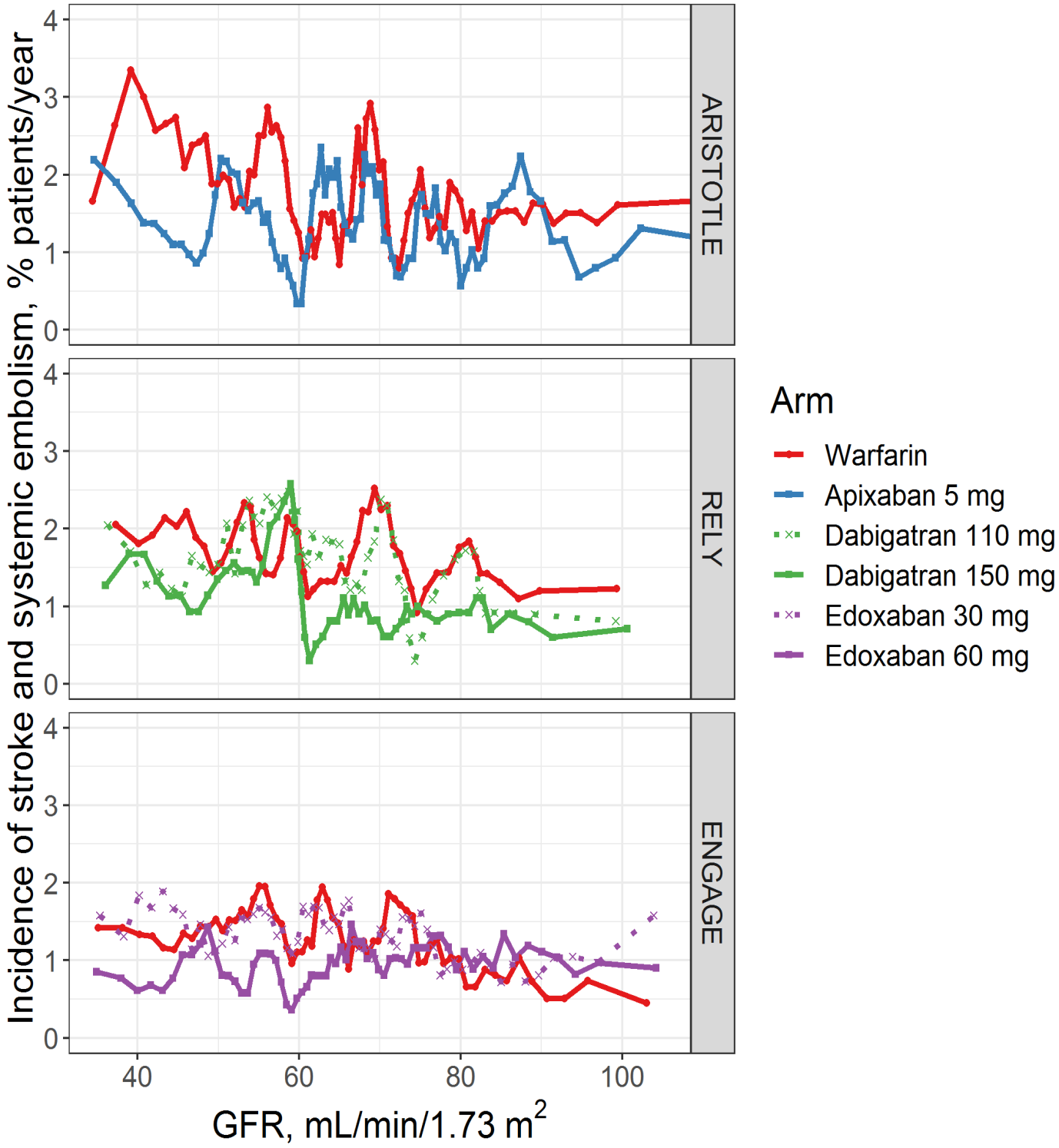
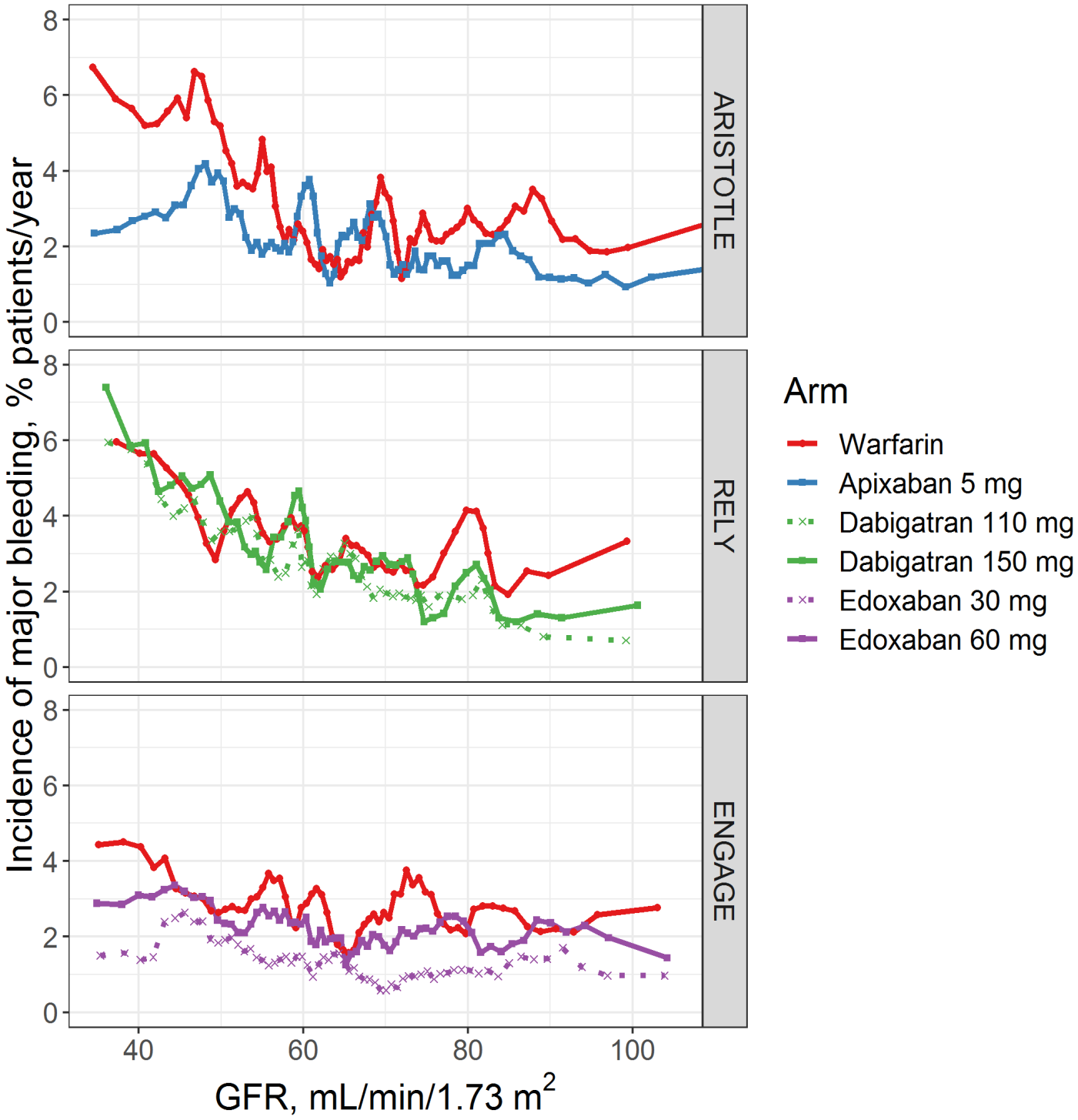
Figure S1: Rolling average incidence of a) stroke/SEE, b) major hemorrhage, and c) composite endpoint versus kidney fucntion for ARITSTOLE (top), RE-LY (middle), and ENGAGE (bottom) trials. Warfarin (solid, red, circles) was a common comparator arm included in each trial. The investigational treatment arms from ARISTOTLE (apixaban 5 mg – blue, solid, circle), RE-LY (dabigatran 110 mg – green, dotted, 'x'; dabigatran 150 mg – green, solid, square), and ENGAGE (edoxaban 30 mg – purple, dotted, 'x'; edoxaban 60 mg – purple, solid, square) are included on each figure.

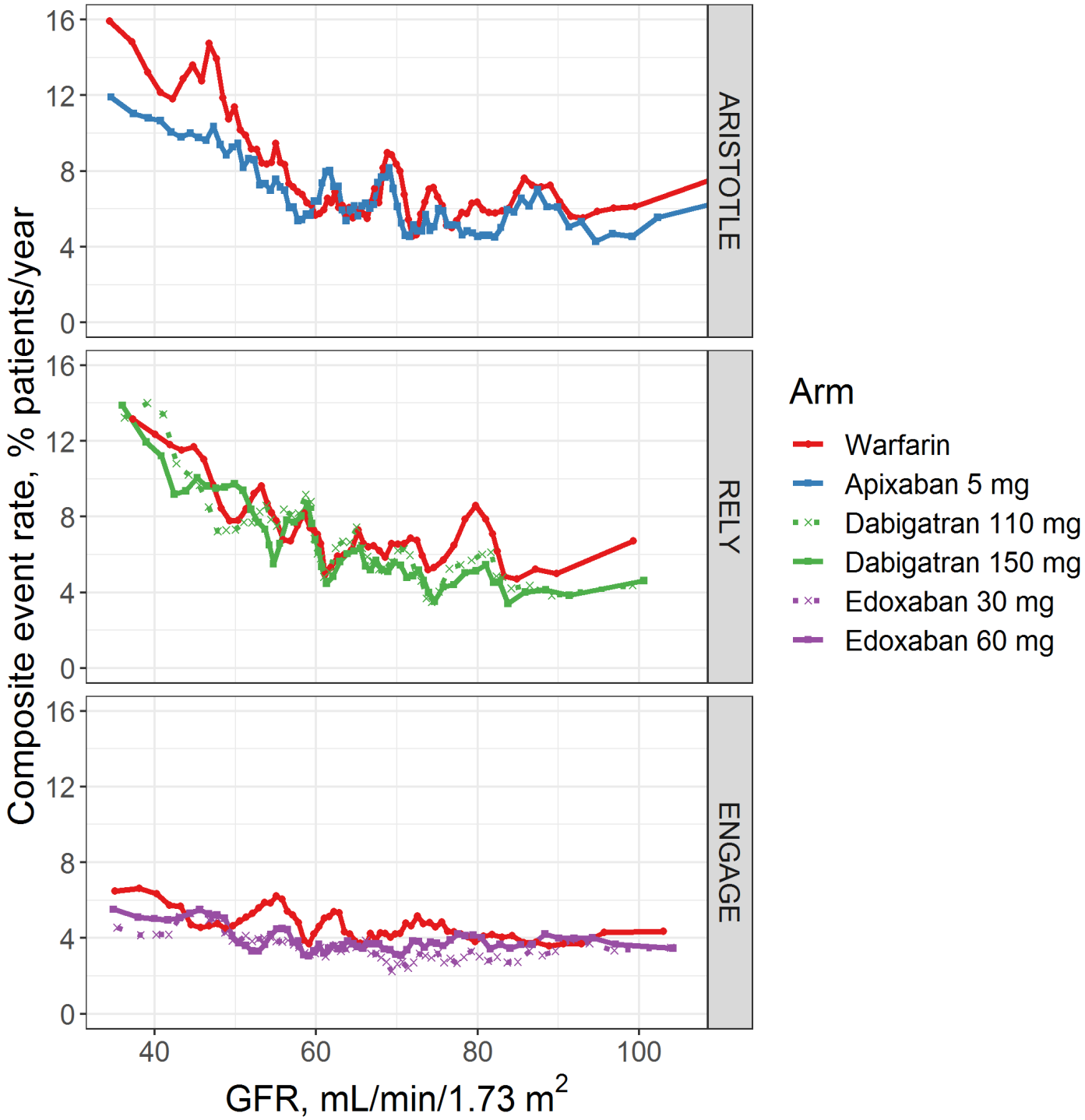
a)



b)


ARISTOTLE
RELY
ENGAGE
Incidence of major bleeding, % patients/year
0
2
4
6
8
40
60
80
100
GFR, mL/min/1.73 m2
Arm
Warfarin
Apixaban 5 mg
Dabigatran 110 mg
Dabigatran 150 mg
Edoxaban 30 mg
Edoxaban 60 mg

c)



Footnote: A moving average[1] of the stroke and systemic embolism (SEE), major bleeding and composite (stroke/SEE/major bleeding/death) endpoint versus GFR was calculated for each treatment arm to depict the continuous relationship between event rate and this independent variable. Subjects in each treatment arm were ordered sequentially from lowest GFR to highest GFR value. The event rate and median GFR was calculated for the first 1000 patients (window width of 1000 patients) and plotted on the figure. The window was then shifted forward, removing the last 100 patients from the sequence and including the next 100 patients in the sequence (window frame of 100 patients). This process was repeated until the last patient in the treatment arm was reached.

1 Ref: Weisstein, Eric W. "Moving Average." From MathWorld--A Wolfram Web Resource. http://mathworld.wolfram.com/MovingAverage.html