it is important that the sensitivity and negative predictive value of a screening approach are high enough not to falsely
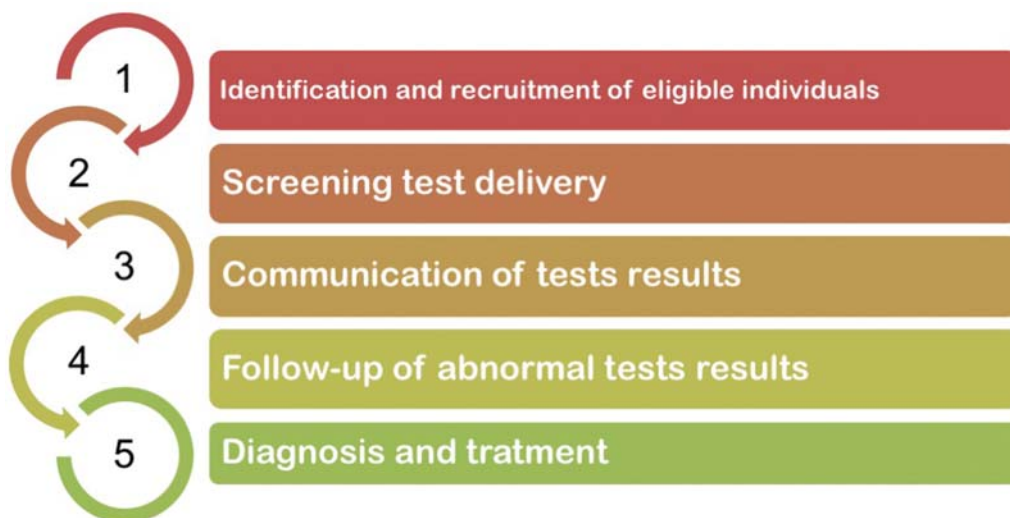
Screening process. Adapted from Beaber EF, Kim JJ, Schapira MM, et al; Population-based Research Optimizing Screening.

Fig. 1 Screening process.

reassure those with a normal screening, while a high specificity and a positive predictive value are needed to limit the number of additional diagnostic tests. Notably, this situation is different from population-based screening with a low cancer prevalence, in which specificity of screening tests is more important than sensitivity to minimize false-positive findings. With respect to the diagnosis and treatment steps in the PROSPR model, it is important that a cancer diagnosis following abnormal screening results confers improvements in morbidity or mortality. Cancers detected by screening after unprovoked VTE appear to be stage III or IV cancers in approximately 50% of cases,[6] which have cast doubt about the potential benefit of screening in this population. Obviously, the greatest benefit is likely to be achieved when early-stage cancers are detected given the potential for curation. Yet, patients with late-stage cancer may also increasingly benefit from an earlier diagnosis in terms of both morbidity and mortality in view of the ongoing, rapid advancements in cancer treatment.

Imaging-Based Strategies for Occult Cancer in Patients with Unprovoked Venous Thromboembolism

Given the substantial risk of an underlying malignancy in patients with unprovoked VTE, many studies have evaluated cancer-screening strategies in this group only rather than in all VTE patients. Screening often consisted of additional testing on top of the generally accepted "limited screening," which consists of medical history, thorough physical examination, basic laboratory testing, and a chest X-ray. The premise is that detection of cancers in an earlier, less advanced stage more often results in curation, thus less morbidity and improved survival. One of the challenges of screening for occult cancer in patients with unprovoked VTE is the wide variation in cancer types diagnosed. A systematic review and individual patient data meta-analysis of more than 2,000 patients with unprovoked VTE showed that no less than 25 different types of hematological or solid cancer were reported in the first year after the diagnosis, with the most frequent being colorectal (17%), lung (15%), and pancreatic cancer (11%).[6] Therefore, screening approaches should target various organ systems to optimize sensitivity. Over the past two decades, several trials compared imaging-based screening strategies with a more limited cancer screening.

The early SOMIT study was an Italian randomized controlled trial that evaluated a combination of multiple screening tests compared with standard of care in patients with unprovoked VTE in whom initial limited testing, including history taking, physical examination, laboratory assessment, and or chest radiograph, was negative for cancer.[23] The extensive screening group underwent computed tomography (CT) scanning of the abdomen and pelvis, gastroscopy or barium swallowing, colonoscopy or sigmoidoscopy, fecal occult blood testing, sputum cytology, and testing for three tumor markers. Unfortunately, the study was terminated early after enrolment of 201 patients, which was approximately 20% of the targeted sample size.

Reasons for termination were the lower than anticipated number of participating centers, and an increasing tendency among physicians in study centers to perform screening tests for occult cancer in control patients. Nonetheless, the study suggested benefit of extensive screening over standard of care, since no less than 13 patients (13%) in the intervention group were diagnosed with cancer at baseline. During the 2-year follow-up, 10 patients (10%) in the control group were diagnosed with cancer compared with only one patient (1%) who had received extensive screening ($p < 0.01$). Importantly, cancers diagnosed by extensive screening tests tended to be less advanced and cancer-related mortality in this group was a nonsignificant 50% lower than in the control group. Despite concerns about the risk of selection bias and crossover in the study, these findings fueled later studies to evaluate cancer screening in patients with unprovoked VTE.

The Trousseau study was a Dutch concurrently controlled, nonrandomized study that also evaluated an imaging-based screening strategy using CT scanning of chest and abdomen in 630 patients with unprovoked VTE.[24] Unlike the SOMIT trial, there was no clear benefit of extensive screening: six additional cancers (2%) were diagnosed in the extensive screening group of which only three were in a potentially curable stage. During a median 2.5 years of follow-up, there was no significant difference in cancers diagnosed or mortality between the limited and extensive screening groups.

More recently, a well-conducted, Canadian, randomized, open-label trial (SOME) also did not show clinical benefit of extensive screening by a CT of the abdomen and pelvis in patients with a first unprovoked VTE.[25] Carrier and colleagues randomly allocated 854 of such patients to either limited occult-cancer screening, which also included age- and gender-specific testing such as prostate-specific antigen and mammography, or limited occult-cancer screening plus a comprehensive CT of the abdomen and pelvis including virtual gastroscopy and colonoscopy. Of overall, the 1-year period prevalence of cancer was only 3.9%. During the 1-year follow-up, 29% of cancers appeared to be missed at baseline in the limited screening group compared with 26% in the extensive screening group ($p = 1.0$). There was also no difference in mortality. Notably, patients undergoing the comprehensive CT scanning were exposed to 31 millisieverts equaling 442 chest radiographs.

Finally, a French randomized, open-label trial (MVTEP) evaluated 18-FDG positron emission tomography/computed tomography (PET/CT) scanning for detection of occult cancer in 399 patients with unprovoked VTE.[26] The conclusion of the trial was not unequivocal. Although PET/CT scanning did not detect cancer in a significantly higher proportion of patients (5.6%) than in those randomized to limited screening only (2.0%) at baseline ($p = 0.07$), the number of patients diagnosed with cancer during 2-year follow-up was lower in the PET/CT-scanning group (0.5 vs. 4.7%; $p = 0.01$). The lower than anticipated rate of cancer diagnosis and substantial number of patients in the PET/CT-scanning group not receiving their allocated imaging likely contributed to the study not meeting the primary endpoint. Also, the trial would have been regarded

as "positive" if it would have used the same primary analysis as in the SOME trial. The MVTEP study therefore did not close the book on a potential role for 18-FDG PET/CT scanning in patients with unprovoked VTE.

The potential benefit of extensive screening was summarized in a systematic review and meta-analysis of patient-level data on 2,316 patients with unprovoked VTE enrolled in 10 prospective studies.[6] When the extensive screening strategies in Trousseau, SOME, and MVTEP were considered together, such an approach was associated with a significantly twofold higher probability of cancer detection than when using limited screening only (odds ratio [OR]: 2.0; 95% CI: 1.2–3.4). This comes at the cost of additional, targeted testing for cancer in 26% of patients receiving extensive screening compared with 17% in those undergoing limited screening ($p = 0.11$). After 1 year following the unprovoked VTE, there was no significant difference between limited (4.2%) and extensive screening (5.6%) in the number of patients who were diagnosed with cancer (OR: 1.4; 95% CI: 0.89–2.1). In addition, a subsequent analysis did not show an effect of extensive occult-cancer screening on survival among 1,830 patients enrolled in Trousseau, SOME, and MVTEP. Of the 56 patients diagnosed with cancer following extensive screening, 27 (48%) had died after a median 3 years of follow-up compared with 23 of 42 patients (55%) in the limited screening groups (hazard ratio [HR]: 0.83;

95% CI: 0.48–1.5).[27] When the authors compared overall mortality in patients whose cancer was missed at initial screening, they found a nonsignificant trend toward 41% reduction in mortality in favor of extensive screening (HR: 0.59; 95% CI: 0.22–1.57; $p = 0.29$). A recent Cochrane systematic review also concluded that current evidence is insufficient to draw conclusions about the effectiveness in reducing cancer-related morbidity or mortality of screening for cancer in patients with unprovoked VTE.[28]

An important notion is that the incidence of cancer diagnosis was substantially lower than anticipated in all more recently performed trials evaluating imaging-based cancer screening. Whereas the 1-year risk of a cancer diagnosis following unprovoked VTE appeared to be approximately 10% in earlier studies,[5] it dropped to approximately 5% when only contemporary studies performed after the year 2000 were taken into account.[6] ►**Fig. 2** shows the decrease in cancer incidence following unprovoked VTE based on a meta-regression analysis. In parallel, the yield of extensive screening is also likely to decrease when provided to all patients with unprovoked VTE. Consequently, recent efforts have focused on identifying groups of patients with a higher-than-average risk of a cancer diagnosis in whom extensive screening may be beneficial due to a lower number needed to screen.
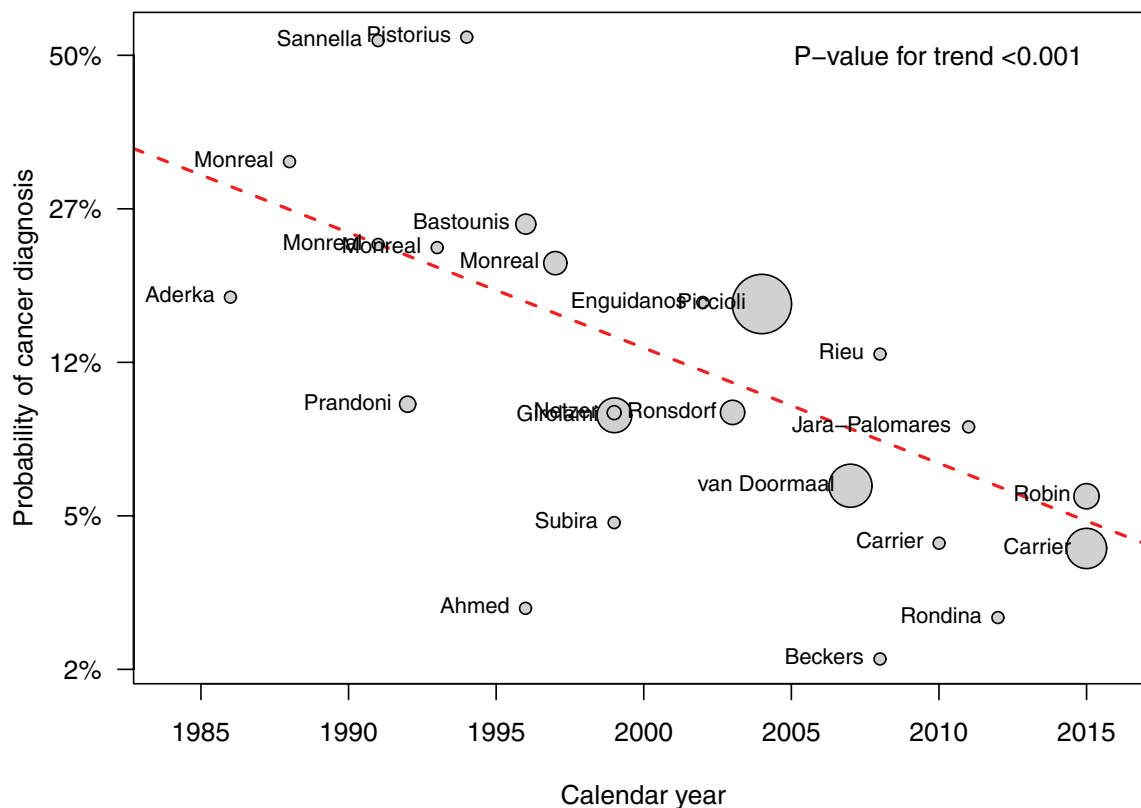

Fig. 2 One-year probability of a cancer diagnosis in patients with unprovoked venous thromboembolism by calendar year. Size of the circles represent weights in the meta-analysis.

Table 1 Factors associated with occult cancer in patients with venous thromboembolism

Clinical and laboratory factors	Odds ratio, hazard ratio, or relative risk for cancer diagnosis in univariable analysis
Unprovoked venous thromboembolism[8,10]	3.3–4.0
Male sex[8,9,29]	1.3–3.7
Age > 50 y[6,29]	7.1–9.0
Age > 60 y[30]	2.9
Age > 70 y[8,9]	1.9–4.0
Chronic lung disease[9,31]	1.7–4.0
Smoking[6,13,30]	1.5–2.2
Diabetes mellitus[30]	2.9
Hypertension[30]	2.1
Anemia[9,13]	1.7
Leukocytosis[9,29]	1.2–3.4
Thrombocytosis[9,29]	1.4–3.1
Recent surgery[8,9,21]	0.3–0.6
Hormone therapy[6,9,13]	0.2–0.4
Prior venous thromboembolism[9]	0.7
Prior provoked venous thromboembolism[30]	3.6
Previous cancer[13,30,31]	2.9–5.2

Risk Factors for Presence of Occult Cancer in Patients with Venous Thromboembolism

The risk of an underlying malignancy varies greatly across different age categories, from approximately 1% in patients younger than 50 years to 7% in those 50 years or older (OR: 7.1; 95% CI: 3.1–16).[6] Although clinicians are often especially concerned in younger patients about an underlying malignancy, this is not supported by the low risk in this group. Conversely, there may be groups of patients in whom the risk of an underlying malignancy is considerable and exceeds the overall 5%. Besides older age, a post-hoc analysis of MVTEP showed that the risk of occult cancer was higher in males and in patients with elevated platelet or leukocyte counts.[29] A post-hoc analysis of the SOME trial revealed that previous provoked VTE and

current smoking were also associated with occult cancer.[30] A history of cancer should also alert clinicians for cancer, which could be either new or recurrent disease.[30,31] Finally, D-dimer levels obtained at VTE diagnosis also appear to be positively correlated with the risk of occult cancer.[11,32] For example, in a retrospective study of 824 VTE patients, cancer was diagnosed four times more frequently in those with D-dimer levels >4,000 ng/mL than in those with levels <2,000 ng/mL.[32] The risk of an occult cancer seems not to depend too much on the location nor on extent of VTE, with similar rates observed in patients presenting with pulmonary embolism and proximal or distal DVT.[6,12,30] Risk factors for cancer are summarized in ►Table 1.

Besides single clinical observations that may lower the threshold for cancer suspicion, a more structured risk assessment approach combining risk factors could be helpful in identifying VTE patients in whom the risk of an underlying cancer is high. Ideally, such a tool should be used after an initial limited cancer screening is negative to guide decisions about subsequent extensive, imaging-based testing. The Registro Informatizado de Enfermedad Tromboembolica (RIETE) score was derived with this purpose using data from 5,863 patients with acute provoked or unprovoked VTE of whom 444 (7.6%) were diagnosed with cancer between 1 and 24 months post-VTE. On multivariable analysis, the items male sex (+1 points), age >70 years (+2 points), chronic lung disease (+1 point), anemia (+2 points), thrombocytosis (+1 point), prior VTE (−1 point), and recent surgery (−2 point) were retained in the model. About 29% of patients were classified as high risk (≥3 points) based on the sum score. Although overall discrimination was modest (C-statistic: 0.64), the risk of a cancer diagnosis was approximately twofold greater in these high-risk patients (12%) than in those with a low-risk score (5.8%). Following these encouraging findings, four independent studies evaluated the RIETE score in more than 10,000 patients with provoked VTE in various settings.[13–15,31] A random-effects meta-analysis of the performance of the dichotomized RIETE score confirms that the risk of an underlying cancer is approximately twofold higher in those with 3 points or more (in summary, RR: 2.09; 95% CI: 1.57–2.78; ►Fig. 3).

Taken together, this shows that the RIETE score could serve as a tool to identify patients in whom more extensive cancer screening may be warranted. Some aspects of the score deserve further consideration though. Some multivariable analyses suggest that the performance of the score is mainly driven only by few items, including older age, anemia, and thrombocytosis.[13,15] Notably, unexplained anemia and
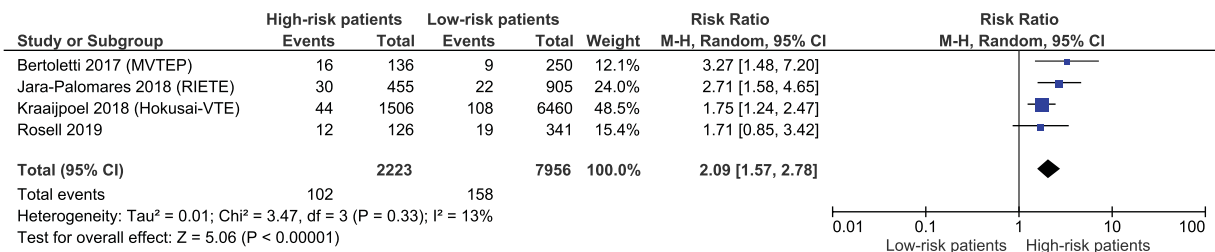
Fig. 3 Random-effects meta-analysis of the discriminatory performance of the dichotomized RIETE score.

thrombocytosis will often invoke targeted testing for cancer in clinical practice anyway. This suggests that perhaps a simple selection based on age might be as effective as calculating the RIETE score. Nonetheless, the RIETE score appears to be a simple tool to identify high-risk patients. Future management studies are needed to determine whether the use of the RIETE score in clinical practice will result in clinical benefit.

Liquid Biopsies

Recent technical advances have led to the development of various blood-based assays that aim to either directly or indirectly reveal the presence of cancer. The hope is that these methods, which are collectively referred to as "liquid biopsies," may provide a simple, cheap, and noninvasive way to diagnose or screen for cancer, monitor recurrence after surgery, or evaluate response to cancer treatment. Examples of liquid biopsies include circulating tumor cells, cell-free tumor DNA (ctDNA), proteomics, and platelet messenger RNA (mRNA) sequencing. In the setting of cancer screening in patients with VTE, liquid biopsies could either replace current screening tests for cancer altogether or serve as an add-on test. In both scenarios, it should have a high sensitivity to detect even early-stage cancer as well as a good specificity to reduce the number of false-positive findings.

The various liquid biopsies all have their specific advantages and disadvantages. For example, circulating tumor cells are less abundant in early-stage cancers resulting in a lower sensitivity. Indeed, a small pilot study in patients with unprovoked VTE showed that three RNA markers (TWIST1, EPCAM, and KRT19) in circulating tumor cells were not able to detect cancer.[16]

Circulating tumor DNA holds promise as a more sensitive test. The test relies on the detection of cell-free DNA, which is largely derived from apoptotic cells such as leukocytes in healthy individuals. In the presence of cancer, tumor cells also contribute to the pool of cell-free DNA. Mutant cell-free DNA originating from tumor cells can be detected by DNA isolation and sequencing, provided that the amount of ctDNA is large enough. Not surprisingly, the performance of this test increases when cancer is more advanced (and the amount of ctDNA higher) and varies substantially across tumor types. For example, in a study of 640 patients with various cancer types, sensitivity ranged from 47% in early-stage cancers to 82% in metastatic cancers.[17] Test performance was better in patients with gastrointestinal cancers than in those with primary brain or prostate cancers.

Another promising, pan-cancer biomarker for cancer is the so-called tumor-educated platelets. The hypothesis is that the mRNA profile of circulating platelets is altered upon confrontation with tumor cells, either by transfer of oncogenic mRNA to platelets by extracellular vesicles or by queue-specific splicing of pre-mRNA in platelets induced by the tumor. A proof-of-concept study including 228 cancer patients and 55 healthy individuals revealed a very high sensitivity of 97% and specificity of 94% for diagnosing various tumor types.[18] In addition, it appeared that the test might be able to correctly identify the tumor location in a substantial number of patients. The influence of concomitant inflammatory comorbidities did not appear to affect the test accuracy significantly.[19]

Finally, an elegant way to improve the performance of liquid biopsies is to combine different analyses in a single test. CancerSEEK is such a test that can be used to identify eight common cancer types by analyzing not only ctDNA, but also levels of well-circulating tumor markers such as CA-125, CEA, and CA 19.9.[20] In a case–control study of 1,005 patients with nonmetastatic cancer, sensitivities ranged from 33% in women with breast cancer to almost 100% in patients with ovarian or liver cancer.

Taken together, many promising, innovative tests for cancer detection are on the horizon. Yet, one has to realize that the sensitivity of all of these tests may be suboptimal, especially for early-stage cancers. Other questions that need to be addressed before they can be introduced in clinical practice concern the clinical benefit and costs of these tests. Future studies should establish whether the application of these tests will reduce morbidity and mortality in the setting of VTE, and whether they are cost-effective.

Ongoing Studies and Closing Remarks

Three interesting ongoing studies in the field of occult cancer in unprovoked VTE are of special note. The PLATO-VTE study (NCT02739867) is a prospective, international, observational cohort study including consecutive patients of 40 years of age or older with symptomatic unprovoked VTE (►Fig. 4A). This study will evaluate whether platelet mRNA sequencing could serve as a pan-cancer diagnostic tool, possibly enabling clinical advances in blood-based "liquid biopsies."[31] Other biomarkers that will be assessed include ctDNA and a proteomics-based approach. The study aims to include 462 patients who will be followed for 12 months. All patients receive limited screening at baseline, but results from the plasma biomarkers are disclosed neither to patients nor to clinicians during the study. Results are expected in 2020.

SOME-RIETE is an open-label, randomized controlled trial (NCT03937583) that uses the RIETE score to select patients with unprovoked VTE at high risk of cancer (≥3 points). Patients with a high-risk score will be randomly allocated to limited or extensive screening (including 18-FDG PET/CT) and followed for 3 years. The main outcome is the number of cancers diagnosed using extensive screening. The study just began patient recruitment in September 2019 and has a target sample size of 650 patients (►Fig. 4B).

Finally, the French–Canadian MVTEP2 is an open-label, randomized controlled trial that will evaluate 18-FDG PET/CT scanning in patients older than 50 years of age with a first unprovoked episode of VTE. Patients in the control group will receive limited screening including age- and gender-specific tests. The primary outcome is the number of false-negative findings (i.e., "missed" cancers) in both groups. The target sample size is 1,276 patients. Recruitment is expected to start in 2020 (►Fig. 4C).
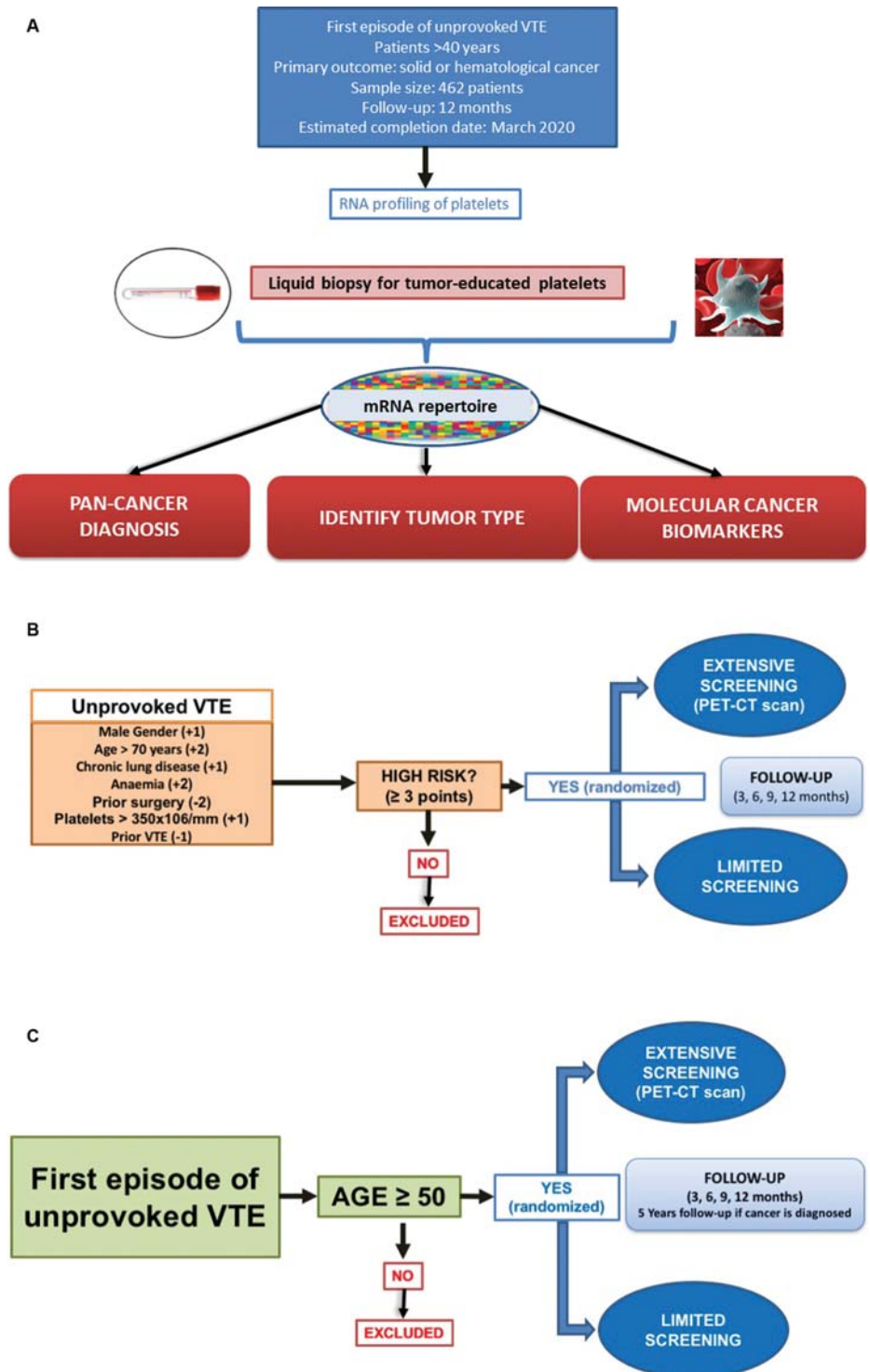
Fig. 4 Design of ongoing studies evaluating screening for cancer in patients with venous thromboembolism. (**A**) PLATO-VTE study. (**B**) SOME-RIETE study. (**C**) MVTEP2 study.

These studies will undoubtedly provide valuable and clinically relevant information on the performance and (potential) clinical utility of various screening tests. A challenge in these studies will be the tendency of clinicians to perform additional screening tests in the control groups, although the negative results of recent studies will hopefully mitigate this potential bias. Given the decreasing prevalence of cancer among patients with VTE (►Fig. 2), selection of

high-risk patients to improve the cost–benefit ratio of cancer screening will become increasingly important. The RIETE has an acceptable performance, although improvements are welcomed. Very sensitive imaging tests for cancer, such as 18-FDG PET/CT scanning, can significantly decrease the number of "missed" cases, but concerns about overdiagnosis (e.g., prostate cancer in elderly men), false-positive findings, and high costs will remain matters of debate. Similar issues

will likely apply to liquid biopsies such as platelet mRNA sequencing and ctDNA assays. In addition, data are needed to show that an early cancer diagnosis following a positive screening actually improves prognosis. While awaiting results from ongoing studies, clinicians should use a thorough medical history and physical examination, basic laboratory testing, chest radiography, and perhaps age- and gender-specific testing in the search for an underlying malignancy, while refraining from other expensive, untargeted, and potentially harmful tests.

Time Capsule

- Risk assessment strategies will be introduced in practice to offer screening only to those patients with (unprovoked) VTE in whom the benefits outweigh the risks and burden.
- The importance of cancer screening is likely to increase as rapid advancements in treatment will render cancer a chronic disease.
- 18-FDG PET/CT scanning is the most sensitive imaging method to screen for cancer, although overdiagnosis and costs will remain sensitive issues.
- Liquid biopsies hold promise as quick, simple, noninvasive tests to screen for cancer, which can also guide the subsequent diagnostic process.

Conflict of Interest
The authors declare, that they have no conflict of interest.

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He has participated in several randomized clinical trials on thromboembolic prophylaxis and treatment. His research activity focuses cancer associated thrombosis and occult cancer in unprovoked venous thromboembolism.

Most notable research support:

Scientific Research Grant FIS 2018 "Detection of cancer with PET/CT in patients with unprovoked venous thromboembolic disease with a high risk of developing cancer. Open randomized clinical trial". (93000€)

More than 80 peer-reviewed publications, highlighting:

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Nick van Es

Nick van Es, MD, is a resident in Internal Medicine at the Amsterdam University Medical Center in Amsterdam, The Netherlands. He completed his PhD-thesis entitled 'Cancer and thrombosis: improvements in strategies

for prediction, diagnosis, and treatment' *cum laude* in 2017 under supervision of Prof. Saskia Middeldorp, vascular medicine specialist, and Prof. Patrick Bossuyt, clinical epidemiologist. He was co-supervised by Prof. Harry Büller and Prof. Marcello Di Nisio, both vascular medicine specialists. During his period as a PhD-student, he visited the Dept. of Medicine at The Ottawa Hospital for a research traineeship supervised by Prof. Marc Carrier and Prof. Phil Wells, which ultimately resulted in publication of a systematic review and individual patient data meta-analysis on screening for cancer in patients with unprovoked venous thromboembolism.

His research primarily focuses on clinical prediction, diagnosis, and treatment of venous thromboembolism in cancer patients, but he also has a broader interest in thrombosis and hemostasis. He completed his training as a Clinical Epidemiologist in 2017 and continues to focus on epidemiological studies. Research is embedded within the Dept. of Vascular Medicine at the Amsterdam University Medical Center, which has a long track record in the field of venous thromboembolism including many clinically oriented studies on diagnosis and treatment. Other research themes within the department are pathophysiology and treatment of atherosclerosis and the effects of gut microbiota on several diseases.

He has a passion for clinical, patient-centered research, preferably by collaborating with various (inter)national researchers. He has a strong ambition to continue his scientific activities in an academic center after completing his training as a vascular medicine specialist in the coming years.

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