## Thrombophilia ad dies vitae

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*Chapter 8*

# Stress-induced hyperglycaemia and venous thromboembolism following total hip or total knee arthroplasty

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## Abstract

*Background*

Stress-induced hyperglycaemia is common during orthopaedic surgery. In addition, hyperglycaemia has recently been shown to activate coagulation. Whether stress-induced hyperglycaemia is associated with symptomatic or asymptomatic venous thromboembolism (VTE), is unknown.

*Objective*

To investigate whether hyperglycaemia measured pre-surgery (day 0) and post-surgery (day1) is associated with an increased risk of VTE.

*Methods*

We performed post-hoc analyses in the four RECORD studies (REgulation of Coagulation in major Orthopaedic surgery reducing the Risk of Deep venous thrombosis and pulmonary embolism). Separate analyses were performed for patients undergoing total hip or knee replacement. Outcome measures were symptomatic VTE and "total VTE" (defined as the composite of symptomatic VTE, asymptomatic DVT and all cause mortality) during the predefined treatment periods. Glucose levels were measured at day 0 and day 1 and categorized into quartiles, based on the distribution in the respective cohorts. The influence of glucose and other relevant covariates on VTE was assessed by stepwise selection (entry/stay level $P$=0.20) in multivariate analyses. Variables for treatment group and study were forced into the model. Adjusted odds ratios (ORs) and 95% confidence intervals were calculated.

*Results*

A total of 12,383 patients were eligible for assessment of symptomatic VTE and 8,512 patients were eligible for assessment of total VTE. Glucose levels measured at day 1 were associated with both symptomatic and total VTE in patients undergoing hip surgery, adjusted OR highest versus lowest quartile 2.6 (95%CI 1.0 to 6.6) and 2.0 (95%CI 1.3 to 3.1), respectively. No association between hyperglycaemia and knee replacement was observed.

*Conclusion*

Hyperglycaemia following total hip replacement was associated with symptomatic and asymptomatic VTE. This was, however, not observed in patients total undergoing knee replacement, which is likely due to the surgical procedure.

## Introduction

Venous thromboembolism (VTE) may manifest as either deep venous thrombosis (DVT) or pulmonary embolism (PE), or a combination of both. VTE affects 2-3 persons per 1,000 inhabitants annually in Western Societies.[1] Acquired risk factors can be identified in approximately 50% of VTE patients, and, in addition, one or more inherited risk factors can be demonstrated in an equal proportion of patients.[2,3] This implies, that in approximately 25% of patients with VTE no risk factors can be identified.

Hyperglycaemia has recently been shown to be associated with VTE in an outpatient population.[4] In several reports, acute hyperglycaemia was shown to cause coagulation activation in an experimental setting as demonstrated by increased levels of thrombin-antithrombin complexes and soluble tissue factor.[5,6] During acute illness or surgery, a phenomenon called stress hyperglycaemia may occur independently of the presence of known diabetes.[7] Indeed, hip surgery has been shown to induce hyperglycaemia peaking the days after the procedure, followed by post-operative procoagulant activity peaking on the third and fourth postoperative days.[8] Whether stress-hyperglycaemia is associated with VTE in hospitalized patients, such as orthopaedic patients, has not been previously addressed. The associated risk of hyperglycaemia could be of particular interest in surgical patients, since the coagulation system is already activated due to the surgical procedure.[9] Furthermore, VTE is a frequently occurring complication following orthopaedic surgery. Despite anticoagulant prophylaxis, symptomatic VTE occurs in approximately 2% of all patients undergoing hip or knee replacements.[10] In this study we aimed to assess whether pre- and postoperative hyperglycaemia is associated with (a)symptomatic VTE.



## Methods

### *Patients*

For the present analysis we made use of the large phase III trial programme: "REgulation of Coagulation in major Orthopaedic surgery reducing the Risk of Deep venous thrombosis and pulmonary embolism studies" (RECORD 1-4).[11-14] These trials compared the efficacy and safety of Rivaroxaban (a direct factor Xa inhibitor) 10 mg o.d. relative to standard treatment with Enoxaparin 40 mg o.d.[11-13] or 30 mg b.i.d.[14] As efficacy and safety outcomes, as well as independent, blinded adjudication committees were the same in all RECORD studies, the studies allow pooling of the data. Patients were eligible if they were aged 18 years or older and were scheduled for elective total hip or total knee arthroplasty. Major exclusion criteria included active bleeding or high risk of bleeding, significant liver disease,

anticoagulant therapy that could not be interrupted, use of HIV-protease-inhibitors and a contraindication for prophylaxis with enoxaparin or a condition that would require a dose adjustment for enoxaparin. Detailed in- and exclusion criteria were reported in the original publications of the RECORD studies.[11-14]

*Procedures*

Deep-vein thrombosis was assessed per protocol, by ascending, bilateral venography with a standardized technique.[15] This was performed at day 36 (range 32 to 40) in patients with total hip replacements (RECORD 1 and 2)[11,12] and at day 13 (range 11 to 15) in patients with total knee replacement (RECORD 3 and 4).[13,14] Symptomatic VTE was objectively confirmed by standard imaging techniques. Treatment duration was 5 weeks for RECORD study 1 and 2 (including the 3 weeks of placebo treatment in the comparator group). Treatment duration in RECORD 3 and 4 was 2 weeks. Patients were followed up for 30–35 days after the last dose. Glucose levels were sampled upon admission (day 0) and 6 hours after surgery (day 1). All samples were analyzed in the central laboratory.

*Outcomes*

The aim of this study was to assess whether hyperglycaemia (measured pre- and post-surgery) was associated with an increased risk of VTE. We assessed the effect of hyperglycaemia on symptomatic VTE in the participants included in the safety population of the four RECORD studies. The safety population was defined as patients who had undergone surgery and had received at least one dose of study medication. Furthermore, we investigated the association between hyperglycaemia and total VTE, which was defined as the composite outcome of symptomatic VTE and asymptomatic DVT as detected by per protocol venography and all cause mortality. The analyses for total VTE were performed in the modified intention to treat (mITT) population, compromising all patients from the safety analyses with adequate assessment of both proximal and distal veins on venography. Only events occurring in the treatment phase of the studies were considered.

*Statistical Analyses*

Descriptive results are presented as mean ± standard deviation (SD) or median with interquartile range (IQR).

To investigate the association of hyperglycaemia and VTE multiple logistic regression analyses were performed separately for patients undergoing total hip and total knee

arthroplasty. Separate analyses were carried out to assess the influence of glucose on Day 0 (pre-surgery) and Day 1 (post-surgery), and of the difference in glucose levels (Day 1-Day 0) on symptomatic and total VTE. In all analyses glucose levels were categorized into quartiles, based on the distribution in the respective cohorts. Glucose quartiles and other relevant covariates (BMI (<25, 25-<35, ≥35), age (<65, 65-75, ≥75), gender and concomitant known diabetes mellitus) were screened via stepwise selection (entry/stay level $P$=0.20) for the creation of the logistic regression models. Variables for treatment group and study were not screened but forced into the model. Odds ratios (OR) and p-values of the likelihood ratio test for testing whether the selected variables have a significant influence on the outcome were calculated. All statistical analyses were performed in SAS version 9.1 (SAS institute, Cary, NC). All outcomes are reported as adjusted ORs.

**Table 1. Baseline characteristics of both study cohorts**

| | **Total hip arthroplasty (RECORD 1&2)[11,12] (n=6890)** | **Total knee arthroplasty (RECORD 3&4)[13,14] (n=5493)** |
|---|---|---|
| **Age – years (mean ± SD)** | 63 (12) | 66 (10) |
| **Sex, female n (%)** | 3780 (55%) | 3652 (66%) |
| **Body-mass index – kg/m² (mean ± SD)** | 28 (5) | 30 (6) |
| **History of VTE, n (%)** | 132 (2%) | 156 (3%) |
| **Previous orthopaedic surgery, n (%)** | 1447 (21%) | 1690 (31%) |
| **Type of surgery, n (%)** | | |
| Primary | 6562 (95%) | 5329 (97%) |
| Revision | 254 (4%) | 119 (2%) |
| Missing/no surgery | 74 (1%) | 45 (1%) |
| **Type of anaesthesia** | | |
| General only | 1983 (29%) | 1034 (19%) |
| General and regional | 619 (9%) | 1126 (21%) |
| Regional only | 4215 (61%) | 3292 (60%) |
| Missing | 73 (1%) | 0 (0%) |
| None | 0 (0%) | 41 (1%) |
| **Duration of surgery – minutes (mean ± SD)** | 98 (48) | 99 (40) |
| **Time to mobilization – days (mean ± SD)** | 2.2 (4) | 1.6 (2) |
| **Ethnic origin, n (%)** | | |
| White | 5687 (83%) | 4037 (73%) |
| Asian | 498 (7%) | 736 (14%) |
| Hispanic | 329 (5%) | 353 (6%) |
| Black | 103 (1%) | 181 (3%) |
| Other/missing | 273 (4%) | 186 (3%) |
| **Randomization allocation, n (%)** | | |
| Rivaroxaban | 3437 (50%) | 2746 (50%) |
| Comparator (enoxaparin) | 3453 (50%) | 2747 (50%) |
| **On glucose lowering therapy, n (%)** | 407 (6%) | 654 (12%) |
| **Diabetes Mellitus n (%)** | 532 (8%) | 890 (16%) |

VTE=venous thromboembolism, SD=standard deviation, N.A.=not available.

## Results

*Baseline characteristics*

The safety population of the four RECORD studies consisted of 12,383 patients, of whom 6,890 underwent total hip arthroplasty and 5,493 total knee arthroplasty, respectively. The baseline characteristics of both cohorts are shown in Table 1. High BMI and female gender were more common in the knee arthroplasty cohort (mean BMI 30.3 kg/m$^2$ vs. 27.5 kg/m$^2$, and 66% vs. 55%, respectively). Mean age was slightly higher in the knee surgery cohort: 66 years vs. 63 years. The mITT population comprised 8,512 patients (hip replacement 4,886 patients, knee replacement 3,626 patients).

*Total hip arthroplasty*

Median pre-operative glucose level (day 0) was 97 mg/dL (IQR 88-114) (Table 2). Glucose levels on Day 0 were not associated with either symptomatic VTE or total VTE, as the variable "glucose" was not maintained in the regression model following stepwise selection regression analysis (Table 2).

At day 1 (post surgery), the median glucose level was 117 mg/dL (IQR 99 to 142). Glucose levels in the highest quartile (>142 mg/dL) were associated with both symptomatic VTE and total VTE, when compared to the lowest glucose quartile (≤99 mg/dL): adjusted OR 2.6 (95%CI 1.0 to 6.6) and OR 2.0 (95%CI 1.3 to 3.1), respectively. The p-value of the Likelihood Ratio test for glucose on Day 1 was significant for both outcomes (p=0.0142 for symptomatic VTE and p<0.0001 for total VTE). In addition, the amount of increase of the glucose level between day 1 and day 0 was associated with total VTE (p=0.0082). Median difference of glucose levels between these two time points was 16 mg/dL (IQR -5 to 40). The highest quartile of this difference was associated with a nearly twofold increased risk for total VTE compared to the lowest quartile (adjusted OR 1.8, 95%CI 1.2 to 2.8). The adjusted OR for symptomatic VTE was not maintained in the regression model (see Table 2).

*Total knee arthroplasty*

The distribution in glucose levels at day 0 and day 1 in patients undergoing knee arthroplasty was comparable to that in the hip surgery cohort. Median glucose was 99 mg/dL (IQR 88 to 115) at day 0 and 123 mg/dL (IQR 103 to 150) at day 1 (Table 3).

For glucose levels measured at day 0, there was no association between glucose levels and symptomatic VTE.

**Table 2. Odds Ratio for glucose levels measured at day 0, day 1 and difference in glucose levels between day 1 and day 0 in relation to symptomatic VTE and total VTE in hip surgery patients (RECORD 1&2)[11,12]**

| **quartiles glucose levels measured at day 0 (mg/dL)** | **≤88** | **>88 to 97** | **>97 to 114** | **>114** |
|---|---|---|---|---|
| **all patients (N)** | 1487 | 1713 | 2014 | 1630 |
| symptomatic VTE (n) | 5 | 13 | 11 | 6 |
| crude OR (95%CI) | 1 (ref) | 1.2 (0.6 to 2.5) | 0.8 (0.4 to 1.8) | 1.3 (0.6 to 2.8) |
| adjusted OR (95%CI) | glucose not maintained in the regression model | | | |
| LR test | p>0.20 | | | |
| **patients valid for the modified intention to treat analyses (N)** | 1051 | 1220 | 1449 | 1141 |
| total VTE (n) | 37 | 41 | 60 | 35 |
| crude OR (95%CI) | 1 (ref) | 1.2 (0.9 to 1.7) | 1.1 (0.8 to 1.6) | 1.5 (1.1 to 2.0) |
| adjusted OR (95%CI) | glucose not maintained in the regression model | | | |
| LR test | p>0.20 | | | |
| **quartiles glucose levels measured at day 1 (mg/dL)** | **≤99** | **>99 to 117** | **>117 to 142** | **>142** |
| **all patients (N)** | 1590 | 1722 | 1671 | 1697 |
| symptomatic VTE (n) | 6 | 4 | 6 | 17 |
| crude OR (95%CI) | 1 (ref) | 0.6 (0.2 to 2.2) | 0.9 (0.3 to 2.9) | 2.6 (1.0 to 6.6) |
| adjusted OR (95%CI) | 1 (ref) | 0.6 (0.2 to 2.2) | 0.9 (0.3 to 2.9) | 2.6 (1.0 to 6.6) |
| LR test | p=0.0142 | | | |
| **patients valid for the modified intention to treat analyses (N)** | 1148 | 1241 | 1219 | 1210 |
| total VTE (n) | 32 | 31 | 33 | 75 |
| crude OR (95%CI) | 1 (ref) | 0.9 (0.5 to 1.4) | 0.9 (0.6 to 1.5) | 2.2 (1.4 to 3.4) |
| adjusted OR (95%CI) | 1 (ref) | 0.9 (0.5 to 1.4) | 0.9 (0.5 to 1.5) | 2.0 (1.3 to 3.1) |
| LR test | p<0.0001 | | | |
| **quartiles difference in glucose levels day 1 - day 0 (mg/dL)** | **≤-5** | **>-5 to 16** | **>16 to 40** | **>40** |
| **all patients (N)** | 1633 | 1655 | 1699 | 1661 |
| symptomatic VTE (n) | 5 | 6 | 8 | 14 |
| crude OR (95%CI) | 1 (ref) | 1.2 (0.4 to 3.9) | 1.5 (0.5 to 4.6) | 2.7 (1.0 to 7.5) |
| adjusted OR (95%CI) | glucose not maintained in the regression model | | | |
| LR test | p>0.20 | | | |
| **patients valid for the modified intention to treat analyses (N)** | 1169 | 1192 | 1241 | 1197 |
| total VTE (n) | 33 | 30 | 43 | 64 |
| crude OR (95%CI) | 1 (ref) | 0.9 (0.5 to 1.5) | 1.2 (0.7 to 1.8) | 1.8 (1.1 to 2.8) |
| adjusted OR (95%CI) | 1 (ref) | 0.9 (0.6 to 1.6) | 1.2 (0.7 to 1.9) | 1.8 (1.2 to 2.8) |
| LR test | p=0.0082 | | | |

VTE=venous thromboembolism; OR=Odds Ratio, LR test=Likelihood Ratio test for testing whether increase in glucose levels (in quartiles) has a significant influence on the occurrence of VTE. Total VTE is the composite of symptomatic VTE, asymptomatic DVT and all cause mortality.

Again, the variable "glucose" was not maintained in the regression model (Table 3). A non-significant trend was observed for total VTE at day 0: adjusted OR 1.4 (95%CI 1.0 to 1.9, Likelihood Ratio test: p=0.16). Furthermore, glucose levels measured at day 1 were not significantly associated with symptomatic VTE: adjusted OR 1.6 (95%CI 0.7 to 3.6), nor with total VTE (see Table 3). In addition, no association was found between the increase in glucose levels (median difference 19 mg/dL, IQR -3 to 46) and VTE: adjusted OR for symptomatic VTE: 0.8 (95%CI 0.3 to 1.8), the variable "glucose" was not maintained in the regression model for total VTE (Table 3).

**Table 3. Odds Ratio for glucose levels measured at day 0, day 1 and difference in glucose levels between day 1 and day 0 in relation to symptomatic VTE and total VTE in knee surgery patients (RECORD 3&4)[13,14]**

| **quartiles glucose levels measured at day 0 (mg/dL)** | **≤88** | **>88 to 99** | **>99 to 115** | **>115** |
|---|---|---|---|---|
| **all patients (N)** | 1216 | 1480 | 1320 | 1417 |
| symptomatic VTE (n) | 12 | 18 | 11 | 19 |
| crude OR (95%CI) | 1 (ref) | 1.2 (0.6 to 2.5) | 0.8 (0.4 to 1.8) | 1.3 (0.6 to 2.8) |
| adjusted OR (95%CI) | glucose not maintained in the regression model | | | |
| LR test | p>0.20 | | | |
| **patients valid for the modified intention to treat analyses (N)** | 813 | 996 | 878 | 903 |
| total VTE (n) | 72 | 115 | 93 | 124 |
| crude OR (95%CI) | 1 (ref) | 1.2 (0.9 to 1.7) | 1.1 (0.8 to 1.6) | 1.5 (1.1 to 2.0) |
| adjusted OR (95%CI) | 1 (ref) | 1.2 (0.9 to 1.7) | 1.1 (0.8 to 1.5) | 1.4 (1.0 to 1.9) |
| LR test | p=0.16 | | | |
| **quartiles glucose levels measured at day 1 (mg/dL)** | **≤103** | **>103 to 123** | **>123 to 150** | **>150** |
| **all patients (N)** | 1476 | 1300 | 1266 | 1281 |
| symptomatic VTE (n) | 10 | 22 | 12 | 14 |
| crude OR (95%CI) | 1 (ref) | 2.5 (1.2 to 5.3) | 1.4 (0.6 to 3.2) | 1.6 (0.7 to 3.6) |
| adjusted OR (95%CI) | 1 (ref) | 2.5 (1.2 to 5.3) | 1.4 (0.6 to 3.2) | 1.6 (0.7 to 3.6) |
| LR test | p=0.08 | | | |
| **patients valid for the modified intention to treat analyses (N)** | 1005 | 876 | 846 | 831 |
| total VTE (n) | 103 | 93 | 99 | 107 |
| crude OR (95%CI) | 1 (ref) | 1.0 (0.8 to 1.4) | 1.1 (0.8 to 1.5) | 1.3 (0.9 to 1.7) |
| adjusted OR (95%CI) | glucose not maintained in the regression model | | | |
| LR test | p>0.20 | | | |
| **quartiles difference in glucose levels day 1 - day 0 (mg/dL)** | **≤-3** | **>-3 to 19** | **>19 to 46** | **>46** |
| **all patients (N)** | 1331 | 1304 | 1347 | 1290 |
| symptomatic VTE (n) | 13 | 21 | 13 | 10 |
| crude OR (95%CI) | 1 (ref) | 1.6 (0.8 to 3.3) | 1.0 (0.4 to 2.1) | 0.8 (0.3 to 1.8) |
| adjusted OR (95%CI) | glucose not maintained in the regression model | | | |
| LR test | p>0.20 | | | |
| **patients valid for the modified intention to treat analyses (N)** | 887 | 899 | 902 | 840 |
| total VTE (n) | 100 | 100 | 102 | 95 |
| crude OR (95%CI) | 1 (ref) | 1.0 (0.8 to 1.4) | 1.0 (0.8 to 1.4) | 1.0 (0.8 to 1.4) |
| adjusted OR (95%CI) | glucose not maintained in the regression model | | | |
| LR test | p>0.20 | | | |

VTE=venous thromboembolism; OR=Odds Ratio, LR test=Likelihood Ratio test for testing whether increase in glucose levels (in quartiles) has a significant influence on the occurrence of VTE. Total VTE is the composite of symptomatic VTE, asymptomatic DVT and all cause mortality.

## Discussion

This study shows an association between post–operative glucose levels and both symptomatic VTE and total VTE in patients undergoing total hip arthroplasty. In addition, the increase of glucose levels from pre to post operative was also significantly associated with total VTE in these patients. In contrast, after adjustment for potential confounders, these associations were not found in patients undergoing knee arthroplasty. Only a non-significant trend was observed for total VTE and glucose levels, measured either at day 0 or day 1.

The association between preoperatively elevated glucose levels and VTE in patients undergoing orthopaedic surgery has previously been reported.[16] Mraovic and colleagues found that preadmission glucose levels exceeding 200 mg/dL independently increased the risk of pulmonary embolism (OR=3.19, 95%CI 1.25 to 8.10) when compared to glucose levels of less than 110mg/dL in patients who underwent hip or knee arthroplasty. We did not find a relation between preoperative hyperglycaemia and VTE. However, 200 mg/dL is well above the cut-off value of the highest quartile in our cohort, 145 mg/dL, and is likely to reflect patients with undiagnosed diabetes mellitus before surgery, a known risk factor for postsurgical complications[17] We also assessed the influence of post-operative stress-induced glucose increase in relation to the development of VTE to investigate whether stress-hyperglycaemia is an independent risk factor for VTE following orthopaedic surgery.

Available pathophysiological evidence supports the relation between (acute) hyperglycaemia and hypercoagulability. In patients with diabetes mellitus, the concentration of several procoagulant factors are increased (fibrinogen, von Willebrand antigen, factor VII antigen, factor VIII) and antifibrinolytic factors are decreased, such as plasminogen activator inhibitor-1 (PAI-1).[18] Furthermore, hip surgery has been shown to induce hyperglycaemia, which preceded a rise of factor VIII clotting activity, von Willebrand ristocetin cofactor activity, von Willebrand factor antigen and prothrombin fragment 1+2.[8] In healthy volunteers, acute hyperglycaemia activates the coagulation system in an experimental setting.[5]

In this study, only those hip surgery patients in the highest quartile of post-operative stress-induced hyperglycaemia were at increased risk for VTE, instead of a linear increase in risk. This implies that glucose levels apparently need to exceed a certain threshold to reach a significant association with VTE. Interestingly, the cut-off between the third and fourth quartiles, 142 mg/dL, is close to the classic cut-off for impaired glucose tolerance following the glucose tolerance test, 140 mg/dL.[19]

Hyperglycaemia was not clearly associated with VTE in patients undergoing TKR, in contrast with patients undergoing THR. This discrepancy cannot be explained by major differences in patients' characteristics, as these were included as covariates in the regression model. The most important factor may concern the surgical procedure. TKR is performed with application of a tourniquet, occluding arterial and venous flow.[20] Tourniquet use is related to the formation of thrombi.[21-24] It is thus possible that the effect of hyperglycaemia is completely outweighed by other risk factors for VTE in patients undergoing TKR.

Although preoperative glucose samples were drawn at predefined time points, patients were not mandatory in a fasting state. We have, however, no reason to assume that there was a difference in distribution in fasting/non-fasting samples in patients with- or without VTE. Furthermore, this substudy involved a non-prespecified analysis. Nevertheless, we have investigated a prospective database, with a very large sample size. In addition, the most important assessments, VTE and glucose, were collected prospectively and comprehensively. The outcome "total VTE" not only included symptomatic VTE and asymptomatic DVT, but also "all cause mortality". As the number of subjects who died during follow up is very low in the four RECORD studies (n=23/8,512, 0.3%), it is not likely that the inclusion of the latter outcome measure affected the results.

In conclusion, stress-induced postoperative hyperglycaemia is associated with asymptomatic and symptomatic VTE following hip replacement. Future studies should assess whether the risk of VTE can be decreased by glucose lowering therapy in patients with postoperative hyperglycaemia.

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