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## Vitamin K supplementation to improve vascular stiffness in CKD

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## **Supplemental Material**

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### 1. Supplementary Table: Details of assays used in the trial

| Assay                                     | Manufacturer                 | Coefficient of variation             |                                     |
|---|------------------------------|--------------------------------------|-------------------------------------|
|   |                              | Intra-assay                          | Inter-assay                         |
| Fetuin A                                  | R+D Systems Quantikine ELISA | 3.5-4.2%                             | 8.5-8.8%                            |
| Fibroblast Growth Factor 23               | Immutopics C-terminal ELISA  | 3.3-11.5%                            | 3.3-11.5%                           |
| Osteocalcin                               | R+D Systems Quantikine ELISA | 5.2-5.4%                             | 7.3-13.8%                           |
| Insulin                                   | Alpco ELISA                  | 4.8-6.9%                             | 4.9-13.5%                           |
| 25-hydroxyvitamin D                       | Diasorin LIAISON             | 2.9-8.4%                             | 5.6-10.1%                           |
| 1,25 dihydroxyvitamin D                   | Diasorin LIAISON XL          | 5.3-8.4%                             | 8.2-8.8%                            |
| dp-ucMGP                                  | IDS-iSYS InaKtif MGP         | ≤ 5.0% (between 910 and 7312 pmol/L) | ≤ 7.3% between 939 and 7386 pmol/L) |
| Tartrate-resistant acid phosphatase-5b    | Cusabio ELISA                | 6.9%                                 | 6.3-14.3%                           |
| N-terminal pro B-type natriuretic peptide | Meso Scale Discovery ELISA   | 8.0%                                 | 13.2-15.5%                          |

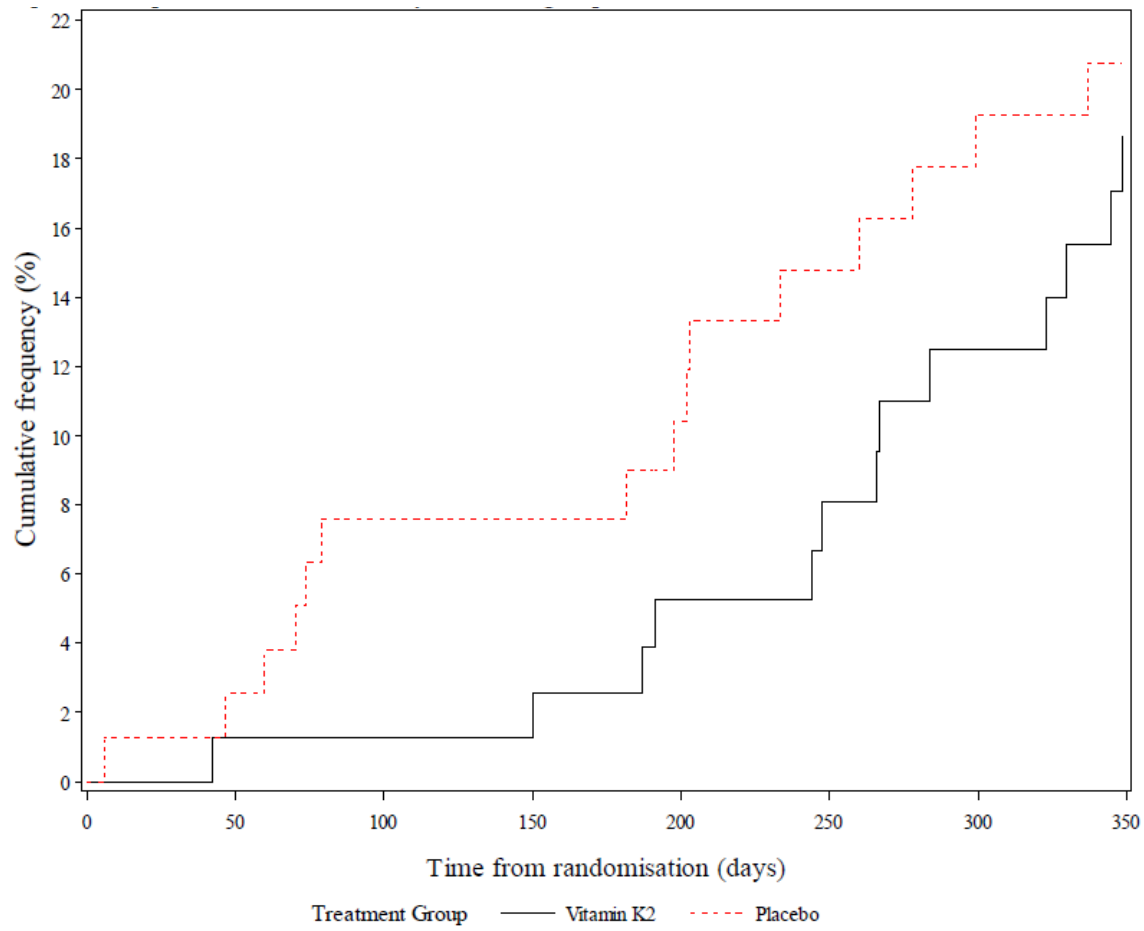
dp-ucMGP: desphospho-uncarboxylated matrix Gla protein

\*A threshold of 900 pmol/L was used as the lowest reportable concentration of dp-ucMGP. Assay performance below this concentration was found to be non-linear on dilution testing, thus values below 900 pmol/L cannot be reported with accuracy.

## 2. Supplementary Table: Details of studies included in the meta-analysis

| Author                    | Year | Country     | Baseline N | Population   | Intervention                      | Dose (mcg/day) | Comparator                    | Duration (months) | Outcome measure                               |
|---------------------------|------|-------------|------------|--|-----------------------------------|----------------|-------------------------------|-------------------|---|
| Braam <sup>33</sup>       | 2004 | Netherlands | 121        | Healthy  | K1 +Multivitamin (incl vitamin D) | 1000           | Multivitamin (incl vitamin D) | 36                | Compliance coefficient (mm <sup>2</sup> /kPa) |
| Shea <sup>34</sup>        | 2009 | USA         | 295        | Older adults   | K1 +Multivitamin (incl vitamin D) | 500            | Multivitamin (incl vitamin D) | 36                | Coronary artery calcification score           |
| Knapen <sup>35</sup>      | 2015 | Netherlands | 244        | Postmenopausal women                                       | K2-MK7                            | 180            | Placebo                       | 36                | Pulse wave velocity (SphygmoCor)              |
| Kurnatowska <sup>16</sup> | 2015 | Poland      | 40         | CKD  | K2-MK7 + Vitamin D                | 90             | Vitamin D                     | 9                 | Coronary artery calcification score           |
| Fulton <sup>18</sup>      | 2016 | Scotland    | 80         | Older adults, vascular disease                             | K2-MK7                            | 100            | Placebo                       | 6                 | Pulse wave velocity (SphygmoCor)              |
| Brandenburg <sup>36</sup> | 2017 | Germany     | 72         | Aortic stenosis or sclerosis                               | K1                                | 2000           | Placebo                       | 12                | Aortic valve calcification score              |
| Oikonomaki <sup>37</sup>  | 2019 | Greece      | 102        | Patients undergoing haemodialysis                          | K2-MK7                            | 200            | Usual care                    | 12                | Abdominal aortic calcification score          |
| Zwakenberg <sup>39</sup>  | 2019 | Netherlands | 68         | Patients with type 2 diabetes mellitus                     | K2-MK7                            | 360            | Placebo                       | 6                 | Femoral artery calcification score            |
| De Vriese <sup>38</sup>   | 2020 | Belgium     | 88         | Patients undergoing haemodialysis with atrial fibrillation | K2-MK7 + Rivaroxaban              | 857            | Rivaroxaban                   | 18                | Coronary artery calcification score           |

### 3. Supplementary Figure. Time to first fall



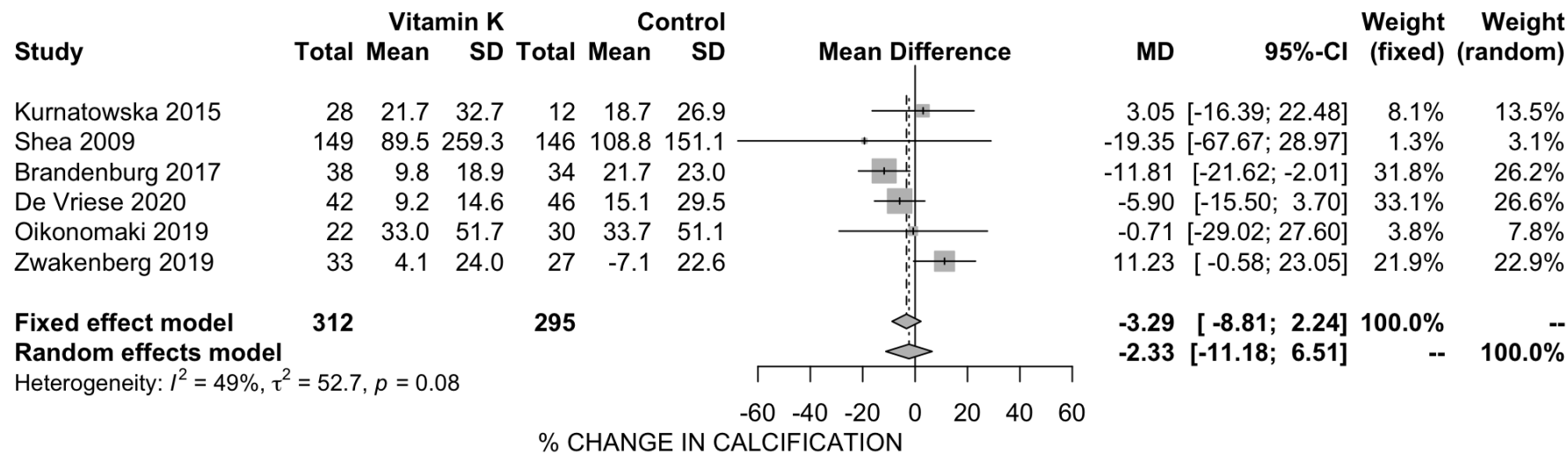
Time to first fall: HR 0.79 (95% CI 0.37 to 1.69, p=0.54)

#### 4. Vascular calcification results

|  | Vitamin K<br>Mean (SD) | Placebo<br>Mean (SD) | Treatment effect* (95% CI)     | p    |
|--|------------------------|----------------------|--------------------------------|------|
| Mean Aortic calcification score (SD)<br>at 12 months                           | 4.8 (5.1)              | 4.2 (5.3)            | -0.3 (-0.8 to 0.2)             | 0.31 |
| [Median (Q1,Q3)]   | [3 (0,8)]              | [3 (0,5)]            |                                |      |
| Mean Aortic calcification score (SD)<br>at 12 months (excluding zero scores)   | 7.0 (4.8)              | 6.5 (5.3)            | -0.3 (-1.1. to 0.42)           | 0.37 |
| Change in aortic calcification score<br>between baseline and 12 months<br>(SD) | 0.0 (1.4)              | 0.3 (1.4)            | -0.3 (-0.8 to 0.2)             | 0.31 |
| No detectable calcification at<br>baseline (%)                                 | 18 (30.0)              | 22 (36.7)            | Odds ratio<br>0.2 (0.0 to 4.3) | 0.30 |
| No detectable calcification at 12<br>months (%)                                | 19 (31.7)              | 21 (35.6)            |                                |      |

## 5. Forest plots – vascular calcification

### a) Excluding current trial



b) Including current trial

