**Supplementary data**

**Determination of risk factors**

Hypertension was defined as the use of any antihypertensive medication or blood pressure higher than 140/90 mmHg on more than two occasions during the follow-up period. Diabetes mellitus was defined as the use of any antidiabetic medication or haemoglobin A1c (NGSP) > 6.5%. Dyslipidaemia was defined as the use of any lipid-lowering agents or an elevated serum low-density lipoprotein concentration > 140 mg/dl. Glucocorticosteroid treatment was defined as the use of any oral or intravenous corticosteroid therapy for more than three consecutive months at any time of the follow-up. Current cigarette smoking was defined as any cigarette or cigar during the follow-up period.

**Determination of antiphospholipid antibodies and the antiphospholipid score (aPL-S)**

For lupus anticoagulant (LA), mixing tests of three clotting assays were performed using a semiautomated hemostasis analyzer (STart 4; Diagnostica Stago) according to the guidelines recommended by the Subcommittee on Lupus Anticoagulant/Antiphospholipid Antibody of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis [1]. For measurement of the activated Partial Thromboplastin Time (APTT), PTT-LA test (Diagnostica Stago) was used for screening and confirmed with mixing test using Staclot LA kit (Diagnostica Stago). The Dilute Russell's viper venom time (dRVVT) was screened and confirmed by the Gradipore LA test (Sydney New South Wales, Australia) and the kaolin clotting time (KCT) using a kaolin solution (Dade Behring, Liederbach, Germany).

Anticardiolipin antibodies (aCL) immunoglobulins (Ig) G and M, anti-beta2 glycoprotein I antibodies (aβ2GPI) IgG and IgM, and phosphatidylserine-dependent antiprothrombin antibodies (aPS/PT) IgG and IgM were assayed by enzyme-linked immunosorbent assay (ELISA) as described previously [2-4].

**References**

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Table S1. Antiplatelet agents

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Antiplatelet agents | Total (N=90) | Wf (N=13) | AP (N=41) | Wf + AP (N=21) | DAPT (N=15) |
| Aspirin (maximum dose 100mg/day ) | 64 (71.1%) | - | 34 (83.9%) | 18 (85.7%) | 12 (80.0%) |
| Ticlopidin (200 - 300mg/day) or Clopidogrel (50 - 75mg/day) | 12 (13.3%) | - | 2 (4.9%) | 0 (0%)) | 10 (66.7%) |
| Cilostazol (100 - 200mg/day) | 10 (11.1%) | - | 4 (9.8%) | 1 (4.8%) | 5 (33.3%) |
| Other antiplatelet agents\* | 6 (6.7%) | - | 1 (2.4%) | 2 (9.5%) | 3 (20.0%) |

\*Other antiplatelet agents included dipyridamole (maximum dose 400mg/day), beraprost sodium　(maximum dose 120μg/day), sarpogrelate hydrochloride (maximum dose 300mg/day) or dilazep dihydrochloride (maximum dose 150mg/day).

Results are presented as number of patients and percentage in each group. N: number of patients, Wf: warfarin monotherapy, AP: antiplatelet monotherapy, Wf + AP: warfarin and antiplatelet combination therapy, DAPT: dual antiplatelet therapy.

Table S2. Antiphospholipid score and antiphospholipid antibody profiles

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | Total (N=90) | Wf (N=13) | AP (N=41) | Wf + AP (N=21) | DAPT (N=15) | P-value |
| **aPL-S** | | 31 [14-50.5] | 33 [13.0-71.0] | 26 [13.0-42.0] | 35 [15.0-54.5] | 33 [20.0-41.0] | 0.434 |
| **aPL-S** ≥ **30** | | 47 (54.4%) | 8 (61.5%) | 18 (43.9%) | 13 (61.9%) | 8 (53.3%) | 0.493 |
| **Lupus anticoagulant** | | 74 (82.2%) | 9 (69.2%) | 32 (78.1%) | 19 (90.5%) | 14 (93.3%) | 0.214 |
|  | PTT-LA | 62 (68.9%) | 5 (38.5%) | 27 (65.9%) | 17 (81.0%) | 13 (86.7%) | 0.024＊ |
|  | KCT | 63 (70.0%) | 7 (53.9%) | 23 (56.1%) | 19 (90.5%) | 14 (93.3%) | 0.002＊ |
|  | dRVVT | 48 (53.3%) | 7 (53.9%) | 23 (56.1%) | 12 (57.1%) | 6 (40.0%) | 0.724 |
| **aCL (IgG or IgM)** | | 43 (47.8%) | 8 (61.5%) | 18 (43.9%) | 12 (57.1%) | 5 (33.3%) | 0.353 |
|  | IgG | 24 (26.7%) | 5 (38.5%) | 9 (22.0%) | 7 (33.3%) | 3 (20.0%) | 0.540 |
|  | IgM | 6 (6.7%) | 1 (7.7%) | 2 (4.9%) | 2 (9.5%) | 1 (6.7%) | 0.920 |
|  | IgG and IgM | 13 (14.4%) | 2 (15.4%) | 7 (17.1%) | 3 (14.3%) | 1 (6.7%) | 0.773 |
| **antiβ2GPI (IgG or IgM)** | | 49 (54.4%) | 11 (84.6%) | 21 (51.2%) | 8 (38.1%) | 9 (60%) | 0.047＊ |
|  | IgG | 35 (38.9%) | 8 (61.5%) | 12 (29.3%) | 7 (33.3%) | 8 (53.3%) | 0.115 |
|  | IgM | 7 (7.8%) | 1 (7.7%) | 5 (12.2%) | 0 | 1 (6.7%) | 0.222 |
|  | IgG and IgM | 7 (7.8%) | 2 (15.4%) | 4 (9.8%) | 1 (4.8%) | 0 | 0.287 |
| **aPS/PT (IgG or IgM)** | | 62 (68.9%) | 8 (61.5%) | 30 (73.2%) | 13 (61.9%) | 11 (73.3%) | 0.734 |
|  | IgG | 38 (42.2%) | 5 (38.5%) | 18 (43.9%) | 7 (33.3%) | 8 (53.3%) | 0.667 |
|  | IgM | 7 (7.8%) | 0 | 4 (9.8%) | 3 (14.3%) | 0 | 0.124 |
|  | IgG and IgM | 17 (18.9%) | 3 (23.1%) | 8 (19.5%) | 3 (14.3%) | 3 (20.0%) | 0.924 |

Results of antibody test are presented as number of antibody positive patients and percentage in each group.＊P-values <0.05. P-values are multiple comparison between 4 groups and were estimated using Kruskal-Wallis test. aPL-S: Antiphospholipid score aPL-S are presented as the median (IQR: Interquartile range 25th -75th). aPL: antiphospholipid antibodies, PTT-LA: Activated Partial Thromboplastin Time, KCT: Kaolin Clotting Time, dRVVT: Diluted Russell Viper Venom time, aCL: anticardiolipin antibodies, antiβ2GPI: anti-β2Glycoprotein I antibodies, aPS/PT: Phosphatidylserine-dependent antiprothrombin antibody, N: number of patients, Wf: warfarin monotherapy, AP: antiplatelet monotherapy, Wf + AP: warfarin and antiplatelet combination therapy, DAPT: dual antiplatelet therapy.

Table S3. Recurrent thrombosis, severe bleeding and death

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | Total (N=90) | Wf (N=13) | AP (N=41) | Wf + AP (N=21) | DAPT (N=15) | P-value |
| **Arterial thrombosis** | |  |  |  |  |  |  |
|  | Cerebral infarction | 29 (32.2%) | 9 (69.2%) | 13 (31.7%) | 6 (28.6%) | 1 (6.7%) | 0.004＊ |
|  | Coronary heart disease | 3 (3.3%) | 0 | 3 (7.3%) | 0 | 0 | 0.184 |
|  | Arterial ischemia in legs | 1 (1.1%) | 1 (7.7%) | 0 | 0 | 0 | 0.268 |
|  | Central retinal artery occlusion | 2 (2.2%) | 0 | 0 | 1 (4.8%) | 1 (6.7%) | 0.285 |
| **Venous thrombosis** | |  |  |  |  |  |  |
|  | Deep vein thrombosis | 3 (3.3%) | 1 (7.7%) | 2 (4.9%) | 0 | 0 | 0.352 |
|  | Branch retinal vein occlusion | 1 (1.1%) | 0 | 0 | 0 | 1 (6.7%) | 0.303 |
|  | Superficial thrombophlebitis | 1 (1.1%) | 0 | 0 | 1 (4.8%) | 0 | 0.345 |
| **Severe bleeding** | | 9 (10.0%) | 0 | 5 (12.2%) | 2 (9.5%) | 2 (13.3%) | 0.373 |
|  | Cerebral haemorrhage | 4 (4.4%) | 0 | 2 (4.9%) | 1 (4.8%) | 1 (6.7%) |  |
|  | Cardiovascular system haemorrhage | 2 (2.2%) | 0 | 1 (2.4%) | 0 | 1 (6.7%) |  |
|  | Alveolar haemorrhage | 1 (1.1%) | 0 | 0 | 1 (4.8%) | 0 |  |
|  | Gastrointestinal haemorrhage | 1 (1.1%) | 0 | 1 (2.4%) | 0 | 0 |  |
|  | Multiple subcutaneous haemorrhage | 1 (1.1%) | 0 | 1 (2.4%) | 0 | 0 |  |
| **Mortality** | | 14 (15.6%) | 1 (7.7%) | 5 (12.2%) | 4 (19.1%) | 4 (26.7%) | 0.476 |
|  | Related to bleeding | 3 (3.3%) | 0 | 1 (2.4%) | 1 (4.8%) | 1 (6.7%) |  |
|  | Related to thrombosis recurrence | 2 (2.2%) | 1 (7.7%) | 0 | 1 (4.8%) | 0 |  |

＊P-values <0.05. P-values are multiple comparison between 4 groups and were estimated using Kruskal-Wallis test. Severe bleeding event was defined as the events that required hospitalization and/or blood transfusion. N: number of patients, Wf: warfarin monotherapy, AP: antiplatelet monotherapy, Wf + AP: warfarin and antiplatelet combination therapy, DAPT: dual antiplatelet therapy

Table S4. Risk factors for recurrent thrombosis

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | **Univariate analysis** | |  | **Multivariate analysis** | |  |
|  | | Unadjusted Hazard Ratio | (95％ CI) | P value | Adjusted Hazard Ratio | (95％ CI) | P value |
| Warfarin monotherapy | | 2.93 | ( 1.394 - 5.731) | 0.007\* | 4.23 | ( 1.686 – 10.378) | 0.003\* |
| Male | | 1.50 | ( 0.672 - 3.046 ) | 0.302 | 1.05 | ( 0.442 - 2.296 ) | 0.909 |
| Age > 50 | | 1.16 | ( 0.618 - 2.218 ) | 0.654 | 1.46 | ( 0.727 – 3.077 ) | 0.295 |
| Steroid | | 1.09 | ( 0.554 - 2.253 ) | 0.813 | 1.01 | ( 0.492 - 2.175 ) | 0.984 |
| Smoking | | 1.43 | ( 0.722 - 2.714 ) | 0.295 | 1.63 | ( 0.782 - 3.271 ) | 0.188 |
| Hypertension | | 1.34 | ( 0.715 - 2.608 ) | 0.364 | 1.18 | ( 0.602 - 2.382 ) | 0.637 |
| Dyslipidemia | | 1.06 | ( 0.559 - 1.980 ) | 0.859 | 1.49 | ( 0.692 – 3.317 ) | 0.314 |
| Diabetes Mellitus | | 1.41 | ( 0.565 - 3.045 ) | 0.436 | 1.76 | ( 0.683 – 4.036 ) | 0.225 |
| aPL-S ≥ 30 | | 1.04 | ( 0.559 - 1.985 ) | 0.895 | 1.01 | ( 0.484 - 2.063 ) | 0.990 |

＊P-values <0.05. P-values were estimated using Cox Regression Analysis. aPL-S: the antiphospholipid score, CI: Confidence Interval

Figure legend

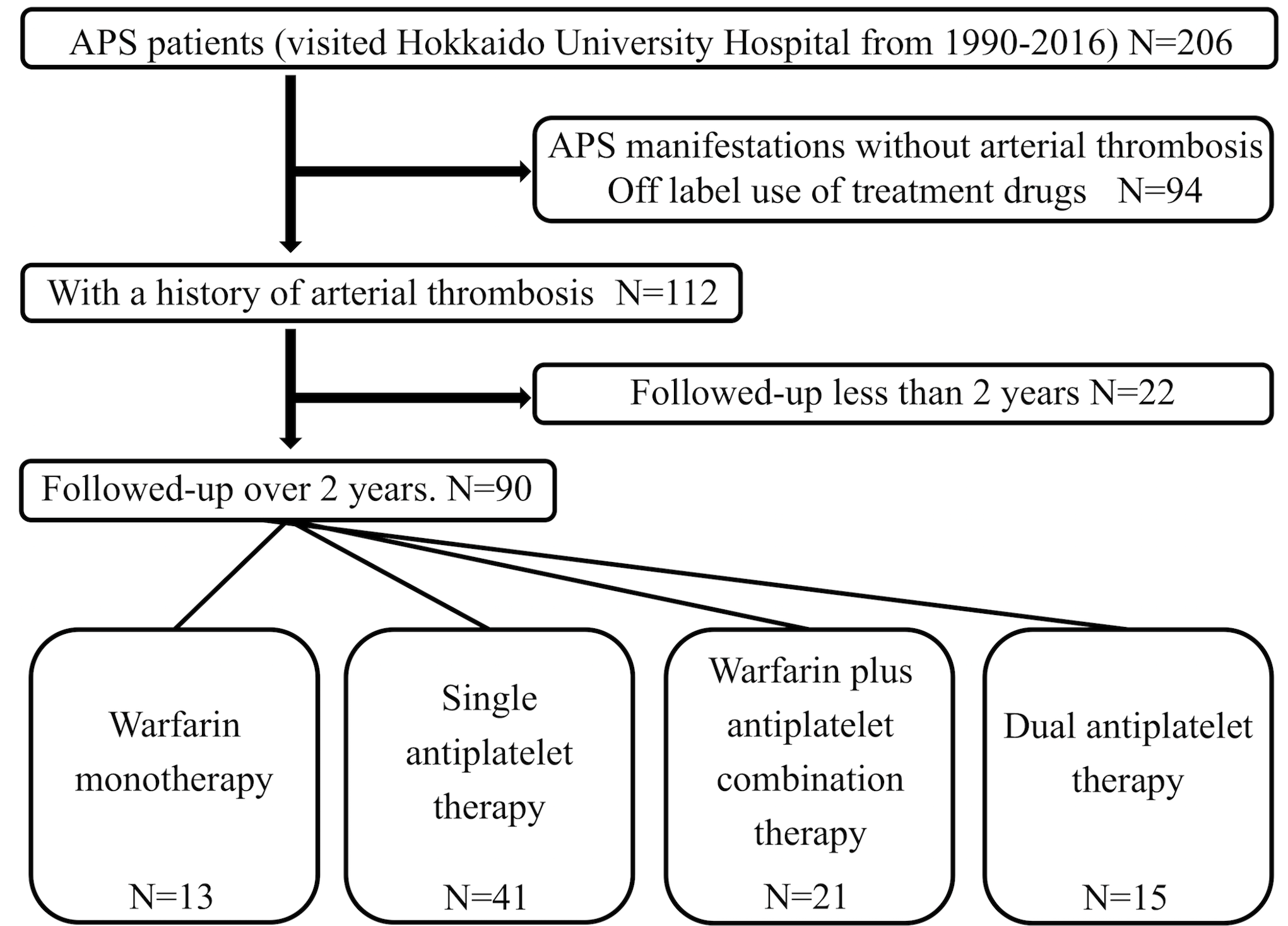


Figure S1. Flow chart of the study design

Patients were categorized into four groups according to the therapy used for secondary prevention of thrombosis. APS: antiphospholipid syndrome, N: number of patients.

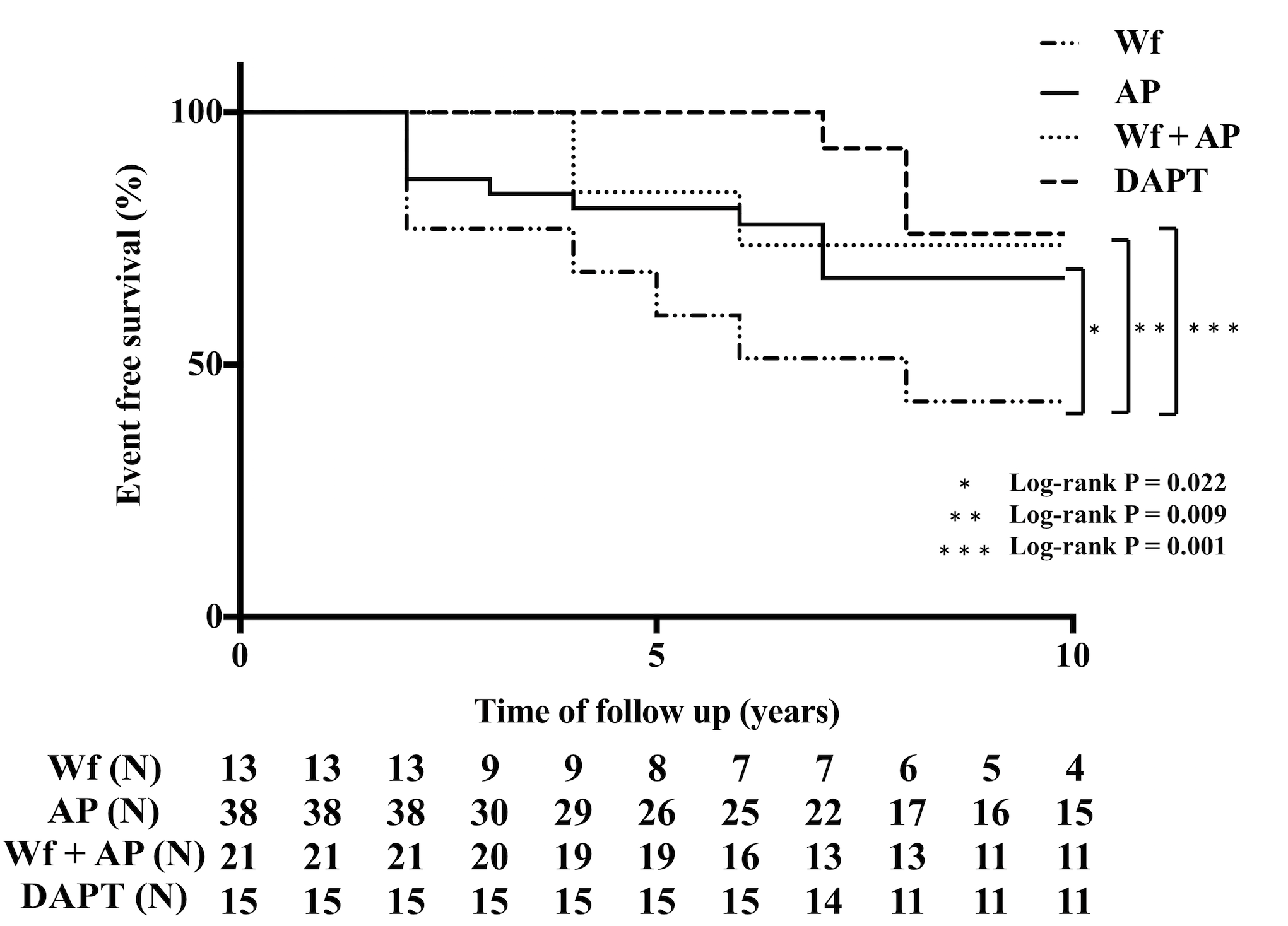


Figure S2. Ten-years thrombosis-free survival (sub-analysis)

Data were estimated using the Kaplan-Meier curves. P-values <0.05. The sub-analysis excluding patients with recurrence of cardiac events were performed. Warfarin (Wf) was less effective for prevention of thrombosis than other treatment options.

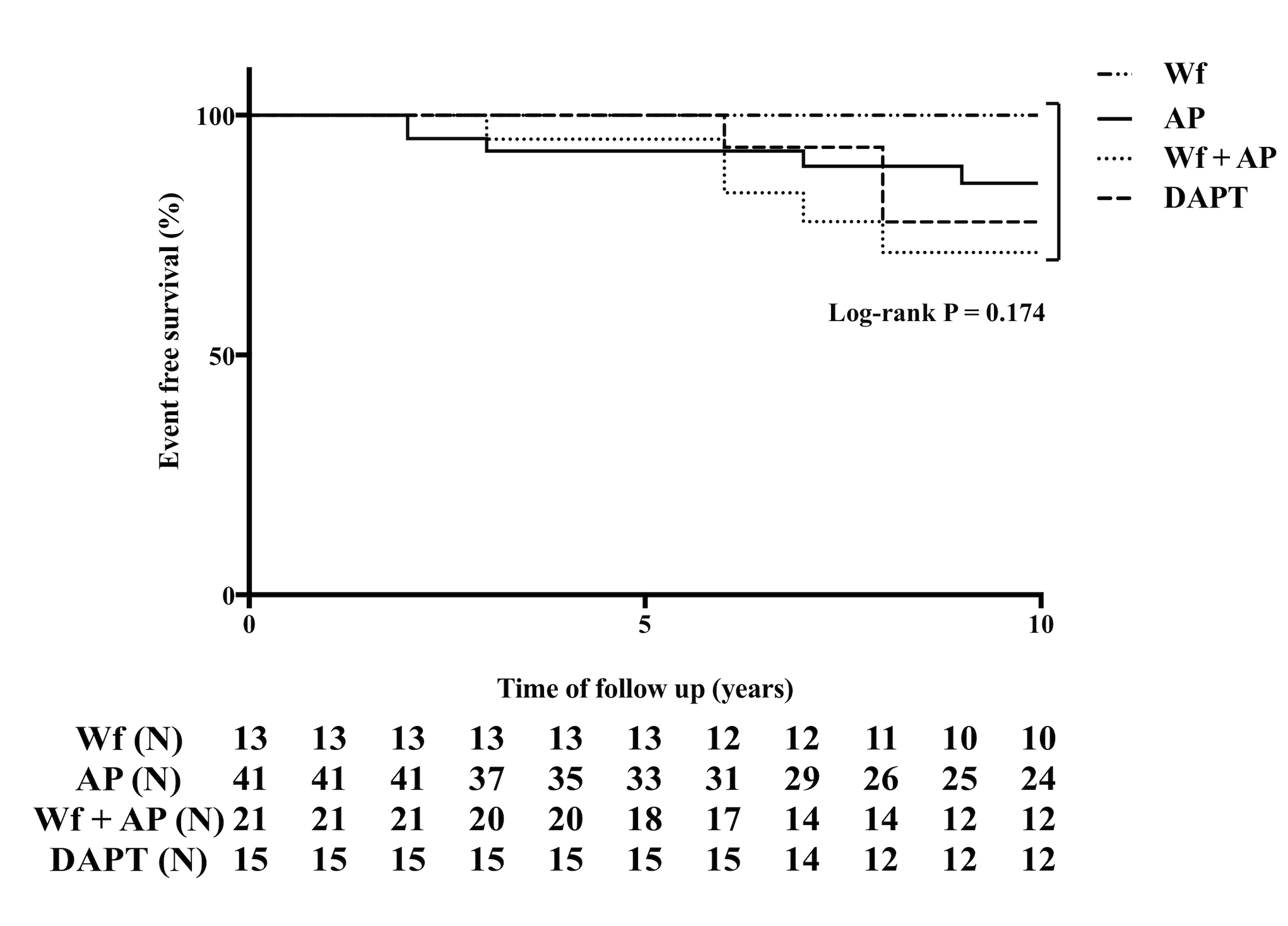


Figure S3. Ten-years adverse events-free survival

Data were estimated using the Kaplan-Meier curves. P-values <0.05. Adverse events-free survival curves. Adverse events were defined as severe bleeding and death. No statistically significant difference in frequency of adverse events was observed between the 4 groups (Log-rank p = 0.174). The case of mortality in Wf monotherapy died 15 years later from the start of the observation. N: number of patients, Wf: warfarin monotherapy, AP: antiplatelet monotherapy, Wf + AP: warfarin and antiplatelet combination therapy, DAPT: dual antiplatelet therapy.