

## Supplementary Online Content

Sleem A, Efron MB, Stebbins A, et al. Effectiveness and safety of enteric coated vs uncoated aspirin in patients with cardiovascular disease: a secondary analysis of the ADAPTABLE randomized clinical trial. Published online October 4, 2023. *JAMA Cardiol*. doi:10.1001/jamacardio.2023.3364

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This supplementary material has been provided by the authors to give readers additional information about their work.

| eTable 1. Demographic and Presenting Characteristics, Medical History, and Medications by Aspirin Formulation Regardless of Dose |   |                             |                       |         |
|--|---|-----------------------------|-----------------------|---------|
| Characteristic <sup>a</sup>  | All participants reporting formulation of ASA used (N=10,678) | Enteric coated ASA (N=7366) | Uncoated ASA (N=3312) | P value |
| Age (yrs)  |   |                             |                       | <.0001  |
| n  | 10678   | 7366                        | 3312                  |         |
| Median (25th, 75th)  | 68.0 (61.3, 73.7)   | 68.3 (61.8, 73.8)           | 67.2 (60.4, 73.3)     |         |
| Female   | 3393 (31.8%)  | 2304 (31.3%)                | 1089 (32.9%)          | 0.10    |
| Randomized Dose  |   |                             |                       | <.0001  |
| 81-mg  | 5374 (50.3%)  | 4074 (55.3%)                | 1300 (39.3%)          |         |
| 325mg  | 5304 (49.7%)  | 3292 (44.7%)                | 2012 (60.7%)          |         |
| History of PAD   |   |                             |                       | 0.14    |
| No   | 7980 (76.6%)  | 5539 (77.0%)                | 2441 (75.7%)          |         |
| Yes  | 2436 (23.4%)  | 1652 (23.0%)                | 784 (24.3%)           |         |
| Race   |   |                             |                       | 0.49    |
| White  | 8965 (84.0%)  | 6218 (84.4%)                | 2747 (82.9%)          |         |
| Black or African American  | 900 (8.4%)  | 592 (8.0%)                  | 308 (9.3%)            |         |

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|--|---|-----------------------------|-----------------------|---------|
| Characteristic <sup>a</sup>  | All participants reporting formulation of ASA used (N=10,678) | Enteric coated ASA (N=7366) | Uncoated ASA (N=3312) | P value |
| Other  | 482 (4.5%)  | 331 (4.5%)                  | 151 (4.6%)            |         |
| Prefer not to say or missing   | 331 (3.1%)  | 225 (3.1%)                  | 106 (3.2%)            |         |
| Ethnicity  |   |                             |                       | 0.23    |
| Hispanic   | 270 (2.5%)  | 181 (2.5%)                  | 89 (2.7%)             |         |
| Non-hispanic   | 10051 (94.2%)   | 6954 (94.4%)                | 3097 (93.6%)          |         |
| Did not respond  | 354 (3.3%)  | 231 (3.1%)                  | 123 (3.7%)            |         |
| Current Smoker   | 1006 (9.4%)   | 640 (8.7%)                  | 366 (11.1%)           | 0.0001  |
| Baseline P2Y <sub>12</sub> inhibitor use   | 2300(22.0%)   | 1587(22.0%)                 | 713(22.0%)            | 0.99    |
| <b>EHR and Claims Information</b>  |   |                             |                       |         |
| Weight (kg) (N)  | 9313  | 6451                        | 2862                  |         |
| Median (IQR)   | 90.0 (78.2, 103.6)  | 90.0 (78.2, 103.6)          | 90.9 (78.6, 104.5)    | 0.09    |
| BMI (N)  | 9074  | 6293                        | 2781                  |         |
| Median (IQR)   | 30.0 (26.7, 34.2)   | 30.0 (26.6, 34.1)           | 30.2 (26.9, 34.5)     | 0.03    |
| Atrial Fibrillation/Flutter  | 884 (8.5%)  | 611 (8.5%)                  | 273 (8.5%)            | 0.96    |

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|--|---|-----------------------------|-----------------------|---------|
| Characteristic <sup>a</sup>  | All participants reporting formulation of ASA used (N=10,678) | Enteric coated ASA (N=7366) | Uncoated ASA (N=3312) | P value |
| History of Bleeding <sup>†</sup>   | 894 (8.6%)  | 595 (8.3%)                  | 299 (9.3%)            | 0.09    |
| Significant GI Bleed   | 661 (6.3%)  | 446 (6.2%)                  | 215 (6.7%)            | 0.37    |
| History of ICH   | 155 (1.5%)  | 105 (1.5%)                  | 50 (1.6%)             | 0.73    |
| History of bleeding disorder   | 126 (1.2%)  | 73 (1.0%)                   | 53 (1.6%)             | 0.007   |
| Prior CABG   | 2525 (24.2%)  | 1763 (24.5%)                | 762 (23.6%)           | 0.33    |
| CHF  | 2392 (23.0%)  | 1646 (22.9%)                | 746 (23.1%)           | 0.79    |
| Chronic Kidney Disease   | 1835 (17.6%)  | 1265 (17.6%)                | 570 (17.7%)           | 0.92    |
| COPD   | 1938 (18.6%)  | 1329 (18.5%)                | 609 (18.9%)           | 0.63    |
| Diabetes   | 3988 (38.3%)  | 2696 (37.5%)                | 1292 (40.1%)          | 0.01    |
| Hypertension   | 8873 (85.2%)  | 6147 (85.5%)                | 2726 (84.5%)          | 0.20    |
| Hyperlipidemia   | 9232 (88.6%)  | 6426 (89.4%)                | 2806 (87.0%)          | <0.001  |
| Prior MI   | 3739(35.9%)   | 2547 (35.4%)                | 1192 (37.0%)          | 0.13    |
| Peptic Ulcer Disease   | 312 (3.0%)  | 211 (2.9%)                  | 101 (3.1%)            | 0.58    |
| PCI/CABG   | 5648 (54.2%)  | 3911 (54.4%)                | 1737 (53.9%)          | 0.62    |

eTable 1. Demographic and Presenting Characteristics, Medical History, and Medications by Aspirin Formulation Regardless of Dose

| Characteristic <sup>a</sup> | All participants reporting formulation of ASA used (N=10,678) | Enteric coated ASA (N=7366) | Uncoated ASA (N=3312) | P value |
|-----------------------------|---|-----------------------------|-----------------------|---------|
| Prior Aspirin Use           | 10275 (96.2%)   | 7127 (96.8%)                | 3148 (95.0%)          | <.0001  |
| Prior Aspirin Dose          |   |                             |                       | <.0001  |
| 81-mg                       | 8714 (84.9%)  | 6125 (86.0%)                | 2589 (82.5%)          |         |
| 162 mg                      | 250 (2.4%)  | 179 (2.5%)                  | 71 (2.3%)             |         |
| 325 mg                      | 1295 (12.6%)  | 815 (11.4%)                 | 480 (15.3%)           |         |
| Other                       | 16 (0.2%)   | 8 (0.1%)                    | 8 (0.3%)              |         |
| ARM                         | 2767(38.4%)   | 2767(38.4%)                 | 1137(35.1%)           | <0.002  |

<sup>a</sup> All values n (CIR%) except as noted

<sup>b</sup> History of bleeding includes GI Bleed, ICH and Bleeding disorder

ARM – acid reducing medication, ASA – aspirin, BMI - body mass index, CABG – coronary artery bypass graft surgery, CHF – congestive heart failure, COPD – chronic obstructive pulmonary disease, EHR – electronic health record, GI – gastrointestinal, ICH – intracranial hemorrhage, MI – myocardial infarction, PAD – peripheral arterial disease, PCI – percutaneous coronary intervention

| <b>eTable 2. Clinical End Points by Aspirin Formulation [Adjusted] Regardless of Dose</b> |                          |                          |                           |                |
|---|--------------------------|--------------------------|---------------------------|----------------|
|   | <b>Uncoated ASA</b>      | <b>Coated ASA</b>        | <b>Adjusted Cox Model</b> |                |
|   | <b>Event (CI rate %)</b> | <b>Event (CI rate %)</b> | <b>HR (95% CI)</b>        | <b>P Value</b> |
| Death/MI/Stroke   | 266 (7.9%)               | 543 (6.8%)               | 0.94 (0.80, 1.09)         | 0.40           |
| All-cause mortality   | 155 (4.3%)               | 301 (3.7%)               | 0.91 (0.75, 1.11)         | 0.35           |
| MI  | 101 (3.4%)               | 219 (2.9%)               | 0.99 (0.78, 1.26)         | 0.94           |
| Stroke  | 43 (1.2%)                | 90 (1.2%)                | 0.93 (0.64, 1.35)         | 0.69           |
| Major Bleeding  | 24 (0.7%)                | 45 (0.6%)                | 0.82 (0.49, 1.37)         | 0.46           |
| PCI or CABG   | 195 (6.4%)               | 477 (6.4%)               | 1.10 (0.92, 1.30)         | 0.29           |
| TIA   | 4 (0.1%)                 | 24 (0.3%)                | 2.61 (0.90, 7.54)         | 0.08           |
| GI Bleed  | 54 (1.5%)                | 88 (1.2%)                | 0.72 (0.51, 1.02)         | 0.06           |

Cumulative Incidence is reported at 26.2 months from randomization [the median follow up time for all-cause mortality in Adaptable]. Primary endpoint, nonfatal MI, all-cause mortality and revascularization adjustment measures are randomized treatment, age, current smoking, randomized follow up strata, no internet use at randomization, race, ethnicity, history of CAD, MI, CABG, PCI, CVD, hypertension, hyperlipidemia, atrial fibrillation, CHF, PAD, prior aspirin use, diabetes, history of bleeding, BMI, and baseline P2Y<sub>12</sub> inhibitor use. Stroke, TIA and GI bleeding adjustment measures are randomized treatment, age, current smoking, ethnicity, race, history of CAD, CVD, hypertension, hyperlipidemia, atrial fibrillation, CHF, PAD, diabetes, prior aspirin use, baseline P2Y<sub>12</sub>, diabetes, history of bleeding, and BMI.

ASA - aspirin, BMI – body mass index, CAD – coronary artery disease, CABG - coronary artery bypass grafting, CVD – cardiovascular disease, GI – gastrointestinal, MI – myocardial infarction, PAD - peripheral arterial disease, TIA – transient ischemic attack

**eTable 3. Interaction of Acid Reducing Medication and Aspirin Formulation Type Regardless of Aspirin Dose on the Cumulative Incidence of Study End Points**

|                     | Enteric coated Aspirin | Uncoated Aspirin  | Adjusted Cox model  |
|---------------------|------------------------|-------------------|---------------------|
|                     | Event (CI rate %)      | Event (CI rate %) | Interaction P Value |
| Death/MI/stroke     | 543 (6.8%)             | 266 (7.9%)        | 0.55                |
| All-cause mortality | 301 (3.7%)             | 155 (4.3%)        | 0.75                |
| MI                  | 219 (2.9%)             | 101 (3.4%)        | 0.49                |
| Stroke              | 90 (1.2%)              | 43 (1.2%)         | 0.10                |
| Major bleeding      | 45 (0.6%)              | 24 (0.7%)         | 0.52                |
| PCI or CABG         | 477 (6.4%)             | 195 (6.4%)        | 0.45                |
| TIA                 | 24 (0.3%)              | 4 (0.1%)          | 0.91                |
| GI bleed            | 88 (1.2%)              | 54 (1.5%)         | 0.64                |

CI reported at 26.2 months from randomization (median follow-up time for all-cause mortality in ADAPTABLE)

Primary endpoint, MI, all-cause mortality, and revascularization adjustment measures are randomized treatment, age, current smoking, randomized follow-up strata, no internet use at randomization, race, ethnicity, history of CAD, MI, CABG, PCI, CVD, hypertension, hyperlipidemia, atrial fibrillation, CHF, PAD, prior aspirin use, BMI, and baseline P2Y<sub>12</sub> inhibitor.

Major bleeding adjustment measures are randomized treatment, diabetes, age, sex, hypertension, baseline P2Y<sub>12</sub> inhibitor, and BMI.

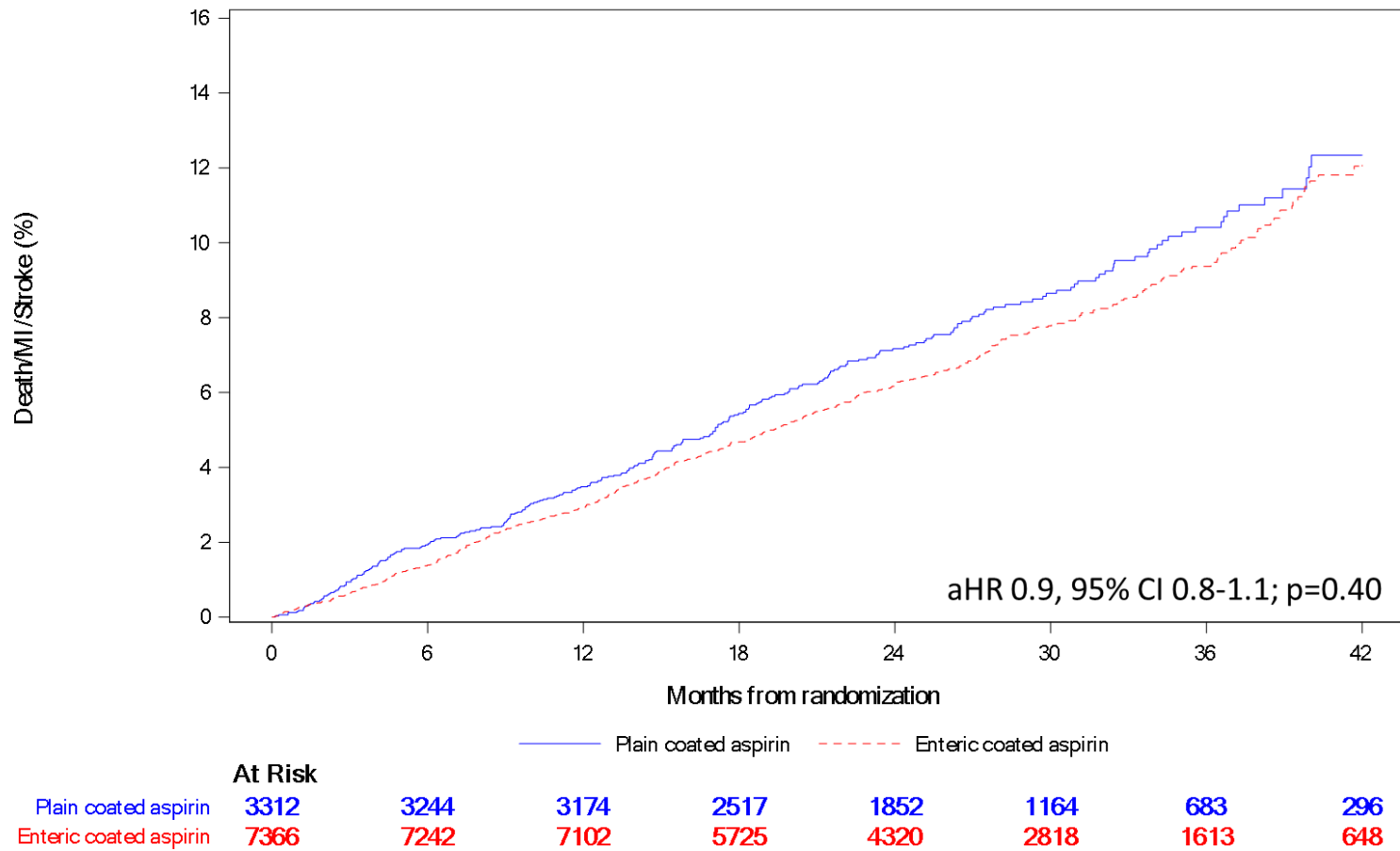
Stroke, TIA, and GI bleeding adjustment measures are randomized treatment, age, current smoking, ethnicity, race, history of CAD, CVD, hypertension, hyperlipidemia, atrial fibrillation, CHF, PAD, diabetes, prior aspirin use, baseline P2Y<sub>12</sub> inhibitor, and BMI.

ASA – aspirin, BMI - body mass index, CAD - coronary artery disease, CABG – coronary artery bypass graft surgery, CHF – congestive heart failure, CI – cumulative incidence, COPD – chronic obstructive pulmonary disease, CVD – cardiovascular disease, EHR – electronic health record, GI – gastrointestinal, ICH – intracranial hemorrhage, MI – myocardial infarction, PAD – peripheral arterial disease, PCI – percutaneous coronary intervention

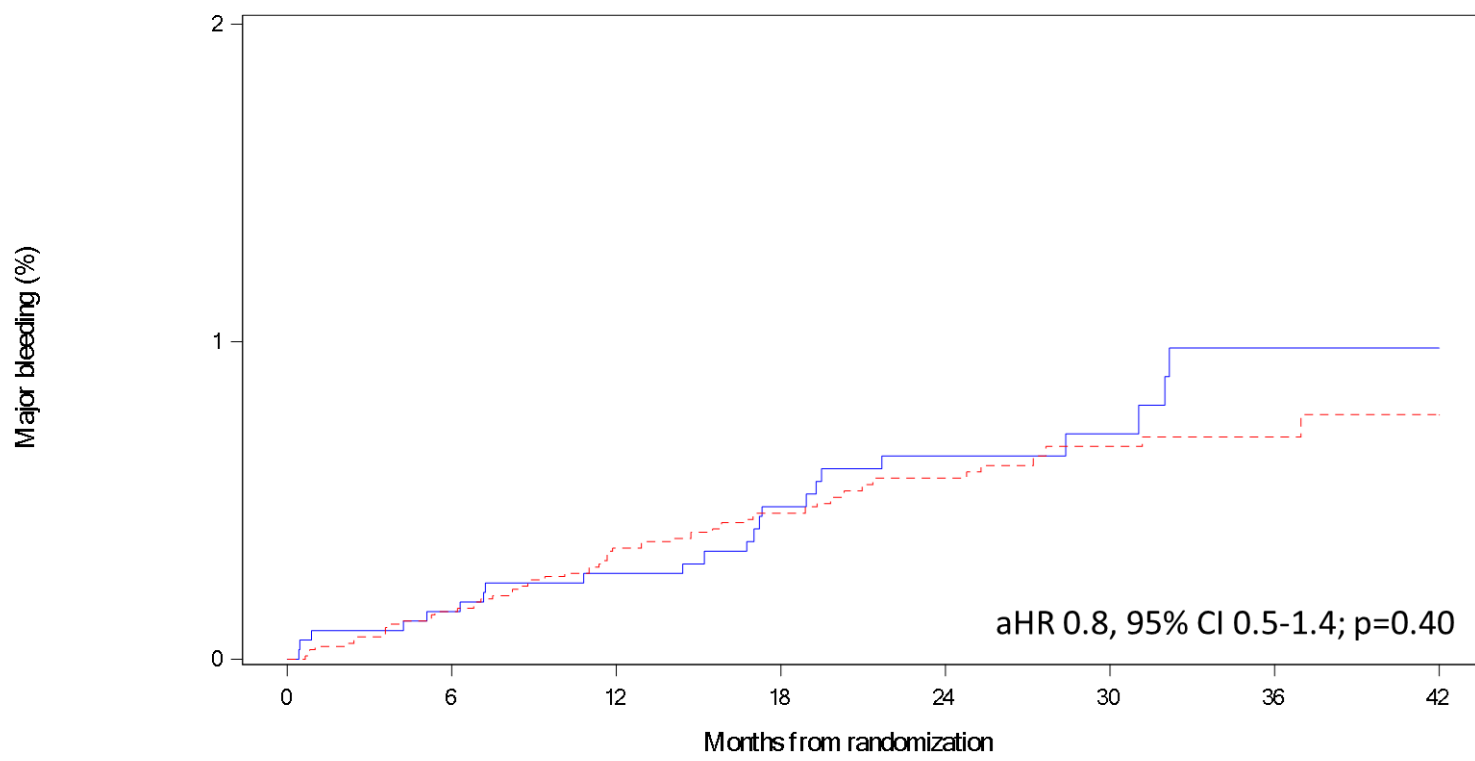


| eTable 4. Event Rates of Study End Points by Formulation Type and Time-Dependent Reported Aspirin Use   |                       |                        |                   |         |                   |         |
|---|-----------------------|------------------------|-------------------|---------|-------------------|---------|
|   |                       |                        | Unadjusted Model  |         | Adjusted Model    |         |
|   | Taking 81 mg rate (N) | Taking 325 mg rate (N) | HR (95% CI)       | P Value | HR (95% CI)       | P Value |
| Primary Endpoint [Death,MI,Stroke]<br>Overall interaction p value   |                       |                        |                   | 0.85    |                   | 0.87    |
| Enteric coated  | 3.7 (340)             | 2.8 (129)              | 1.30 (1.06, 1.60) | 0.01    | 1.27 (1.03, 1.55) | 0.02    |
| Uncoated  | 3.8 (141)             | 3.2 (66)               | 1.16 (0.87, 1.56) | 0.32    | 1.12 (0.83, 1.50) | 0.45    |
| All Cause Death: Overall interaction p value  |                       |                        |                   | 0.96    |                   | 0.95    |
| Enteric coated  | 1.9 (183)             | 1.4 (67)               | 1.28 (0.97, 1.70) | 0.08    | 1.22 (0.92, 1.61) | 0.17    |
| Uncoated  | 2.3 (88)              | 1.5 (31)               | 1.47 (0.98, 2.22) | 0.06    | 1.38 (0.91, 2.08) | 0.12    |
| Primary Safety Endpoint [Major bleeding]:<br>Overall interaction p value  |                       |                        |                   | 0.86    |                   | 0.88    |
| Enteric coated  | 0.28 (26)             | 0.3 (13)               | 1.02 (0.52, 1.99) | 0.95    | 1.04 (0.53, 2.02) | 0.92    |
| Uncoated  | 0.35 (13)             | 0.2 (4)                | 1.83 (0.60, 5.63) | 0.29    | 1.79 (0.58, 5.48) | 0.32    |
| Rates and HR reflect the effect of the time-varying reported dose on the end point. Rates are calculated as annualized event rates (events per 100 patient-years).  |                       |                        |                   |         |                   |         |
| Adjustment model includes age, race, ethnicity, prior aspirin dose, prior MI, prior PCI, history of atrial fibrillation, non-internet user at randomization, history of bleeds, and baseline P2Y <sub>12</sub> use. |                       |                        |                   |         |                   |         |
| CI – confidence interval, HR- hazard ratio, MI – myocardial infarction, N - number  |                       |                        |                   |         |                   |         |

eFigure 1. Cumulative Incidence of the Primary End Point (All-Cause Death, Myocardial Infarction, or Stroke) by EC-ASA and Uncoated (Plain Coated) ASA Regardless of Aspirin Dose



eFigure 2. Cumulative Incidence Function of Major Bleeding by EC-ASA and Uncoated (Plain Coated) ASA Regardless of Aspirin Dose



|                        | 0    | 6    | 12   | 18   | 24   | 30   | 36   | 42  |
|------------------------|------|------|------|------|------|------|------|-----|
| <b>At Risk</b>         |      |      |      |      |      |      |      |     |
| Plain coated aspirin   | 3312 | 3274 | 3231 | 2578 | 1912 | 1214 | 710  | 320 |
| Enteric coated aspirin | 7366 | 7298 | 7200 | 5862 | 4443 | 2911 | 1672 | 676 |