**Supplementary Material**

**Brazilian Guidelines for the Pharmacological Treatment of Pulmonary Embolism. Official document of the Brazilian Society of Pulmonology and Phthisiology based on the GRADE methodology.**

**Chart S1 - Tables with search strategies for PICO questions:**

Question 1 - Should home anticoagulation be used compared to hospitalization in patients with low-risk PE?

| **Structured question** |
| --- |
| P: Acute low-risk PE and initiation of treatment with low molecular weight heparin or DOACS (Apixaban, Rivaroxaban, Edoxaban, Dabigatran) |
| I: Outpatient treatment |
| C: In-hospital treatment |
| O: Recurrence of PE or Hemodynamic Instability or Severe Bleeding or Clinically Relevant Bleeding or Mortality |
| **Medline/EMBASE strategy** |
| (Pulmonary Embolism OR Pulmonary Embolisms OR Pulmonary Thromboembolisms OR Pulmonary Thromboembolism) AND (Heparin, Low-Molecular-Weight OR LMWH OR Low Molecular Weight Heparin) OR (Dalteparin OR Enoxaparin OR Nadroparin OR Tinzaparin) OR (Apixaban OR Rivaroxaban OR Edoxaban OR Dabigatran) AND (home OR house OR residence OR domicile OR habitation OR Outpatient OR Ambulatory) AND (Random*) |

Question 2 - Should anticoagulation with DOACs* be used compared to anticoagulation with LMWH in patients with PE and diagnosed with cancer?

| **Structured question** |
| --- |
| P: Cancer patient diagnosed with PE |
| I: DOACS (Apixaban, Rivaroxaban, Edoxaban, Dabigatran) |
| C: Low molecular weight heparin |
| O: Recurrence of PE or Hemodynamic Instability or Severe Bleeding or Clinically Relevant Bleeding or Mortality |

**Medline/Embase straregy**

(Pulmonary Embolism OR Pulmonary Embolisms OR Pulmonary Thromboembolisms OR Pulmonary Thromboembolism) AND (Tumor OR Neoplasm OR Tumors OR Neoplasia OR Neoplasias OR Cancer OR Cancers OR Malignancy OR Malignancies OR Neoplasms) AND (Heparin, Low-Molecular-Weight OR LMWH OR Low Molecular Weight Heparin) AND (Dalteparin OR Enoxaparin OR Nadroparin OR Tinzaparin OR Apixaban OR Rivaroxaban OR Edoxaban OR Dabigatran)

OR

(Pulmonary Embolism OR Pulmonary Embolisms OR Pulmonary Thromboembolisms OR Pulmonary Thromboembolism) AND (Tumor OR Neoplasm OR Tumors OR Neoplasia OR Neoplasias OR Cancer OR Cancers OR Malignancy OR Malignancies OR Neoplasms) AND (Heparin, Low-Molecular-Weight OR LMWH OR Low Molecular Weight Heparin) OR (Dalteparin OR Enoxaparin OR Nadroparin OR Tinzaparin OR Apixaban OR Rivaroxaban OR Edoxaban OR Dabigatran) AND Random*

Question 3 - Should it be recommended to maintain extended anticoagulation versus comparator (ASA or placebo) in patients diagnosed with unprovoked PE, who have completed at least 3 months of anticoagulation?

**Structured question**

P: Patient diagnosed with low-risk PE, low-intermediate risk, high-intermediate risk, after stabilization or high risk, after reperfusion and stabilization

I: DOACS (Apixaban, Rivaroxaban, Edoxaban, Dabigatran)

C: LMWH in combination with antivitamin K

O: VTE recurrence, Severe bleeding, Clinically relevant bleeding, Mortality

**Estratégia Medline/Embase**

(Pulmonary Embolism OR Pulmonary Embolisms OR Pulmonary Thromboembolisms OR Pulmonary Thromboembolism) AND ((Heparin, Low-Molecular-Weight OR LMWH OR Low Molecular Weight Heparin) AND vitamin K) AND (Dalteparin OR Enoxaparin OR Nadroparin OR Tinzaparin OR Apixaban OR Rivaroxaban OR Edoxaban OR Dabigatran) AND (low OR intermediate OR high OR reperfusion OR stabilization OR stabilized)

OR

(Pulmonary Embolism OR Pulmonary Embolisms OR Pulmonary Thromboembolisms OR Pulmonary Thromboembolism) AND ((Heparin, Low-Molecular-Weight OR LMWH OR Low Molecular Weight Heparin) AND vitamin K) AND (Dalteparin OR Enoxaparin OR Nadroparin OR Tinzaparin OR Apixaban OR Rivaroxaban OR Edoxaban OR Dabigatran) AND random*

OR

(Pulmonary Embolism OR Pulmonary Embolisms OR Pulmonary Thromboembolisms OR Pulmonary Thromboembolism) AND (Heparin, Low-Molecular-Weight OR LMWH OR Low Molecular Weight Heparin) AND ((Heparin, Low-Molecular-Weight OR LMWH OR Low Molecular Weight Heparin) AND vitamin K) AND (recurrence OR bleeding OR mortality)

Question 4 - Treatment (3 to 6 months) with DOACs* should be recommended compared to conventional anticoagulation (LMWH or UFH initially followed by warfarin), in patients diagnosed with low-risk PE, low-intermediate risk, high-intermediate risk, after stabilization or high risk, after reperfusion and stabilization?

**Structured question**

P: Patient diagnosed with low-risk PE, low-intermediate risk, high-intermediate risk, after stabilization or high risk, after reperfusion and stabilization

I: DOACS (Apixaban, Rivaroxaban, Edoxaban, Dabigatran)

C: LMWH in combination with antivitamin K

O: VTE recurrence, Severe bleeding, Clinically relevant bleeding, Mortality

**Medline/Embase Strategy**

(Pulmonary Embolism OR Pulmonary Embolisms OR Pulmonary Thromboembolisms OR Pulmonary Thromboembolism) AND ((Heparin, Low-Molecular-Weight OR LMWH OR Low Molecular Weight Heparin) AND vitamin K) AND (Dalteparin OR Enoxaparin OR Nadroparin OR Tinzaparin OR Apixaban OR Rivaroxaban OR Edoxaban OR Dabigatran) AND (low OR intermediate OR high OR reperfusion OR stabilization OR stabilized)

OR

(Pulmonary Embolism OR Pulmonary Embolisms OR Pulmonary Thromboembolisms OR Pulmonary Thromboembolism) AND ((Heparin, Low-Molecular-Weight OR LMWH OR Low Molecular Weight Heparin) AND vitamin K) AND (Dalteparin OR Enoxaparin OR Nadroparin OR Tinzaparin OR Apixaban OR Rivaroxaban OR Edoxaban OR Dabigatran) AND random*

OR

(Pulmonary Embolism OR Pulmonary Embolisms OR Pulmonary Thromboembolisms OR Pulmonary Thromboembolism) AND (Heparin, Low-Molecular-Weight OR LMWH OR Low Molecular Weight Heparin) AND ((Heparin, Low-Molecular-Weight OR LMWH OR Low Molecular Weight Heparin) AND vitamin K) AND (recurrence OR bleeding OR mortality)

Question 5 - Should systemic thrombolysis be recommended compared to isolated anticoagulation (LMWH or UFH) in patients with intermediate-high risk PE?

**Structured question**

P: Patients diagnosed with high-intermediate risk PE or submassive PE

I: Systemic thrombolysis (streptokinase, rTpa, alteplase, urokinase, tenecteplase)

C: LMWH or UFH

O: VTE recurrence, Severe bleeding, Clinically relevant bleeding, Mortality, CTEPH

**Medline/Embase Strategy**

(Pulmonary Embolism OR Pulmonary embolisms OR Pulmonary Thromboembolisms OR Pulmonary Thromboembolisms

AND

(Heparin, Low-Molecular-Weight OR LMWH OR Low Molecular Weight Heparin OR Heparin OR unfractionated Heparin OR anticoagulation)

AND

(Tenecteplase OR r-tPA OR Alteplase OR Streptokinase OR Urokinase OR Thrombolysis OR Thrombolytic OR Reperfusion) AND random*

AND

(recurrence OR hemodynamic decompensation OR hemodynamic collapse OR bleeding OR mortality OR chronic thromboembolic pulmonary hypertension OR CTEPH)

1.6-Question 6 - Should systemic thrombolysis be recommended compared to isolated anticoagulation (LMWH, UFH) in patients with high-risk PE?

**Structured question**

P: Patients diagnosed with high-risk PE or massive PE

I: Systemic thrombolysis (streptokinase, rTpa, alteplase, urokinase, tenecteplase)

C: LMWH or UFH

O: VTE recurrence, Severe bleeding, Clinically relevant bleeding, Mortality, CTEPH

**Medline/Embase Strategy**

(Pulmonary Embolism OR Pulmonary embolisms OR Pulmonary Thromboembolisms OR Pulmonary Thromboembolisms

AND

(Heparin, Low-Molecular-Weight OR LMWH OR Low Molecular Weight Heparin OR Heparin OR unfractionated Heparin OR anticoagulation)

AND

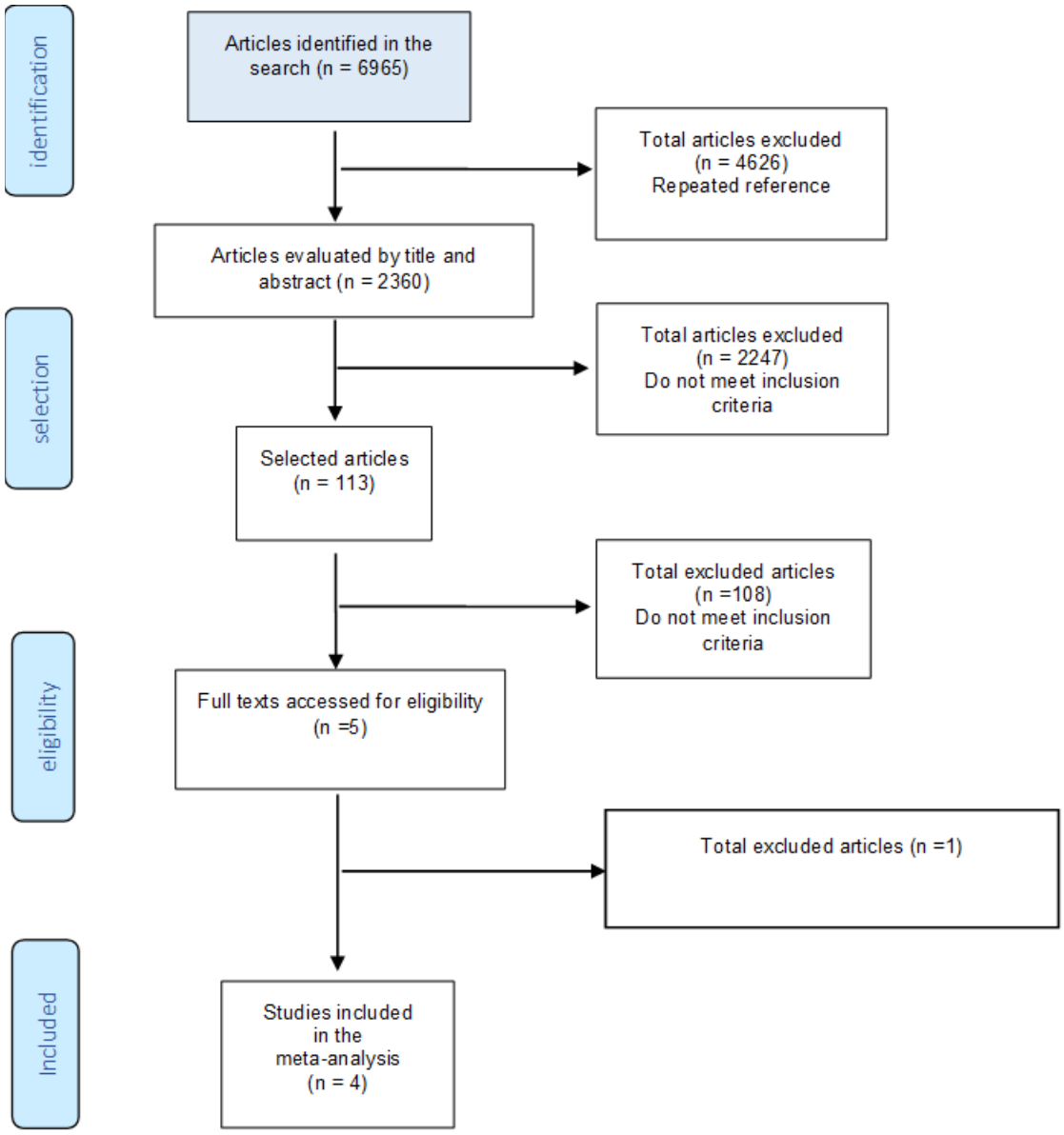
(Tenecteplase OR r-tPA OR Alteplase OR Streptokinase OR Urokinase OR Thrombolysis OR Thrombolytic OR Reperfusion) AND random*

AND

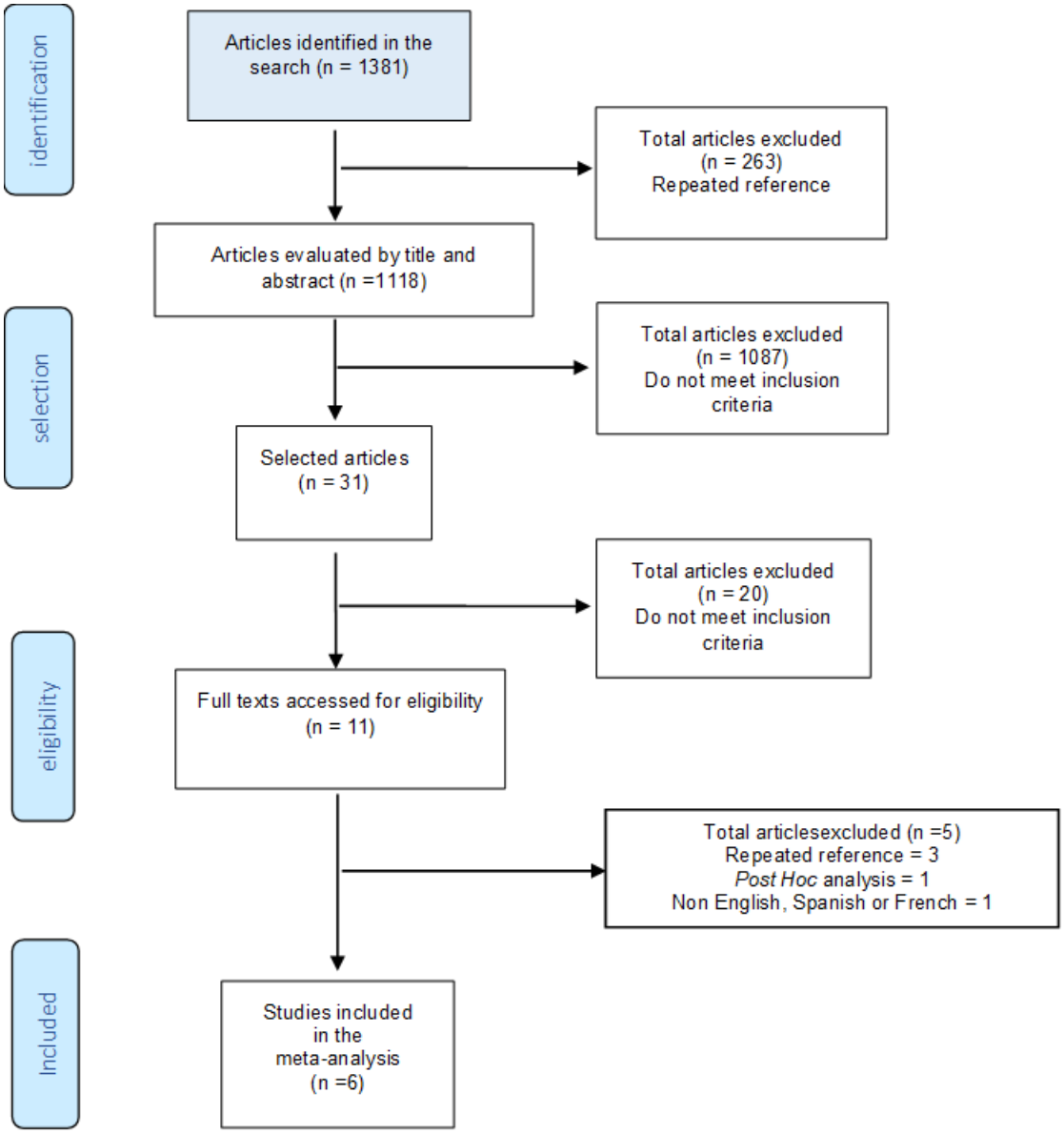
(recurrence OR hemodynamic decompensation OR hemodynamic collapse OR bleeding OR mortality OR chronic thromboembolic pulmonary hypertension OR CTEPH)

**Figure S1 - Flowcharts of the selection of the recovered papers on the virtual bases of scientific information for the PICO questions**

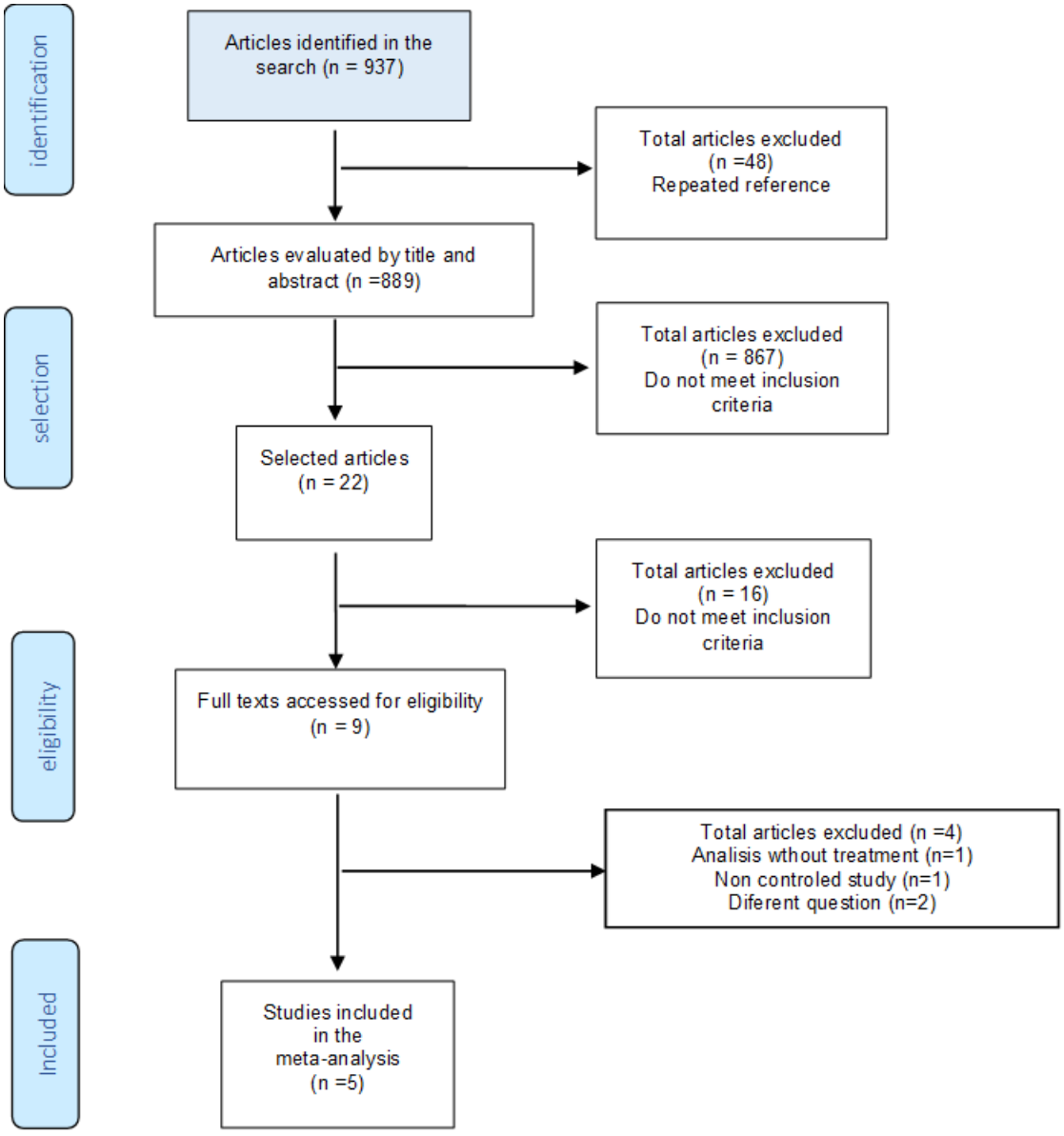
Question 1 - Should home anticoagulation be used compared to hospitalization in patients with low-risk PE?



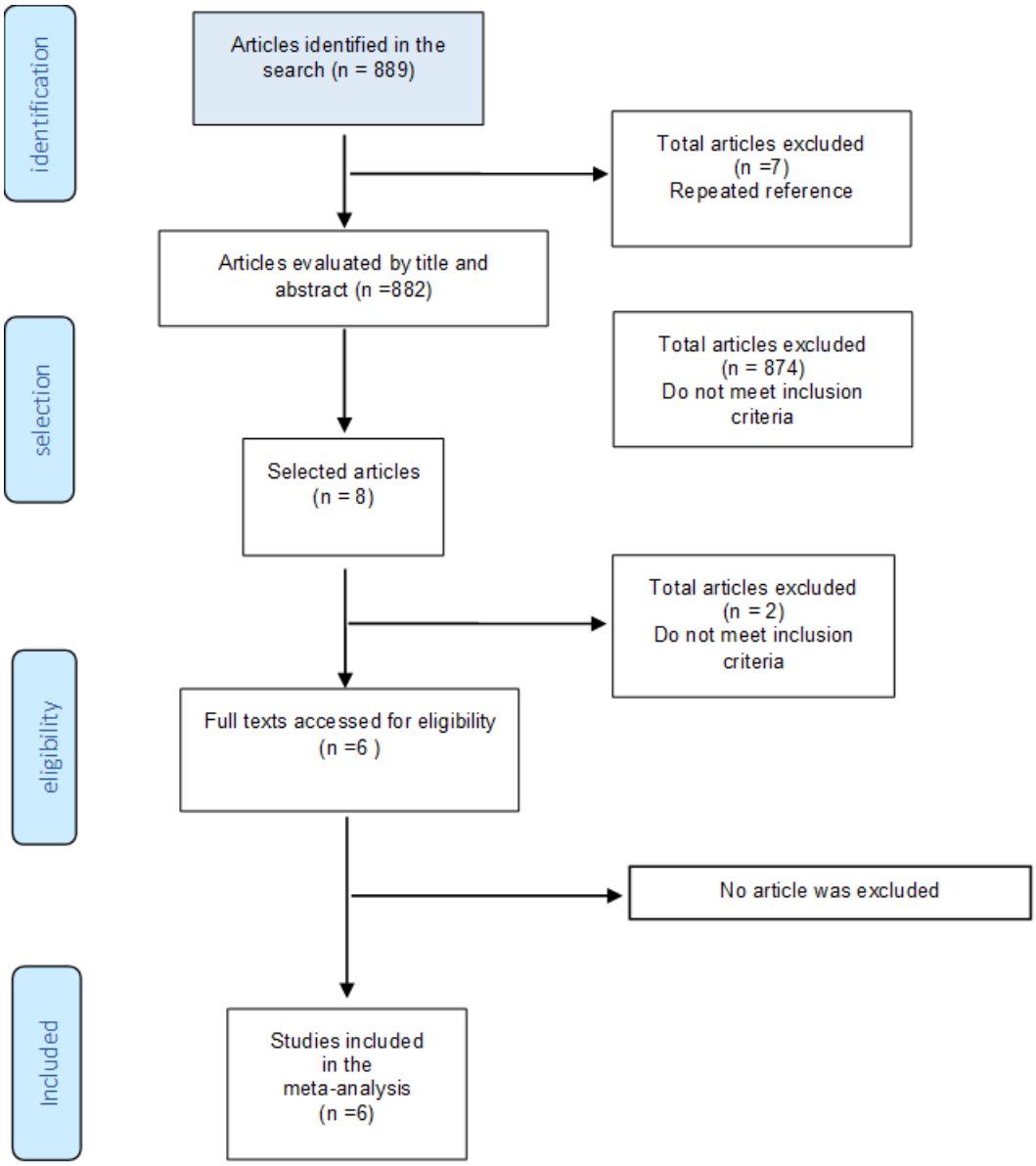
Question 2 - Should anticoagulation with DOACs be used compared to anticoagulation with LMWH in patients with PE and diagnosed with cancer?



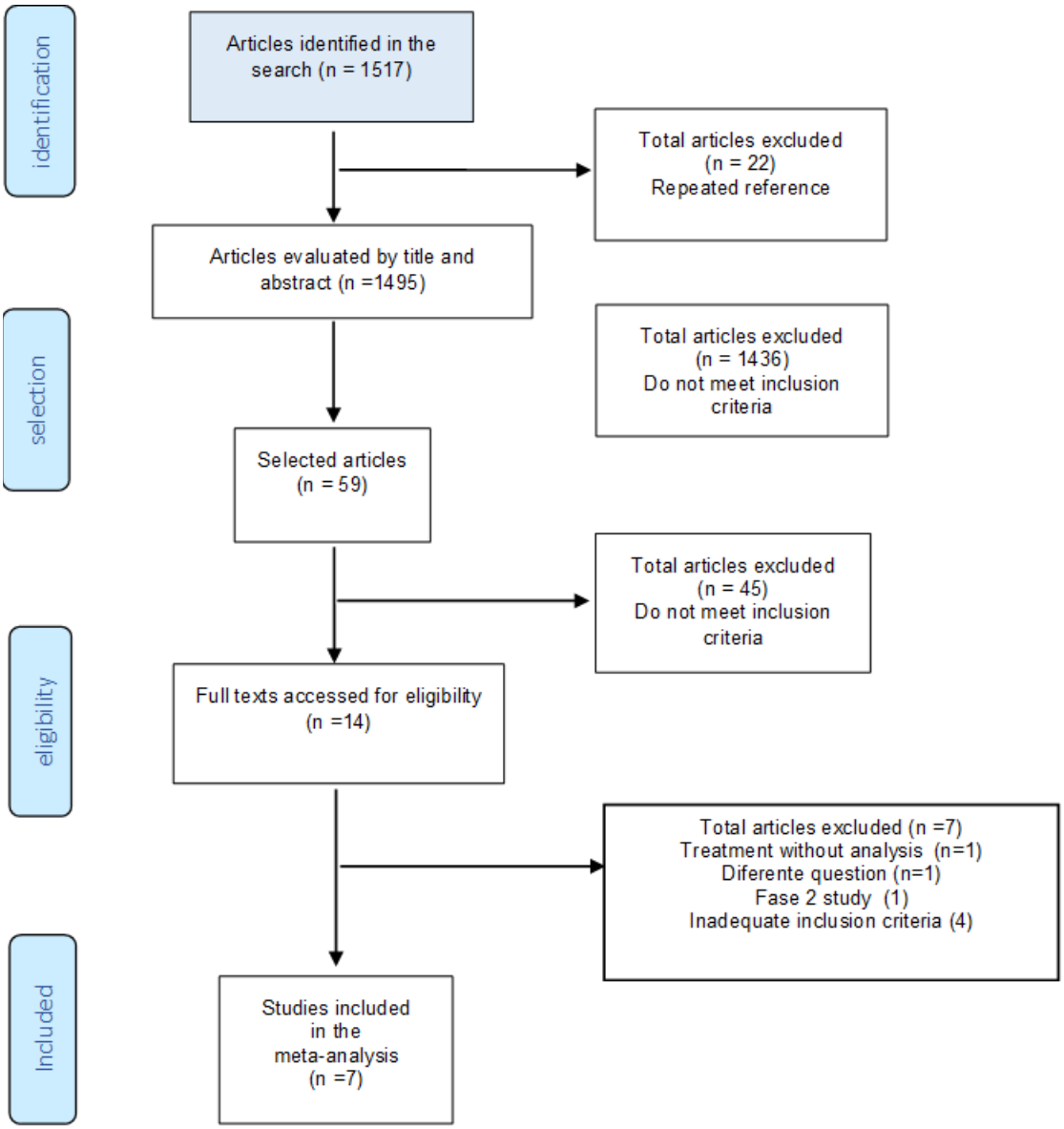
Question 3 - Should it be recommended to maintain extended anticoagulation versus comparator (ASA or placebo) in patients diagnosed with unprovoked PE, who have completed at least 3 months of anticoagulation?



Question 4 - Treatment (3 to 6 months) with DOACs* should be recommended compared to conventional anticoagulation (LMWH or UFH initially followed by warfarin), in patients diagnosed with low-risk PE, low-intermediate risk, high-intermediate risk, after stabilization or high risk, after reperfusion and stabilization?



Question 5 - Should systemic thrombolysis be recommended compared to isolated anticoagulation (LMWH or UFH) in patients with intermediate-high risk PE?



Question 6 - Should systemic thrombolysis be recommended compared to isolated anticoagulation (LMWH, UFH) in patients with high-risk PE?

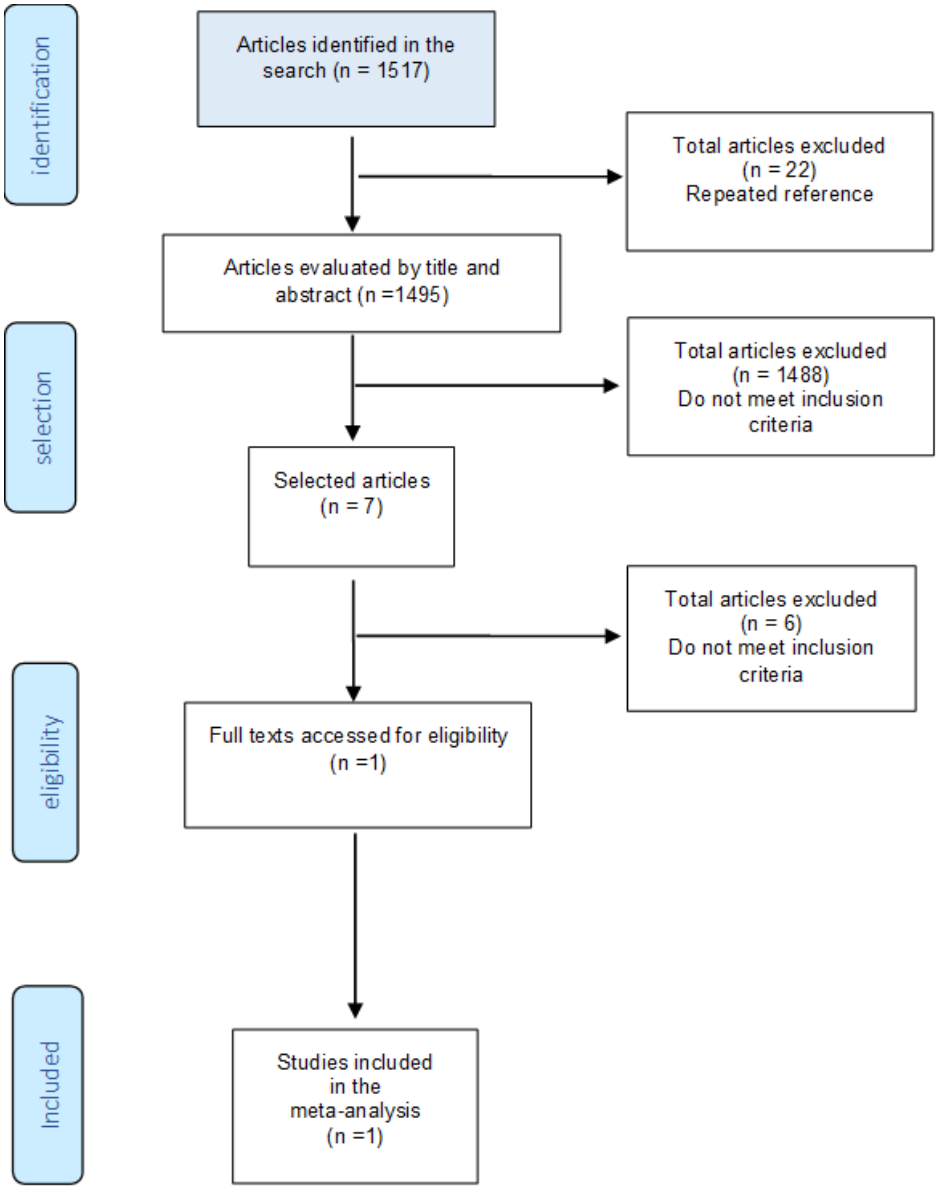


**Chart S2 - Tabelas com a descrição dos estudos incluídos na análise quantitativa das questões PICO.**

Question 1 - Should home anticoagulation be used compared to hospitalization in patients with low-risk PE?

| Study | Study design | Population | Intervention | Comparator | Outcome | Time |
|---|---|---|---|---|---|---|
| Lancet 2011; 378: 41-48. | Open, randomized, non-inferiority clinical trial. Multicenter, involving 19 emergency departments in 4 countries. Number of patients: 344 | Patients diagnosed with acute, symptomatic PE, with a low risk of death (conventional PESI - score I or II). | Discharged from hospital within 24 hours or less, after randomization, using LMWH, followed by VKA, for at least 90 days. | Usual hospitalization starting with LMWH, followed by VKA, for at least 90 days. | Primary outcome: confirmed symptomatic VTE recurrence. Secondary: major bleeding (14-90 days); mortality from any cause (within 90 days). | 90 days (evaluations at 14,30,60 and 90 days). Study design |
| Am J Respir Crit Care Med 2016; 194: 998-1006. | Open, randomized, non-inferiority clinical trial. Multicenter, involving 17 hospitals in the Netherlands. Number of patients: 558 | Patients diagnosed with acute, symptomatic PE, with low risk of death and/or adverse events (negative Hestia score for all questions). | Patients who had NT-proBNP lower than 500pg/ml were discharged 24 hours after confirming the diagnosis of PE and patients with levels higher than this value were hospitalized . | Usual hospitalization starting with LMWH, followed by VKA, for at least 90 days . | Primary outcome: Adverse outcome defined by: PE-related death, bleeding-related mortality. Cardiopulmonary resuscitation, admission to intensive care, need for thrombolysis or surgical embolectomy. Secondary: symptomatic recurrence of VTE, major bleeding, death from any cause within 3 months. | 90 days (evaluations at 4-6 weeks and 90 days). |

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| Academic Emergency Medicine 2018; 25: 995-1003. | Open, randomized clinical trial. Multicenter, involving 60 centers in the United States of America. Number of patients: 114 | Patients diagnosed with acute, symptomatic PE, with low risk of death and/or adverse events (negative Hestia score for all questions). | Discharged from hospital 12-24 hours after screening (screening < 12 hours from diagnosis), using rivaroxaban 15mg every 12 hours for 21 days, followed by a reduction to 20mg until the end of the study. | Hospitalization and usual treatment at medical discretion (LMWH and VKA or DOAC). | Primary outcome: duration in hours of hospital stay for VTE or bleeding in the first 30 days of the study. Primary safety outcome: major bleeding Secondary: symptomatic recurrence of VTE, VTE-related death, number of unscheduled visits for VTE-related symptoms and/or bleeding, duration of initial hospitalization and other hospitalizations for any cause, non-major bleeding, and patient satisfaction with care. | 90 days (evaluations in 7, 14, 30 and 90 days). |

AVK: anti-vitamin K; DOAC: direct-acting oral anticoagulant; LMWH: low molecular weight heparin; NT-proBNP: N-terminal fragment of type B natriuretic peptide; PESI: Pulmonary Embolism Severity Index; PE: pulmonary embolism; VTE: venous thromboembolism.

Question 2 - Should anticoagulation with DOACs be used compared to anticoagulation with LMWH in patients with PE and diagnosed with cancer?

| Study | Study design | Population | Intervention | Comparator | Outcome | Time |
|---|---|---|---|---|---|---|
| J Thromb Haemost. 2020; 18:411-421. | Open, randomized clinical trial of superiority in relation to the risk of bleeding. Multicenter, involving 28 centers in the United States of America. Number of patients: 300. | Patients > 18 years old, diagnosed with active cancer, life expectancy greater than 60 days and diagnosed with acute VTE | Apixaban 10 mg every 12 hours for 7 days, followed by a dose of 5 mg every 12 hours. | Dalteparin 200UI/Kg/day in the first month, followed by a dose of 150UI/Kg. | Primary outcome: any bleeding episode. Secondary: recurrence of VTE, death due to PE or arterial thromboembolism. | 6 months (monthly assessments) |

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| N Engl J Med 2020; 382:1599-1607. | Open, randomized, non-inferiority clinical trial. Multicenter, involving 119 centers in 9 European countries, in addition to Israel and the United States of America. Number of patients: 1170. | Adults, with a diagnosis of active cancer and a new diagnosis of VTE (incidental or symptomatic). | Apixaban 10 mg every 12 hours for 7 days, followed by a dose of 5 mg every 12 hours | Dalteparin 200UI/Kg/day in the first month, followed by a dose of 150UI/Kg. | Primary outcome: VTE recurrence. Main safety outcome: major bleeding. | Six months of treatment (evaluations at 4 weeks, 3 months, 6 months and 7 months). |
| Chest 2022: 161: 781-790. | Pilot, open, randomized, non-inferiority clinical trial. Multicenter, involving 18 centers in France. Number of patients: 158. | Adults, with a diagnosis of active cancer and a new diagnosis of VTE (incidental or symptomatic). | Rivaroxaban 15mg every 12 hours for 3 weeks, followed by a dose of 20mg daily. | Dalteparin 200UI/Kg/day in the first month, followed by a dose of 150UI/Kg. | Primary efficacy outcome: VTE recurrence. Secondary: Lower limb DVT, major bleeding or clinically relevant, non-major bleeding. | Three months (1 and 3 month assessments). . |
| J Clin Oncol 2018; 36:2017-2023. | Pilot, open, randomized clinical trial. Multicentre, involving 58 UK centres. Number of patients: 406. | Adults, with a diagnosis of active cancer and a new diagnosis of VTE (incidental or symptomatic). | Rivaroxaban 15mg every 12 hours for 3 weeks, followed by a dose of 20mg daily. | Dalteparin 200UI/Kg/day in the first month, followed by a dose of 150UI/Kg. | Primary efficacy outcome: VTE recurrence. Secondary: Lower limb DVT, major bleeding or clinically relevant, non-major bleeding. | Treatment for 6 months (quarterly assessments until completing 12 months. Subsequently, every six months until completing 24 months). |

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| N Eng J Med 2018: 378:615-624. | Open, randomized, non-inferiority clinical trial. Multicenter, involving 114 centers in 13 countries. Number of patients: 1050. | Adults, with a diagnosis of active cancer and a new diagnosis of VTE (incidental or symptomatic). | LMWH 5 days after diagnosis, followed by edoxaban 60mg/day. | Dalteparin 200UI/Kg/day in the first month, followed by a dose of 150UI/Kg. | Primary outcome: composite of VTE recurrence or major bleeding. Secondary: VTE recurrence, DVT recurrence, PE recurrence, Major bleeding, clinically relevant non-major bleeding, death from any cause and event-free survival. | Treatment for 6 to 12 months (assessments: 31 days after randomization, 3, 6, 9 and 12 months. Minimum until the ninth month). |
| JAMA 2023; 329: 1924-1933. | Open, randomized, non-inferiority clinical trial. Multicenter, involving 67 centers in the USA. Number of patients: 671. | Adults, with a diagnosis of active cancer and a new diagnosis of VTE (incidental or symptomatic). | DOACS according to patient preference and convenience. | LMWH according to patient preference and convenience. | Primary efficacy outcome: VTE recurrence. Secondary: major bleeding, non-major and clinically relevant bleeding, minor bleeding, incidence of death and survival in the 6 months of follow-up, quality of life (SF12) and perception of harms and benefits of anticoagulation, based on a specific questionnaire. | Treatment for 6 months (evaluations at 3 and 6 months). |

AVK: anti-vitamin K; DOAC: direct-acting oral anticoagulant; LMWH: low molecular weight heparin; LL: lower limbs; PE: pulmonary embolism; VTE: venous thromboembolism; DVT: deep vein thrombosis.

Question 3: Should it be recommended to maintain extended anticoagulation versus comparator (ASA or placebo) in patients diagnosed with unprovoked PE, who have completed at least 3 months of anticoagulation?

| Study | Study design | Population | Intervention | Comparator | Outcome | Time |
|---|---|---|---|---|---|---|
| N Engl J Med | Double-blind, randomized, | Adult patients, previously | Apixaban 2.5mg every | Placebo | Combined primary efficacy endpoint of: | Treatment time: 12 |

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| 2013: 368:699-708 | multicenter clinical trial involving 328 hospitals in 28 countries. Number of patients: 2486. | diagnosed with VTE, treated for at least 6 to 12 months with standard treatment or apixaban or enoxaparin and warfarin (such as participants in the AMPLIFY study) | 12 hours or Apixaban 5mg every 12 hours. | | VTE recurrence or death from any cause. Primary safety outcome: major bleeding. Secondary outcomes: recurrence of symptomatic VTE, death related to VTE, combined outcome of recurrence of symptomatic VTE, acute myocardial infarction, stroke or death related to cardiovascular disease. | months. Monthly telephone contacts were made for 12 months and 1 month after the end of treatment. |
| N Engl J Med 2017: 376:1211-1222 | Double-blind, randomized clinical trial involving 244 centers in 31 countries. Number of patients: 3396. | Adult patients, with a previous diagnosis of VTE, treated for at least 6 to 12 months with VKA or DOACS (dabigatran, rivaroxaban, apixaban or edoxaban. | Rivaroxaban 20mg per day or Rivaroxaban 10mg per day. | Aspirin 100mg daily | Primary efficacy outcome: combination of VTE recurrence and death of unknown cause for which PE could not be excluded. Primary efficacy outcome: major bleeding. Secondary safety outcomes: acute myocardial infarction, ischemic stroke, systemic embolism, other venous thrombosis, in addition to lower limb DVT and death from any cause. Secondary safety endpoints: non-major bleeding, composite outcome of major bleeding or non-major but clinically relevant bleeding, and non-major bleeding that led to interruption of study drug for more than 14 days. | Treatment time: 1 year. Telephone contacts were made on days 30, 90, 180, 270, 360 from randomization and 30 days after stopping the study drug. |
| N Engl J Med 2013; | Double-blind, randomized clinical trial | Adult patients, with a previous | Dabigatran 150mg every 12 hours. | Placebo | Primary efficacy outcome: combination of recurrence of | Treatment time: 6 months. |

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| 368: 709-718. | involving 147 centers in 21 countries. Number of patients: 1353. | diagnosis of VTE, treated for at least 3 months with an anticoagulant approved for the treatment of VTE. | | | symptomatic VTE and death of unknown cause for which PE could not be excluded. Safety outcome: major bleeding and non-major but clinically relevant bleeding. | Assessment was carried out 12 months after randomization. |
| N Engl J Med 1999; 340: 901-907. | Double-blind, randomized clinical trial involving 14 centers in Canada and the USA. Number of patients: 162. | Adult patients, with a previous diagnosis of VTE, without identified risk factors, treated for at least 3 months with VKA. | Warfarin in a dose sufficient to maintain the INR between 2.0-3.0 | Placebo | Primary efficacy outcome: recurrence of symptomatic VTE. Secondary outcomes: Major bleeding, non-major bleeding and death. | Treatment time: 24 months. |
| JAMA 2015; 314: 31-40 | Double-blind, randomized clinical trial involving 14 centers in France. Number of patients: 371. | Adult patients, with a previous diagnosis of VTE, without identified risk factors, treated for at least 6 months with VKA. | Warfarin in a dose sufficient to maintain the INR between 2.0-3.0 | Placebo | Combined primary outcome of symptomatic VTE recurrence and major bleeding. Secondary outcomes: death not related to PE or major bleeding, recurrence of symptomatic VTE, major bleeding. | Treatment time: 18 months. Patients were followed up for an average of 24 months after the end of treatment. Follow-up visits were made at 3, 6, 12, 18, 30 and 42 months after randomization. Telephone contact at 24 and 36 months. |

AVK: anti-vitamin K; DOAC: direct-acting oral anticoagulant; LL: lower limbs; PE: pulmonary embolism; VTE: venous thromboembolism; DVT: deep vein thrombosis.

Question 4 - Treatment (3 to 6 months) with DOACs should be recommended compared to conventional anticoagulation (LMWH or UFH initially followed by warfarin), in patients diagnosed with low-risk PE, low-intermediate risk, high-intermediate risk, after stabilization or high risk, after reperfusion and stabilization?

| Study | Study design | Population | Intervention | Comparator | Outcome | Time |
|---|---|---|---|---|---|---|
| Circulation 2014; 129: 764 | Multicenter, double blind, double dummy, randomized, non-inferiority clinical study involving European American and Asian centers. Number of patients: 2589. | Adult patients diagnosed with acute, symptomatic VTE. | Dabigatran 150mg every 12 hours. | Warfarin with target INR between 2 - 3 | Primary outcome: recurrence of symptomatic VTE. Secondary: Major bleeding, non-major but relevant bleeding and other bleeding. | Treatment time: 6 months. Assessments every 7 days and monthly until 6 months. |
| N Engl J Med 2013; 369: 1406-1415 | Estudo clínico multicêntrico, duplo cego, randomizado, de não inferioridade, envolvendo 439 centros em 37 países. Nº de pacientes: 8292. | Adult patients diagnosed with acute, symptomatic VTE. | Edoxaban 60mg per day. | Warfarin with target INR between 2 - 3 | Primary efficacy outcome: recurrence of symptomatic VTE. Secondary efficacy endpoints: combination of recurrence or death from cardiovascular causes or death from any cause.<br><br>Primary safety outcome: Clinically relevant bleeding (combination of major bleeding or clinically relevant non-major bleeding). | Treatment time from 3 to 12 months, according to the attending physician. Visits were scheduled for 5, 12, 30 and 60 days. Subsequently, the visits were monthly, if the patient was undergoing treatment, or |

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| | | | | | | quarterly if the treatment had been suspended for up to 12 months. |
| N Engl J Med 2013; 369: 799 – 808. | Multicenter, double-blind, randomized, non-inferiority clinical study involving 358 centers in 28 countries. Number of patients: 5400. | Adult patients diagnosed with acute, symptomatic VTE. | Apixaban 5mg every 12 hours | Warfarin with target INR between 2 - 3 | Combined primary efficacy endpoint: symptomatic VTE recurrence or thromboembolism-related death. Secondary efficacy outcomes: symptomatic VTE recurrence, thromboembolism-related death, cardiovascular death, death from any cause, or VTE-related death and major bleeding. Desfecho primário de segurança: sangramento maior. Desfechos secundários de segurança: composto de sangramento clinicamente relevante (combinação de sangramento maior ou sangramento não maior clinicamente relevante). | Treatment time of 6 months. Visits scheduled at weeks 2, 4, 8, 12, 16, 20 and 24, after randomization and 30 days after the expected end of treatment. |

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|---|---|---|---|---|---|---|
| N Engl J Med 2009; 361:2342-2352 | Multicenter, double-blind, double-dummy, randomized, non-inferiority clinical study involving 228 centers in 29 countries. Number of patients: 2564. | Adult patients diagnosed with acute, symptomatic VTE. | Dabigatran 150mg every 12 hours. | Warfarin with target INR between 2 - 3 | Primary efficacy outcome: symptomatic VTE recurrence or thromboembolism-related death. Secondary efficacy outcomes: recurrence of symptomatic DVT, recurrence of symptomatic PE, VTE-related death, and death from any cause. Safety endpoints: Major bleeding, major bleeding or clinically relevant non-major bleeding, any bleeding. | Treatment time: 6 months. Assessments every 7 days and monthly until 6 months. An assessment was carried out 30 days after the end of treatment. |
| N Engl J Med 2010; 363:2499-510. | Multicenter, open, randomized, non-inferiority clinical study. Number of patients: 3449. | Pacientes adultos, com diagnóstico de TVP aguda, sintomática. | Rivaroxaban 20mg/day | Warfarin with target INR between 2 - 3 | Primary efficacy outcome: recurrence of symptomatic VTE.<br><br>Primary safety outcome: major bleeding or clinically relevant non-major bleeding. Secondary safety outcomes: major bleeding, clinically relevant non-major bleeding, death from any cause, vascular events (acute coronoary syndrome, stroke, TIA or systemic embolic event) and other adverse events. | Treatment time in 3 strata: 3, 6 and 12 months. |
| N Engl J Med 2012; 366:1287-97. | Multicenter, open, randomized, non-inferiority clinical study. Number of patients: 4832. | Adult patients diagnosed with acute, symptomatic VTE. | Rivaroxaban 20mg/day | Warfarin with target INR between 2 - 3 | Primary efficacy outcome: recurrence of symptomatic VTE.<br><br>Primary safety outcome: major bleeding or clinically relevant non-major bleeding. Secondary outcomes: major bleeding, death | Treatment time in 3 strata: 3, 6 and 12 months. |

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| | | | | | from any cause, vascular events (acute coronary syndrome, ischemic stroke, TIA or systemic embolic event) and clinical benefit composed of VTE recurrence or major bleeding. | |

TIA: transient ischemic attack; DOAC: direct-acting oral anticoagulant; VTE: venous thromboembolism; DVT: deep vein thrombosis.

Question 5 - Should systemic thrombolysis be recommended compared to isolated anticoagulation (LMWH or UFH) in patients with intermediate-high risk PE?

| Study | Study design | Population | Intervention | Comparator | Outcome | Time |
|---|---|---|---|---|---|---|
| Am J Med Sci 2011; 341: 33-39. | Randomized, double-blind, single-center clinical study. In patients: 72. | Adult patients diagnosed with submassive PE (signs of RV dysfunction on echocardiogram and ECG, with hemodynamic stability) and onset of symptoms up to 6 hours before randomization. | Alteplase 100mg. Maintained UFH 1000U/h, IV, adjusted according to aPTT. Long-term treatment with warfarin. | Placebo. Maintained UFH 1000U/h, IV, adjusted according to aPTT. Long-term treatment with warfarin. | Primary efficacy outcome: improvement in RV dysfunction assessed by echocardiogram at admission and up to 180 days from randomization. Secondary outcomes: recurrence of PE or clinical deterioration (need for infusion of vasoactive drugs due to persistent hypotension, intubation, CPR, emergency embolectomy or embolectomy for hemodynamic intervention. Safety outcomes: major and non-major bleeding. | Assessme t of patien up to 180 days after randomiza on. |

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|---|---|---|---|---|---|---|
| J Thromb Haemost 2014; 12: 459-468 | Randomized, double-blind, multicenter clinical study, No patients: 83. | Adult patients diagnosed with moderate-high risk PE (RV hypokinesia on echocardiogram and elevated troponin I or T or BNP or NT-proBNP). | All patients initially received LMWH in addition to the study drug: tenecteplase. Long-term treatment was with warfarin unless there were any contraindications. | All patients initially received LMWH in addition to the study drug: placebo. Long-term treatment was with warfarin unless there were any contraindications. | Outcome related to PE, up to 5 days of hospitalization: death, shock or need for intubation. Treatment-related outcomes, up to 5 days of hospitalization: death due to bleeding, major bleeding or clinically relevant non-major bleeding. Long-term outcomes, 90 days: VTE recurrence; reduced functional capacity (signs of IVD on echocardiogram or exercise intolerance); quality of life (SF36 and VEINES QOL). | In-hospita assessme t – 5 days Long-term evaluation – 90 days |
| JACC 2017; 69:1536-1544 | Randomized, double-blind, multicenter clinical study involving 76 centers in 13 countries. Number of patients: 1005. | Adult patients diagnosed with PE and symptom onset within the previous 15 days. RV dysfunction assessed by echocardiogram or signs observed on CT angiography and myocardial injury confirmed by troponins I or T. | Tenecteplase (dose calculated according to weight, according to the leaflet) bolus, followed by IV UFH, for 48 hours. Subsequently, anticoagulant medication followed the service routine. | Bolus of placebo, followed by IV UFH, for 48 hours. Subsequentl y, anticoagulan t medication followed the service routine. | Primary efficacy outcome: death within the first 30 days of follow-up and death at any point between randomization and 24 months. Secondary outcome: CTEPH | Evaluation in 30 days and 24 months. |

| | | | | | | |
|---|---|---|---|---|---|---|
| N Engl J Med 2002; 347: 1143-1150 | Randomized, double-blind, multicenter clinical study involving 49 centers in Germany. Number of patients: 256. | Adult patients diagnosed with acute PE and signs of right ventricular dysfunction assessed by echocardiogram, invasive hemodynamics or new signs of right ventricular overload on ECG. | Alteplase 100mg. Maintained UFH 1000U/h, IV, adjusted according to aPTT (2.0 to 2.5 times the upper limit of normal). Long-term treatment with VKA, with target INR of 2.5 and 3.0. | Placebo. Maintained UFH 1000U/h, IV, adjusted according to aPTT (2.0 to 2.5 times the upper limit of normal). Long-term treatment with VKA, with target INR of 2.5 and 3.0. | Primary efficacy outcome: death during hospitalization or clinical deterioration requiring therapeutic escalation (need for vasoactive drugs, rescue thrombolysis, intubation, CPR and surgical embolectomy or catheter thrombus fragmentation). Secondary outcomes: VTE recurrence and major bleeding. | Assessme t at hospit discharge or 30 days after randomiza on, whichever came first |
| N Engl J Med 2014; 370: 1402-1411. | Randomized, double-blind, multicenter clinical study involving 76 centers in 13 countries. Number of patients: 1005. | Adult patients diagnosed with PE and symptom onset within the previous 15 days. RV dysfunction assessed by echocardiogram or signs observed on CT angiography and myocardial injury confirmed by troponins I or T. | Tenecteplase (dose calculated according to weight, according to the leaflet) bolus, followed by IV UFH, for 48 hours. Subsequently, anticoagulant medication followed the service routine. | Bolus placebo, followed by IV UFH, for 48 hours. Subsequentl y, anticoagulan t medication followed the service routine. | Primary efficacy outcome: death from any cause or hemodynamic decompensation within 7 days of randomization. Secondary efficacy outcomes: death within 7 days of randomization, hemodynamic decompensation within 7 days of randomization, VTE recurrence within 7 days of randomization, death within 30 days of randomization, and major adverse effects within 30 days of randomization. Safety outcomes: hemorrhagic stroke within 7 days of randomization, major extracranial bleeding within 7 days of randomization and serious adverse events within 30 days of randomization. | Assessme ts at 7 day and 30 days after randomiza on. |

| | | | | | | |
|---|---|---|---|---|---|---|
| J Th Univ Heart Ctr 2014; 9: 104-108. | Randomized clinical study, blinded only to the patient. Unicentric, No patients: 50. | Adult patients diagnosed with submassive PE (right ventricular dysfunction on echocardiogram) | Alteplase 100mg or streptokinase 1,500,000 u/2 hours, in addition to enoxaparin 1mg/kg twice a day. | Placebo and enoxaparin 1mg/kg twice a day. | Primary efficacy outcome: death during hospitalization or clinical deterioration, requiring therapeutic escalation (at least one of the conditions: catecholamine infusion, rescue thrombolysis, intubation, CPR, emergency surgical embolectomy or thrombus fragmentation by catheter). Secondary outcomes: major bleeding, pulmonary hypertension assessed by echocardiography and ventricular dilation at the end of the first week after randomization. | Echocardiographic assessment one week after randomization and at hospital discharge |
| J Clin Med res 2017; 9:163-169. | Randomized clinical study. Unicentric, No patients: 86. | Adult patients diagnosed with acute PE, with onset of symptoms within 14 days of randomization, hemodynamically stable, with signs of right ventricular dysfunction assessed by echocardiogram and/or myocardial injury by biomarkers. | Tenecteplase (dose calculated according to weight, according to the leaflet) bolus, followed by IV UFH, with a target aPTT between 2 – 2.5 times the upper limit of normality. | Placebo, followed by IV UFH, bolus, followed by infusion with aPTT target between 2 – 2.5 times the upper limit of normal. | Primary efficacy outcome: composite of death from any cause, hemodynamic decompensation within 7 days of randomization. Secondary efficacy outcomes: composition of the primary outcome and recurrence of PE, within 7 days after randomization; death and re-hospitalization within 30 days since randomization. Safety endpoints: ischemic or hemorrhagic stroke or major extracranial bleeding within 7 days after randomization. | Assessments on the 7th and 30th days after randomization. |

BNP: B-type natriuretic peptide; ECG: electrocardiogram; LMWH: low molecular weight heparin; UFH: unfractionated heparin; CTEPH: chronic thromboembolic pulmonary hypertension; NT-proBNP: N-terminal fragment of type B natriuretic peptide; CPR: cardiopulmonary resuscitation;

PE: pulmonary embolism; VTE: venous thromboembolism; aPTT: activated partial thromboplastin time; RV: right ventricle.

Question 6 - Should systemic thrombolysis be recommended compared to isolated anticoagulation (LMWH, UFH) in patients with high-risk PE?

| Study | Study design | Population | Intervention | Comparator | Outcome | Time |
|---|---|---|---|---|---|---|
| Journal of Thrombosis and Thrombolysis 1995; 2: 227-229 | Randomized, single-center clinical study, No patients: 8. | Patients with massive PE (more than 9 obstructed segments according to V/Q scintigraphy assessment, with or without hypotension, but with RV dysfunction*. | Streptokinase 1,500,000UI, followed by UFH. | UFH | Hospital mortality | Hospital admission and 2 years after randomization. |

*All patients had hemodynamic instability.

V/Q scintigraphy: ventilation and perfusion scintigraphy; UFH: unfractionated heparin; PE: pulmonary embolism; RV: right ventricle.

## Chart S3- Evidence tables for decisions

| **Question 1** | Should home anticoagulation be used compared to hospitalization in patients with low-risk PE? | |
|---|---|---|
| | **Question of interest** | **Answer options** |
| Importance of the problem | Is the problem a priority? | ☐ No<br>☐ Probably not<br>☐ Probably yes<br>X Yes<br>☐ Varies |

| | | |
|---|---|---|
| | | ☐ Unknown |
| Desirable effects | What is the magnitude of the desirable effects? | ☐ Trivial<br>X Small<br>☐ Moderate<br>☐ Large<br>☐ Varies<br>☐ Unknown |
| Undesirable effects | What is the magnitude of the undesirable effects? | ☐ Trivial<br>X Small<br>☐ Moderate<br>☐ Large<br>☐ Varies<br>☐ Unknown |
| General certainty of evidence | How certain is the evidence (level of evidence for the set of evidence)? | X Very low<br>☐ Low<br>☐ Moderate<br>☐ High |
| Balance between risks and benefits | Does the balance between risks and benefits favor the intervention or the comparator? | ☐ Favors the comparator<br>☐ Probably favors the comparator<br>X Does not favor the comparator or the intervention<br>☐ Probably favors intervention<br>☐ Encourages intervention<br>☐ Varies<br>☐ Unknown |
| Feasibility | Is the intervention feasible for implementation? | ☐ No<br>☐ Probably not<br>X Probably yes<br>☐ Yes<br>☐ Varies<br>☐ Unknown |
| **Conclusion** | For low-risk thromboembolism patients, who meet access to healthcare requirements, we suggest home treatment (conditional recommendation, very low quality of evidence) | |

| **Question 2** | Should anticoagulation with DOACs be used compared to anticoagulation with LMWH in patients with PE and diagnosed with cancer? | |
|---|---|---|
| | **Question of interest** | **Answer options** |
| Importance of the problem | Is the problem a priority? | ☐ No<br>☐ Probably not<br>☐ Probably yes<br>X Yes<br>☐ Varies<br>☐ Unknown |
| Desirable effects | What is the magnitude of the desirable effects? | ☐ Trivial<br>☐ Small<br>X Moderate<br>☐ Large<br>☐ Varies<br>☐ Unknown |
| Undesirable effects | What is the magnitude of the undesirable effects? | ☐ Trivial<br>☐ Small<br>X Moderate<br>☐ Large<br>☐ Varies<br>☐ Unknown |
| General certainty of evidence | How certain is the evidence (level of evidence for the set of evidence)? | ☐ Very low<br>X Low<br>☐ Moderate<br>☐ High |
| Balance between risks and benefits | Does the balance between risks and benefits favor the intervention or the comparator? | ☐ Favors the comparator<br>☐ Probably favors the comparator<br>☐ Does not favor the comparator or the intervention<br>X Probably favors intervention<br>☐ Encourages intervention<br>☐ Varies<br>☐ Unknown |
| Feasibility | Is the intervention feasible for implementation? | ☐ No<br>☐ Probably not |

| | | |
|---|---|---|
| | | X Probably yes<br>☐ Yes<br>☐ Varies<br>☐ Unknown |
| **Conclusion** | For patients with thromboembolism and cancer, we suggest direct-acting oral anticoagulants (conditional recommendation, low quality of evidence). | |

| **Question 3** | Should it be recommended to maintain extended anticoagulation versus comparator (ASA or placebo) in patients diagnosed with unprovoked PE, who have completed at least 3 months of anticoagulation? | |
|---|---|---|
| | **Question of interest** | **Answer options** |
| Importance of the problem | Is the problem a priority? | ☐ No<br>☐ Probably not<br>☐ Probably yes<br>X Yes<br>☐ Varies<br>☐ Unknown |
| Desirable effects | What is the magnitude of the desirable effects? | ☐ Trivial<br>☐ Small<br>☐ Moderate<br>X Large<br>☐ Varies<br>☐ Unknown |
| Undesirable effects | What is the magnitude of the undesirable effects? | ☐ Trivial<br>X Small<br>☐ Moderate<br>☐ Large<br>☐ Varies<br>☐ Unknown |
| General certainty of evidence | How certain is the evidence (level of evidence for the set of evidence)? | ☐ Very low<br>☐ Low<br>☐ Moderate<br>X High |
| Balance between | Does the balance between | ☐ Favors the comparator |

| | | |
|---|---|---|
| risks and benefits | risks and benefits favor the intervention or the comparator? | ☐ Probably favors the comparator<br>☐ Does not favor the comparator or the intervention<br>☐ Probably favors intervention<br>X Encourages intervention<br>☐ Varies<br>☐ Unknown |
| Feasibility | Is the intervention feasible for implementation? | ☐ No<br>☐ Probably not<br>☐ Probably yes<br>X Yes<br>☐ Varies<br>☐ Unknown |
| **Conclusion** | For patients with thromboembolism who have completed 3 months of anticoagulation we recommend extended anticoagulation (strong recommendation, high quality of evidence) | |

| **Question 4** | Treatment (3 to 6 months) with DOACs should be recommended compared to conventional anticoagulation (LMWH or UFH initially followed by warfarin), in patients diagnosed with low-risk PE, low-intermediate risk, high-intermediate risk, after stabilization or high risk, after reperfusion and stabilization? | |
|---|---|---|
| | **Question of interest** | **Answer options** |
| Importance of the problem | Is the problem a priority? | ☐ No<br>☐ Probably not<br>☐ Probably yes<br>X Yes<br>☐ Varies<br>☐ Unknown |
| Desirable effects | What is the magnitude of the desirable effects? | X Trivial<br>☐ Small<br>☐ Moderate<br>☐ Large<br>☐ Varies<br>☐ Unknown |
| Undesirable effects | What is the magnitude of the | ☐ Trivial |

| | | |
|---|---|---|
| | undesirable effects? | X Small<br>☐ Moderate<br>☐ Large<br>☐ Varies<br>☐ Unknown |
| General certainty of evidence | How certain is the evidence (level of evidence for the set of evidence)? | ☐ Very low<br>☐ Low<br>X Moderate<br>☐ High |
| Balance between risks and benefits | Does the balance between risks and benefits favor the intervention or the comparator? | ☐ Favors the comparator<br>☐ Probably favors the comparator<br>☐ Does not favor the comparator or the intervention<br>X Probably favors intervention<br>☐ Encourages intervention<br>☐ Varies<br>☐ Unknown |
| Feasibility | Is the intervention feasible for implementation? | ☐ No<br>☐ Probably not<br>☐ Probably yes<br>X Yes<br>☐ Varies<br>☐ Unknown |
| **Conclusion** | For patients with stable thromboembolism or after hemodynamic stabilization, we recommend direct-acting oral anticoagulant for 3 to 6 months (strong recommendation, moderate quality of evidence). | |

| **Question 5** | Should systemic thrombolysis be recommended compared to isolated anticoagulation (LMWH or UFH) in patients with intermediate-high risk PE? | |
|---|---|---|
| | **Question of interest** | **Answer options** |
| Importance of the problem | Is the problem a priority? | ☐ No<br>☐ Probably not<br>☐ Probably yes<br>X Yes |

| | | |
|---|---|---|
| | | ☐ Varies<br>☐ Unknown |
| Desirable effects | What is the magnitude of the desirable effects? | X Trivial<br>☐ Small<br>☐ Moderate<br>☐ Large<br>☐ Varies<br>☐ Unknown |
| Undesirable effects | What is the magnitude of the undesirable effects? | ☐ Trivial<br>X Small<br>☐ Moderate<br>☐ Large<br>☐ Varies<br>☐ Unknown |
| General certainty of evidence | How certain is the evidence (level of evidence for the set of evidence)? | ☐ Very low<br>☐ Low<br>X Moderate<br>☐ High |
| Balance between risks and benefits | Does the balance between risks and benefits favor the intervention or the comparator? | ☐ Favors the comparator<br>X Probably favors the comparator<br>☐ Does not favor the comparator or the intervention<br>☐ Probably favors intervention<br>☐ Encourages intervention<br>☐ Varies<br>☐ Unknown |
| Feasibility | Is the intervention feasible for implementation? | ☐ No<br>☐ Probably not<br>X Probably yes<br>☐ Yes<br>☐ Varies<br>☐ Unknown |
| **Conclusion** | For patients with high-intermediate risk thromboembolism, we suggest not using drug thrombolysis (conditional recommendation, moderate quality of evidence). | |

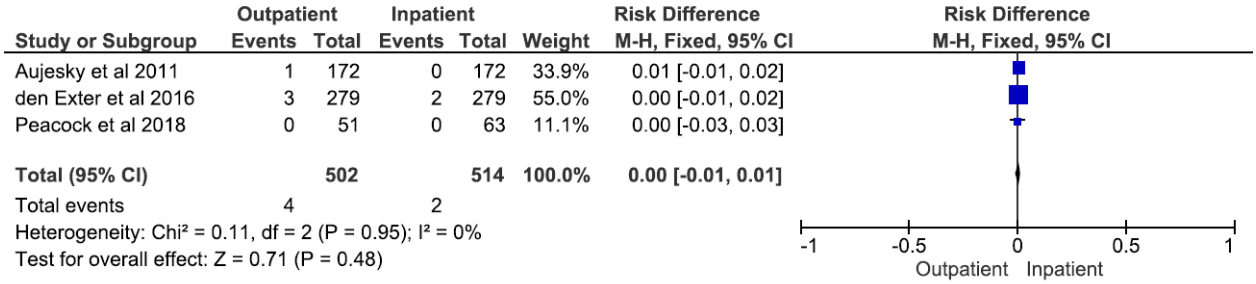
| **Question 6** | Should systemic thrombolysis be recommended compared to isolated anticoagulation (LMWH, UFH) in patients with high-risk PE? | |
|---|---|---|
| | **Question of interest** | **Answer options** |
| Importance of the problem | Is the problem a priority? | ☐ No<br>☐ Probably not<br>☐ Probably yes<br>X Yes<br>☐ Varies<br>☐ Unknown |
| Desirable effects | What is the magnitude of the desirable effects? | ☐ Trivial<br>☐ Small<br>☐ Moderate<br>X Large<br>☐ Varies<br>☐ Unknown |
| Undesirable effects | What is the magnitude of the undesirable effects? | X Trivial<br>☐ Small<br>☐ Moderate<br>☐ Large<br>☐ Varies<br>☐ Unknown |
| General certainty of evidence | How certain is the evidence (level of evidence for the set of evidence)? | X Very low<br>☐ Low<br>☐ Moderate<br>☐ High |
| Balance between risks and benefits | Does the balance between risks and benefits favor the intervention or the comparator? | ☐ Favors the comparator<br>☐ Probably favors the comparator<br>☐ Does not favor the comparator or the intervention<br>X Probably favors intervention<br>☐ Encourages intervention<br>☐ Varies<br>☐ Unknown |
| Feasibility | Is the intervention feasible for | ☐ No |

| | | |
|---|---|---|
| | implementation? | ☐ Probably not<br>☐ Probably yes<br>X Yes<br>☐ Varies<br>☐ Unknown |
| **Conclusion** | For patients with high-risk thromboembolism, we suggest systemic drug thrombolysis (conditional recommendation, very low quality of evidence) | |

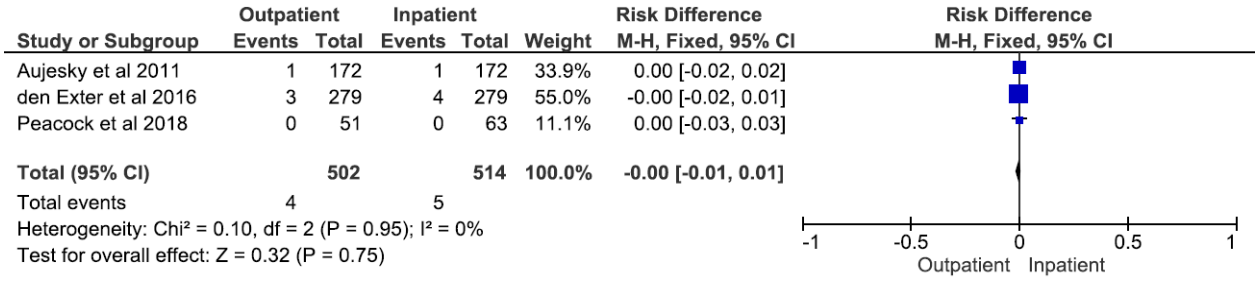
**Figure S2- Forest plots of PICO questions.**

Question 1 - Should home anticoagulation be used compared to hospitalization in patients with low-risk PE?

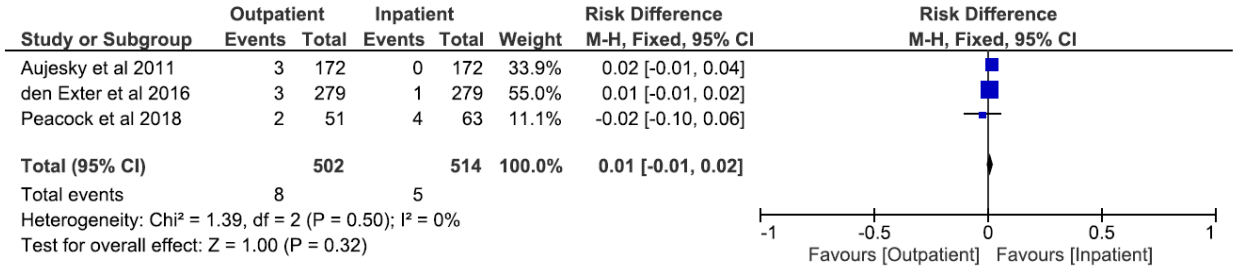
Venous Thromboembolism (VTE) recurrence




Death for any cause

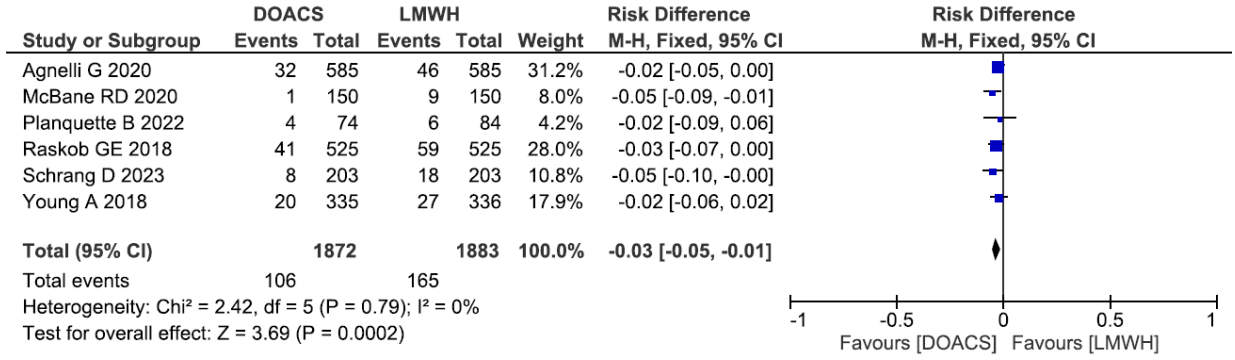


Any bleeding

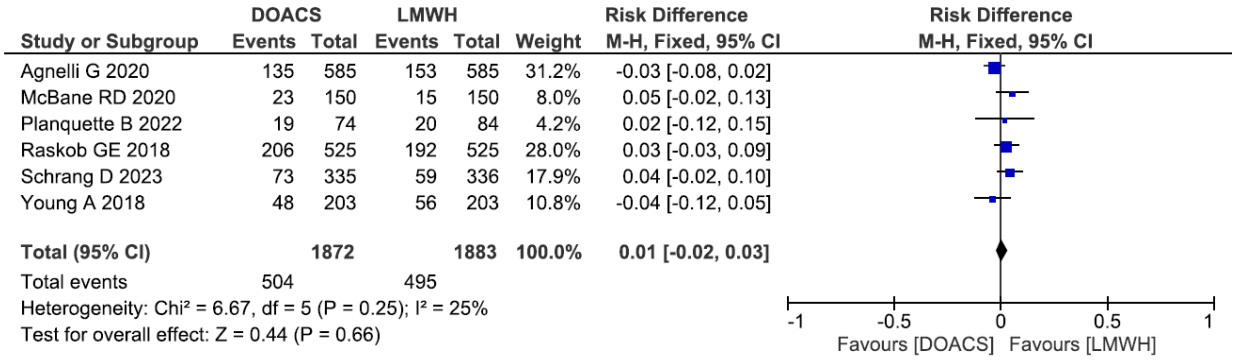



Question 2 - Should anticoagulation with DOACs be used compared to anticoagulation with LMWH in patients with PE and diagnosed with cancer?

TEV recurrence



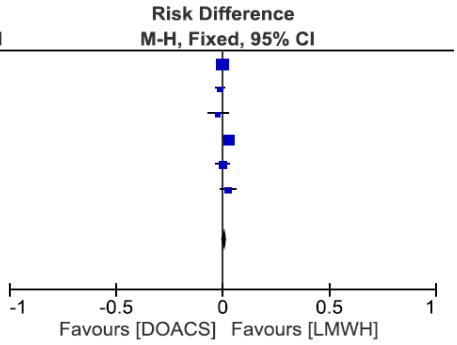

Death for any cause



Major bleeding

| Study or Subgroup | DOACS Events | DOACS Total | LMWH Events | LMWH Total | Weight | Risk Difference M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Agnelli G 2020 | 22 | 585 | 23 | 585 | 31.2% | -0.00 [-0.02, 0.02] |
| McBane RD 2020 | 0 | 150 | 2 | 150 | 8.0% | -0.01 [-0.04, 0.01] |
| Planquette B 2022 | 1 | 74 | 3 | 84 | 4.2% | -0.02 [-0.07, 0.03] |
| Raskob GE 2018 | 36 | 525 | 21 | 525 | 28.0% | 0.03 [0.00, 0.06] |
| Schrang D 2023 | 17 | 335 | 17 | 336 | 17.9% | 0.00 [-0.03, 0.03] |
| Young A 2018 | 11 | 203 | 6 | 203 | 10.8% | 0.02 [-0.01, 0.06] |
| **Total (95% CI)** | | **1872** | | **1883** | **100.0%** | **0.01 [-0.00, 0.02]** |
| Total events | 87 | | 72 | | | |

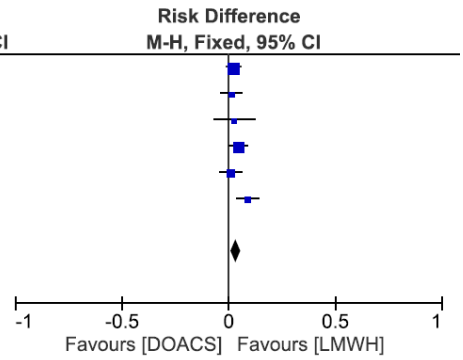
Heterogeneity: Chi² = 8.94, df = 5 (P = 0.11); I² = 44%
Test for overall effect: Z = 1.24 (P = 0.21)




Any bleeding

| Study or Subgroup | DOACS Events | DOACS Total | LMWH Events | LMWH Total | Weight | Risk Difference M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Agnelli G 2020 | 70 | 585 | 56 | 585 | 31.2% | 0.02 [-0.01, 0.06] |
| McBane RD 2020 | 9 | 150 | 7 | 150 | 8.0% | 0.01 [-0.04, 0.06] |
| Planquette B 2022 | 9 | 74 | 8 | 84 | 4.2% | 0.03 [-0.07, 0.12] |
| Raskob GE 2018 | 97 | 525 | 73 | 525 | 28.0% | 0.05 [0.00, 0.09] |
| Schrang D 2023 | 46 | 335 | 43 | 336 | 17.9% | 0.01 [-0.04, 0.06] |
| Young A 2018 | 25 | 203 | 7 | 203 | 10.8% | 0.09 [0.04, 0.14] |
| **Total (95% CI)** | | **1872** | | **1883** | **100.0%** | **0.03 [0.01, 0.05]** |
| Total events | 256 | | 194 | | | |

Heterogeneity: Chi² = 6.42, df = 5 (P = 0.27); I² = 22%
Test for overall effect: Z = 3.20 (P = 0.001)

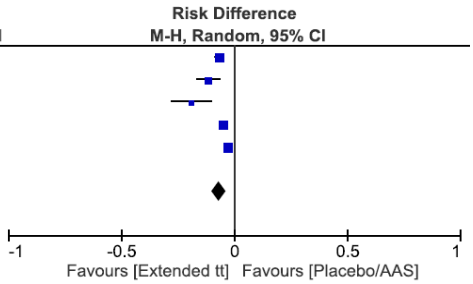



Question 3 - Should it be recommended to maintain extended anticoagulation versus comparator (ASA or placebo) in patients diagnosed with unprovoked PE, who have completed at least 3 months of anticoagulation?

TEV recurrence

| Study or Subgroup | Extended tt* Events | Extended tt* Total | Placebo/AAS** Events | Placebo/AAS** Total | Weight | Risk Difference M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Agnelli G 2013 | 36 | 1657 | 75 | 829 | 24.6% | -0.07 [-0.09, -0.05] |
| Couturaud F 2015 | 3 | 184 | 25 | 187 | 15.4% | -0.12 [-0.17, -0.07] |
| Kearon C 1999 | 1 | 79 | 17 | 83 | 8.2% | -0.19 [-0.28, -0.10] |
| Schulman S 2013 (PC) | 3 | 685 | 37 | 668 | 25.3% | -0.05 [-0.07, -0.03] |
| Weitz JI 2017 | 31 | 2234 | 50 | 1131 | 26.4% | -0.03 [-0.04, -0.02] |
| **Total (95% CI)** | | **4839** | | **2898** | **100.0%** | **-0.07 [-0.10, -0.04]** |
| Total events | 74 | | 204 | | | |

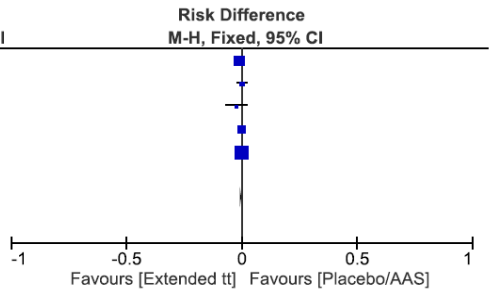
Heterogeneity: Tau² = 0.00; Chi² = 29.90, df = 4 (P < 0.00001); I² = 87%
Test for overall effect: Z = 4.57 (P < 0.00001)



Death for any cause

| Study or Subgroup | Extended tt* Events | Total | Placebo/AAS** Events | Total | Weight | Risk Difference M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Agnelli G 2013 | 11 | 1657 | 14 | 829 | 31.1% | -0.01 [-0.02, -0.00] |
| Couturaud F 2015 | 2 | 184 | 2 | 187 | 5.2% | 0.00 [-0.02, 0.02] |
| Kearon C 1999 | 1 | 79 | 3 | 83 | 2.3% | -0.02 [-0.07, 0.02] |
| Schulman S 2013 (PC) | 0 | 685 | 2 | 668 | 19.1% | -0.00 [-0.01, 0.00] |
| Weitz JI 2017 | 10 | 2234 | 7 | 1131 | 42.3% | -0.00 [-0.01, 0.00] |
| **Total (95% CI)** | | **4839** | | **2898** | **100.0%** | **-0.01 [-0.01, -0.00]** |
| Total events | 24 | | 28 | | | |

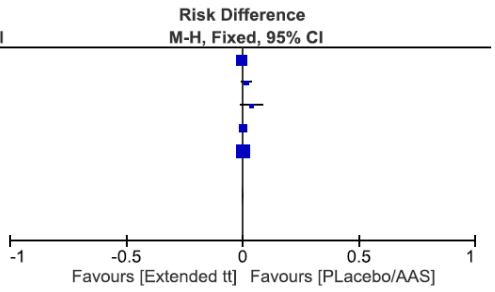
Heterogeneity: Chi² = 4.05, df = 4 (P = 0.40); I² = 1%
Test for overall effect: Z = 2.36 (P = 0.02)




Major Bleeding

| Study or Subgroup | Extended tt* Events | Total | Placebo/AAS** Events | Total | Weight | Risk Difference M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Agnelli G 2013 | 3 | 1657 | 4 | 829 | 31.1% | -0.00 [-0.01, 0.00] |
| Couturaud F 2015 | 4 | 184 | 1 | 187 | 5.2% | 0.02 [-0.01, 0.04] |
| Kearon C 1999 | 3 | 79 | 0 | 83 | 2.3% | 0.04 [-0.01, 0.09] |
| Schulman S 2013 (PC) | 2 | 685 | 0 | 668 | 19.1% | 0.00 [-0.00, 0.01] |
| Weitz JI 2017 | 11 | 2234 | 3 | 1131 | 42.3% | 0.00 [-0.00, 0.01] |
| **Total (95% CI)** | | **4839** | | **2898** | **100.0%** | **0.00 [-0.00, 0.01]** |
| Total events | 23 | | 8 | | | |

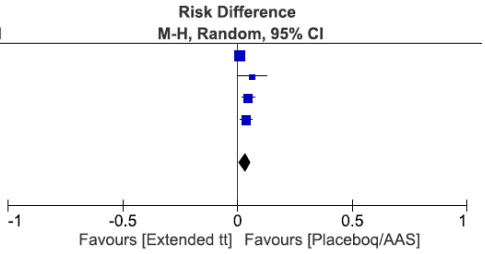
Heterogeneity: Chi² = 7.69, df = 4 (P = 0.10); I² = 48%
Test for overall effect: Z = 1.48 (P = 0.14)




Any bleeding

| Study or Subgroup | Tto estendido* Events | Total | Placebo/AAS** Events | Total | Weight | Risk Difference M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Agnelli G 2013 | 62 | 1657 | 22 | 829 | 34.9% | 0.01 [-0.00, 0.03] |
| Kearon C 1999 | 6 | 79 | 1 | 83 | 11.5% | 0.06 [0.00, 0.13] |
| Schulman S 2013 (PC) | 72 | 685 | 39 | 668 | 25.9% | 0.05 [0.02, 0.08] |
| Weitz JI 2017 | 408 | 2234 | 165 | 1131 | 27.7% | 0.04 [0.01, 0.06] |
| **Total (95% CI)** | | **4655** | | **2711** | **100.0%** | **0.03 [0.01, 0.06]** |
| Total events | 548 | | 227 | | | |

Heterogeneity: Tau² = 0.00; Chi² = 9.97, df = 3 (P = 0.02); I² = 70%
Test for overall effect: Z = 2.59 (P = 0.010)

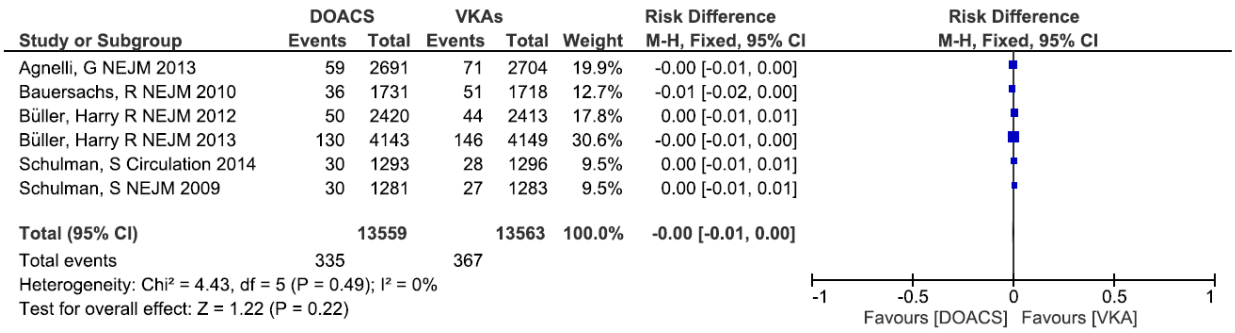



* Anticoagulation after at least 3 months of treatment

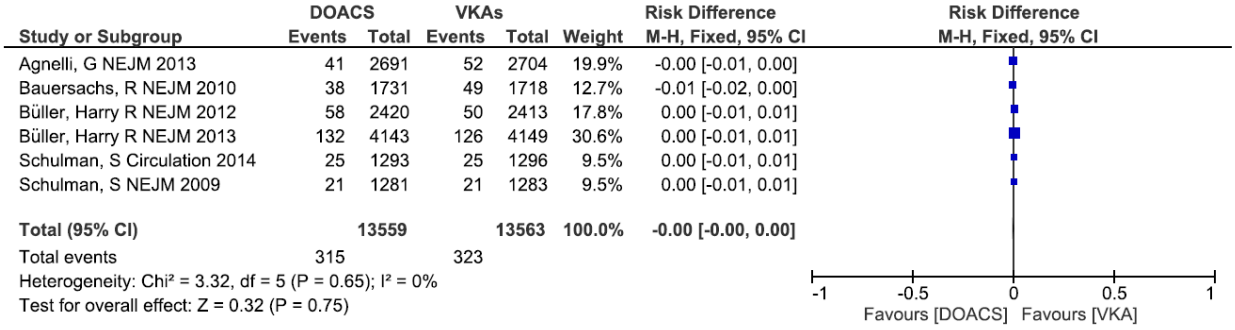
**Placebo or acetyl salicylic acid after at least 3 months of treatment

Question 4 - Treatment (3 to 6 months) with DOACs* should be recommended compared to conventional anticoagulation (LMWH or UFH initially followed by warfarin), in patients diagnosed with low-risk PE, low-intermediate risk, high-intermediate risk, after stabilization or high risk, after reperfusion and stabilization?

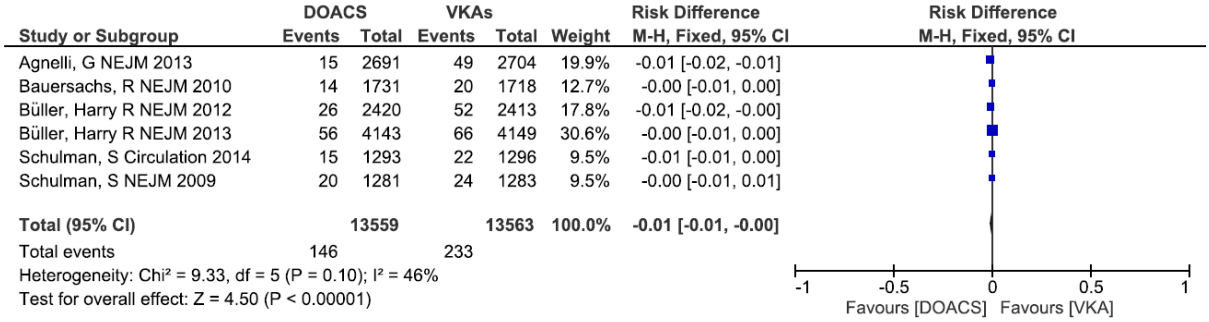
TEV recurrence



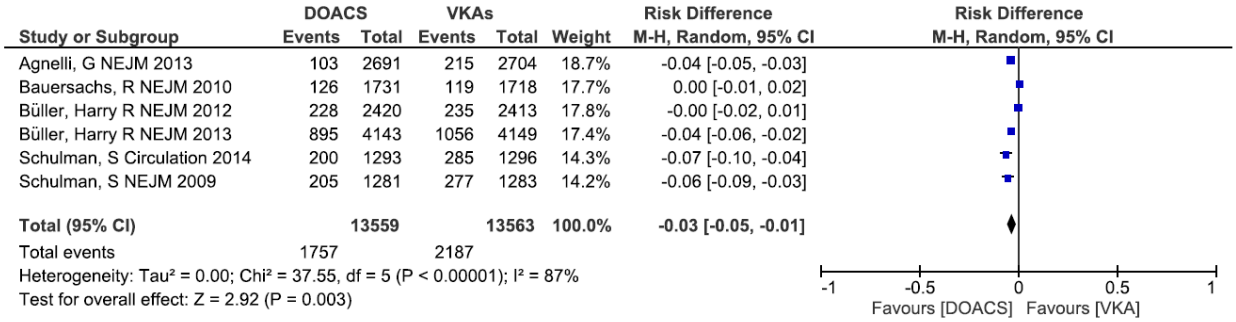

## Death of any cause




## Major bleeding




## Any bleeding

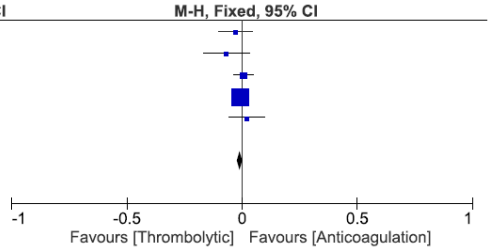



Question 5: Should systemic thrombolysis be recommended compared to isolated anticoagulation (LMWH or UFH) in patients with intermediate-high risk PE?

## TEV recurrence

| Study or Subgroup | Thrombolytic Events | Thrombolytic Total | Anticoagulation Events | Anticoagulation Total | Weight | Risk Difference M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Fesullo, 2011 | 0 | 37 | 1 | 35 | 4.8% | -0.03 [-0.10, 0.05] |
| Kline, JA, 2014 | 1 | 40 | 4 | 43 | 5.5% | -0.07 [-0.17, 0.03] |
| Konstantinides, Stavros 2002 | 4 | 118 | 4 | 138 | 17.0% | 0.00 [-0.04, 0.05] |
| Meyer, Guy, 2014 | 1 | 506 | 5 | 499 | 67.0% | -0.01 [-0.02, 0.00] |
| Sinha, SK, 2017 | 2 | 45 | 1 | 41 | 5.7% | 0.02 [-0.06, 0.10] |
| **Total (95% CI)** | | **746** | | **756** | **100.0%** | **-0.01 [-0.02, 0.00]** |
| Total events | 8 | | 15 | | | |

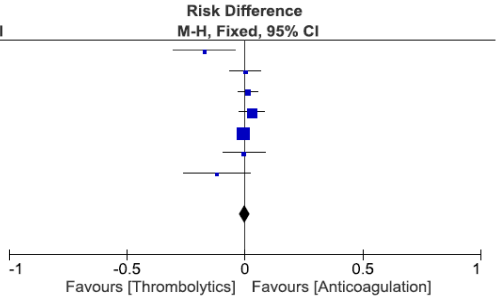
Heterogeneity: Chi² = 2.58, df = 4 (P = 0.63); I² = 0%
Test for overall effect: Z = 1.34 (P = 0.18)




## Death of any cause

| Study or Subgroup | Trombolíticos Events | Trombolíticos Total | Anticoagulação Events | Anticoagulação Total | Weight | Risk Difference M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Fesullo, 2011 | 0 | 37 | 6 | 35 | 3.2% | -0.17 [-0.30, -0.04] |
| Kline, JA, 2014 | 1 | 40 | 1 | 43 | 3.7% | 0.00 [-0.06, 0.07] |
| Konstantinides, Stavros 2002 | 4 | 118 | 3 | 138 | 11.3% | 0.01 [-0.03, 0.05] |
| Konstantinides, Stavros 2017 | 65 | 359 | 53 | 350 | 31.4% | 0.03 [-0.03, 0.08] |
| Meyer, Guy, 2014 | 12 | 506 | 16 | 499 | 44.5% | -0.01 [-0.03, 0.01] |
| Sinha, SK, 2017 | 2 | 45 | 2 | 41 | 3.8% | -0.00 [-0.09, 0.08] |
| Taherkhani, M, 2014 | 0 | 25 | 3 | 25 | 2.2% | -0.12 [-0.26, 0.02] |
| **Total (95% CI)** | | **1130** | | **1131** | **100.0%** | **-0.00 [-0.02, 0.02]** |
| Total events | 84 | | 84 | | | |

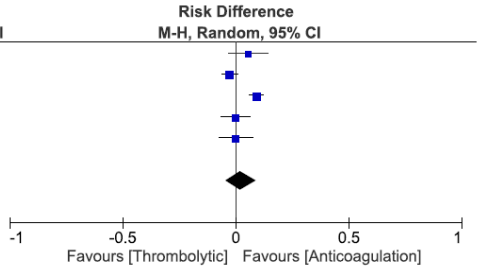
Heterogeneity: Chi² = 11.33, df = 6 (P = 0.08); I² = 47%
Test for overall effect: Z = 0.12 (P = 0.91)




## Major bleeding

| Study or Subgroup | Thrombolytic Events | Thrombolytic Total | Anticoagulation Events | Anticoagulation Total | Weight | Risk Difference M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Fesullo, 2011 | 2 | 37 | 0 | 35 | 16.8% | 0.05 [-0.03, 0.14] |
| Konstantinides, Stavros 2017 | 1 | 118 | 5 | 138 | 22.5% | -0.03 [-0.06, 0.01] |
| Meyer, Guy, 2014 | 58 | 506 | 12 | 499 | 22.8% | 0.09 [0.06, 0.12] |
| Sinha, SK, 2017 | 1 | 45 | 1 | 41 | 19.6% | -0.00 [-0.07, 0.06] |
| Taherkhani, M, 2014 | 0 | 25 | 0 | 25 | 18.3% | 0.00 [-0.07, 0.07] |
| **Total (95% CI)** | | **731** | | **738** | **100.0%** | **0.02 [-0.04, 0.09]** |
| Total events | 62 | | 18 | | | |

Heterogeneity: Tau² = 0.00; Chi² = 33.54, df = 4 (P < 0.00001); I² = 88%
Test for overall effect: Z = 0.69 (P = 0.49)




## Any bleeding

| Study or Subgroup | Thrombolytic Events | Total | Anticoagulation Events | Total | Weight | Risk Difference M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Fesullo, 2011 | 16 | 37 | 9 | 35 | 17.8% | 0.18 [-0.04, 0.39] |
| Meyer, Guy, 2014 | 165 | 506 | 43 | 499 | 32.7% | 0.24 [0.19, 0.29] |
| Sinha, SK, 2017 | 7 | 45 | 5 | 41 | 24.0% | 0.03 [-0.11, 0.18] |
| Taherkhani, M, 2014 | 2 | 25 | 1 | 25 | 25.5% | 0.04 [-0.09, 0.17] |
| **Total (95% CI)** | | **613** | | **600** | **100.0%** | **0.13 [-0.00, 0.26]** |
| Total events | 190 | | 58 | | | |

Heterogeneity: Tau² = 0.01; Chi² = 13.85, df = 3 (P = 0.003); I² = 78%

Test for overall effect: Z = 1.91 (P = 0.06)