## PEER REVIEW HISTORY



## ARTICLE DETAILS

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| **TITLE (PROVISIONAL)** | Health-related quality of life after catheter-directed thrombolysis for deep vein thrombosis; from the CaVenT study (an open RCT) |
| **AUTHORS** | Enden, Tone; Wik, Hilde; Kvam, Ann Kristin; Haig, Ylva; Kløw, Nils-Einar; Sandset, Per Morten |

## VERSION 1 - REVIEW

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| **REVIEWER** | **Broholm, Rikke**<br><br>Rigshospitalet and Gentofte, University of Copenhagen, Copenhagen, Denmark |
| **REVIEW RETURNED** | 03-May-2013 |

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| **THE STUDY** | The CaVenT investigators have reported their results of an open-label randomised controlled trial in a population with high proximal deep vein thrombosis (DVT). Patients were randomised to additional catheter-directed thrombolysis (CDT) with alteplase or to standard treatment with 6 months anticoagulation and 24 months of compression stockings.<br><br>Primary outcome measure included post-thrombotic syndrome (PTS) after 24 months of follow-up and patency of the iliofemoral veins at 6 months. Secondary outcome was quality-of life (QOL) assessed with the generic instrument EQ-5D and the disease specific instrument VEINES-QOL/Sym.<br><br>First, it is important to recognise that the authors now use the term “high proximal DVT” which refers to thrombus in mid-thigh level or higher. It is different from the initial title with iliofemoral DVT that is defined as thrombus in the common femoral, external iliac and common iliac veins. Iliofemoral DVT compared to femoral DVT only is a strong predictor of subsequent PTS. The baseline characteristics of the patients in the CDT and standard treatment groups were 3% and 2% with isolated pelvic vein thrombosis, 42% and 34% with iliofemoral DVT, and 50% and 59% with femoral DVT, respectively. |

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| | Findings:<br>In the present study by Enden and colleagues, 209 patients were recruited and 189 were available for follow-up at 24 months; 90 in the CDT group and 99 controls. The authors found no difference in QOL between the additional CDT and standard treatment; EQ-5D index was 0.80 and 0.84 (p=0.71), VEINES-QOL score was 50.1 and 49.9 (p= 0.60), and VEINES-Sym score was 50.3 and 49.8 (p=0.37), respectively. However, independent of treatment arms, patients with PTS had poorer outcomes than patients without PTS at 24 months; EQ-5D index was 0.77 and 0.86 (p< 0.001), VEINES-QOL score was 45.6 and 54.2 (p< 0.001), and VEINES-Sym score was 45.0 and 54.8 (p< 0.001), respectively.<br><br>Comments:<br>The objective of the study was to investigate whether additional CDT improves long-term quality of life compared to standard treatment alone. However, it is important to consider the basic results from the CaVenT study concerning the incidence of PTS at 24 months. Here, PTS was found among 41% of patients allocated additional CDT whereas 56% in the control group had PTS (p=0.047). Both patient selection (symptoms < 21 days) and procedural technique most likely contributed to this finding. Disappointingly, PTS in the CDT group was not related to the success of lysis. This was likely due to the small number of patients with iliofemoral DVT relative to patients with infrainguinal DVT. Furthermore, only a small proportion of patients received venous stenting (n=15) and 23 patients received angioplasty. Previous studies have shown that up to 70% of patients with iliofemoral DVT has an underlying iliac venous stenosis that has to be treated with a stent to restore venous outflow. The low incidence of venous stenting in the CaVenT study is likely to have diminished the benefit of CDT.<br>In view of the abovementioned data, it is not surprising that Enden and colleagues did not find a difference in QOL between the additional CDT and standard treatment. However, they found poorer QOL among patients with PTS compared to patients without PTS. They recommend that QOL assessment should be among the long-term outcome measures in clinical research on patients who are at risk of developing PTS. This is an important message.<br><br>In the section “Strengths and Limitations” on page 3 line 35 they describe that the study may have been underpowered to detect a clinically meaningful difference in QOL between the two treatment arms. This is a possibility but it might be due to the small number of patients with iliofemoral DVT relative to infrainguinal DVT patients and the relatively small difference in PTS between the two groups. This should be clarified.<br><br>In the “Introduction” section page 4 line 11 and line 18 the terms “proximal deep vein thrombosis” and “high proximal DVT” are |

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| | used. These should be defined and the difference from iliofemoral DVT should be explained.<br><br>Page 4 line 57: symptoms lasted < 21 days. Today, acute DVT is defined as symptoms that have been present for up to 14 days and/or imaging indicating venous thrombosis having occurred within the last 14 days. The purpose of the basic study was to treat acute DVT and this should be described as a limitation of the basic study.<br><br>Page 9 line 10: the sentence "…however, the difference of 3.2 and 2.4 points, respectively, .." should be changed to "…However, the difference of 2.4 and 3.2 points, respectively…".<br><br>Page 12 line 32: "This finding was not supported in our RCT, and long-term QOL may not represent a significant secondary efficacy outcome after CDT". Again, the reason for not finding a difference between the two treatment arms is probably due to the relatively small difference in PTS between the two groups. As previously described, the authors found that PTS in the CDT group was not related to the effect of lysis. This conflicts with the inherent purpose of CDT and previous studies. The authors should elaborate more on this topic in the discussion.<br><br>Page 16 line 16: reference 3: the fifth author name is written in capital letters. This should be corrected.<br><br>Page 17 line 16 and 34: reference 16 and reference 21: the journal number/volume and pages are missing. This should be added.<br><br>Overall, this study has been successfully conducted. However, there are some limitations of the basic study that influence the results of the present study. The authors must especially discuss the present results in light of these limitations. In what degree will the authors treat patients with iliofemoral DVT? Is CDT useless in the future? |

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| **REVIEWER** | **Christensen, Robin**<br><br>Copenhagen University Hospital, Frederiksberg, The Parker Institute: MSU |
| **REVIEW RETURNED** | 06-May-2013 |

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| **THE STUDY** | The authors explicitly state that they did analyses on the Intention-to-Treat population; however, in all the tables they refer to the sample that completes 2-year follow-up.<br><br>I would strongly recommend the authors apply a transparent ITT approach - like Non-responder Imputation. |

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| | The authors only reports results for individual groups with a P-value for the test between them; they've forgotten to report group mean differences (with 95% CIs) |
| **RESULTS AND CONCLUSIONS** | According to CONSORT etc - the authors need to focus on differences between the groups (with 95% CIs) rather than reporting each group individually. |
| **REPORTING ETHICS** | The authors doesn't compare groups with an effect size (+95% CIs). They claim that they've used ITT which they clearly have not. |
| **GENERAL COMMENTS** | The authors investigate whether additional catheter-directed thrombolysis (CDT) improve HRQoL in patients with DVT. Overall the study is well-designed, apparently with a rigorous protocol. Though this paper focus on the secondary outcomes from the trial, without appropriate statistical support.<br><br>I would recommend the authors to apply a more CONSORT-like title for the study:<br><br>Health-related quality of life after catheter-directed thrombolysis for deep vein thrombosis: secondary outcomes of the randomised, non-blinded, parallel-group CaVenT study<br><br>ABSTRACT:<br>The authors should focus on group contrasts in their reporting, rather than giving individual group statistics. It is strongly recommended that the authors report 'Differences between means' with (95% confidence intervals).<br>I understand the authors are tempted to report "P-values", which is acceptable; please include the P-value in each of the above mentioned parentheses with 95%CI.<br><br>Article summary:<br>There is no need to state "Patient-Reported" before Quality of Life; please omit.<br><br>Statistical analysis and sample size:<br>The authors state that they applied an ITT approach! However, I can't see how missing data were imputed; please elaborate.<br>According to the RESULTS section the authors completely ignore the fact that they randomized 209 participants. They clearly state that they include patients with two-year follow-up data; THAT IS NOT THE ITT population (90 vs 99 patients). This needs to be clarified and corrected.<br>I would probably suggest the authors to re-do all the analyses, include all 209 patients in the groups originally assigned; for missing data I would recommend a non-responder imputation- i.e., use the baseline observation carried forward technique.<br><br>Table 1: Demographics and clinical characteristics:<br>In a baseline table, the authors should report measures of central tendency with a measure of dispersion – e.g. Mean and SD (or Median and IQR), not Mean values with 95% CIs (95% CI: measure |

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| | precision – not dispersion)<br><br>Table 1 Cont'd<br>The authors mix baseline characteristics and outcome measures in Table 1. It is strongly recommended that these are split into separate Tables (please see CONSORT statement).<br><br>Table 2 AND Table 3:<br>The authors report individual group results and a column with a P-value. This is not the recommended approach. The authors should report individual group estimates, a column with group mean differences (and 95% CIs), and then maybe also the column with the P-value (please see CONSORT statement for further guidance on statistical Tables in biomedical journals).<br><br>OVERALL RECOMMENDATION:<br>The trial report represent a rigorous project. However, there are substantial statistical inadequacies that needs to be corrected: Either the authors perform correct statistical analyses on the – as stated –ITT population, or they have to change the wording into something like "the Per Protocol population".<br>The authors have completely ignored that the correct way to address statistical analyses in 2-arm trials is to focus on the group mean difference with 95% CIs. It is less important what happens in the individual groups.<br><br>Robin Christensen; Senior Biostatistician<br>Copenhagen, Denmark. |

## VERSION 1 – AUTHOR RESPONSE

Dear Editor

Many thanks for the thorough and comprehensive review allowing us to improve and submit a revision of our manuscript "Health-related quality of life after catheter-directed thrombolysis for deep vein thrombosis; from the CaVenT study (an open RCT)" to BMJ Open. We have revised the manuscript in accordance to the reviewers' comments, and our specific point by point responses are clarified in the following sections. We hope that with this we are meeting the reviewers' concerns about our manuscript, and the standards for publication in your journal.

Best regards, Tone Enden, tone.enden@medisin.uio.no

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Reviewer I: Dr Alison Walker, BMJ Open associate editor

Q1. Well reported and appears well conducted. Trial reg says that one of the (12) secondary outcomes is 'effects on quality of life at 2 and 5 years'. Why have they reported this at only 2 years and then say as a limitation that more longitudinal studies are needed – aren't they planning to report this at 5 years?

R1. Yes, we are planning to report quality of life results when the ongoing 5 years follow-up of the study is completed. In terms of limitation of longitudinal assessments we meant more frequent

study visits/data points in addition to the 6, 24, and 60 months visits; this has now been added to the Strength and limitations and the Discussion sections.

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Reviewer II: Rikke Broholm, MD, Ph.D

Q1. In the section “Strengths and Limitations” on page 3 line 35 they describe that the study may have been underpowered to detect a clinically meaningful difference in QOL between the two treatment arms. This is a possibility but it might be due to the small number of patients with iliofemoral DVT relative to infrainguinal DVT patients and the relatively small difference in PTS between the two groups. This should be clarified.

R1. We consider lack of statistical power to be an important limitation which together with other limitations can explain our findings, and as suggested by the reviewer this has now been clarified: “The study was designed to detect a difference in the frequency of post-thrombotic syndrome between the two treatment arms and may have been underpowered to detect a clinically meaningful difference in quality of life. Other possible explanations include a relatively small effect on the reduction in post-thrombotic syndrome and the small proportion presenting with iliofemoral DVT relative to infrainguinal DVT.”

Q2. In the “Introduction” section page 4 line 11 and line 18 the terms “proximal deep vein thrombosis” and “high proximal DVT” are used. These should be defined and the difference from iliofemoral DVT should be explained.

R2. We agree with the reviewer and the following clarifications have been made in the Introduction: “… a proximal deep vein thrombosis (DVT), i.e., DVT in the popliteal vein or above” and “… high proximal DVT localized in the mid-thigh level or above, …”.

Q3. Page 4 line 57: symptoms lasted < 21 days. Today, acute DVT is defined as symptoms that have been present for up to 14 days and/or imaging indicating venous thrombosis having occurred within the last 14 days. The purpose of the basic study was to treat acute DVT and this should be described as a limitation of the basic study.

R3. The Society of Interventional Radiology have stated an arbitrary maximum of 14 days of symptoms for acute DVT and we agree that accordingly our population may also include patients with sub-acute DVT, ie, 15—28 days, as suggested in the SIR standards. However, the mean duration of symptoms in our study was 6.6 days (SD 4.6) indicating that the study participants are a representative population for acute DVT. This is now clarified in the discussion: “As our eligibility criteria allowed for study participants to enroll with up to 21 days of symptoms, this meant that patients with sub-acute DVT, that is more than 14 days of symptoms, may have entered the study and possibly contributed to the overall high PTS frequency and lack of treatment group differences in the QOL scores [19]. However, as the mean symptom duration was less than 7 days and only 15 patients (hereunder 8 controls) had more than 14 days of symptom, we find this unlikely.”

Q4. Page 9 line 10: the sentence “…however, the difference of 3.2 and 2.4 points, respectively, ..” should be changed to “…However, the difference of 2.4 and 3.2 points, respectively…”.

R4. Thanks, this error has been corrected.

Q5 Page 12 line 32: “This finding was not supported in our RCT, and long-term QOL may not represent a significant secondary efficacy outcome after CDT”. Again, the reason for not finding a difference between the two treatment arms is probably due to the relatively small difference in PTS between the two groups. As previously described, the authors found that PTS in the CDT group was not related to the effect of lysis. This conflicts with the inherent purpose of CDT and previous

studies. The authors should elaborate more on this topic in the discussion.
R5. We agree that the relation between PTS and effective thrombolysis are up for discussion, or even better, for more research. As outcomes more related to this have been studied and presented in detail in other publications from the CaVenT study, we do not think the current report with focus on quality of life is suited for a more emphasized discussion on this topic, but again point to our remaining responses and the extended discussion in the revised manuscript.
Q6. Page 16 line 16: reference 3: the fifth author name is written in capital letters. This should be corrected. Page 17 line 16 and 34: reference 16 and reference 21: the journal number/volume and pages are missing. This should be added.
R7. Thanks, this has now been corrected.
Q7. Overall, this study has been successfully conducted. However, there are some limitations of the basic study that influence the results of the present study. The authors must especially discuss the present results in light of these limitations. In what degree will the authors treat patients with iliofemoral DVT? Is CDT useless in the future?
Q7. In addition to the discussions, and in particular the limitations, now elaborated in the revised manuscript, we refer to the previous publications based on the CaVenT study for other conclusive remarks on the use of CDT in patients with extensive DVT.

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Reviewer 3: Robin Christensen, BSc, MSc, PhD; Senior Biostatistician.
Q1. The authors explicitly state that they did analyses on the Intention-to-Treat population; however, in all the tables they refer to the sample that completes 2-year follow-up. I would strongly recommend the authors apply a transparent ITT approach - like Non-responder Imputation.
R1. Our Intention-to-Treat analyses and approach have previously been presented in details in our publication on the main clinical findings of the CaVenT study (Lancet 2012). For clarity we have now added this information in the statistical analyses section and a flow chart of the trial profile in the results section. We are aware of different possible statistical approaches for missing outcome data in ITT analyses including non-responder imputation; however in addition to our argumentation in the revised statistics section, the follow up periods of 6 and then 18 months covered long enough time spans to represent quite different phases and stages of acute, sub-acute, and chronic symptoms from DVT and post-thrombotic sequelae, respectively. Finally, only one patient who completed 24 months follow-up did not complete 6 months follow-up. And so, overall, we do not find the non-responder imputation approach appropriate for our study.
Q2. The authors only reports results for individual groups with a P-value for the test between them; they've forgotten to report group mean differences (with 95% CIs). According to CONSORT etc - the authors need to focus on differences between the groups (with 95% CIs) rather than reporting each group individually. The authors doesn't compare groups with an effect size (+95% CIs). They claim that they've used ITT which they clearly have not.
R2. We originally chose to report the results for the VEINES-QOL/Sym in particular, but also on QOL scores in general, in a manner previously reported, ie., by both Kahn, Lamping, and Broholm. But as pointed out by the reviewer, this does not comply with the CONSORT statement, and we now report the mean differences between groups (=mean effect size) with 95% CIs (precision of mean effect size) for all outcomes. However, we have not removed the p-values, as the CONSORT statement allows this when given in addition to the mean effect size with precision. Regarding ITT, please see our responses to Qs 1 and 10.

Q3. I would recommend the authors to apply a more CONSORT-like title for the study:
Health-related quality of life after catheter-directed thrombolysis for deep vein thrombosis: secondary outcomes of the randomised, non-blinded, parallel-group CaVenT study
R3. The title has been changed as suggested by the reviewer.
Q4. ABSTRACT: The authors should focus on group contrasts in their reporting, rather than giving individual group statistics. It is strongly recommended that the authors report 'Differences between means' with (95% confidence intervals). I understand the authors are tempted to report "P-values", which is acceptable; please include the P-value in each of the above mentioned parentheses with 95%CI.
R4. The effect measures are now presented as suggested by the reviewer and in accordance with the CONSORT statement; please also see our response to Q2 above.
Q5. Article summary: There is no need to state "Patient-Reported" before Quality of Life; please omit.
R5. OK.
Q6. Statistical analysis and sample size: The authors state that they applied an ITT approach! However, I can't see how missing data were imputed; please elaborate. According to the RESULTS section the authors completely ignore the fact that they randomized 209 participants. They clearly state that they include patients with two-year follow-up data; THAT IS NOT THE ITT population (90 vs 99 patients). This needs to be clarified and corrected. I would probably suggest the authors to re-do all the analyses, include all 209 patients in the groups originally assigned; for missing data I would recommend a non-responder imputation- i.e., use the baseline observation carried forward technique.
R6. Please, see our responses to the reviewer's Qs 1 and 10.
Q7. Table 1: Demographics and clinical characteristics: In a baseline table, the authors should report measures of central tendency with a measure of dispersion – e.g. Mean and SD (or Median and IQR), not Mean values with 95% CIs (95% CI: measure precision – not dispersion)
R7. This has now been changed accordingly in table 1.
Q8. Table 1 Cont'd. The authors mix baseline characteristics and outcome measures in Table 1. It is strongly recommended that these are split into separate Tables (please see CONSORT statement).
R8. OK; the non-baseline measures have been removed from table 1 and since they cover only three variables, we have chosen to present them in the text in the section following the table.
Q9. Table 2 AND Table 3: The authors report individual group results and a column with a P-value. This is not the recommended approach. The authors should report individual group estimates, a column with group mean differences (and 95% CIs), and then maybe also the column with the P-value (please see CONSORT statement for further guidance on statistical Tables in biomedical journals).
R9. A column with group mean differences with the corresponding 95% CIs has been added to tables 2 and 3; please also see our responses above to Qs 2 and 4.
Q10 OVERALL RECOMMENDATION: The trial report represents a rigorous project. However, there are substantial statistical inadequacies that needs to be corrected: Either the authors perform correct statistical analyses on the – as stated –ITT population, or they have to change the wording into something like "the Per Protocol population". The authors have completely ignored that the correct way to address statistical analyses in 2-arm trials is to focus on the group mean difference with 95% CIs. It is less important what happens in the individual groups.
R10. Please, see our responses above. As argued in our previous publications and the present

revised version of the manuscript, we consider our analyses to be by ITT and not by “Per Protocol” approach.