Dear Sir,

I have read with interest the article by Rajan and coworkers, recently published in Thrombosis & Haemostasis (1). By examining the long-term follow-up of a cohort of patients with deep-vein thrombosis (DVT) enrolled in a trial addressing the duration of anticoagulant therapy (2), they failed to detect an increased difference of newly diagnosed cancer in idiopathic DVT (13/152, 8.6%) as compared to secondary DVT (8/112, 7.1%). Moreover, patients with recurrent venous thromboembolism (VTE) did not appear at a higher risk of developing subsequent malignancy when compared with those who did not develop recurrences. Accordingly, the policy of aggressive screening for cancer in patients with idiopathic thromboembolism is questioned.

As acknowledged by the same authors, their results are in striking contrast with all available literature. As shown in the enclosed table, all available papers addressing this issue revealed a highly statistically significant association between idiopathic VTE and underlying malignancy (3-12). It is one of the strongest associations between two clinical conditions existing in the medical field, and there is no need for meta-analysis of pooled data for arriving at a generally accepted conclusion. As an interesting side note, one of these papers (10) reports the experience of nine different groups distributed in Europe and in Australia, involved in a multicentre trial addressing the treatment of DVT (13). The table includes also recent data (and, therefore, not available at the time of the publication by Rajan et al.) from Monreal et al. who, once again, strongly confirmed this association by investigating the long-term follow-up of almost 700 consecutive patients with VTE (12). Two of the studies quoted by the authors (14, 15) did not compare idiopathic versus secondary thrombosis, and therefore they cannot be claimed to warrant any conclusion on this matter.

I agree with the authors that there are important differences in the study designs of available investigations, accounting for the different rates of newly diagnosed malignancies. For example, the definition of “idiopathic” VTE has varied considerably over time, current information on a number of thrombophilic defects not being available at the time of investigations performed before ’90s. Furthermore, in the studies in which no extensive screening procedures were performed, the incidence of newly diagnosed malignancy was considerably lower than that observed in studies in which an extensive investigation for occult malignancy was carried out (4, 5, 7, 8, 10, 12). But all data are fully consistent with the hypothesis that an underlying cancer is to be expected at a far greater extent in patients with apparently unexplained thrombosis than in patients with thrombosis secondary to known risk factors.

How to explain, therefore, the results of Rajan and associates? First of all, it might merely be a chance effect. It should, however, be noted that they established their cohort one month after the qualifying episode of thrombosis. As acknowledged by the same authors, several cases of cancer did indeed occur during this four-week period and were excluded from the inception cohort. Unfortunately, however, they do not say whether the new malignancies that were observed in the first month following the thrombotic episode developed in patients with idiopathic DVT or in patients with secondary disease. I highly suspect that they belonged to the former group. My suspicion derives not only from my long clinical experience but also by the careful analysis of the majority of available papers, that consistently reported a close timely association between unexplained thrombosis and cancer.

It is well demonstrated that patients with cancer exhibit a high risk of VTE recurrences while being under anticoagulant therapy (16, 17). For this reason, all clinicians are alerted to suspect an underlying malignancy in patients with thrombosis who develop symptomatic recurrences while correctly anticoagulated. If one looks carefully at the clinical study carried out in Padua in collaboration with investigators from Amsterdam University (6), the large majority of recurrent thrombotic episodes in patients with underlying malignancies developed in the first weeks after DVT, while patients were fully anticoagulated. The failure to include in the observation period the first four weeks following the episode of thrombosis is, therefore, likely to have resulted in the exclusion of a substantial rate of VTE recurrences. If this is true, any reliable conclusion on the lack of association between recurrent thromboembolism and newly diagnosed malignancy is virtually precluded.

The association between idiopathic VTE and occult malignancy cannot be questioned, and is further supported even by the authors’ data. In fact, despite the exclusion from the analysis of patients developing cancer in the first month, Rajan and associates were able to identify a new malignancy in 8.6% of patients with idiopathic DVT, which is fully consistent with data from other investigations (6, 9, 10, 11). Nevertheless, I agree with the authors that at present time it is still unclear whether an extensive screening for occult malignancies is justified. In fact, it remains unclear whether identified malignancies are potentially treatable and whether treatment could favourably influence

### Table 1 Incidence of cancer in the follow-up of patients with idiopathic and secondary VTE

<table>
<thead>
<tr>
<th>Frequency of cancer</th>
<th>Idiopathic VTE (%)</th>
<th>Secondary VTE (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aderka et al., 1986 (3)</td>
<td>12/35 (34.3)</td>
<td>2/46 (4.2)</td>
</tr>
<tr>
<td>Montereal et al., 1988 (4)</td>
<td>3/16 (18.7)</td>
<td>0/67 (0)</td>
</tr>
<tr>
<td>Montereal et al., 1991 (5)</td>
<td>7/31 (22.6)</td>
<td>5/82 (6.1)</td>
</tr>
<tr>
<td>Prasad et al., 1992 (6)</td>
<td>11/145 (7.6)</td>
<td>2/105 (1.9)</td>
</tr>
<tr>
<td>Monreal et al., 1993 (7)</td>
<td>6/21 (28.6)</td>
<td>3/51 (5.9)</td>
</tr>
<tr>
<td>Bastounis et al., 1996 (8)</td>
<td>21/84 (25)</td>
<td>8/202 (4)</td>
</tr>
<tr>
<td>Ahmed et al., 1996 (9)</td>
<td>3/113 (2.7)</td>
<td>0/83 (0)</td>
</tr>
<tr>
<td>Hettiarachchi et al., 1997 (10)</td>
<td>10/155 (6.4)</td>
<td>3/171 (1.7)</td>
</tr>
<tr>
<td>Achkar et al., 1997 (11)</td>
<td>13/76 (16.7)</td>
<td>5/154 (3.2)</td>
</tr>
<tr>
<td>Monreal et al., 1997 (12)</td>
<td>13/105 (12.4)</td>
<td>10/569 (1.8)</td>
</tr>
<tr>
<td>Rajan et al., 1998 (1)</td>
<td>13/152 (8.6)</td>
<td>8/112 (7.1)</td>
</tr>
</tbody>
</table>

**ALL** 112/931 (12.0) 46/1644 (2.8)

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life expectancy or quality of life. An international multicentre random-ized trial in which patients with unexplained thrombosis, but asympto-matic for malignant disease are randomized to either extensive screening or standard clinical care without screening, is currently in progress, and has the potential to identify an effect of screening for malignancy on the survival of these patients (18). While waiting for the results of this trial, it is appropriate to maintain a low threshold of suspicion for malignancy when treating patients with unexplained VTE. The unexpectedly high rate of cancers who developed in the follow-up of Canadian patients with secondary thrombosis (7.1%) suggests that, under some circumstances, an occult malignancy might be suspected also in patients experiencing an episode of thrombosis in concomitance with recognized risk factors.

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References


Complex Control of Vascular Smooth Muscle Cell Growth by Thromboxane A

Dear Sir,

Activated platelets release a variety of mitogens. These growth fac-tors are known to synergize in stimulating vascular smooth muscle cell (SMC) proliferation. For example, thromboxane A
mimetics, such as U46619, have been shown to potentiate PDGF- and thrombin-induced SMC mitogenesis (1, 2). Interestingly, in these as well as in other stud-ies (3, 4), bell-shaped concentration-response curves of U46619 were found. However, none of these studies has addressed this issue thus far. Since we have demonstrated that the cloned bovine thromboxane A
receptor is coupled to an adenylyl cyclase stimulating pathway (5), we hypothesized that cAMP formation may counteract stimulatory effects of TXA
mimetics on SMC proliferation.

We have, therefore, compared the effects of U46619 on the potentiation of PDGF-induced DNA synthesis in bovine coronary artery SMC with the effects on cAMP formation. Interestingly, there was a marked stimulation of cAMP formation by higher concentrations of the TXA
mimetic (Fig. 1) which was significantly (p <0.05) suppressed by the TXA
receptor antagonist SQ 29548 (10 μM).

It is concluded that, depending on the concentration, TXA
can exhibit both stimulatory and inhibitory effects on SMC proliferation. Thus, for the overall mitogenic response of SMC to platelet-derived growth factors, complex interactions need to be considered. This might be of importance for platelet-dependent SMC proliferation in athero-sclerosis and restenosis.

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