Direct Oral Anticoagulants: Drug Selection by Means of the SOJA Method

Robert Janknegt*, Esther Metting, Johan Kooistra and Richard Dekhuijzen
1Hospital Pharmacist, Clinical Pharmacologist Sittard, The Netherlands
2Epidemiologist/Behavioral Scientist, University Medical Center, Groningen, The Netherlands
3BENU Pharmacies, Maarssen, The Netherlands
4Pulmonologist, Nijmegen, The Netherlands

*Corresponding Author: Robert Janknegt, Hospital Pharmacist, Clinical Pharmacologist Sittard, The Netherlands.

Part 2

| Medicines | Duration Days (days) | N      | First dose, timing (hours) | Age | Female (%) | Design | Duration of follow-up | Ref |
|-----------|----------------------|--------|----------------------------|-----|------------|--------|----------------------|-----|
| Api 2.5 mg bid or Enox 30 mg bid sc War INR 1.8-3 or | 10-14 | 111 | 12-24 post | 68 | 68 | DB | 10-14 days | [26] |
| Api 2.5 mg bid or Enox 30 mg bid sc | 10-14 | 1599 | 12-24 post | 66 | 62 | DB | 70 days | [27] |
| Api 2.5 mg bid or Enox 40 mg qd sc | 10-14 | 1528 | 12-24 post | 67 | 71 | DB, DD | 10-14 days | [28] |
| Api 2.5 mg bid or Enox 40 mg qd sc | 35 | 2708 | 12-24 post | 61 | 53 | DB, DD | 95 days | [29] |
| Dabi 150 mg bid | 6-10 | 390 | 1-4 post | 66 | 65 | DB, DD | 6-10 | [30] |
| Dabi 225 mg bid | 6-10 | 393 | 12 before | 66 | 58 | DB, DD | 6-10 | [30] |
| Dabi 150 mg qd Dabi 220 mg qd Enox 40 mg qd | 6-10 | 703 | 1-4 post evening before | 68 | 64 | DB, DD | 3 months | [31] |
| Dabi 150 mg qd Dabi 220 mg qd Enox 40 mg qd | 28-35 | 1163 | 1-4 post evening before | 63 | 57 | DB, DD | 28-35 | [32] |

Citation: Robert Janknegt, et al. "Direct Oral Anticoagulants: Drug Selection by Means of the SOJA Method". Acta Scientific Pharmaceutical Sciences 4.12 (2020): 145-175.
### Table 1: Comparative studies in orthopaedic surgery, baseline data and design.

| Medicines | BMI | Arthritis (%) | Duration of Surgery (h) | Surgery | Primary endpoint | Ref |
|-----------|-----|----------------|-------------------------|---------|------------------|-----|
| Api 2.5 mg bid or Enox 30 mg bid sc War INR 1.8-3 or | 31 | 70 | 1.4 | Knee | VTE-A + VTE-S + PE-NF | [26] |
| | 30 | 71 | 1.6 |
| | 30 | 72 | 1.6 |
| Api 2.5 mg bid or Enox 30 mg bid sc | 31 | 81 | 1.5 | Knee | VTE-A + VTE-S + PE-NF + death | [27] |
| | 31 | 80 | 1.5 |
| Api 2.5 mg bid or Enox 40 mg qd sc | 29 | 63 | 1.6 | Knee | VTE + PE-NF + death | [28] |
| | 29 | 63 | 1.6 |
| Api 2.5 mg bid or Enox 40 mg qd sc | 28 | 57 | 1.5 | Hip | VTE + PE-NF + death | [29] |
| | 28 | 58 | 1.5 |

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### Table 2: Comparative studies in orthopaedic surgery, baseline data and design.

| Drug Combination | SOJA Score | Location | Outcome | Reference |
|------------------|------------|----------|---------|-----------|
| Dabi 150 mg bid  | 1.5        | Hip and knee | VTE during treatment | [30] |
| Dabi 225 mg bid  | 1.4        | Hip and knee | VTE + mortality | [31] |
| Enox 40 mg qd    |            | Hip       | VTE + mortality | [32] |
| Dabi 150 mg qd   | 1.5        | Knee     | VTE + mortality | [33] |
| Dabi 220 mg qd   | 1.5        | Knee     | VTE + mortality | [34] |
| Enox 40 mg qd    | 1.5        | Knee     | VTE | [35] |
| Edo 15 mg qd     | 1.4        | Knee     | VTE | [36] |
| Edo 30 mg qd     | 1.4        | Knee     | VTE | [37] |
| Dalte 5000 IU qd | 1.4        | Knee     | VTE | [38] |
| Edo 30 mg bid    | 1.5        | Knee     | VTE | [39] |
| Edo 15 mg qd     | 1.5        | Knee     | VTE | [40] |
| Edo 30 mg qd     | 1.5        | Knee     | VTE | [41] |
| Edo 15 mg qd     | 1.4        | Knee     | VTE | [42] |
| Edo 30 mg qd     | 1.4        | Knee     | VTE | [43] |

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| Medicines                  | DVT-A (%) | DVT-S (%) | DVT-M (%) | DVT-P (%) | DVT (%) | VTE (%) | PE (%) | Fatal PE (%) | Mortality (%) | Composite Efficacy (%) | Reference |
|----------------------------|-----------|-----------|-----------|-----------|---------|---------|--------|-------------|---------------|------------------------|-----------|
| Api 2.5 mg bid             | 8.3       | 0.9       | 0.9       | 10        | 0       | 0.7     | 1.8    |             |               |                        | [26]      |
| Enox 30 mg bid             | 12.8      | 0.9       | 2.8       | 17        | 1.8     | 0       | 4.6    |             |               |                        | [27]      |
| War INR 1.8-3              | 25.7      | 0.9       | 1.8       | 29        | 0       | 0       | 1.8    | (VTE-P + PE + death) |            |                        | [28]      |
| Api 2.5 mg bid             | 0.2       | 0.4       | 0.7       | 7.8       | 1.0     | 0.1     | 0.2    |             |               |                        | [29]      |
| Enox 30 mg bid             | 0.2       | 0.4       | 0.9       | 8.2       | 0.4     | 0       | 0.2    |             |               |                        | [30]      |
| (all results after 10-14 days) |          |           |           |           |         |         |        |             |               |                        |           |
| Api 2.5 mg bid             | <0.1      | 0.5       | 0.8       | 14.6      | 0.3     | 0.1     | 0.13   |             |               | 15.1 (VTE + PE + death) | [31]      |
| Enox 40 mg qd              | 0.2       | 0.5       | 2.2       | 24.4      | 0       | 0       | 8.8    |             |               | 24.4 (VTE + PE + death) | [32]      |
| (all results after 35 days) |          |           |           |           |         |         |        |             |               | P<0.0001               |           |
| Dabi 150 mg bid            | 3.3       | 1.7       | 5.6       | 16.8      | 13.1    | 17.4    | 4.0    |             |               |                        | [33]      |
| Dabi 225 mg bid            | 39.7      | 36.0      | 36.0      | 0.4       | 0.1     | 0.1     | 1.7    |             |               |                        |           |
| Enox 40 mg qd              | 0.4       | 2.6       | 5.6       | 3.4       | 2.6     | 0.3     | 5.6    | (DVT/PE)    |               |                        |           |
|                              |           |           |           |           |         |         |        |             |               |                        |           |
|                              |           |           |           |           |         |         |        |             |               |                        |           |
|                              |           |           |           |           |         |         |        |             |               |                        |           |
|                              |           |           |           |           |         |         |        |             |               |                        |           |
| Dabi 220 mg qd             | 3.2       | 3.1       | 3.1       | 0.1       | 0.1     | 0.3     | 8.6    |             |               |                        | [34]      |
| Enox 40 mg qd              | 0.8       | 1.2       | 1.2       | 0.8       | 0.4     | 0.3     | 6.0    |             |               |                        | [35]      |
| (all results after 35 days) |          |           |           |           |         |         |        |             |               |                        | [36]      |
|                              | 2.1       | 0.4       | 0.1       | 7.6       | 0.1     | 0       | 3.1    |             |               |                        | [37]      |
|                              | 3.9       | 0.2       | 0.3       | 8.6       | 0.2     | 0.1     | 6.7    |             |               |                        | [38]      |
|                              |           |           |           |           |         |         |        |             |               |                        |           |
|                              | 0         | 0         | 0         | 0         | 0       | 0       | 7.7    |             |               |                        |           |
|                              | 0.4       | 0.1       | 0         | 0         | 0       | 0       | 8.7    |             |               |                        |           |
|                              |           |           |           |           |         |         |        |             |               |                        |           |

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| Drug Combination | Dabi 150 mg qd | Dabi 220 mg qd | Enox 40 mg qd | (all results after 12-15 days) | Edo 15 mg qd | Edo 30 mg qd | Dalte 5000 IU qd | (VTE-M) | P=0.036 | P<0.001 | P=0.02 | P<0.001 | VTE + death | P=0.036 | P<0.001 | 0 | 0.2 | 33.7 | 31.1 | 25.3 | VTE + death |
|------------------|----------------|----------------|----------------|---------------------------------|--------------|--------------|-----------------|---------|---------|---------|---------|---------|----------------|---------|---------|---|----|-------|-------|-------|----------------|
|                  |                |                |                |                                 |              |              |                 |         |         |         |         |         | (all results after 36 days) |         |         | ---|----|-------|-------|-------|----------------|
|                  |                |                |                |                                 |              |              |                 |         |         |         |         |         | (all results after 36 days) |         |         | ---|----|-------|-------|-------|----------------|
|                  |                |                |                |                                 |              |              |                 |         |         |         |         |         | (all results after 36 days) |         |         | ---|----|-------|-------|-------|----------------|
|                  |                |                |                |                                 |              |              |                 |         |         |         |         |         | (all results after 36 days) |         |         | ---|----|-------|-------|-------|----------------|
|                  |                |                |                |                                 |              |              |                 |         |         |         |         |         | (all results after 36 days) |         |         | ---|----|-------|-------|-------|----------------|
|                  |                |                |                |                                 |              |              |                 |         |         |         |         |         | (all results after 36 days) |         |         | ---|----|-------|-------|-------|----------------|
|                  |                |                |                |                                 |              |              |                 |         |         |         |         |         | (all results after 36 days) |         |         | ---|----|-------|-------|-------|----------------|
|                  |                |                |                |                                 |              |              |                 |         |         |         |         |         | (all results after 36 days) |         |         | ---|----|-------|-------|-------|----------------|
|                  |                |                |                |                                 |              |              |                 |         |         |         |         |         | (all results after 36 days) |         |         | ---|----|-------|-------|-------|----------------|
|                  |                |                |                |                                 |              |              |                 |         |         |         |         |         | (all results after 36 days) |         |         | ---|----|-------|-------|-------|----------------|
|                  |                |                |                |                                 |              |              |                 |         |         |         |         |         | (all results after 36 days) |         |         | ---|----|-------|-------|-------|----------------|
|                  |                |                |                |                                 |              |              |                 |         |         |         |         |         | (all results after 36 days) |         |         | ---|----|-------|-------|-------|----------------|
|                  |                |                |                |                                 |              |              |                 |         |         |         |         |         | (all results after 36 days) |         |         | ---|----|-------|-------|-------|----------------|
|                  |                |                |                |                                 |              |              |                 |         |         |         |         |         | (all results after 36 days) |         |         | ---|----|-------|-------|-------|----------------|
|                  |                |                |                |                                 |              |              |                 |         |         |         |         |         | (all results after 36 days) |         |         | ---|----|-------|-------|-------|----------------|
|                  |                |                |                |                                 |              |              |                 |         |         |         |         |         | (all results after 36 days) |         |         | ---|----|-------|-------|-------|----------------|
|                  |                |                |                |                                 |              |              |                 |         |         |         |         |         | (all results after 36 days) |         |         | ---|----|-------|-------|-------|----------------|
|                  |                |                |                |                                 |              |              |                 |         |         |         |         |         | (all results after 36 days) |         |         | ---|----|-------|-------|-------|----------------|
|                  |                |                |                |                                 |              |              |                 |         |         |         |         |         | (all results after 36 days) |         |         | ---|----|-------|-------|-------|----------------|

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Table 3: Comparative studies in orthopaedic surgery, results.

DVT-A: Asymptomatic deep vein thrombosis
DVT-S: Severe/symptomatic deep vein thrombosis
DVT-M: Major deep vein thrombosis
DVT-P: Proximal deep vein thrombosis
PE: Pulmonary embolism
PE-NF: Non-fatal pulmonary embolism
PE-F: Fatal pulmonary embolism
VTE: Venous thromboembolism (deep vein thrombosis plus pulmonary embolism).

| Medicines         | Withdrawal AE (%) | AE (%) | AE drug related (%) | AE-S (%) | Wound related infections (%) | MI (%) | Stroke (%) | ALT>3ALN | ALT>3ALN And bili >2ALN | Reference |
|-------------------|-------------------|--------|---------------------|----------|-------------------------------|--------|------------|----------|------------------------|-----------|
| Api 2.5 mg bid    | 87                | 7.8    | 1.3                 | 1.3      | 1.3                           | 0.7    | 2.6        | 0        | 0                      | [26]      |
| Enox 30 mg bid    | 87                | 6.7    | 0.7                 | 0        | 0                             | 0      | 2.7        | 0        | 0                      | [27]      |
| War INR 1.8-3     | 89                | 6.0    | 2.0                 | 0.7      | 0                             | 0      | 2.0        | 0.7      | 0                      | [28]      |
| Api 2.5 mg bid    | 87                | 8.5    | 1.3                 | 0.1      | 0                             | 0      | 1.0        | 0        | 1                      | [29]      |
| Enox 30 mg bid    | 87                | 8.6    | 0.7                 | 0.3      | 0.1                           | 0      | 1.6        | 0.1      | 0                      | [29]      |
| Api 2.5 mg bid    | 3                 | 52     | 14                  | 5        | 0.1                           | 0.1    | 2          | 0.2      | 0.2                    | [28]      |
| Enox 40 mg qd     | 3                 | 55     | 14                  | 6        | 0.1                           | 0      | 1          | 0.1      | 0.1                    | [29]      |
| Api 2.5 mg bid    | 3                 | 52     | 14                  | 5        | 0.1                           | 0.1    | 2          | 0.2      | 0.2                    | [28]      |
| Enox 40 mg qd     | 3                 | 55     | 14                  | 6        | 0.1                           | 0      | 1          | 0.1      | 0.1                    | [29]      |

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| Drug Combination       | AE1  | AE2  | AE3  | AE4  | AE5  | AE6  |
|------------------------|------|------|------|------|------|------|
| Dabi 150 mg bid        | 3.7  | 1.0  | 3.7  | [30] |
| Dabi 225 mg bid        | 3.7  | 0.4  | 3.7  |      |
| Enox 40 mg qd          | 4.6  | 0.5  | 4.6  |      |
| Dabi 150 mg qd         | 8    | 77   | 8    | [31] |
| Dabi 220 mg qd         | 6    | 77   | 8    |      |
| Enox 40 mg qd          | 6    | 77   | 7    |      |
| Dabi 220 mg qd         | 5.9  | 68   | 9.1  | 5.6  | <0.1 | 0    | 3.8  | 0.2  | [32] |
| Enox 40 mg qd          | 5.2  | 69   | 9.5  | 5.9  | <0.1 | 0    | 5.6  | 0    |      |
| Dabi 150 mg qd         | 5    |      |      | 1.0  |      |      | 0.7  |      | [33] |
| Dabi 220 mg qd         | 5    |      |      | 0.9  |      |      | 1.0  |      |      |
| Eno 30 mg bid          | 1.6  | 35   | 8.9  | 4.2  |      | 4.2  | 0.5  |      | [34] |
| Edo 30 mg qd           | 0.6  | 28   | 4.7  | 2.9  |      | 2.4  | 0.6  |      |      |
| Dalte 5000 IU qd       | 1.2  | 36   | 8.1  | 1.7  |      | 2.9  | 0.6  |      |      |
| Edo 30 mg qd           |      |      |      | 0.6  |      | 5.7  | 0.3  |      | [35] |
| Eno 20 mg bid          |      |      |      |      |      | 0.4  |      |      |      |
| Edo 15 mg qd           | 65   | 18   | 0    |      |      | 0.4  |      |      | [36] |
| Edo 30 mg qd           | 71   | 26   | 0    |      |      | 0.3  |      |      |      |
| Eno 20 mg bid          | 83   | 53   | 1.1  |      |      | 1.2  |      |      |      |
| Edo 30 mg qd           | 65   |      |      | 2.6  |      |      |      |      | [37] |
| Eno 20 mg bid          | 77   |      |      | 10   |      |      |      |      |      |
| Riva 10 mg qd          | 64   | 12   | 0.4  | 0.1  | 0.1  | 2.0  | 0.1  |      | [38] |
| Eno 40 mg qd           | 65   | 12   | 0.4  | 0.3  | 0.1  | 2.7  | 0.1  |      |      |
| Riva 10 mg qd          | 3.8  | 60   | 1.1  | 7.3  | 0.7  | 0.3  | 0.2  | 1.6  | 0.2  | [39] |
| Eno 40 mg qd           | 5.3  | 62   | 1.4  | 10.7 | 0.5  | 0.2  | 0.1  | 4.7  | 0.3  |      |
| Riva 10 mg qd          |      |      |      | 12.013.0 | 0.6 | 0.1  | 0.2 |      |      |      | [40] |
| Eno 40 mg qd           |      |      |      |      | 0.9  | 0.2  | 0  |      |      |      |      |
| Riva 10 mg qd          | 80   | 20   | 5.2  | 0.3  | 0.1  | 0.1  | 1.3  | 0.1  |      | [41] |
| Eno 30 mg bid          | 81   | 20   | 7.0  | 0.2  | 0    | 0    | 2.6  | 0.2  |      |      |

**Table 4:** Comparative studies in orthopaedic surgery, safety results.

AE: Adverse Events

AE-S: Severe Adverse Events

MI: Myocardial Infarction.

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| Medicines          | Major bleeding (%) | Overt bleeding (%) | Minor bleeding (%) | Non-major bleeding (%) | All bleeding (%) | Bleeding with surgical intervention (%) | Fatal bleeding (%) | Bleeding at critical site (%) | Bleeding at surgical site (%) | Reference |
|--------------------|---------------------|--------------------|-------------------|------------------------|-------------------|----------------------------------------|--------------------|------------------------------|---------------------------------|-----------|
| Api 2.5 mg bid     | 0                   | 3.9                | 0                 | 3.0                    | 0                 | 0                                      | 0                  | 0.1                         | 0.5                             | [26]      |
| Enox 30 mg bid     | 0                   | 4.0                | 0                 | 4.0                    | 0                 | 0                                      | 0                  | 0.1                         | 0.9                             |          |
| War INR 1.8-3      | 0                   | 5.3                | 0                 | 5.3                    | 0                 | 0                                      | 0                  | 0.1                         | 0.9                             |          |
| Api 2.5 mg bid     | 0.7                 | 0.6                | 2.4               | 5.3                    | 0                 | 0                                      | 0                  | 0.1                         | 0.5                             | [27]      |
| Enox 30 mg bid     | 1.4                 | 1.4                | 2.5               | 6.8                    | <0.1              | 0.1                                    | 0.1                | 0.1                         | 0.9                             |          |
| Api 2.5 mg bid     | 0.6                 | 0.5                | 3.4               | 6.9                    | 0                 | 0                                      | 0                  | 0.1                         | 0.5                             | [28]      |
| Enox 40 mg qd      | 0.9                 | 0.9                | 3.6               | 8.4                    | 0                 | 0                                      | 0                  | 0.1                         | 0.7                             |          |
| Api 2.5 mg bid     | 0.8                 | 6.9                | 11.7              | 12.6                   | <0.1              | 0                                      | 0                  | 0.1                         | 0.6                             | [29]      |
| Enox 40 mg qd      | 0.7                 | 7.3                |                   |                        |                   |                                        |                    |                              |                                  |          |
| Dabi 150 mg bid    | 4.1                 | 7.9                | 12.0              |                        |                   |                                        | 12.0               |                              |                                  | [30]      |
| Dabi 225 mg bid    | 3.8                 | 9.7                | 13.5              |                        |                   |                                        |                    |                              |                                  |          |
| Enox 40 mg qd      | 2.0                 | 6.4                |                   |                        |                   |                                        |                    |                              |                                  |          |
| Dabi 150 mg qd     | 1.3                 | 8.4                | 6.8               | 0.1                    | 0                 | 0.1                                    | 0                  | 0.1                         | 0.9                             | [31]      |
| Dabi 220 mg qd     | 1.5                 | 8.8                | 5.9               | 0.2                    | 0                 | 0                                      | 0                  | 0.1                         | 0.9                             |          |
| Enox 40 mg qd      | 1.3                 | 9.9                | 5.3               | 0.1                    | 0                 | 0                                      | 0                  | 0.1                         | 0.9                             |          |
| Dabi 150 mg qd     | 1.3                 | 6.2                | 4.7               | 0.3                    | 0.1               | 0                                      | 0.1                | 0.1                         | 0.9                             | [32]      |
| Dabi 220 mg qd     | 2.0                 | 6.1                | 4.2               | 0.2                    | 0.1               | 0                                      | 0.1                | 0.1                         | 0.9                             |          |
| Enox 40 mg qd      | 1.6                 | 6.4                | 3.5               | 0.3                    | 0                 | 0                                      | 0.3                | 0.1                         | 0.9                             |          |
| Dabi 220 mg qd     | 1.4                 | 1.3                | 6.0               | 2.3                    | 9.7               | 0                                      | 0                  | 0.1                         | 0.9                             | [33]      |
| Enox 40 mg qd      | 0.9                 | 0.7                | 5.4               | 2.0                    | 8.3               | 0                                      | 0                  | 0.1                         | 0.9                             |          |
| Dabi 150 mg qd     | 0.6                 | 2.5                |                   | 0                      | 0                 | 0                                      | 0.2                | 0.1                         | 0.9                             | [34]      |
| Dabi 220 mg qd     | 0.6                 | 2.7                |                   | 0                      | 0                 | 0                                      | 0.3                | 0.1                         | 0.9                             |          |
| Enox 40 mg qd      | 1.4                 | 2.4                |                   | 0.1                    | 0                 | 0                                      | 1.4                | 0.1                         | 0.9                             |          |
| Edo 15 mg qd       | 0.5                 | 1.2                | 2.1               |                        |                   |                                        |                    |                              |                                  | [35]      |
| Edo 30 mg qd       | 0.6                 | 1.0                | 1.8               |                        |                   |                                        |                    |                              |                                  |          |
| Dalte 5000 IU qd   | 0                   | 1                  | 0.6               |                        |                   |                                        |                    |                              |                                  |          |
| Edo 30 mg qd       | 1.1                 | 5.1                | 6.2               |                        |                   |                                        |                    |                              |                                  | [36]      |
| Enox 20 mg bid     | 0.3                 | 3.4                | 3.7               |                        |                   |                                        |                    |                              |                                  |          |
| Medicines                  | N     | Age (%) | Inclusion                                      | Blood pressure S/D | BMI | Design   | Duration of follow-up (years) | CHAD score mean | Endpoint                        | Ref     |
|---------------------------|-------|---------|-----------------------------------------------|-------------------|-----|----------|--------------------------------|-----------------|---------------------------------|---------|
| Api 5 mg bid              | 2808  | 70      | 41 AF at risk for stroke, not suitable for Vit K antagonist | 132               | 28  | Open     | 1.1                            | 2.0             | Stroke or SE                    | [44]    |
| Warfarin INR 2-3          | 9081  | 70      | 36 AF at least one risk factor for stroke     | 130               | 130 | Open     | 1.8                            | 2.1             | Stroke or SE                    | [45]    |
| Dab 110 mg bid            | 6015  | 71      | 36 AF, at risk for stroke                     | 131               | 131 | DB       | 2.0                            | 2.1             | Stroke or SE                    | [46]    |
| Warfarin INR 2-3          | 6076  | 71      | 37                                            | 131               | 131 | DB       | 2.2                            | 2.1             | Stroke or SE                    | [46]    |
| Dab 150 mg bid            | 6022  | 72      | 37                                            | 131               | 131 | Open     | 2.1                            | 2.2             | Stroke or SE                    | [46]    |
| Warfarin INR 2-3          | 317   | 59      | 27 AF, ablation                               | 131               | 131 | Open     | 2.0                            | 2.2             | Bleeding                        | [47]    |
| Dab 150 mg bid            | 318   | 59      | 22                                            | 131               | 131 | Open     | 8 weeks                        | 2.0             | MI, stroke, SE                  | [48]    |
| Warfarin/Aspirin          | 981   | 72      | 26                                            | 131               | 131 | Open     | 14 months                      | 3.7             | MI, stroke, SE                  | [48]    |
| Warfarin/Aspirin          | 981   | 72      | 23                                            | AF, PCI           | 131 | Open     | 3.8                            | 3.8             | MI, stroke, SE                  | [48]    |
| Dab 150 mg bid            | 763   | 69      | 22                                            | Combi with ticagrelor or clopidogrel | 131 | 131 | 3.3                            | 3.6             | MI, stroke, SE                  | [48]    |
| Warfarin/Aspirin          | 764   | 69      | 22                                            |                   |     |          |                                |                 |                                 |         |

**Table 5:** Comparative studies in orthopaedic surgery, safety results: bleeding.
### Table 6: Comparative studies in atrial fibrillation, baseline data and design.

| Medicines | Type of AF (%) | Previous stroke (%) | Heart failure (%) | Diabetes | Hypertension | Ref |
|-----------|----------------|---------------------|-------------------|----------|--------------|-----|
| Api 5 mg bid | Persistent | 21 | Paroxysmal | 27 | Permanent | 52 | 14 | 40 | 19 | 86 | [44] |
| Aspirin 81-324 mg qd | | 21 | | 27 | | 52 | 13 | 38 | 20 | 87 | |
| Api 5 mg bid | | 85 | | 15 | | 19 | 36 | 25 | 87 | | [45] |
| Warfarin INR 2-3 | | 84 | | 16 | | 20 | 35 | 25 | 88 | |
| Dab 110 mg bid | | 32 | | 32 | | 35 | 20 | 32 | 23 | 79 | [46] |
| Dab 150 mg bid | | 31 | | 33 | | 36 | 20 | 32 | 23 | 79 | |
| Warfarin INR 2-3 | | 32 | | 34 | | 34 | 20 | 32 | 23 | 79 | |
| Dab 150 mg bid | | 27 | | 67 | | 6 | 3 | 10 | 10 | 52 | [47] |
| Warfarin INR 2-3 | | 26 | | 69 | | 6 | 3 | 11 | 11 | 56 | |
| Dab 110 mg bid | | 18 | | 50 | | 33 | 8 | 11 | 37 | | [48] |
| Warfarin/Aspirin | | 18 | | 49 | | 32 | 10 | 10 | 38 | |
| Dab 150 mg bid | | 17 | | 50 | | 33 | 7 | 10 | 34 | |
| Warfarin/Aspirin | | 20 | | 49 | | 31 | 10 | 10 | 40 | |
| Edo 30 mg qd | | 26 | | 29 | | 29 | 57 | 36 | 94 | [49] |
| Edo 60 mg qd | | 25 | | 28 | | 28 | 58 | 36 | 94 | |
| Warfarin INR 2-3 | | 25 | | 28 | | 28 | 58 | 36 | 94 | |
| Riv 20 mg qd | | 81 | | 18 | | 55 | 63 | 40 | 90 | [50] |
| Warfarin INR 2-3 | | 81 | | 18 | | 55 | 62 | 40 | 91 | |
| Riv 20 mg qd | | 56 | | 17 | | 3 | 3 | 20 | 20 | 65 | [51] |
| Vit K antag INR 2-3 | | 50 | | 23 | | 5 | 4 | 15 | 21 | 69 | |

### Table 7: Comparative studies in atrial fibrillation, baseline data and design.

**Citation:** Robert Janknegt, et al. "Direct Oral Anticoagulants: Drug Selection by Means of the SOJA Method". *Acta Scientific Pharmaceutical Sciences* 4.12 (2020): 145-175.
### Table 8: Comparative studies in atrial fibrillation, baseline data and design.

| Medicines           | Stroke | Stroke ischaemic or unspecified | Stroke Hemorrhagic | Stroke disabling or fatal | SE | Stroke or SE | TIA | Ref       |
|---------------------|--------|---------------------------------|--------------------|---------------------------|----|--------------|-----|-----------|
| Api 5 mg bid        | 1.6/yr | 1.1/yr                          | 0.2/yr             | 1.0/yr                    | 0.1/yr | 1.6/yr       |     | [44]      |
| Aspirin 81-324 mg qd| 3.4/yr | 3.0/yr                          | 0.3/yr             | 2.3/yr                    | 0.4/yr | 3.7/yr       |     | [44]      |
|                     | p<0.001| p<0.001                         | p<0.001            | P<0.001                   |     |              |     |           |
| Api 5 mg bid        | 1.19/yr| 0.97/yr                         | 0.24/yr            | 0.09/yr                   | 1.27/yr | 0.09/yr       |     | [45]      |
| Warfarin INR 2-3    | 1.51/yr| 1.05/yr                         | 0.47/yr            | 0.10/yr                   | 1.60/yr | 0.10/yr       |     |           |
|                     | P=0.01 | P<0.001                         | P<0.001            | P=0.01                    |     |              |     |           |
| Dab 110 mg bid      | 1.44/yr| 1.34/yr                         | 0.12/yr            | 0.94/yr                   | 1.53/yr | 0.94/yr       |     | [46]      |
| Dab 150 mg bid      | 1.01/yr| 0.92/yr                         | 0.10/yr            | 0.66/yr                   | 1.11/yr | 0.66/yr       |     |           |
| Warfarin INR 2-3    | 1.57/yr| 1.20/yr                         | 0.38/yr            | 1.00/yr                   | 1.69/yr | 1.00/yr       |     |           |
|                     | P=0.01 | P<0.001                         | P<0.001            | NI p=0.02 for 150 mg vs warfarin |     |              |     |           |

**Citation:** Robert Janknegt, *et al.* "Direct Oral Anticoagulants: Drug Selection by Means of the SOJA Method*. Acta Scientific Pharmaceutical Sciences 4.12 (2020): 145-175.
| Medicines              | MI   | CV hospitalization | Death CV | Death total | Composite Stroke, SE, death | Composite Stroke, SE, MI, death | Ref |
|-----------------------|------|--------------------|----------|-------------|-----------------------------|---------------------------------|-----|
| Api 5 mg bid          | 0.8  | 12.6               | 2.7      | 3.5         | 4.6                         |                                 | [44]|
| Aspirin 81-324 mg qd  | 0.9  | 15.9               | 3.1      | 4.4         | 7.2                         |                                 |     |
|                       |      |                    |          | P<0.001     |                             |                                 |     |
| Api 5 mg bid          | 0.53/yr | P<0.001          | 3.52/yr  | 4.49/yr     | 4.85/yr                     |                                 | [45]|
| Warfarin INR 2-3      | 0.61/yr |                 | 3.94/yr  | 5.05/yr     | 5.49/yr                     |                                 |     |
|                       |      |                    | P<0.05   | P=0.02      | P=0.01                      |                                 |     |
| Dab 110 mg bid        | 0.72/yr |                | 2.43/yr  | 3.75/yr     |                             |                                 | [46]|
| Dab 150 mg bid        | 0.74/yr |                | 2.28/yr  | 3.64/yr     |                             |                                 |     |
| Warfarin INR 2-3      | 0.53/yr |                | 2.69/yr  | 4.31/yr     |                             |                                 |     |
| Dab 150 mg bid        | 1.7%  |                    |          |             |                             |                                 |     |
| Warfarin/Aspirin      | 1.3%  |                    |          |             |                             |                                 |     |
| Dab 150 mg bid        | 1.2%  |                    |          |             |                             |                                 |     |
| Warfarin/Aspirin      | 1.0%  |                    |          |             |                             |                                 |     |
| Edo 30 mg qd          | 1.91/yr | 1.77/yr            | 0.16/yr  | 0.80/yr     | 1.61/yr                     |                                 | [49]|
| Edo 60 mg qd          | 1.49/yr | 1.25/yr            | 0.26/yr  | 0.69/yr     | 1.18/yr                     |                                 |     |
| Warfarin INR 2-3      | 1.69/yr | 1.25/yr            | 0.47/yr  | 0.71/yr     | 1.50/yr                     |                                 |     |
|                       |      | P<0.001            |          |             |                             |                                 |     |
| Riv 20 mg qd          | 2.1/yr | 2.1/yr             | 0.41     | 0.81/yr     | 1.7/yr                      |                                 | [50]|
| Warfarin INR 2-3      | 2.4/yr | 2.3/yr             | 0.71     | 1.09/yr     | 2.2/yr                      |                                 |     |
|                       |      | P<0.01             |          | P=0.024     | NI: p<0.001                 |                                 |     |
| Riv 20 mg qd          | 0.20  |                    | 0.20     | 0           | 0.51                        |                                 | [51]|
| Vit K antag INR 2-3   | 0.41  | 0.41               | 0        | 0.20        | 1.02                        |                                 |     |

Table 9: Comparative studies in atrial fibrillation, results.
| Medicines                  | Withdrawal AE (%) | AE (%) | AE drug related (%) | AE-S (%) | ALT>3ALN | ALT>3ALN And bili >2ALN | Reference |
|---------------------------|-------------------|--------|---------------------|----------|----------|-------------------------|-----------|
| Api 5 mg bid              |                   |        |                     |          |          |                         | [44]      |
| Aspirin 81-324 mg qd      |                   | 22     | 1.4                 | 0.2      | [45]      |
| Warfarin INR 2-3          |                   | 27     | 1.6                 | 0.4      |          |                         |           |
| Warfarin INR 2-3          |                   |        |                     |          |          |                         |           |
| Apixaban 5 mg bid         |                   | 81     | 35                  | 1.1      | 0.3      |                         | [45]      |
| Warfarin INR 2-3          |                   | 83     | 37                  | 1.0      | 0.4      |                         |           |
| Dab 110 mg bid            |                   | 2.7    | 2.1                 | 0.2      | [46]      |
| Warfarin INR 2-3          |                   | 2.7    | 1.9                 | 0.2      |          |                         |           |
| Dab 150 mg bid            |                   | 1.7    | 2.2                 | 0.3      | [47]      |
| Warfarin INR 2-3          |                   | 2      |                     |          |          |                         |           |
| Dab 110 mg bid            |                   | 6      | 43                  | 2.1      | 0.2      |                         | [48]      |
| Warfarin/Aspirin          |                   | 6      | 42                  |          |          |                         |           |
| Dab 150 mg bid            |                   | 6      | 40                  |          |          |                         |           |
| Warfarin/Aspirin          |                   | 6      | 42                  |          |          |                         |           |
| Edoxaban 30 mg qd         |                   | 16     | 10                  | 18       | 2.1      | 0.2                     | [49]      |
| Edoxaban 60 mg qd         |                   | 17     | 11                  | 17       | 2.2      | 0.2                     | [49]      |
| Warfarin INR 2-3          |                   | 17     | 12                  | 18       | 2.1      | 0.1                     |           |
| Riv 20 mg qd              |                   | 81     |                      | 0.5      | [50]      |
| Warfarin INR 2-3          |                   | 82     |                      | 0.5      | [50]      |
| Vit K antag INR 2-3       |                   |        |                     |          |          |                         | [51]      |

**Table 10:** Comparative studies in atrial fibrillation, results.

**Table 11:** Comparative studies in atrial fibrillation, safety results.

**Citation:** Robert Janknegt, et al. "Direct Oral Anticoagulants: Drug Selection by Means of the SOJA Method". Acta Scientific Pharmaceutical Sciences 4.12 (2020): 145-175.
### Table 12: Comparative studies in atrial fibrillation, safety results, bleeding.

| Medicines                        | Major bleeding | Intracranial bleeding | Fatal bleeding | Clinically relevant non-major | Major or Clinically relevant non-major | Minor bleeding | Any bleeding | Bleeding in critical organ | Ref |
|----------------------------------|----------------|-----------------------|----------------|------------------------------|----------------------------------------|----------------|--------------|----------------------------|-----|
| Api 5 mg bid                     | 1.4            | 0.4                   | 0.1            | 3.1                          |                                        | 6.3            |              |                            | [44]|
| Aspirin 81-324 mg qd             | 1.2            | 0.4                   | 0.2            | 2.7                          |                                        | 5.0            |              |                            |     |
| Api 5 mg bid                     | 2.13/yr        | 0.33/yr               | 0.3            | 4.07/yr                      |                                        | 18.1/yr        |              |                            | [45]|
| Warfarin INR 2-3                 | 3.09/yr        | 0.80/yr               | 0.8            | 6.01/yr                      |                                        | 25.8/yr        |              |                            |     |
| ISTH                             |                |                       |                |                              |                                        |                |              |                            |     |
|                                  |                |                       |                |                              |                                        |                |              |                            |     |
| Dab 110 mg bid                   | 2.71/yr        | 0.23/yr               | 0.23           | 13.2/yr                      |                                        | 19%            |              |                            | [46]|
| Dab 150 mg bid                   | 3.11/yr        | 0.30/yr               | 0.30           | 14.8/yr                      |                                        | 17%            |              |                            |     |
| Warfarin INR 2-3                 | 3.36/yr        | 0.74/yr               | 0.74           | 16.4/yr                      |                                        | 17%            |              |                            |     |
|                                  |                |                       |                |                              |                                        |                |              |                            |     |
| Dab 150 mg bid                   | 1.6%           | 6.9%                  | 6.9%           | 19%                          |                                        | 19%            |              |                            | [47]|
| Warfarin INR 2-3                 |                |                       |                |                              |                                        | 17%            |              |                            |     |
|                                  |                |                       |                |                              |                                        |                |              |                            |     |
| Dab 110 mg bid                   | 5.0%           | 0.3%                  | 0.3%           | 19%                          |                                        | 17%            |              |                            | [48]|
| Warfarin/Aspirin                 | 9.2%           | 1.0%                  | 1.0%           | 19%                          |                                        | 17%            |              |                            |     |
| Dab 150 mg bid                   | 5.6%           | 0.1%                  | 0.1%           | 19%                          |                                        | 17%            |              |                            |     |
| Warfarin/Aspirin                 | 8.4%           | 1.0%                  | 1.0%           | 19%                          |                                        | 17%            |              |                            |     |
| Edo 30 mg qd                     | 1.61/yr        | 0.26/yr               | 0.26           | 6.60/yr                      |                                        | 3.52/yr        |              |                            | [49]|
| Edo 60 mg qd                     | 2.75/yr        | 0.39/yr               | 0.39           | 8.67/yr                      |                                        | 4.12/yr        |              |                            |     |
| Warfarin INR 2-3                 | 3.43/yr        | 0.85/yr               | 0.85           | 10.2/yr                      |                                        | 4.89/yr        |              |                            |     |
|                                  |                |                       |                |                              |                                        |                |              |                            |     |
| Riv 20 mg qd                     | 3.6/yr         | 0.5/yr                | 0.5            | 11.8/yr                      |                                        | 0.8            |              |                            | [50]|
| Warfarin INR 2-3                 | 3.4/yr         | 0.7/yr                | 0.7            | 11.4/yr                      |                                        | 1.2            |              |                            |     |
|                                  |                |                       |                |                              |                                        |                |              |                            |     |
| Riv 20 mg qd                     | 0.61           | 0.20                  | 0.20           | 0.20                         |                                        | 0.60           |              |                            | [51]|
| Vit K antag INR 2-3              | 0.80           | 0.20                  | 0.20           | 0.20                         |                                        | 0.60           |              |                            |     |

**Citation:** Robert Janknegt, *et al.* "Direct Oral Anticoagulants: Drug Selection by Means of the SOJA Method". *Acta Scientific Pharmaceutical Sciences* 4.12 (2020): 145-175.
| Medicines                     | N  | Age | Female (%) | Body Weight (kg) | Inclusion                  | DVT (%) | PE (%) | DVT + PE (%) | Design | Duration of follow-up (months) | Ref |
|------------------------------|----|-----|------------|------------------|----------------------------|---------|--------|--------------|--------|--------------------------------|-----|
| Api 10/5 mg bid               | 2691 | 57  | 42         | 85               | Acute DVT                  | 65      | 25     | 9            | DB, DD | 6                              | [52]|
| Enox 1mg/kg/Warfarin INR 2-3 | 2704 | 57  | 41         | 85               |                            | 66      | 25     | 8            | DB, DD |                                |     |
| Api 2.5 mg bid                | 840  | 57  | 42         | 86               | Acute DVT previous 6-12 months treatment | 65      | 35     | 35           | DB, DD | 12                             | [53]|
| Api 5 mg bid                  | 813  | 57  | 42         | 86               |                            | 65      | 35     | 35           | DB, DD |                                |     |
| Placebo                       | 829  | 57  | 43         | 85               |                            | 67      | 34     |              | DB, DD |                                |     |
| Api 2.5 mg bid 30 days        | 3255 | 67  | 50         |                   | Medically ill + risk factor for VTE | 4.3     | 3.8    |              | DB, DD | 1                              | [54]|
| Enox 40 qd 6-14 days          | 3273 | 67  | 52         |                   |                            |         |        |              |        |                                |     |
| Dabi 150 mg bid               | 1273 | 55  | 42         | 86               | Acute DVT after parenteral treatment for 9 days | 69      | 21     | 10           | DB, DD | 6                              | [55]|
| Warfarin INR 2-3              | 1266 | 54  | 41         | 84               |                            | 69      | 21     | 10           | DB, DD |                                |     |
| Dabi 150 mg bid               | 1280 | 56  | 39         | 80               | Acute DVT after parenteral treatment for 5-11 days | 69      | 23     | 8            | DB, DD | 6                              | [56]|
| Warfarin INR 2-3              | 1288 | 57  | 40         | 81               |                            | 68      | 23     | 9            | DB, DD |                                |     |
| Dabi 150 mg bid               | 1430 | 55  | 39         | 86               | Acute VTE after treatment for > 3 months | 66      | 23     | 12           | DB, DD | 6-36                           | [57]|
| Warfarin INR 2-3              | 1426 | 54  | 39         | 86               |                            | 65      | 24     | 12           | DB, DD |                                |     |
| Dabi 150 mg bid               | 681  | 56  | 44         | 84               | Acute VTE after treatment for > 6 months | 63      | 27     | 7            | DB, DD | 12                             | [57]|
| Placebo                       | 662  | 56  | 45         | 84               |                            | 67      | 27     | 5            |        |                                |     |
| Edox 60 mg qd                 | 4118 | 56  | 43         |                   | Acute DVT after parenteral treatment for > 5 days | 66      | 34     | 33           | DB, DD | 3-12                           | [58]|
| Warfarin INR 2-3              | 4122 | 56  | 43         |                   |                            | 65      | 33     |              |        |                                |     |
| Edox 60 mg qd                 | 522  | 64  | 47         |                   | DVT in cancer patients     | 37      |        | 63           | Open   | 6-12                           | [59]|
| Dalteparin 150 IU/kg          | 524  | 64  | 45         |                   |                            | 37      |        | 63           | Open   |                                |     |
| Riv 15 mg bid, 20 mg qd       | 1731 | 56  | 43         |                   | Acute DVT                  | 99      | 1      |              | Open   | 3-12                           | [60]|
| Enox 1mg/kg/Warfarin INR 2-3  | 1718 | 56  | 44         |                   |                            | 99      | 1      |              |        |                                |     |
| Riv 20 mg qd                  | 602  | 58  | 41         |                   | Acute DVT after treatment for 6-12 months | 64      | 36     | 40           | DB, DD | 6-12                           | [60]|
| Placebo                       | 594  | 58  | 43         |                   |                            | 60      |        | 40           |        |                                |     |

**Citation:** Robert Janknegt, et al. "Direct Oral Anticoagulants: Drug Selection by Means of the SOJA Method". *Acta Scientific Pharmaceutical Sciences* 4.12 (2020): 145-175.
Riv 15 mg bid, 20 mg qd
Enox 1mg/kg/ Warfarin INR 2-3

| Medicines          | CCR >50 ml/min % | Previous VTE (%) | Unprovoked VTE (%) | Active cancer (%) | Coronary artery disease (%) | Diabetes (%) | Heart failure (%) | Immobilised (%) | Primary endpoint | Ref |
|--------------------|------------------|------------------|-------------------|------------------|--------------------------|--------------|------------------|-----------------|-----------------|-----|
| Api 10/5 mg bid    | 84               | 17               | 90                | 2.5              |                         |              |                  |                 | VTE-RS or VTE-D | [52]|
| Enox 1mg/kg/ Warfarin INR 2-3 | 85 | 15 | 90 | 2.8 | | | | | VTE-RS or VTE-D | [52]|
| Api 2.5 mg bid     | 91               | 12               | 93                | 1.8              |                         |              |                  |                 | VTE-RS or death | [53]|
| Api 5 mg bid       | 92               | 15               | 91                | 1.1              |                         |              |                  |                 | VTE-RS or death | [53]|
| Placebo            | 91               | 12               | 91                | 2.2              |                         |              |                  |                 | VTE-RS or death | [53]|
| Api 2.5 mg bid 30 d| 43               | 3.5              |                   |                 |                         |              |                  |                 | VTE-D or PE or DVT-S or DVT-P | [54]|
| Enox 40 qd 6-14 d  | 3.8              | 3.0              |                   |                 |                         |              |                  |                 | VTE-D or PE or DVT-S or DVT-P | [54]|
| Dabi 150 mg bid    | 26               | 5.0              |                   |                 |                         |              |                  |                 | VTE-RS or VTE-D | [55]|
| Warfarin INR 2-3   | 25               | 4.5              |                   |                 |                         |              |                  |                 | VTE-RS or VTE-D | [55]|
| Dabi 150 mg bid    | 19               | 3.9              |                   |                 |                         |              |                  |                 | VTE-RS or VTE-D | [56]|
| Warfarin INR 2-3   | 16               | 3.9              |                   |                 |                         |              |                  |                 | VTE-RS or VTE-D | [56]|
| Dabi 150 mg bid    | 4.2              | 8.4              | 10.5              | 6.6              |                         |              |                  |                 | VTE-RS or VTE-D | [57]|
| Warfarin INR 2-3   | 4.1              | 6.1              | 7.6               | 7.3              |                         |              |                  |                 | VTE-RS or VTE-D | [57]|
| Dabi 150 mg bid    | 6.3              | 8.4              |                   | 7.8              |                         |              |                  |                 | VTE-RS or VTE-D | [57]|
| Placebo            | 5.7              | 7.6              |                   | 5.4              |                         |              |                  |                 | VTE-RS or VTE-D | [57]|
| Edox 60 mg qd      | 19               | 66               | 9.2               |                 |                         |              |                  |                 | VTE-RS or VTE-D | [58]|
| Warfarin INR 2-3   | 18               | 65               | 9.5               |                 |                         |              |                  |                 | VTE-RS or VTE-D | [58]|

Table 13: Comparative studies in deep venous thrombosis, baseline data and design.

Citation: Robert Janknegt, et al. “Direct Oral Anticoaguulants: Drug Selection by Means of the SOJA Method”. *Acta Scientific Pharmaceutical Sciences* 4.12 (2020): 145-175.
### Table 14: Comparative studies in deep venous thrombosis, baseline data and design.

**UA:** Instable Angina

**VTE-RS:** VTE recurrent symptomatic thromboembolism

**VTE-D:** VTE related death.

| Medicines                | VTE-RS or VTE-D (%) | VTE-RS or death (%) | VTE-D or PE or DVT-S or DVT-P | CV-D, MI, stroke | PE-NF (%) | PE-F (%) | VTE-S (%) | DVT-P (%) | Death (%) | VTE-D (%) | Ref  |
|--------------------------|---------------------|---------------------|-------------------------------|------------------|-----------|----------|-----------|-----------|-----------|-----------|------|
| Api 10/5 mg bid          | 2.3                 |                     |                               |                  |           |          |           |           |           |           | [52] |
| Enox 1mg/kg/Warfarin INR 2-3 | 2.7                 |                     |                               |                  |           |          |           |           |           |           | [52] |
| Api 2.5 mg bid           | 1.7                 | 3.8                 |                               | 0.5              | 1.0       | <0.1     |           |           | 1.5       |           | [53] |
| Api 5 mg bid             | 1.7                 | 4.2                 |                               | 0.6              | 0.5       | 0        |           |           | 0         |           | [53] |
| Placebo                  | 8.8                 | 11.6                |                               | 1.3              | 1.8       | 0        |           |           | 0         |           | [53] |

**Citation:** Robert Janknegt, *et al.* "Direct Oral Anticoagulants: Drug Selection by Means of the SOJA Method". *Acta Scientific Pharmaceutical Sciences* 4.12 (2020): 145-175.
| Drug Combination | 2.71 | 0.22 | 0.15 | 2.40 | 4.1 | 0.06 | [54] |
|------------------|------|------|------|------|-----|------|------|
| Api 2.5 mg bid 30 d |      |      |      |      |     |      |      |
| Enox 40 qd 6-14 d | 2.4  | 1.0  | 1.3  | 1.6  | 0.1 | 0.2  | [55] |
| Dabi 150 mg bid | 2.1  | 0.6  | 1.4  | 1.7  | 0.2 | [56] |
| Warfarin INR 2-3 | 2.3  | 0.5  | 2.0  | 2.0  | 0.2 | [57] |
| Dabi 150 mg bid | 2.3  | 1.0  | 1.3  | 1.9  | 0   | [58] |
| Warfarin INR 2-3 | 1.8  | 0.7  | 1.2  | 1.2  | 0.1 | [59] |
| Dabi 150 mg bid | 1.3  | 0.4  | 1.3  | 1.3  | 0.1 | [60] |
| Placebo | 0.4  | 0.1  | 0.3  |      |     | [61] |
|              | 5.6  | 2.1  | 3.3  |      |     |       |
|              | P<0.01 |      |      |      |     |       |
| Edox 60 mg qd | 3.2  | 1.2  | 1.4  | 0.5  | 0.5 | [62] |
| Warfarin INR 2-3 | 3.5  | 1.4  | 1.5  | 0.5  | 0.5 | [63] |
| Dalteparin 150 IU/kg | 7.9  | 5.2  | 40  | 0.6  |     | [64] |
|                  | 11.3 | 5.3  | 37  | 0.6  |     |       |
| Riv 15 mg bid, 20 mg qd | 1.2  | 1.1  | 2.1  | 2.2  | 2.9 | [65] |
| Enox 1mg/kg/ Warfarin INR 2-3 | 1.2  | 1.1  | 3.0  |      |     |       |
| Riv 20 mg qd | 0.3  | 0.2  | 1.3  | 0.2  | 0.3 | [66] |
| Placebo | 2.8  | 0.2  | 7.1  |      |     |       |
| P<0.001 |     |      |     |      |     |       |
| Riv 15 mg bid, 20 mg qd | 0.9  | 0.7  | 2.1  | 2.4  | 2.1 | [67] |
| Enox 1mg/kg/ Warfarin INR 2-3 | 0.9  | 0.7  | 1.8  |      |     |       |
| Riv 10 mg qd 35 days | 1.8  | 0.3  | 4.4  | 3.5  | 5.1 | [68] |
| Enox 40 mg qd 10 days | 1.6  | 0.5  | 5.7  | 4.4  | 4.8 | [69] |
| Riv 10 mg | 1.6  | 0.4  | 0.4  | 0.2  | 0.7 | [70] |
| Riv 20 mg | 1.5  | 0.5  | 0.5  |      |     |       |
| Aspirin 100 mg | 4.4  | 5.0  | 1.7  | 0.6  |     | [71] |
|                  | P<0.001 |      |      |      |     |       |

**Table 15**: Comparative studies in deep venous thrombosis, results.

**Citation**: Robert Janknegt, et al. "Direct Oral Anticoagulants: Drug Selection by Means of the SOJA Method". *Acta Scientific Pharmaceutical Sciences* 4.12 (2020): 145-175.
### Medicines

| Medicines                  | Withdrawal AE (%) | AE (%) | AE drug related (%) | AE-S (%) | ALT>3ALN And bili >2ALN (%) | MI (%) | Stroke (%) | Ref |
|---------------------------|-------------------|--------|---------------------|----------|----------------------------|--------|------------|-----|
| Api 10/5 mg bid           | 6.1               | 67     | 16                  | 1.9      | 0.2                        | 0.5    | 0.3        | [52]|
| Enox 1 mg/kg/ Warfarin INR 2-3 | 7.4               | 72     | 15                  | 5.6      | 0.1                        | 0.3    | 0.1        | [53]|
| Api 2.5 mg bid            | 8                 | 71     | 13                  | 0        | 0.2                        | 0.1    | 0.1        | [54]|
| Api 5 mg bid              | 7                 | 67     | 13                  | 0.1      | 0.4                        | 0.4    | 0.1        | [55]|
| Placebo                   | 16                | 73     | 19                  | 0.4      | 0.5                        | 0.6    | 0.3        | [56]|
| Api 2.5 mg bid 30 d       |                   |        |                     |          |                            |        |            | [57]|
| Enox 40 qd 6-14 d         |                   |        |                     |          |                            |        |            | [58]|
| Dabi 150 mg bid           | 7.9               | 63     | 12                  | 2.9      | 0.2                        | 0.2    | 0.3        | [59]|
| Warfarin INR 2-3          | 9.0               | 65     | 13                  | 3.4      | 0.2                        | 0.3    | 0.1        | [60]|
| Dabi 150 mg bid           | 7.8               | 67     | 12                  | 0.1      | 0.3                        |        |            | [61]|
| Warfarin INR 2-3          | 7.8               | 71     | 12                  | 0.2      | 0.2                        |        |            | [62]|
| Dabi 150 mg bid           | 10.1              | 72     | 15.9                | 1.7      | 0.1                        | 0.9    | 0.1        | [63]|
| Warfarin INR 2-3          | 8.8               | 71     | 15.7                | 1.8      | 0.1                        | 0.2    |            | [64]|
|                            |                   |        |                     |          |                            |        |            | [65]|
| Dabi 150 mg bid           | 7.3               | 51     | 6.9                 | 0.6      | 0.1                        | 0.3    | 0.3        | [66]|
| Placebo                   | 12.3              | 50     | 9.1                 | 0.6      | 0.2                        | 0.2    |            | [67]|
| Edox 60 mg qd             | 2.9               | 69     | 12.2                | 2.1      | 0.2                        | 0.5    |            | [68]|
| Warfarin INR 2-3          | 2.5               | 71     | 13.2                | 2.3      | <0.1                       | 0.3    |            | [69]|
| Riv 15 mg bid, 20 mg qd   | 4.9               | 63     | 12.0                | 1.5      | 0.1                        | 0.3    | 0.1        | [70]|
| Enox 1 mg/kg/ Warfarin INR 2-3 | 4.7               | 63     | 13.6                | 3.8      | 0.2                        | 0.2    |            | [71]|
| Riv 20 mg qd              | 2.0               |        |                     |          |                            |        |            | [72]|
| Placebo                   | 0.5               |        |                     |          |                            |        |            | [73]|
| Riv 15 mg bid, 20 mg qd   | 5.1               | 81     | 20                  | 0.6      | 0.6                        | 0.1    |            | [74]|
| Enox 1 mg/kg/ Warfarin INR 2-3 | 4.1               | 79     | 20                  | 0.9      | 0.9                        |        |            | [75]|
| Riv 10 mg qd 35 days      |                   |        |                     |          |                            |        |            | [76]|
| Enox 40 mg qd 10 days     |                   |        |                     |          |                            |        |            | [77]|
| Riv 10 mg                 |                   |        |                     |          |                            |        |            | [78]|
| Riv 20 mg                 |                   |        |                     |          |                            |        |            | [79]|
| Aspirin 100 mg            |                   |        |                     |          |                            |        |            | [80]|

**Table 16:** Comparative studies in deep venous thrombosis, safety results.

**Citation:** Robert Janknegt, et al. “Direct Oral Anticoagulants: Drug Selection by Means of the SOJA Method”. *Acta Scientific Pharmaceutical Sciences* 4.12 (2020): 145-175.
### Medicines

| Medicines | Major bleeding | Intra-cranial bleeding | Fatal bleeding | Clinically relevant non-major | Major or Clinically relevant non-major | Minor bleeding | Any bleeding | Bleeding in critical organ | Ref |
|-----------|----------------|------------------------|----------------|-------------------------------|----------------------------------------|---------------|-------------|--------------------------|-----|
| Api 10/5 mg bid | 0.6 | 0.1 | <0.1 | 3.8 | 4.3 | | | 16 | [52] |
| Enox 1mg/kg/ Warfarin INR 2-3 | 1.8 | 0.2 | 0.1 | 8.0 | 9.7 | | | 26 | P<0.001 |
| Api 2.5 mg bid | 0.2 | 0 | 0 | 3.0 | 3.2 | | | 0.2 | [53] |
| Api 5 mg bid | 0.1 | 0 | 0 | 4.2 | 4.3 | | | 0 | P<0.001 |
| Placebo | 0.5 | 0 | 0 | 2.3 | 2.7 | | | 0.2 | [54] |
| Api 2.5 mg bid 30 d | 0.47 | 0 | 0 | 2.2 | 2.7 | | | 7.7 | P<0.001 |
| Enox 40 qd 6-14 d | 0.19 | 0.1 | 0.1 | 1.9 | 2.1 | | | 6.8 | P<0.001 |
| Dabi 150 mg bid | 1.6 | 0 | 0.1 | 4.0 | 5.6 | | | 16.1 | P<0.001 |
| Warfarin INR 2-3 | 1.9 | 0.3 | 0.1 | 6.9 | 8.8 | | | 21.9 | P<0.001 |
| Dabi 150 mg bid | 1.2 | 0.2 | 0 | 5.0 | | | | 0.5 | P<0.001 |
| Warfarin INR 2-3 | 1.7 | 0.2 | 0.1 | 7.9 | | | | 0.3 | P<0.001 |
| Dabi 150 mg bid | 0.9 | 0 | 0 | 5.6 | 19.4 | | | 0.5 | P<0.001 |
| Warfarin INR 2-3 | 1.8 | 0.1 | | 10.2 | 26.2 | | | 0.9 | P<0.001 |
| Dabi 150 mg bid | 0.3 | 0 | | 5.3 | 10.5 | | | 0.5 | P<0.001 |
| Placebo | 0 | | | | | | | | |
| Edox 60 mg qd | 1.4 | 0.1 | <0.1 | 7.2 | 21.7 | | | 0.3 | [C58] |
| Warfarin INR 2-3 | 1.6 | 0.4 | 0.2 | 8.9 | 25.6 | | | 0.6 | P<0.001 |
| Edox 60 mg qd | 6.9 | 15 | 19 | | | | | | |
| Dalteparin 150 IU/kg | 4.0 | 11 | 14 | | | | | | |
| Riv 15 mg bid, 20 mg qd | 0.8 | 0.1 | | 7.3 | | | | 0.2 | [60] |
| Enox 1mg/kg/ Warfarin INR 2-3 | 1.2 | 0.3 | | 7.0 | | | | 0.2 | P<0.001 |
| Riv 20 mg qd | 0.7 | 0 | 0 | 5.4 | | | | 0 | P<0.001 |
| Placebo | 0 | 0 | 1.2 | | | | | | |
| Riv 15 mg bid, 20 mg qd | 1.1 | 0.1 | | 9.5 | | | | 0.3 | P<0.001 |
| Enox 1mg/kg/ Warfarin INR 2-3 | 2.2 | 0.1 | 0.1 | 9.8 | | | | 1.1 | P<0.001 |

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**Citation:** Robert Janknegt, et al. "Direct Oral Anticoagulants: Drug Selection by Means of the SOJA Method". *Acta Scientific Pharmaceutical Sciences* 4.12 (2020): 145-175.
### Table 17: Comparative studies in deep venous thrombosis, safety results, bleeding.

| Medicines       | N   | Age | Female (%) | Design | Diabetes (%) | Previous MI (%) | CV disease (%) | LVHF (%) | Peripheral vascular disease (%) | Duration of follow-up | Ref |
|-----------------|-----|-----|------------|--------|--------------|-----------------|---------------|----------|----------------------------------|----------------------|-----|
| Api 5 mg bid    | 3705| 67  | 33         | DB     | 49           | 25              | 10            | 28       | 18                               | 1.25 years           | [64]|
| Placebo         | 3687| 67  | 32         | DB     | 47           | 28              | 10            | 29       | 18                               |                      |     |
| Riva 2.5 mg bid | 5174| 62  | 35         | DB     | 32           | 26              | 10            | 29       | 18                               | 13-31 months         | [65]|
| Riva 5 mg bid   | 5176| 62  | 36         | DB     | 32           | 27              | 10            | 29       | 18                               |                      |     |
| Placebo         | 5176| 62  | 35         | DB     | 32           | 27              | 10            | 29       | 18                               |                      |     |
| Riva 2.5 mg bid | 1519| 62  | 25         | DB     | 29           | 21              | 10            | 29       | 18                               | 390 days             | [66]|
| Aspirin 100 mg qd | 1518| 63  | 25         | DB     | 30           | 23              | 10            | 29       | 18                               |                      |     |

### Table 18: Comparative studies in acute coronary syndromes, baseline data and design.

| Medicines       | Type of ACS | Time from event to randomisation (days) | Medication | Primary Endpoint | Ref |
|-----------------|-------------|----------------------------------------|------------|------------------|-----|
| Api 5 mg bid    | STEMI       | 6.0                                    | ACE/A2A    | CV-D, MI, I-S    | [64]|
| Placebo or      | N-STEMI     | 6.0                                    | Beta blocker |                  |     |
| Riva 2.5 mg bid | UA          | 24                                     | Statin     | CV-D, MI, Stroke | [65]|
| Riva 5 mg bid   | ACE/ A2A    | 6.0                                    | Parenteral Antithrombotic agents |       |
| Placebo         | Beta blocker| 6.0                                    | PPI        | CV-D, MI, I-S    | [64]|
| Riva 2.5 mg bid | Statin      | 6.0                                    | Parenteral |                  |     |
| Aspirin 100 mg qd | PPI        | 6.0                                    | Antithrombotic agents | TIMI | [66]|

### Table 19: Comparative studies in acute coronary syndromes, baseline data and design.

**Citation:** Robert Janknegt, et al. "Direct Oral Anticoagulants: Drug Selection by Means of the SOJA Method". *Acta Scientific Pharmaceutical Sciences* 4.12 (2020): 145-175.
| Medicines                                      | Composite (%) | Death (%) | CV-D (%) | MI (%) | I-S (%) | Stent thrombosis (%) | Ref |
|-----------------------------------------------|---------------|-----------|----------|--------|---------|----------------------|-----|
| Api 5 mg bid or Placebo or UA                 | CV-D, MI, I-S | CV-D, MI, stroke |          |        |         |                      |     |
|                                               | 7.5           | 9.5       | 7.9      | 10.0   | 4.2     | 4.8                  | 0.6 |
|                                               | 4.2           | 3.9       | 3.9      | 4.8    | 9.2     | 1.6                  | 1.3 |
| Riva 2.5 mg bid                               | CV-D, MI, I-S | CV-D, MI, stroke |          |        |         |                      |     |
|                                               | 9.1           | 8.8       | 10.7     | 4.2    | 4.5     | 4.1                  | 2.2 |
|                                               | 2.9           | 4.4       | 2.9      | 7.5    | 4.0     | 2.3                  | 2.3 |
|                                               | P=0.02 (2.5 mg vs placebo) | P=0.002 (2.5 mg vs placebo) | P=0.002 (2.5 mg vs placebo) |       |         |                      |     |
| Riva 2.5 mg bid                               | CV-D, MI, I-S | CV-D, MI, stroke |          |        |         |                      |     |
|                                               | 5             | 5         | 5        | 5      | 0.6     | 3.6                  | 0.6 |
|                                               | 5             | 5         | (including stent thrombosis) |        | 0.6     | 3.3                  | 0.8 |

**Table 20:** Comparative studies in acute coronary syndromes, results.

| Medicines                                      | Major bleeding (%) | Major or clinically relevant non-major bleeding (%) | Severe bleeding (%) | Severe or moderate bleeding (%) | Fatal bleeding (%) | Intracranial bleeding (%) | Any bleeding (%) | Ref |
|-----------------------------------------------|--------------------|-----------------------------------------------------|---------------------|--------------------------------|-------------------|--------------------------|-----------------|-----|
| Api 5 mg bid or Placebo or                     | 1.3                | 2.7                                                 | 3.2                 | 1.8                             | 0.1               | 0.6                      | 18.5            | [64]|
|                                               | P<0.001            | P<0.001                                             | P<0.001             | P<0.001                         | P=0.03            | P<0.001                  |                 |     |
| Riva 2.5 mg bid                               | 1.8                | 1.1                                                 | 1.2                 | 0.6                             | 0.4               | 0.7                      | 0.4             | [65]|
|                                               | P<0.001            | P<0.001                                             | P<0.001             | P<0.001                         | P=0.009           |                         |                 |     |
| Riva 5 mg bid                                 | 2.4                | 0.6                                                 | 0.2                 | 0.2                             | 0.1               | 0.1                      | 0.7             |     |
|                                               | P=0.04 for 2.5 mg vs 5 mg Riva |                         |                     | P=0.009                         |                   |                         |                 |     |
| Placebo                                       | 0.6                | 2.0                                                 | 0.2                 | 0.1                             | 0.1               | 0.1                      | 0.0             |     |
|                                               | 0.5                | 2.0                                                 | 0.2                 | 0.1                             | 0.1               | 0.1                      | 0.0             | [66]|

**Table 21:** Comparative studies in acute coronary syndromes, safety results, bleeding.
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Conflicts of Interest

None reported.

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