

# Clinical trials of antithrombotics for DVT prophylaxis in orthopedic surgery

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## 1 antivitamins K

| Trial   | Treatments  | Patients    | Trials design and methods |
|---|---|-------------|---------------------------|
| <b>vs no treatment</b>  |   |             |                           |
| <b>Borsgtrom , 1965</b><br>n=29/29<br>follow-up: 65279;34 weeks | 65279;Dicoumarol<br>versus<br>65279;No treatment                          | HFS         | Open                      |
| <b>Phenindione vs no treatment</b>                              |   |             |                           |
| <b>Eskeland , 1966</b><br>n=100/100<br>follow-up: 3 months      | Phenindione<br>versus<br>No treatment                                     | HFS         | Open                      |
| <b>Hamilton , 1970</b><br>n=38/38<br>follow-up: 310 months      | Phenindione<br>versus<br>No treatment                                     | HFS         | Open                      |
| <b>Warfarin vs no treatment</b>                                 |   |             |                           |
| <b>Pinto , 1970</b><br>n=25/25<br>follow-up: >3 weeks           | Warfarin<br>versus<br>No treatment  | Hip surgery | Open                      |
| <b>Hume , 1973</b><br>n=17/19<br>follow-up: Discharge           | Warfarin<br>versus<br>No treatment  | THR         | Open                      |
| <b>Morris , 1976</b><br>n=80/80<br>follow-up: 3 months          | Warfarin<br>versus<br>No treatment  | HFS         | Open                      |
| <b>Powers , 1989</b><br>n=65/63<br>follow-up: 3 months          | Warfarin<br>versus<br>No treatment  | HFS         | Open                      |
| <b>Warfarin vs placebo</b>                                      |   |             |                           |
| <b>Myrhe , 1969</b><br>n=50/55<br>follow-up: 3 weeks            | Wwarfarin<br>versus<br>Placebo  | HFS         | double blind              |
| <b>Warfarin vs Ardeparin</b>                                    |   |             |                           |
| <b>RD Heparin , 1994</b><br>n=403/770<br>follow-up: 3 months    | Warfarin<br>versus<br>Ardeparin 50 anti-Xa IU /kg or 90 anti-Xa IU /kg x1 | THR or TKR  | Open                      |
| <b>Heit , 1997</b><br>n=279/554<br>follow-up: Days 514          | Warfarin<br>versus<br>Ardeparin 25, 35, 50 anti-Xa U /kg x2               | TKR         | double blind              |
| <b>Warfarin vs Aspirin</b>                                      |   |             |                           |

continued...

| <b>Trial</b>  | <b>Treatments</b>                                   | <b>Patients</b>               | <b>Trials design and methods</b> |
|---|---|-------------------------------|----------------------------------|
| Lotke , 1997<br>n=146/166<br>follow-up: 6 months      | Warfarin<br>versus<br>Aspirin 325 mg x2             | THR or TKR (stratified)       | Open                             |
| Powers , 1989<br>n=65/66<br>follow-up: 3 months       | Warfarin<br>versus<br>Aspirin 650 mg x2             | HFS                           | Open                             |
| <b>Warfarin vs Dalteparin</b>                         |   |                               |                                  |
| Francis , 1997<br>n=292/288<br>follow-up: Day 7 2     | Warfarin<br>versus<br>Dalteparin 5000 anti-Xa IU x1 | THR                           | Open                             |
| Hull , 2000<br>n=489/983<br>follow-up: Day 6 2        | Warfarin<br>versus<br>Dalteparin 5000 anti-Xa IU x1 | THR                           | double blind                     |
| <b>Warfarin vs Danaparoid</b>                         |   |                               |                                  |
| Gerhart , 1991<br>n=131/132<br>follow-up: 9 days      | Warfarin<br>versus<br>Danaparoid 750 U x2           | HFS                           | Open                             |
| van Comp , 1998<br>n=247/241<br>follow-up: 3 months   | Warfarin<br>versus<br>Danaparoid 750 U x2           | THR                           | Open                             |
| <b>Warfarin vs Dextran</b>                            |   |                               |                                  |
| Harris , 1972<br>n=114/113<br>follow-up: NA           | Warfarin<br>versus<br>Dextran 40                    | THR                           | Open                             |
| Barber , 1977<br>n=58/51<br>follow-up: 1114 days      | Warfarin<br>versus<br>Dextran 70                    | THR                           | Open                             |
| Francis , 1983<br>n=57/43<br>follow-up: 57 days       | Warfarin<br>versus<br>Dextran 40                    | THR or TKR (stratified)65279; | Open                             |
| Myrhe , 1969<br>n=50/55<br>follow-up: 3 weeks         | Warfarin<br>versus<br>Dextran 70                    | HFS                           | double blind                     |
| <b>Warfarin vs Enoxaparin</b>                         |   |                               |                                  |
| Leclerc , 1996<br>n=334/336<br>follow-up: 6 months    | Warfarin<br>versus<br>Enoxaparin 30 mg x2           | TKR                           | double blind                     |
| Colwell , 1999<br>n=1495/1516<br>follow-up: 3 months  | Warfarin<br>versus<br>Enoxaparin 30 mg x2           | THR                           | Open                             |
| Fitzgerald , 2001<br>n=176/173<br>follow-up: 3 weeks  | Warfarin<br>versus<br>Enoxaparin 30 mg x2           | TKR                           | Open                             |
| <b>Warfarin vs Intermittent pneumatic compression</b> |   |                               |                                  |

continued...

| <b>Trial</b>  | <b>Treatments</b>  | <b>Patients</b>               | <b>Trials design and methods</b> |
|---|--|-------------------------------|----------------------------------|
| Francis , 1992<br>n=103/98<br>follow-up: 68 days                    | Warfarin<br>versus<br>IPC                                  | THR                           | Open                             |
| Paiement , 1987<br>n=80/83<br>follow-up: 12 days                    | Warfarin<br>versus<br>IPC                                  | THR                           | Open                             |
| Bailey , 1991<br>n=45/50<br>follow-up: 57 days                      | Warfarin<br>versus<br>IPC                                  | THR                           | Open                             |
| Kaempffe , 1991<br>n=52/48<br>follow-up: At least 2 months          | Warfarin<br>versus<br>IPC                                  | THR or TKR (stratified)       | Open                             |
| <b>Warfarin vs Logiparin</b>  |  |                               |                                  |
| Hull , 1993<br>n=721/715<br>follow-up: 65279;Day 14 or<br>discharge | Warfarin<br>versus<br>Logiparin 75 anti-Xa IU /kg x1       | 65279;THR or TKR (stratified) | double blind                     |
| <b>Acenocoumarol vs Nadroparin</b>                                  |  |                               |                                  |
| Hamulyak , 1994<br>n=342/330<br>follow-up: Day 10 2                 | Acenocoumarol<br>versus<br>Nadroparin 60 anti-Xa IU /kg x1 | THR or TKR (stratified)       | single blind                     |
| <b>Acenocoumarol vs Reviparin</b>                                   |  |                               |                                  |
| Samama , 2001<br>n=645/644<br>follow-up: 6 weeks                    | Acenocoumarol<br>versus<br>Reviparin 4200 anti-Xa IU x1    | THR                           | Open                             |
| <b>Warfarin vs Sudoxicam</b>  |  |                               |                                  |
| Hume , 1973<br>n=52/51<br>follow-up: Discharge                      | Warfarin<br>versus<br>Sudoxicam                            | THR                           | single blind                     |
| <b>Acenocoumarol vs unfractionated heparin</b>                      |  |                               |                                  |
| van Geloven , 1977<br>n=11/11<br>follow-up: NA                      | Acenocoumarol<br>versus<br>UFH 4000 x2                     | THR                           | double blind                     |
| <b>Warfarin vs unfractionated heparin</b>                           |  |                               |                                  |
| Hume , 1973<br>n=17/18<br>follow-up: Discharge                      | Warfarin<br>versus<br>UFH 5000 x3                          | THR                           | Open                             |
| Barber , 1977<br>n=58/19<br>follow-up: 1114 days                    | Warfarin<br>versus<br>UFH 5000 x2                          | THR                           | Open                             |

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## 2 direct factor Xa inhibitors

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| Trial  | Treatments  | Patients   | Trials design and methods                       |
|--|---|--|---|
| <b>edoxaban vs placebo</b>   |   |  |   |
| DU176b-04 <i>ongoing</i><br>[NCT01203072]<br>n=NA<br>follow-up:              | edoxaban 5, 15, 30, 60 mg once daily for 2 weeks<br>versus<br>placebo   | elective total knee arthroplasty                           | parallel groups<br>double-blind<br>Japan        |
| <b>apixaban vs enoxaparin</b>  |   |  |   |
| ADVANCE 3 , 2010<br>[NCT00423319]<br>n=2708/2699<br>follow-up: 35 days (+60) | apixaban 2.5mg twice daily for 35 days<br>versus<br>enoxaparin 40mg once daily for 35 days  | patients undergoing elective total hip replacement surgery | Parallel groups<br>double blind<br>21 countries |
| <b>edoxaban vs enoxaparin</b>  |   |  |   |
| DU176b-B-J302 <i>ongoing</i><br>[NCT01181102]<br>n=NA<br>follow-up:          | edoxaban 30mg once daily<br>versus<br>enoxaparin sodium (enoxaparin sodium 20mg(=2000IU)/0.2ml twice daily, subcutaneous injection) | elective total knee arthroplasty                           | parallel groups<br>double-blind<br>Japan        |
| DU176b-B-J303 <i>ongoing</i><br>[NCT01181141]<br>n=NA<br>follow-up:          | edoxaban 30mg once daily<br>versus<br>Enoxaparin sodium 20mg(=2000IU)/0.2ml twice daily, subcutaneous injection                     | elective hip fracture surgery                              | open<br>Japan                                   |

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| <b>Trial</b>  | <b>Treatments</b>  | <b>Patients</b>  | <b>Trials design and methods</b>                          |
|---|--|--|---|
| <b>DU176b-B-J304</b> <i>ongoing</i><br>[NCT01181167]<br>n=NA<br>follow-up:                    | edoxaban 30mg once daily<br>versus<br>(enoxaparin sodium 20mg(=2000IU)/0.2ml<br>twice daily, subcutaneous injection                                    | elective total hip arthroplasty  | parallel groups<br>double-blind<br>Japan                  |
| <b>rivaroxaban vs enoxaparin</b>  |  |  |   |
| <b>RECORD 1 , 2008</b><br>[NCT00329628]<br>n=2266/2275<br>follow-up: 36 days (range<br>30-42) | rivaroxaban 10mg once daily for 35 days<br>versus<br>enoxaparin 40mg subcutaneous once daily for<br>31-39 days   | patients undergoing total hip arthroplasty                                     | Parallel groups<br>double blind<br>27 countries worldwide |
| <b>apixaban vs enoxaparin (europe regimen)</b>  |  |  |   |
| <b>ADVANCE 2 , 2010</b><br>[NCT00452530]<br>n=1528/1529<br>follow-up: 12 days                 | apixaban 2.5mg twice daily during 12 days<br>versus<br>enoxaparin 40mg once daily 12 days  | patients undergoing elective unilateral or<br>bilateral total knee replacement | Parallel groups<br>double blind<br>27 countries           |
| <b>rivaroxaban vs enoxaparin (europe regimen)</b>   |  |  |   |
| <b>RECORD 3 , 2008</b><br>[NCT00361894]<br>n=1254/1277<br>follow-up: 13-17 days               | rivaroxaban 10 mg once daily for 10- 14 days<br>versus<br>enoxaparin 40 mg subcutaneous once daily<br>for 10-14 days                                   | patients undergoing total knee arthroplasty                                    | Parallel groups<br>double blind<br>19 countries worldwide |
| <b>edoxaban vs enoxaparin (short duration)</b>  |  |  |   |
| <b>STARS J-V</b><br>[NCT01181167]<br>n=255/248<br>follow-up:                                  | edoxaban 30 mg once daily for 11 to 14 days<br>versus<br>subcutaneous enoxaparin 2,000 IU, equivalent<br>to 20 mg, twice daily (BID) for 11 to 14 days | total hip arthroplasty   | Parallel groups<br>double-blind<br>japan                  |
| <b>rivaroxaban vs enoxaparin (short duration)</b>   |  |  |   |
| <b>ODIXa-HIP 10mg , 2006</b><br>n=142/157<br>follow-up: 5-9 days                              | rivaroxaban 10mg daily for 59 days<br>versus<br>once-daily subcutaneous enoxaparin dose of<br>40 mg for 59 days  | patients undergoing elective total hip<br>replacement                          | Parallel groups<br>double blind<br>Europe, Israel         |
| <b>rivaroxaban (long duration) vs enoxaparin (short duration)</b>                             |  |  |   |
| <b>RECORD 2 , 2008</b><br>[NCT00332020]<br>n=1252/1257<br>follow-up: 30-42 days               | extended thromboprophylaxis with<br>rivaroxaban 10mg once daily for 31-39 days<br>versus<br>enoxaparin 40mg subcutaneous once daily for<br>10-14 days  | patients undergoing elective total hip<br>replacement                          | Parallel groups<br>double blind<br>21 countries worldwide |
| <b>apixaban vs enoxaparin (US regimen)</b>  |  |  |   |
| <b>APROPOS 2.5mg , 2007</b><br>[NCT00097357]<br>n=153/152<br>follow-up: 12 days               | apixaban 2.5mg BID for 12 days<br>versus<br>enoxaparin 30mg twice daily for 12 days  | patients undergoing elective total knee<br>replacement surgery                 | Parallel groups<br>double blind                           |
| <b>rivaroxaban vs enoxaparin (US regimen)</b>   |  |  |   |

continued...

| <b>Trial</b>   | <b>Treatments</b>   | <b>Patients</b>  | <b>Trials design and methods</b>                 |
|--|---|--|--|
| <b>ODIXa-KNEE , 2005</b><br>n=102/105<br>follow-up: 5-9 days                 | BAY 59-7939 5mg b.i.d. for 59 days<br>versus<br>enoxaparin 30 mg b.i.d. for 59 days   | patients undergoing elective total knee<br>replacement       | Parallel groups<br>double blind<br>North America |
| <b>RECORD 4 , 2009</b><br>[NCT00362232]<br>n=1584/1564<br>follow-up: 40 days | rivaroxaban 10mg once daily for 10 to 14 days<br>versus<br>enoxaparin 30 mg twice daily by<br>subcutaneous injection for 10-14 days | patients who had undergone<br>total-knee-replacement surgery | Parallel groups<br>double blind<br>12 countries  |

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#### **ADVANCE 3, 2010:**

Lassen MR, Gallus A, Raskob GE, Pineo G, Chen D, Ramirez LM Apixaban versus Enoxaparin for Thromboprophylaxis after Hip Replacement. N Engl J Med 2010;363:2487-2498 [21175312] [10.1056/NEJMoa1006885](https://doi.org/10.1056/NEJMoa1006885)

#### **DU176b-B-J302, 0:**

#### **DU176b-B-J303, 0:**

#### **DU176b-B-J304, 0:**

#### **RECORD 1, 2008:**

Eriksson BI, Borris LC, Friedman RJ, Haas S, Huisman MV, Kakkar AK, Bandel TJ, Beckmann H, Muehlhofer E, Misselwitz F, Geerts W Rivaroxaban versus enoxaparin for thromboprophylaxis after hip arthroplasty N Engl J Med 2008;358:2765-75 [18579811] [10.1056/NEJMoa0800374](https://doi.org/10.1056/NEJMoa0800374)

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**3 extended prophylaxis**

| <b>Trial</b>  | <b>Treatments</b>  | <b>Patients</b> | <b>Trials design and methods</b> |
|---|--|-----------------|----------------------------------|
| <b>out of hospital Ardeparin vs standard prophylaxis</b>  |  |                 |                                  |
| Heit , 2000<br>n=589/572                                  | 65279;in hospital thromboprophylaxis followed by out of hospital Ardeparin 100 IU/kg once a day for a total duration of 42 days versus Ardeparin 50 IU/kg twice a day for 4-10 days                      | THR or TKR      |                                  |
| <b>out of hospital Dalteparin vs standard prophylaxis</b> |  |                 |                                  |
| Dahl , 1997<br>n=134/131                                  | 65279;in hospital thromboprophylaxis followed by out of hospital Dalteparin 5000 IU once a day for a total duration of 35 days versus Dalteparin 5000 IU once a day for 7 days (dextran day 0 and day 1) | THR             |                                  |
| Lassen , 1998<br>n=140/141                                | 65279;in hospital thromboprophylaxis followed by out of hospital Dalteparin 5000 IU once a day for a total duration of 35 days versus Dalteparin 5000 IU once a day for 7 days                           | THR             |                                  |
| Hull , 2000<br>n=389/180                                  | 65279;in hospital thromboprophylaxis followed by out of hospital Dalteparin 5000 IU once a day for a total duration of 35 days versus Dalteparin 5000 IU once a day or warfarin for 6 days               | THR             |                                  |
| <b>out of hospital Enoxaparin vs standard prophylaxis</b> |  |                 |                                  |
| Bergqvist , 1996<br>n=117/116                             | 65279;in hospital thromboprophylaxis followed by out of hospital Enoxaparin 40 mg once a day for a total duration of 30 days versus 65279;Enoxaparin 40 mg once a day for 10-11 days                     | 65279;THR       |                                  |
| Planes , 1996<br>n=90/89                                  | 65279;in hospital thromboprophylaxis followed by out of hospital Enoxaparin 40 mg once a day for a total duration of 35 days versus Enoxaparin 40 mg once a day for 13-15 days                           | THR             |                                  |

continued...

| Trial   | Treatments  | Patients   | Trials design and methods |
|---|---|------------|---------------------------|
| <b>Comp , 2001</b><br>n=441/432                           | 65279;in hospital thromboprophylaxis followed by out of hospital Enoxaparin 40 mg once a day for a total duration of 27-29 days versus Enoxaparin 30 mg twice a day for 7-10 days | THR or TKR |                           |
| <b>out of hospital Nadroparin vs standard prophylaxis</b> |   |            |                           |
| <b>NPHDO , 1998</b><br>n=173/173                          | 65279;in hospital thromboprophylaxis followed by out of hospital Nadroparin weight-adjusted for a total duration of 37-38 days versus Nadroparin weight-adjusted for 16-17 days   | THR        |                           |
| <b>out of hospital UFH vs standard prophylaxis</b>        |   |            |                           |
| <b>Manganelli , 1998</b><br>n=79/80                       | 65279;in hospital thromboprophylaxis followed by out of hospital UFH 5000 IU three times a day for a total duration of 30 days versus UFH 5000 IU three times a day for 15 days   | THR        |                           |

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## 4 Graduated compression stockings

| Trial  | Treatments  | Patients  | Trials design and methods                            |
|--|---|---|--|
| <b>compression stocking group vs control (on top fondaparinux)</b> |   |   |  |
| <b>Cohen (L8405) , 2007</b><br>n=426/430<br>follow-up: 42 days     | fondaparinux 2.5mg plus graduated compression stockings versus fondaparinux 2.5mg daily | patients undergoing elective or emergency hip surgery | Parallel groups open<br>Brazil, UK, Hong Kong, Spain |

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## 5 Low molecular weight heparin

| Trial   | Treatments   | Patients             | Trials design and methods |
|---|--|----------------------|---------------------------|
| <b>semuloparin vs enoxaparin</b>                                      |  |                      |                           |
| <b>SAVE-HIP1 , 2012</b><br>[NCT00697099]<br>n=1161/1165<br>follow-up: | Semuloparin 20 mg once-daily versus Enoxaparin 40 mg once-daily  | -                    |                           |
| <b>SAVE-KNEE , 2012</b><br>[NCT00718224]<br>n=-576/574<br>follow-up:  | Semuloparin 20 mg once-daily versus Enoxaparin 30 mg twice-daily | -                    |                           |
| <b>SAVE-HIP 2 , 2012</b><br>[NCT00721760]<br>n=500/503<br>follow-up:  | Semuloparin 20 mg once-daily versus Enoxaparin 40 mg once-daily  | hip fracture surgery | Parallel groups           |

continued...

| Trial   | Treatments   | Patients     | Trials design and methods |
|---|--|--------------|---------------------------|
| <b>enoxaparin vs no treatment</b>                               |  |              |                           |
| Warwick , 1995<br>n=78/78<br>follow-up: 8-10 days               | enoxaparin 4000x1 + elastic stockings<br>versus<br>no treatment + elastic stockings            | Elective hip | open                      |
| <b>nadroparin vs no treatment</b>                               |  |              |                           |
| Yoo , 1997<br>n=50/50<br>follow-up: 10 days                     | nadroparin 41/kgx1 days 1-3, 62/kg x1 days<br>4-11+elastic stockings<br>versus<br>no treatment | Elective hip | open                      |
| <b>ardeparin vs placebo</b>                                     |  |              |                           |
| Levine , 1996<br>n=122/124<br>follow-up: 14 days                | ardeparin 50/kgx2 +elastic stockings<br>versus<br>Placebo+elastic stockings                    | Knee         | double blind              |
| <b>dalteparin vs placebo</b>                                    |  |              |                           |
| Jorgensen , 1989<br>n=30/38<br>follow-up: 9 days                | dalteparin 5000 x1<br>versus<br>Placebo  | Hip fracture | double blind              |
| Torholm , 1991<br>n=58/54<br>follow-up: 9 days                  | dalteparin 5000x1<br>versus<br>Placebo   | Elective hip | double blind              |
| <b>enoxaparin vs placebo</b>                                    |  |              |                           |
| Kalodiki , 1996<br>n=13/14<br>follow-up: discharge (8-12 days ) | enoxaparin 4000x1<br>versus<br>Placebo   | Elective hip | double blind              |
| Leclerc , 1991<br>n=65/64<br>follow-up: 14 days                 | Enoxaparin 3000 x2<br>versus<br>Placebo  | Knee         | double blind              |
| Samama , 1997<br>n=85/85<br>follow-up: 8-12 days                | enoxaparin 4000x1+elastic stockings<br>versus<br>Placebo+elastic stockings                     | Elective hip | double blind              |
| Turpie , 1986<br>n=50/50<br>follow-up: 14 days or<br>discharge  | Enoxaparin 3000 x2<br>versus<br>Placebo  | Elective hip | double blind              |
| <b>nadroparin vs placebo</b>                                    |  |              |                           |
| Sourmelis , 1995<br>n=72/78<br>follow-up: 10-12 days            | nadroparin 3075x1 preop, 6150x1 post op<br>versus<br>Placebo                                   | Hip fracture | double blind              |
| <b>tinzaparin vs placebo</b>                                    |  |              |                           |
| Lassen , 1991<br>n=105/105<br>follow-up: 8-10 days              | tinzaparin 50/kg x1 +elastic stockings<br>versus<br>Placebo+elastic stockings                  | Elective hip | double blind              |
| <b>dalteparin vs Dextran</b>                                    |  |              |                           |

continued...

| <b>Trial</b>                                      | <b>Treatments</b>                                     | <b>Patients</b> | <b>Trials design and methods</b> |
|---|---|-----------------|----------------------------------|
| Matzsch , 1991<br>n=120/123                       | dalteparin<br>versus<br>Dextran                       | Elective hip    |                                  |
| Eriksson , 1988<br>n=50/50                        | dalteparin<br>versus<br>Dextran                       | Elective hip    |                                  |
| Matzsch , 1988<br>n=48/52                         | dalteparin<br>versus<br>Dextran                       | Elective hip    |                                  |
| <b>enoxaparin vs Dextran</b>                      |   |                 |                                  |
| DES Group , 1991<br>n=120/126                     | Enoxaparin<br>versus<br>Dextran                       | Elective hip    |                                  |
| <b>certoparin + DHE vs Unfractionated heparin</b> |   |                 |                                  |
| Haas , 1987<br>n=80/80                            | Sandoz +0.5mg DHE<br>versus<br>Unfractionated heparin | Elective hip    |                                  |
| Lassen , 1989<br>n=68/71<br>follow-up: 6 days     | certoparin 3000+0.5mg DHE x1<br>versus<br>placebo     | Hip fracture    | double blind                     |
| Lassen , 1988<br>n=118/122<br>follow-up: 6 days   | certoparin 3000+0.5mg DHE, x1<br>versus<br>Placebo    | Elective hip    | double blind                     |
| <b>dalteparin vs Unfractionated heparin</b>       |   |                 |                                  |
| Binsack , 1986<br>n=48/47                         | dalteparin<br>versus<br>Unfractionated heparin        | Elective hip    |                                  |
| Barre , 1987<br>n=40/40                           | dalteparin<br>versus<br>Unfractionated heparin        | Elective hip    |                                  |
| Dechavanne , 1989<br>n=82/40                      | dalteparin<br>versus<br>Unfractionated heparin        | Elective hip    |                                  |
| Eriksson , 1989<br>n=67/69                        | dalteparin<br>versus<br>Unfractionated heparin        | Elective hip    |                                  |
| Haas , 1985<br>n=65/65                            | dalteparin<br>versus<br>Unfractionated heparin        | Elective hip    |                                  |
| Monreal , 1989<br>n=46/44                         | dalteparin<br>versus<br>Unfractionated heparin        | Hip             |                                  |
| <b>enoxaparin vs Unfractionated heparin</b>       |   |                 |                                  |

continued...

| Trial                                       | Treatments                                     | Patients     | Trials design and methods |
|---|--|--------------|---------------------------|
| Levine , 1991<br>n=333/332                  | Enoxaparin<br>versus<br>Unfractionated heparin | Elective hip |                           |
| Planes , 1988<br>n=124/113                  | Enoxaparin<br>versus<br>Unfractionated heparin | Elective hip |                           |
| <b>fluxum vs Unfractionated heparin</b>     |  |              |                           |
| Chiapuzzo , 1988<br>n=70/70                 | Fluxum<br>versus<br>Unfractionated heparin     | Elective hip |                           |
| Pini , 1989<br>n=25/24                      | Fluxum<br>versus<br>Unfractionated heparin     | Hip          |                           |
| <b>nadroparin vs Unfractionated heparin</b> |  |              |                           |
| Leyvraz , 1991<br>n=203/206<br>follow-up:   | Fraxiparin<br>versus<br>Unfractionated heparin | Elective hip |                           |

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## 6 oral direct thrombin inhibitor

| Trial  | Treatments  | Patients  | Trials design and methods                       |
|--|---|---|---|
| <b>ximelagatran vs Dalteparin</b>  |   |   |   |
| <b>METHRO I , 2002</b><br>n=103<br>follow-up: 69 days  | Melagatran 14 mg s.c. immediately before surgery, melagatran at 20.00 hours, then ximelagatran 624 mg orally b.d. for 69 days versus<br>Dalteparin 5000 IU o.d., started evening before surgery for 69 days | adults undergoing hip or knee replacement         | parallel group<br>open<br>Swedish               |
| <b>METHRO II , 2002</b><br>n=1495/381<br>follow-up: 710 days   | Melagatran 13 mg s.c. immediately before surgery, melagatran same day, then ximelagatran 824 mg orally b.d. for 710 days versus<br>Dalteparin 5000 IU o.d., started evening before surgery for 710 days     | undergoing hip or knee replacement                | Parallel groups<br>double-blind                 |
| <b>dabigatran 150mg vs enoxaparin</b>  |   |   |   |
| <b>RE-NOVATE (150mg) , 2007</b><br>[NCT00168818]<br>n=1174/1162<br>follow-up: 28-35 days, median 33d | dabigatran etexilate 150 mg q.d. 28-35 days versus<br>Enoxaparin 40 mg q.d. for 28-25 days  | Total hip replacement                             | double blind<br>Europe, Australia, South Africa |
| <b>dabigatran 220mg vs enoxaparin</b>  |   |   |   |
| <b>RE-NOVATE 2 unpublished</b><br>[NCT00657150]<br>n=1010/1003<br>follow-up: 28-35 days (mean 32d)   | dabigatran 220mg once daily for 28-35 Days versus<br>enoxaparin 40mg subcutaneous once daily for 28-35 Days   | patients undergoing total hip-replacement surgery | Parallel groups<br>double-blind                 |

continued...



| <b>Trial</b>   | <b>Treatments</b>   | <b>Patients</b>  | <b>Trials design and methods</b>  |
|--|---|--|---|
| <b>RE-NOVATE (220mg) , 2007</b><br>[NCT00168818]<br>n=1157/1162<br>follow-up: 28-35 days, median 33d | dabigatran etexilate 220 mg q.d. for 28-35 days<br>versus<br>Enoxaparin 40 mg q.d. for 23-35 days   | Total hip replacement  | Parallel groups<br>double blind<br>Europe, Australia, South Africa                    |
| <b>ximelagatran vs Enoxaparin</b>  |   |  |   |
| <b>Platinum (Colwell) , 2003</b><br>n=906/910<br>follow-up: 712 days                                 | Ximelagatran 24 mg orally b.d., starting at least 12 h after surgery for 712 days<br>versus<br>Enoxaparin 30 mg s.c. b.d.,starting at least 12 h after surgery for 712 days   | adults undergoing hip replacement  | parallel group<br>double-blind<br>USA, Canada, Israel, Mexico,Argentina, South Africa |
| <b>METHRO III , 2002</b><br>n=2788<br>follow-up: 811 days  | Melagatran 3 mg s.c. 412h after surgery, then ximelagatran24 mg orally b.d. for 710 days<br>versus<br>Enoxaparin 40 mg s.c. o.d. 12 h before surgery for 710 days   | hip or knee replacement  | double-blind<br>Europe, South Africa  |
| <b>Phase II (Heit) , 2001</b><br>n=600<br>follow-up: 612 days  | Ximelagatran 8, 12, 18 or 24 mg orally b.d., at least 12 h after surgery for 612 days<br>versus<br>Enoxaparin 30 mg s.c. b.d.,starting at least 12 h after surgery for 612 days   | adults (age>18 years and weight at least 40 kg) undergoing knee replacements | parallel group<br>double-blind<br>North American                                      |
| <b>EXPRESS , 2003</b><br>n=2835<br>follow-up: 811 days   | Melagatran 2 mg s.c. up to 30 min before surgery, then melagatran 3 mg at least 8 h after surgery, then ximelagatran 24 mg orally b.d. for 811 days<br>versus<br>Enoxaparin 40 mg s.c. o.d.,starting 12 h before surgery for 811 days | hip or knee replacement  | parallel group<br>double-blind<br>Europe  |
| <b>dabigatran 150mg vs enoxaparin (europe regimen)</b>   |   |  |   |
| <b>RE-MODEL (150mg) , 2007</b><br>n=708/699<br>follow-up: 6-10 days, mean 8 days                     | dabigatran etexilate 150 mg q.d. for 6-10 days<br>versus<br>Enoxaparin 40 mg q.d. for 6-10 days   | Total knee replacement   | Parallel groups<br>double blind<br>Europe, Australia, South Africa                    |
| <b>dabigatran 220mg vs enoxaparin (europe regimen)</b>   |   |  |   |
| <b>RE-MODEL (220mg) , 2007</b><br>n=694/699<br>follow-up: 6-10 days, mean 8 days                     | dabigatran etexilate 220 mg q.d. 6-10 days<br>versus<br>Enoxaparin 40 mg q.d. for 6-10 days   | patients undergoing total knee replacement                                   | double blind<br>Europe, Australia, South Africa                                       |
| <b>dabigatran 150mg vs enoxaparin (US regimen)</b>   |   |  |   |
| <b>RE-MOBILIZE (150mg) , 2008</b><br>n=877/876<br>follow-up: 12-15 days, median 14d                  | dabigatran etexilate 150 mg q.d. for 12-15 days<br>versus<br>enoxaparin 30 mg SC BID after surgery for 12-15 days   | Total knee replacement   | double blind<br>US, Canada, Mexico, UK  |
| <b>dabigatran 220mg vs enoxaparin (US regimen)</b>   |   |  |   |

continued...

| Trial  | Treatments   | Patients               | Trials design and methods                                 |
|--|--|------------------------|---|
| RE-MOBILIZE (220mg) , 2008<br>n=862/876<br>follow-up: 12-15 days, median 14d | dabigatran etexilate 220 mg for 12-15 days versus<br>Enoxaparin 30mg SC BID after surgery for 12-15 days | Total knee replacement | Parallel groups<br>double blind<br>US, Canada, Mexico, UK |

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## 7 platelet aggregation inhibitors

19

| Trial   | Treatments  | Patients                            | Trials design and methods |
|---|---|-------------------------------------|---------------------------|
| <b>Aspirin vs no treatment</b>                                    |   |                                     |                           |
| <a href="#">Pasteryer , 1977</a><br>n=20/20<br>follow-up: 2 weeks | Aspirin 1000mg daily + Hep<br>versus<br>control (Hep alone)   | Elective orthopaedic surgery        | Parallel groups           |
| <a href="#">Rocha , 1986</a><br>n=60/30<br>follow-up: 1 weeks     | Aspirin 250mg or 1000mg daily<br>versus<br>control (combination of heparin plus<br>dihydroergotamine) | total hip replacement               | Parallel groups<br>open   |
| <b>aspirin + dipyridamol vs no treatment</b>                      |   |                                     |                           |
| <a href="#">Morris-B , 1977</a><br>n=32/32<br>follow-up:          | Aspirin 900 mg daily + dipyridamole<br>versus<br>control  | elderly patients with hip fractures | Parallel groups<br>open   |
| <a href="#">Lyon-I , 1975</a><br>n=20/20<br>follow-up: 2 weeks    | Aspirin 1500 mg daily + Dipyridamole<br>versus<br>control   | Elective orthopaedic surgery        |                           |
| <b>dipyridamol vs no treatment</b>                                |   |                                     |                           |
| <a href="#">Morris-A , 1977</a><br>n=24/24<br>follow-up:          | dipyridamole<br>versus<br>control   | elderly patients with hip fractures | Parallel groups<br>open   |
| <b>Flurbiprofen vs no treatment</b>                               |   |                                     |                           |
| <a href="#">Mocris-C , 1977</a><br>n=20/20<br>follow-up:          | Flurbiprofen<br>versus<br>control   | elderly patients with hip fractures | Parallel groups<br>open   |

continued...

| <b>Trial</b>   | <b>Treatments</b>  | <b>Patients</b>  | <b>Trials design and methods</b>   |
|--|--|--|--|
| <b>Hydroxychloroquine vs no treatment</b>                    |  |  |  |
| Massachusetts-I , 1981<br>n=50/25<br>follow-up:              | Aspirin 1200mg daily, Aspirin 1200mg daily + hydroxychloroquine 300 mg b.i.d.<br>versus<br>control | patients with upper femoral fractures                                  | Parallel groups<br>open  |
| <b>aspirin vs placebo</b>                                    |  |  |  |
| Zekert-I , 1974<br>n=138/140<br>follow-up:                   | Aspirin 1500mg daily<br>versus<br>placebo  | patients undergoing surgery of hip-joint proximal fractures            | Parallel groups<br>double-blind  |
| Powers , 1976<br>n=66/63                                     | A1300<br>versus<br>placebo   | traumatic orthopaedic surgery  |  |
| Erfurt-B , 1979<br>n=44/44<br>follow-up:                     | A1500<br>versus<br>placebo   | traumatic orthopaedic surgery  | double-blind   |
| PEP hip-fracture , 2000<br>n=6679/6677<br>follow-up: 35 days | aspirin 160mg/d started preoperatively and continued for 35 days<br>versus<br>placebo              | patients undergoing surgery for hip fracture                           | Parallel groups<br>Double blind<br>Australia, New Zealand, South Africa, |
| Stockholm-I , 1975<br>n=26/25<br>follow-up: 2 weeks          | Aspirin 2000mg daily<br>versus<br>placebo  | elective surgery of the hip  | double blind   |
| Harris-I , 1977<br>n=58/59<br>follow-up: 1 weeks             | Aspirin 1200mg daily<br>versus<br>placebo  | patients over 40 years of age, who had undergone total hip replacement | Parallel groups<br>double-blind  |
| McKenna-I , 1980<br>n=24/12<br>follow-up: 2 weeks            | Aspirin 975mg or 3900mg daily<br>versus<br>placebo   | total knee replacement   | Parallel groups<br>double-blind  |
| Sautter , 1983<br>n=68/77<br>follow-up: 3 weeks              | Aspirin 900mg daily + sulfapyrazone<br>versus<br>placebo   | patient with total hip replacement                                     | Parallel groups  |
| McBride , 1983<br>n=21/22<br>follow-up: 1 weeks              | A1800+Dipyridamole<br>versus<br>placebo  | Elective orthopaedic surgery   |  |
| <b>aspirin + dipyridamol vs placebo</b>                      |  |  |  |
| Encke-II , 1976<br>n=34/25<br>follow-up:                     | Aspirin 1500mg daily, Aspirin 990mg daily + dipyridamol<br>versus<br>placebo                       | patients with abdominal operations                                     | Parallel groups<br>double-blind  |
| Hamburg , 1976<br>n=21/11<br>follow-up: 3 weeks              | A+Dipyridamole,A1000<br>versus<br>placebo  | Elective orthopaedic surgery   |  |
| <b>Hydroxychloroquine vs placebo</b>                         |  |  |  |

continued...

| <b>Trial</b>   | <b>Treatments</b>                                      | <b>Patients</b>   | <b>Trials design and methods</b> |
|--|--|---|----------------------------------|
| Danish-A , 1976<br>n=48/50<br>follow-up:                 | Hydroxychloroquine sulphate<br>versus<br>placebo       | patients with fractures of the hip, pelvis, or<br>thoracolumbar spine                         | Parallel groups<br>double-blind  |
| Danish-B , 1976<br>n=27/28<br>follow-up:                 | Hydroxychloroquine sulphate<br>versus<br>placebo       | patients with fractures of the hip, pelvis, or<br>thoracolumbar spine                         | Parallel groups                  |
| Massachusetts-II , 1976<br>n=51/51<br>follow-up: 3 weeks | Hydroxychloroquine 600mg daily<br>versus<br>placebo    | fractures or orthopaedic operations involving<br>the skeleton between the knee and the pelvis |                                  |
| Cooke , 1977<br>n=25/25<br>follow-up: 2 weeks            | Hydroxychloroquine<br>versus<br>placebo                | elective surgery on the hip   | Parallel groups<br>double-blind  |
| Hume-A , 1977<br>n=20/20<br>follow-up: 2 weeks           | Hydroxychloroquine<br>versus<br>placebo                | total hip replacement   |                                  |
| Stockholm-II , 1981<br>n=18/17<br>follow-up: 2 weeks     | Hydroxychloroquine<br>versus<br>placebo                | total hip replacement   |                                  |
| <b>RA233 vs placebo</b>                                  |  |   |                                  |
| 65279;Wood , 1973<br>n=21/9<br>follow-up:                | RA233; Aspirin 600mg daily +RA233<br>versus<br>placebo | traumatic orthopaedic surgery   |                                  |
| <b>Ticlopidine vs placebo</b>                            |  |   |                                  |
| McKenna-II , 1983<br>n=29/29<br>follow-up: 2 weeks       | Ticlopidine<br>versus<br>placebo                       | Elective orthopaedic surgery  |                                  |
| Lyon-II , 3000<br>n=20/20<br>follow-up: 3 weeks          | Ticlopidine<br>versus<br>placebo                       | Elective orthopaedic surgery  |                                  |
| Gardecki , 3000<br>n=48/46<br>follow-up: 2 weeks         | Ticlopidine<br>versus<br>placebo                       | Elective orthopaedic surgery  |                                  |

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## 8 recombinant hirudin

| Trial  | Treatments  | Patients  | Trials design and methods                 |
|--|---|---|---|
| <b>desirudin vs enoxaparin</b>                           |   |   |   |
| <a href="#">Ericksson , 1997</a><br>n=NA<br>follow-up:   | desirudin 15mg SC twice daily for 8-12 days<br>versus<br>enoxaparin 40mg once daily for 8-12 days | Patients who undergo total hip replacement                  | Parallel groups<br>double blind<br>Europe |
| <b>desirudin vs UFH</b>                                  |   |   |   |
| <a href="#">REVASC , 1997</a><br>n=225/220<br>follow-up: | desirudin 15mg twice daily<br>versus<br>unfractionated heparin 5000 IU three times a<br>day       | patients having a primary elective total hip<br>replacement | Parallel groups                           |

continued...

| Trial  | Treatments  | Patients                                 | Trials design and methods                 |
|--|---|--|---|
| <b>Eriksson , 1996</b><br>n=1119<br>follow-up: | recombinant hirudin, desirudin (CGP 39393) 10, 15, or 20 mg twice daily started just before surgery and continued for 8-11 days versus unfractionated heparin 5000 IU three times daily started just before surgery and continued for 8-11 days | patients undergoing elective hip surgery | Parallel groups<br>double blind<br>Europe |

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## 9 synthetic oligosaccharide

| Trial  | Treatments  | Patients  | Trials design and methods                |
|--|---|---|--|
| <b>fondaparinux vs control</b>   |   |   |  |
| <b>NCT00320398</b> <i>ongoing</i><br>[NCT00320398]<br>n=NA<br>follow-up: | -   | patients undergoing either an elective primary total hip replacement (THR) surgery or a revision of a THR | double-blind<br>Japan                    |
| <b>fondaparinux vs placebo</b>   |   |   |  |
| <b>DRI4757</b><br>n=345/87<br>follow-up: 14 days                         | fondaparinux subcutaneously at 0.75, 1.5, 2.5, and 3.0 mg for at least 10 calendar days, (with a maximum of 14 days) versus placebo | Japanese patients undergoing elective total knee replacement surgery                                      | Parallel groups<br>double blind<br>Japan |
| <b>fondaparinux vs enoxaparin</b>  |   |   |  |
| <b>L8541</b><br>n=119/118<br>follow-up: 9 days (49d)                     | fondaparinux 2.5mg subcutaneous once-daily for 7+/-2 days versus enoxaparin 40mg s.c. once-daily                                    | chinese patients undergoing major orthopaedic surgery of the lower limbs                                  | Parallel groups<br>single-blind<br>China |

continued...



| <b>Trial</b>  | <b>Treatments</b>   | <b>Patients</b>   | <b>Trials design and methods</b>                          |
|---|---|---|---|
| <b>L8635</b><br>n=28/23<br>follow-up: 10 days                                 | Fondaparinux 2.5mg once daily subcutaneously for 7 days<br>versus<br>enoxaparin 40mg once daily SC for 7 days   | Taiwanese patients undergoing elective knee replacement | Parallel groups<br>open, blind assessment<br>Taiwan       |
| <b>PENTAMAKS (Bauer) , 2001</b><br>n=517/517<br>follow-up: 11 days            | fondaparinux 2.5-mg once-daily subcutaneous, starting 6 hours after surgery<br>versus<br>enoxaparin 30mg twice daily (North america recommendation)                 | elective major knee surgery                             | Parallel groups<br>double blind<br>North america          |
| <b>PENTHIFRA (Eriksson) , 2001</b><br>n=831/840<br>follow-up: 11 days         | fondaparinux 2.5-mg once-daily subcutaneous, starting 6 hours after surgery<br>versus<br>enoxaprin 40mg once daily  | hip fracture surgery                                    | Parallel groups<br>double blind<br>21 countries           |
| <b>EPHESUS (Lassen) , 2002</b><br>n=1155/1154<br>follow-up: 11 days (6 weeks) | fondaparinux 2.5-mg once-daily subcutaneous, starting 6 hours after surgery<br>versus<br>enoxaprin 40mg once daily  | elective hip replacement surgery                        | Parallel groups<br>double blind<br>16 European countries  |
| <b>PENTATHLON (Turpie) , 2002</b><br>n=1138/1137<br>follow-up: 11 days        | fondaparinux 2.5-mg once-daily subcutaneous, starting 6 hours after surgery<br>versus<br>enoxaparin 30mg twice daily (North america recommendation)                 | elective hip replacement surgery                        | Parallel groups<br>double blind<br>USA, Canada, Australia |
| <b>Turpie , 2001</b><br>n=673/260<br>follow-up: >15 days                      | pentasaccharide Org31540/SR90107A subcutaneous once daily at doses 0.75 mg, 1.5 mg, 3.0 mg, 6.0 mg, and 8.0 mg<br>versus<br>enoxaparin 30mg once daily subcutaneous | patients undergoing total hip replacement               | Parallel groups<br>double blind<br>US, Canada, Australia  |
| <b>SR123781A vs enoxaparin</b>  |   |   |   |
| <b>DRIVE , 2008</b><br>[NCT00338897]<br>n=854/169<br>follow-up: 5-10 days     | SR123781A for 5-10 days, doses ranging from 0.25 to 4.0 mg daily for 10 days<br>versus<br>enoxaparin 40 mg  | patients undergoing total hip replacement surgery       | Parallel groups<br>double blind<br>12 countries           |
| <b>extended prophylaxis vs standard prophylaxis</b>                           |   |   |   |
| <b>PENTHIFRAPLUS (Eriksson) , 2003</b><br>n=656<br>follow-up: 19-23 days      | 25-31 days of fondaparinux 2.5-mg once-daily<br>versus<br>6-8 days of fondaparinux 2.5-mg once-daily  | patients undergoing hip fracture surgery                | Parallel groups<br>double blind                           |

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## 10 unfractionated heparin

| Trial                        | Treatments   | Patients                     | Trials design and methods |
|------------------------------|--|------------------------------|---------------------------|
| <b>UFH vs no treatment</b>   |  |                              |                           |
| Bergqvist , 1979<br>n=84/77  | UFH twice daily for 5 days<br>versus<br>no treatment         | elective orthopedic surgery  |                           |
| Bergqvist , 1979<br>n=32/23  | UFH twice daily for 5 days<br>versus<br>no treatment         | traumatic orthopedic surgery |                           |
| Dechavanne , 1974<br>n=29/29 | UFH 3 times daily for 10 days<br>versus<br>no treatment      | elective orthopedic surgery  |                           |
| Dechavanne , 1975<br>n=20/21 | UFH 3 times daily for 10 days<br>versus<br>no treatment      | elective orthopedic surgery  |                           |
| Galasko , 1976<br>n=50/50    | UFH twice daily (duration unknown)<br>versus<br>no treatment | traumatic orthopedic surgery |                           |

continued...

| <b>Trial</b>                     | <b>Treatments</b>                                       | <b>Patients</b>              | <b>Trials design and methods</b> |
|----------------------------------|---|------------------------------|----------------------------------|
| Gallus , 1973<br>n=23/23         | UFH 3 times daily for A<br>versus<br>no treatment       | traumatic orthopedic surgery |                                  |
| Mannucci , 1976<br>n=23/24       | UFH 3 times daily for 7 days<br>versus<br>no treatment  | elective orthopedic surgery  |                                  |
| Morris , 1974<br>n=36/36         | UFH twice daily for 10 days<br>versus<br>no treatment   | elective orthopedic surgery  |                                  |
| Morris , 1977<br>n=24/24         | UFH 3 times daily for 10 days<br>versus<br>no treatment | traumatic orthopedic surgery |                                  |
| VTCSG , 1975<br>n=34/30          | UFH twice daily for 10 days<br>versus<br>no treatment   | elective orthopedic surgery  |                                  |
| Welin-Berger , 1982<br>n=20/20   | UFH twice daily for 7 days<br>versus<br>no treatment    | elective orthopedic surgery  |                                  |
| <b>UFH vs placebo</b>            |   |                              |                                  |
| Abraham-Inpijn , 1975<br>n=12/13 | UFH twice daily for 8 days<br>versus<br>placebo         | elective orthopedic surgery  |                                  |
| Hampson , 1974<br>n=48/52        | UFH 3 times daily for 7- 10 days<br>versus<br>placebo   | elective orthopedic surgery  |                                  |
| Lahnborg , 1980<br>n=70/69       | UFH twice daily for 10 days<br>versus<br>placebo        | traumatic orthopedic surgery |                                  |
| Lowe , 1981<br>n=51/49           | UFH twice daily for 16 days<br>versus<br>placebo        | elective orthopedic surgery  |                                  |
| Moskovitz , 1978<br>n=29/23      | UFH 3 times daily for 7 days<br>versus<br>placebo       | traumatic orthopedic surgery |                                  |
| Moskovitz , 1978<br>n=35/32      | UFH 3 times daily for 7 days<br>versus<br>placebo       | elective orthopedic surgery  |                                  |
| Svend-Hansen , 1981<br>n=65/65   | UFH 3 times daily for 14 days<br>versus<br>placebo      | traumatic orthopedic surgery |                                  |
| Williams , 1978<br>n=106/106     | UFH twice daily for 14 days<br>versus<br>placebo        | elective orthopedic surgery  |                                  |

continued...

| Trial                      | Treatments                                       | Patients                     | Trials design and methods |
|----------------------------|--|------------------------------|---------------------------|
| Xabregas , 1977<br>n=27/26 | UFH twice daily for 14 days<br>versus<br>placebo | traumatic orthopedic surgery |                           |

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## 11 About TrialResults-center.org

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