

# Is chronic HIV infection associated with venous thrombotic disease? A systematic review

S.K. Klein<sup>1\*</sup>, E.J. Slim<sup>1</sup>, M.D. de Kruif<sup>1</sup>, T.T. Keller<sup>1</sup>, H. ten Cate<sup>2</sup>, E.C.M. van Gorp<sup>1</sup>, D.P.M. Brandjes<sup>1</sup>

<sup>1</sup>Department of Internal Medicine, Slotervaart Hospital, Amsterdam, the Netherlands,

<sup>2</sup>Department of Internal Medicine and Cardiovascular Research Institute, Maastricht University Hospital, the Netherlands, tel.: +31 (0)20-512 93 33, e-mail: igskk@slz.nl, \*corresponding author

## ABSTRACT

Infection with the human immunodeficiency virus (HIV) is still a major health problem world-wide. HIV infection has changed into a chronic infection with the chance of developing long-term complications. Vascular complications are frequently reported in the current literature. HIV and treatment by highly active antiretroviral therapy (HAART) are associated with many cardiovascular risk factors. An increased risk of arterial cardiovascular complications was found in a number of studies. However, data about the risk of venous thrombotic disease (VTE), including potentially fatal conditions as pulmonary embolism, were limited. In a systematic review of the literature, ten relevant epidemiological studies were identified that investigated the risk of venous thrombotic disease in HIV-infected patients. The incidence was increased two- to tenfold in comparison with a healthy population of the same age. However, these studies were mainly retrospective cohort studies that were prone to selection bias, confounding factors were not always mentioned and in all but three control populations were missing. An increased risk of venous thrombotic disease in HIV-infected patients could be explained by the presence of a hypercoagulable state, characterised by an increase in procoagulant factors, such as endothelial TF expression and thrombogenic properties of microparticles, and a decrease in anticoagulant factors, including AT III, HC II and the protein C pathway. Furthermore, the risk of VTE was associated with an increased risk of infections and autoimmune haemolytic anaemia, and was weakly associated with HAART. All together, quite some evidence pointed towards a relationship between HIV infection and venous thrombotic disease, but the association still needs to be established in properly designed epidemiological studies.

## KEYWORDS

AIDS, coagulation, complication, fibrinolysis, HAART, HIV, thromboembolism, venous thrombosis

## INTRODUCTION

Infection with the human immunodeficiency virus (HIV) is increasingly becoming a chronic disease in the developed world. Treatment with highly active antiretroviral therapy (HAART) has successfully prolonged the life expectancy of HIV-infected patients. However, as a consequence, chronic HIV infection and HAART are now increasingly associated with long-term complications.

HAART is a combination of therapy by protease inhibitors (PI), nucleoside reverse transcriptase inhibitors (NRTI) and non-nucleoside reverse transcriptase inhibitors (NNRTI). In particular the use of PI is complicated by disorders of lipid metabolism, insulin resistance, osteoporosis, nephrotoxicity and neurotoxicity. Furthermore, the use of NRTI is associated with lactic acidosis. HIV infection itself is associated with a number of complications, including increased general risk of infections and various malignancies. Many of these complications are potential risk factors of cardiovascular disease. In the recent literature, the possibility of a relationship between HIV infection and cardiovascular disease has been frequently discussed. A number of studies have shown an increased risk of arterial vascular diseases in HIV patients. A prospective trial in 1551 HIV-infected patients showed an increased risk of coronary artery disease for patients using PIs.<sup>1</sup> A cohort study comprising 4993 patients revealed an incidence of 0.59 to 3.41/1000 patient-years<sup>2</sup> and a very large prospective observational study enrolling 23,468 HIV-positive patients found an incidence

of 3.5/1000 patient-years for myocardial infarction.<sup>3</sup> Apart from research on arterial vascular diseases, a number of case reports were also published describing venous thrombotic events in HIV-infected patients. Recurrent episodes of deep venous thrombosis (DVT) and pulmonary embolism were relatively frequently reported. Further clinical observations in our own clinic raised questions about the possibility of an increased risk of venous thrombotic disorders in HIV-infected patients. Venous thrombotic disorders could be a serious, potentially fatal complication of HIV infection and clear insight is needed into the risk of venous thrombotic disorders in HIV-infected patients to judge the nature of the relationship, mechanism, risk factors and necessity of intervention.

In a systematic review, all relevant articles published from 1986 to 2004 studying the relationship between HIV infection and venous thrombotic disease are presented here. Clinical epidemiological studies are reviewed together with studies investigating the underlying pathogenic mechanisms. Special attention is paid to factors interfering with blood coagulation, which are particularly relevant for the occurrence of venous thromboembolism, whereas their significance for arterial thrombotic complications is still unknown.<sup>4</sup>

## METHODS

Citations were retrieved from English, French and German language based studies from PubMed and MEDLINE databases, from 1986 to 2004. Using the terms "HIV", "AIDS", "infectious disease", "thrombosis", "deep venous thrombosis", "thrombo-embolism", "pulmonary embolism", "coagulation" and "fibrinolysis", in single terms or in combinations, titles, abstracts and references were systematically scanned by two reviewers for relevant articles on the topic of HIV infection associated with venous thrombotic disorders. With the electronic search approximately 500 articles were found. Case reports, letters, comments and abstracts were excluded. Eventually a reference list of 63 articles remained.

## EPIDEMIOLOGY

In the developed world, the risk of DVT in the general population is approximately 0.10% a year.<sup>5,7</sup> This incidence increases sharply with age, from 0.001% a year in childhood to nearly 1% a year in the elderly.<sup>7</sup> Because most HIV-infected people are relatively young,<sup>8</sup> their background risk of DVT should be expected to be lower than the overall incidence.

Ten epidemiological studies reported on the occurrence of DVT and venous thromboembolic complications among

HIV-infected patients (table 1). Most of these studies were retrospective cohort studies. One study was both a retrospective and prospective study and one study did not mention the study design. The population sizes in the studies ranked from 60 to 42,935. The first study by Hassell *et al.* in 1994 reported a high incidence of DVT of 18% in 60 HIV-infected people, and of 6.6% in HIV patients who were followed prospectively over a median follow-up of 12 months.<sup>9</sup> In subsequent studies, the risk varied from 0.19 to 7.63%.<sup>10,11</sup> One very large study containing 42,935 patients found an incidence of 0.26%,<sup>12</sup> the same incidence was found for pulmonary embolism by Howling *et al.*<sup>13</sup> Considering these studies, the overall risk of DVT in patients with HIV infection may be roughly estimated to be a two- to tenfold higher in comparison with a healthy population of comparable age.

An important risk factor for developing venous thrombosis in these patients could be severity of HIV infection. One study reported an incidence of venous thrombosis of 0.96% in 728 patients infected by HIV and a twofold higher incidence of 1.9% in 250 patients suffering from AIDS.<sup>14</sup> A second study found a significantly higher incidence of thromboembolic events of 24% in 37 patients with low CD4 counts (<200/mm<sup>3</sup>) in comparison with 1.1% in 94 patients with higher CD4 counts.<sup>11</sup>

Another risk factor could be related to the introduction of protease inhibitors for the treatment of HIV infection in 1996. George *et al.*<sup>10</sup> found that the incidence of venous thrombotic events increased dramatically from 0.19% before the introduction of protease inhibitors to 1.07% afterwards. However, recently Fultz *et al.*<sup>15</sup> reported finding no significant increase.

## INCREASE IN PROCOAGULANT FACTORS

The increased risk of DVT in HIV-infected patients could be related to increased levels of procoagulant factors. Endothelial cells could play an important role in the activation of the coagulation cascade during HIV infection.<sup>16-18</sup> Activation of endothelial cells, which normally behave as anticoagulant regulators, occurred during infections with viruses including HIV,<sup>19</sup> cytomegalovirus,<sup>20</sup> herpes virus and many others.<sup>21-23</sup> From *in vitro* work it is known that infection initiates intracellular signalling through the NFκB pathway, which results in both stimulation of an inflammatory response and in enhanced expression of tissue factor (TF) on the cell membrane. TF induces the extrinsic pathway of coagulation by binding to factor VIIa and therefore is the major initiator of the coagulation cascade.

Another triggering factor of the coagulation cascade in HIV patients could be stimulation of microparticles.

**Table 1**

*Incidence of deep venous thrombosis and complications in HIV-infected patients: overview of studies*

AUTHOR	YEAR	DESIGN	SIZE	POPULATION	INCIDENCE	ENDPOINTS	DIAGNOSTICS
Jenkins <sup>57</sup>	1991	R	243	AIDS	3.29%	DVT, PE	Phlebography, V/Q scan
Hassell <sup>9</sup>	1994	R+P	60	HIV	18%	DVT, PE, thrombophlebitis, stroke	Doppler, V/Q scan, ICD-9 code
Laing <sup>13</sup>	1996	-	728	HIV	0.96%	DVT	Doppler, MRI, venography, V/Q scan
			250	AIDS	1.60%		
Howling <sup>13</sup>	1999	R	3792	HIV	0.26%	PE	CT, pulmonary angiography, V/Q scan, autopsy
George <sup>10</sup>	1999	R	650	HIV*	1.07%	DVT, PE	Plethysmography, venography, pulmonary angiography, V/Q scan
			1050	HIV**	0.19%		
Sullivan <sup>12</sup>	2000	R	42935	HIV	0.26%	DVT	ICD-9 code
Saber <sup>58</sup>	2001	R	4752	HIV	0.95%	DVT	Doppler, venography
Saif <sup>11</sup>	2001	R	131	HIV	7.63%	DVT, PE	Plethysmography, venography, pulmonary angiography, V/Q scan
Copur <sup>8</sup>	2002	R	362	HIV	2.76%	DVT, PE	Duplex, CT, V/Q scan, ICD-9 code
Fultz <sup>15</sup>	2004	R	13549	HIV**	2%	DVT, PE, phlebitis, thrombophlebitis	ICD-9 code
			5114	HIV*	1.6%		

\*After 1996/ PI introduction, \*\*before 1996/PI introduction. R = retrospective; P = prospective; DVT = deep venous thrombosis; PE = pulmonary embolism.

Microparticles are relatively small cellular remnants circulating in plasma, originating from platelets and endothelial cells. In HIV patients, microparticles also originate from CD4+ lymphocytes, as a direct consequence of HIV infection and possibly as a reflection of CD4+ lymphocyte apoptosis.<sup>24</sup> Elevated concentrations of microparticles were found in HIV-infected individuals,<sup>25</sup> and, in general, high numbers of microparticles are associated with activation of the coagulation cascade.<sup>25</sup> The procoagulant properties of microparticles are believed to be caused by the clustering of coagulation factor complexes on the activated phospholipid surface serving as catalysts of coagulation reactions. Even in the absence of high levels of microparticles, these elements may still contribute to enhanced coagulation activity, as seen in patients with multiple organ dysfunction syndrome and sepsis.<sup>26</sup>

#### DECREASE IN ANTICOAGULANT FACTORS

The increased risk of DVT during HIV infection could also be related to the impaired functioning of several important anticoagulant proteins. In HIV-infected patients with thrombosis, lowered levels of antithrombin (AT)

were reported.<sup>27</sup> AT is the most important physiological inhibitor of activated coagulation factors (IIa, IXa, Xa, XIa and XIIa). An inherited heterozygous deficiency predisposes to venous thrombosis and a homozygous deficiency is not compatible with life. Acquired AT deficiency frequently occurs in the course of disseminated intravascular coagulation (DIC). Acquired deficiencies may occur by different mechanisms, including decreased synthesis by the liver, increased loss via the kidneys in the nephrotic syndrome, or inactivation by proteolytic enzymes. In DIC, a combination of impaired production, increased utilisation and clearance of AT protease complexes and accelerated cleavage may occur simultaneously. In HIV infection, the contributing role of these factors is not known. Other anticoagulant proteins affected by HIV infection are protein C and protein S. These are vitamin K-dependent glycoproteins which are mainly synthesised in the liver. Protein C is a potent anticoagulant which is activated after the binding of thrombin to thrombomodulin on the endothelial cell surface. Activated protein C (APC) inactivates the activated clotting factors V and VIII.<sup>28,29</sup> Protein S has no known enzymatic activity but is an important co-factor for protein C. Most of the plasma protein S is bound to C4 binding protein and approximately 40% is free and active. Reduced concentrations of protein S are associated with an increased risk of DVT.<sup>30</sup> In HIV-infected patients,

a number of abnormalities in this anticoagulant system have been described. Decreased levels of protein C were detected in HIV-infected patients.<sup>31,32</sup> Also, reduced protein S plasma levels and diminished activity were reported.<sup>33,34</sup> In one study, decreased concentrations of protein S were more prevalent in subjects with CD4+ T lymphocyte counts <200/mm<sup>3</sup> compared with patients with counts >200/mm<sup>3</sup>.<sup>35</sup> The reduced total protein S levels in HIV could be related to enhanced activation or apoptosis of circulating T cells, generating microparticles that may bind protein S. This cellular binding process could explain some of the low values of free protein S that were measured by the PEG precipitation technique.<sup>25</sup> Theoretically, lower levels of active protein S could also be caused by downregulation of protein S synthesis<sup>36</sup> or by anti-protein S antibodies.<sup>37</sup> Heparin cofactor II (HC II) is another anticoagulant protein associated with HIV infection. HC II is a natural thrombin inhibitor. Although the relationship between HC II and DVT is still controversial, the congenital deficiency was reported to be associated with recurrent venous thrombosis.<sup>38</sup> The proportion of subjects with presumably acquired HC II deficiency was significantly greater in HIV-positive individuals than in healthy subjects.<sup>27</sup> A link between HC II and immunodeficiency was suggested by a significant correlation between HC II activity and both the absolute number of CD4+ T lymphocytes and the CD4/CD8 ratio. HC II deficiency was significantly more pronounced in AIDS patients compared with HIV patients.<sup>27</sup> Possible reasons for HC II deficiency could be decreased synthesis, enhanced proteolysis or consumption. Antiphospholipid antibodies (APL) are proteins directed against different phosphor-containing lipids, the main constituents of cell membranes. The best known of these APL are anticardiolipin antibodies and lupus anticoagulants. Studies have shown APL to be present in 82 to 92% of patients with AIDS.<sup>39</sup> APL are related to an increased occurrence of both venous and arterial thrombosis.<sup>40,41</sup> However, in 63 HIV-infected patients, Palomo *et al.*<sup>42</sup> could not find a correlation between the presence of APL antibodies and development of thrombosis. The increased risk for thrombosis can at least in part be explained by inhibition of activated protein C by anticardiolipin antibodies and their co-factor  $\beta_2$ -glycoprotein I. Lupus anticoagulants in particular are associated with acute infections by opportunistic organisms such as *Pneumocystis carinii*. However, the presence of APL in HIV-infected patients is not associated with the stage of disease, CD4 cell count, viral load, medication, or with a hypercoagulable state.<sup>9,43</sup> An association described between microparticles and IgG-APL titres may be a consequence of microparticle generation,<sup>24</sup> but the mechanism is not known. Furthermore, increased titres of APL in HIV infection may reflect polyclonal B cell expansion.<sup>44</sup>

## MISCELLANEOUS FACTORS OF HAEMOSTASIS

Endothelial cell activation does not only lead to enhanced expression of procoagulant proteins, but is also related to altered functioning of various other haemostatic factors. In HIV-infected patients, significant increases of von Willebrand factor were described.<sup>45</sup> Von Willebrand factor is a large endothelium-derived protein that mediates platelet adhesion to damaged endothelium, which is the first step in haemostasis.

Furthermore, raised levels of both tissue type plasminogen activator (tPA) and its inhibitor, plasminogen activator inhibitor I (PAI-I), were found in HIV patients.<sup>45,49</sup>

Activation of both proteins indicates a general activation of the fibrinolytic system, probably as a reaction to the enhanced tendency to thrombosis (and secondary fibrinolysis).

Endothelial cell activation was also reflected in the detection of increased levels of soluble thrombomodulin (sTM) in HIV-infected patients. Soluble TM is an important co-factor for protein C, and probably the raised levels should also be considered a reaction to the various haemostatic changes.

## SPECIFIC HIV-RELATED FACTORS

A number of specific HIV infection related factors could also contribute to the higher risk of DVT. Treatment with HAART was epidemiologically linked to an increased risk for DVT in one study but this association could not be confirmed in another study. Thus, it is not yet clear whether the occurrence of these events should be attributed to chance, HIV infection or HAART. The mechanism could be related to increases in PAI-1 and fibrinogen levels that were found in patients treated by HAART<sup>50</sup> and could be associated with increased lipid levels<sup>51,52</sup> and in particular with the lipodystrophy syndrome.<sup>52,55</sup> There are no studies published about the association between other antiretroviral therapy (nucleoside reverse transcriptase inhibitors and non-nucleoside reverse transcriptase inhibitors alone) and venous thrombosis. In one study, no relationship was found between the use of nucleoside analogues, protease inhibitors, or non-nucleoside reverse-transcriptase inhibitors and the risk of cardiovascular or cerebrovascular events.<sup>56</sup>

In spite of the efficacy of HAART, HIV patients are still at increased general risk of infections. These concomitant infections are an additional risk factor for thrombosis.<sup>11,57,58</sup>

Cytomegalovirus infections were associated with pulmonary embolism and cerebral venous thrombosis.<sup>59</sup> In *Pneumocystis carinii* infection, elevated levels of APL were found in up to 94% of infected AIDS patients.<sup>60,61</sup>

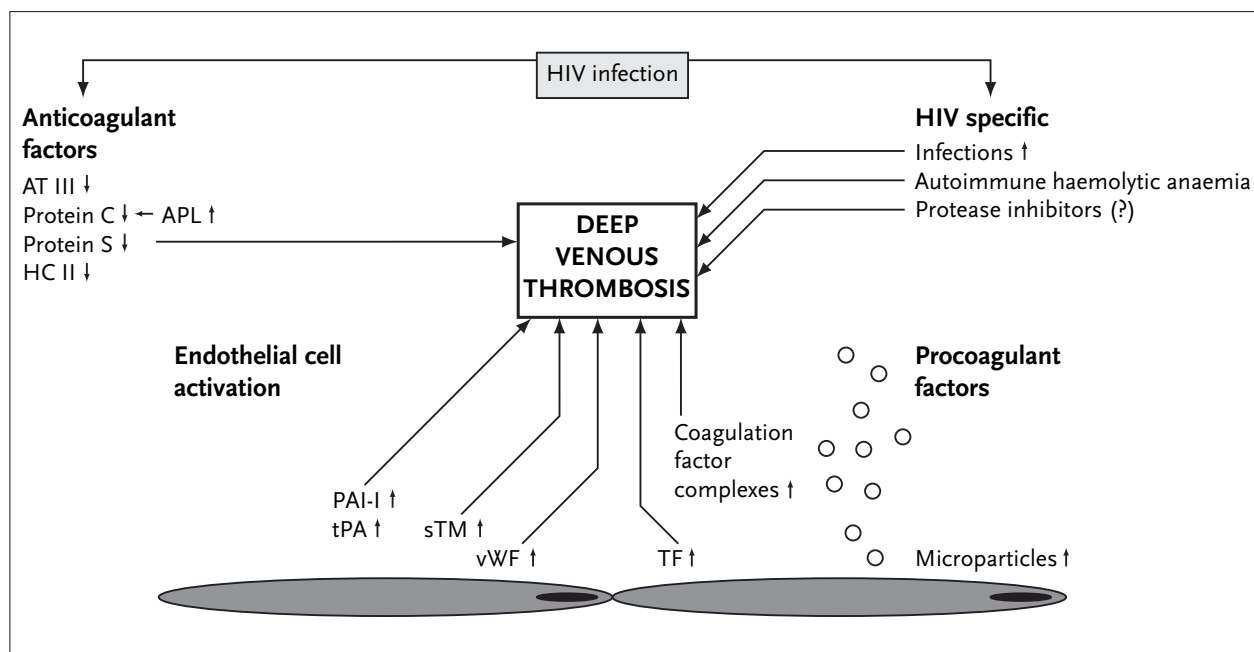
HIV infection can also be complicated by autoimmune haemolytic anaemia. In this condition an increased risk of thromboembolic events, especially during infusion of red blood cells, was reported.<sup>62,63</sup>

## DISCUSSION

A number of case reports suggested that HIV infection was associated with an increased risk for venous thrombosis. In a systematic search of the literature, we retrieved ten relevant studies (table 1) that reported the incidence of venous thrombotic events in HIV-infected patients. These studies suggested that the incidence was probably increased two- to tenfold in comparison with a healthy population of similar age. The increased incidence was associated with various changes in blood coagulation in HIV-infected patients, increased risk of infections and autoimmune haemolytic anaemia. However, the epidemiological studies were limited by some important factors. The power of the studies was limited by the generally low incidence of DVT. Endpoints and the diagnostics used varied greatly, which complicates comparison of the studies. Furthermore, most of the

studies were retrospective cohort studies and included different study populations, including both hospital-based and population-based patient groups, making these studies prone to selection bias. Only three studies compared the results with control populations.<sup>8,15,58</sup> However, these control populations were not always fully described, confounding factors, such as interfering malignancies, were not always mentioned, the diagnostic work-up was not always clear, data may have been incomplete and endpoints included phlebitis in two studies.<sup>9,15</sup>

A considerable number of studies in HIV-infected patients described various haemostatic changes that are associated with the risk of developing venous thrombosis. Procoagulant factors, such as endothelial TF expression and thrombogenic properties of microparticles, were upregulated, whereas anticoagulant factors, including AT, HC II and the protein C pathway, were downregulated. In addition, fibrinolytic proteins were present in elevated concentrations and endothelial sTM production was increased. Taken together, these changes represented a general hypercoagulable state in HIV-infected patients and this state could be responsible for the increased risk of venous thrombosis (figure 1).



**Figure 1**  
Diagram summarising the hypercoagulable state in HIV-infected patients

The hypercoagulable state is associated with an increased risk for developing deep venous thrombosis. Changes in levels of several factors are indicated by arrows upwards and downwards. Continuous lines represent stimulation and dashed lines inhibition. The effect of protease inhibitors is not certain (see text).

HIV = human immunodeficiency virus; AT III = antithrombin; APL = antiphospholipid antibodies; HC II = heparin cofactor II; PAI-I = plasminogen activator inhibitor I; tPA = tissue plasminogen activator; sTM = soluble thrombomodulin; vWF = van Willebrand factor; TF = tissue factor.

In many cases, the origin and mechanism of the haemostatic changes were not clear. The mechanism will probably be related in general to direct triggering of the immune system by HIV and the subsequent stimulation of common pathways involving the inflammatory response and the coagulation system.<sup>64</sup> The hypercoagulable state in HIV patients is also related to the increased risk of other infections. Superimposed infections triggered acquired deficiencies of protein C and protein S and were associated with increased levels of APL. Furthermore, two epidemiological studies showed higher risks for patients with AIDS or with a CD4 count <200/mm<sup>3</sup>. Thus, the increased risk of DVT in HIV-infected patients is probably caused by active ongoing triggering of the immune system by both HIV infection and superimposed infections. HAART was associated with an increased risk of DVT by some investigators but the evidence was weak. Considering the rather consistent evidence that HIV infection in itself is related to DVT, both epidemiological and haematological, and that it is likely to be mediated by direct triggering of the immune system, it seems prudent at the moment not to consider DVT as a direct complication of HAART. However, the evidence that HAART is not associated with DVT is not very strong either and is, in fact, limited to one epidemiological study showing a non-significant increase in risk of DVT by HAART. Because of the potential serious consequence of DVT, further studies are strongly recommended to establish whether or not HAART adds to the risk of DVT in HIV-infected patients. In conclusion, currently available epidemiological evidence suggests that chronic HIV infection is associated with a two- to tenfold increased risk of venous thrombosis in comparison with a general population of the same age. However, these data lack reliability, because the incidence rates were often derived from retrospective cohort studies that were limited by low absolute risk numbers, and because the studies were susceptible to selection bias and they frequently lacked proper control groups. Because of the low absolute risk numbers, it will be difficult to organise adequately powered prospective cohort studies. Well-designed case-control studies could be a suitable alternative to determine the incidence of DVT. In these studies, proper attention should be paid to avoidance of selection bias and to analysis and correction of possible confounding factors, including age and gender, travel history, malignancies, infections, intoxications, PI and other HAART medication use, and inherited and acquired changes in levels of proteins involved in haemostasis. After all, the multiple evidence of a hypercoagulable state in HIV-infected patients renders it likely that an association between DVT and HIV infection does exist. Finally, if the relationship were to be confirmed in well-designed case-control studies, the option of thrombosis prophylaxis should be considered in HIV-infected patients.

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#### ERRATUM

In the article 'PR and QTc interval prolongation on the electrocardiogram after binge drinking in healthy individuals' by A. Lorscheid *et al.* all percentage symbols (%) for the amount of alcohol should be read as permillage symbols (‰).

Lorscheid A, de Lange DW, Hijmering ML, Cramer MJ, van de Wiel A. PR and QTc interval prolongation on the electrocardiogram after binge drinking in healthy individuals. *Neth J Med* 2005;63(2):59-63.