

SUPPLEMENTAL MATERIAL

Table S1. Adjusted Hazards Ratios for Risk of CVD, IHD, Stroke/TIA and Heart Failure Events, and Population Attributable Fraction Associated With PDC by Beneficiaries Taking One vs Two or More Antihypertensives, Medicare 2008-2014 Cohort

Characteristics	Proportion Days Covered			p-trend [†]	Adjusted PAF (95% CI) [‡]
	<40% (low adherence)	40% to 79% (intermediate adherence)	≥80% (high adherence)		
Taking one antihypertensive*					
Number of Medicare beneficiaries and percent (%)	10 306 (10.7%)	32 353 (33.5%)	53 808 (55.8%)		
CVD					
Events [§]	4 311 (4 242)	13 927 (13 792)	12 232 (11 991)		
Total person years	44 871	149 301	292 312		
Crude incidence, per 1000 person years	96.1 (96.0-96.2)	93.3 (93.2-93.3)	41.8 (41.8-41.9)		
HR adjusted for age, sex, and race only (95% CI)	1.0	0.97 (0.94-1.0)	0.42 (0.40-0.43)	<.001	
Fully-adjusted HR	1.0	1.0 (0.96-1.04)	0.45 (0.43-0.46)	<.001	33.8 (32.4-35.1)
IHD					
IHD events [§]	2 398 (2 395)	7 964 (7 961)	6 554 (6 541)		
Total person years	48 542	161 201	300 356		
Crude incidence, per 1000 person years	49.4 (49.3-49.5)	49.4 (49.4-49.4)	21.8 (21.8-21.8)		
HR adjusted for age, sex, and race only (95% CI)	1.0	0.99 (0.95-1.04)	0.43 (0.41-0.45)	<.001	
Fully-adjusted HR	1.0	1.01 (0.96-1.05)	0.45 (0.43-0.47)	<.001	34.3 (32.4-36.1)
Stroke/TIA					
Stroke/TIA events [§]	717 (714)	2 017 (2 013)	1 743 (1 731)		
Total person years	54 910	182 642	313 463		
Crude incidence, per 1000 person years	13.1 (13.0-13.1)	11.0 (11.0-11.1)	5.56 (5.55-5.57)		
HR adjusted for age, sex, and race only (95% CI)	1.0	0.85 (0.78-0.92)	0.42 (0.39-0.46)	<.001	
Fully-adjusted HR	1.0	0.86 (0.79-0.94)	0.44 (0.40-0.48)	<.001	31.4 (27.6-35.0)
Heart failure					
Heart failure events [§]	890 (889)	2 667 (2 658)	2 537 (2 526)		

Total person years	53 324	177 744	310 080		
Crude incidence, per 1000 person years	16.7 (16.7-16.8)	15.0 (15.0-15.1)	8.18 (8.17-8.19)		
HR adjusted for age, sex, and race only (95% CI)	1.0	0.93 (0.86-1.0)	0.52 (0.48-0.56)	<.0001	
Fully-adjusted HR	1.0	1.0 (0.93-1.08)	0.59 (0.55-0.64)	<.0001	23.9 (20.8-27.0)
Taking two or more antihypertensives*					
Number of Medicare beneficiaries and percent (%)	3 593 (6.1%)	14 728 (24.9%)	40 809 (69.0%)		
CVD					
Events [§]	1 636 (1 615)	6 464 (6 395)	8 628 (8457)		
Total person years	15 730	67 968	228 439		
Crude incidence, per 1000 person years	104 (104-105)	95.1 (95.0-95.2)	37.8 (37.7-37.8)		
HR adjusted for age, sex, and race only (95% CI)	1.0	0.93 (0.86-1.0)	0.52 (0.48-0.56)	<.001	
Fully-adjusted HR	1.0	1.0 (0.93-1.08)	0.59 (0.55-0.64)	<.001	25.6 (24.4-26.9)
IHD					
IHD events [§]	881 (881)	3 639 (3 635)	4 555 (4 545)		
Total person years	17 139	73 799	23 4143		
Crude incidence, per 1000 person years	51.4 (51.3-51.5)	49.3 (49.3-49.4)	19.5 (19.4-19.5)		
HR adjusted for age, sex, and race only (95% CI)	1.0	0.93 (0.86-1.0)	0.52 (0.48-0.56)	<.001	
Fully-adjusted HR	1.0	1.0 (0.93-1.08)	0.59 (0.55-0.64)	<.001	26.2 (24.5-27.8)
Stroke/TIA					
Stroke/TIA events [§]	262 (260)	911 (909)	1 104 (1 093)		
Total person years	19 364	84 145	243 497		
Crude incidence, per 1000 person years	13.5 (13.5-13.6)	10.8 (10.8-10.8)	4.53 (4.53-4.54)		
HR adjusted for age, sex, and race only (95% CI)	1.0	0.93 (0.86-1.0)	0.52 (0.48-0.56)	<.001	
Fully-adjusted HR	1.0	1.0 (0.93-1.08)	0.59 (0.55-0.64)	<.001	23.9 (20.6-27.1)
Heart failure					
Heart failure events [§]	379 (379)	1320 (1 314)	1 925 (1 914)		
Total person years	18 636	81 145	240 215		

Crude incidence, per 1000 person years	20.3 (20.3-20.4)	16.3 (16.2-16.3)	8.01 (8.00-8.02)		
HR adjusted for age, sex, and race only (95% CI)	1.0	0.93 (0.86-1.0)	0.52 (0.48-0.56)	<.001	
Fully-adjusted HR	1.0	1.0 (0.93-1.08)	0.59 (0.55-0.64)	<.001	18.2 (15.6-20.8)

Abbreviations: CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; IHD, ischemic heart disease; PAF, population attributable fraction; TIA, transient ischemic attack.

* For the number of antihypertensive medications use, first, we calculated the total days of antihypertensive medications coverage for beneficiaries who took one, two, three or more medications during the period of follow-up respectively, and second, we classified the beneficiaries into one, and two or more medications use groups if he/she took one, or two or more medications for $\geq 75\%$ of days during the follow-up. The beneficiaries who did not fall into the above defined one, or two or more medications use groups were excluded from this sensitivity analysis.

† P-value for trends across the categories of proportion days covered; all tests two-tailed.

‡ PAF adjusted for age, sex, race/ethnicity, urban-rural residence, statins use, number of antihypertensive medications, status of low-income subsidy, out of pocket medications payment/day, Charlson-Comorbidity-Index, and 10 chronic conditions at baseline.

§ CVD events included both fatal and non-fatal events, and numbers in parentheses indicate the non-fatal events.

|| Adjusted for age, sex, race/ethnicity, urban-rural residence, statins use, number of antihypertensive medications, status of low-income subsidy, out of pocket medications payment/day, Charlson-Comorbidity-Index, and 10 chronic conditions at baseline.

Table S2. Adjusted Hazards Ratios for Risk of CVD, IHD, Stroke/TIA and Heart Failure Events, and Population Attributable Fraction Associated With First Year PDC, Medicare 2008-2014 Cohort

Characteristics	Proportion Days Covered*			p-trend [†]	Adjusted PAF (95% CI) [‡]
	<40% (low adherence)	40% to 79% (intermediate adherence)	≥80% (high adherence)		
Number of Medicare beneficiaries and percent (%)	22 044 (14.2%)	30 880 (19.8%)	102 673 (66.0%)		
CVD					
Events [§]	7 165 (7 034)	9 736 (9 593)	30 297 (29 865)		
Total person years	106 313	155 625	536 683		
Crude incidence, per 1000 person years	67.4 (67.3-67.4)	62.6 (62.5-62.6)	56.5 (56.4-56.5)		
HR adjusted for age, sex, and race only (95% CI)	1.0	0.94 (0.91-0.97)	0.85 (0.83-0.88)	<.001	
Fully-adjusted HR	1.0	0.98 (0.95-1.01)	0.96 (0.93-0.98)	0.003	1.4 (0.6- 2.3)
IHD					
IHD events [§]	3 874 (3 870)	5 406 (5 400)	16 711 (16 688)		
Total person years	111 770	162 930	560 481		
Crude incidence, per 1000 person years	34.7 (34.6-34.7)	33.2 (33.2-33.2)	29.8 (29.8-29.8)		
HR adjusted for age, sex, and race only (95% CI)	1.0	0.97 (0.93-1.01)	0.88 (0.84-0.91)	<.001	
Fully-adjusted HR	1.0	0.99 (0.95-1.03)	0.96 (0.93-1.0)	0.047	1.4 (0.3- 2.6)
Stroke/TIA					
Stroke/TIA events [§]	1 154 (1 148)	1 442 (1 436)	4 158 (4 136)		
Total person years	120 483	176 131	601 408		
Crude incidence, per 1000 person years	9.58 (9.56- 9.6)	8.19 (8.17- 8.2)	6.91 (6.91-6.92)		
HR adjusted for age, sex, and race only (95% CI)	1.0	0.87 (0.80-0.94)	0.74 (0.69-0.79)	<.001	
Fully-adjusted HR	1.0	0.90 (0.83-0.97)	0.82 (0.77-0.88)	<.001	5.4 (3.4 - 7.8)
Heart failure					
Heart failure events [§]	1 573 (1 565)	2 021 (2 015)	6 124 (6 100)		
Total person years	118 121	172 504	590 520		
Crude incidence, per 1000 person years	13.3 (13.3-13.3)	11.7 (11.7-11.7)	10.4 (10.4-10.4)		
HR adjusted for age, sex, and race only (95% CI)	1.0	0.91 (0.85-0.98)	0.85 (0.80-0.89)	<.001	
Fully-adjusted HR	1.0	0.98 (0.92-1.05)	0.98 (0.92-1.03)	0.411	N/A

Abbreviations: CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; IHD, ischemic heart disease; PAF, population attributable fraction; TIA, transient ischemic attack.

* We calculated the interval-based cumulative PDC of one or more (≥ 1) antihypertensives on hand during the first year of follow-up or follow-up to the first fatal or nonfatal CVD events for the beneficiaries who had a CVD event within first year of follow-up using information in Medicare Part D drug claim data.

† P-value for trends across the categories of proportion days covered; all tests two-tailed.

‡ PAF adjusted for age, sex, race/ethnicity, urban-rural residence, statins use, number of antihypertensive medications, status of low-income subsidy, out of pocket medications payment/day, Charlson-Comorbidity-Index, and 10 chronic conditions at baseline.

§ CVD events included both fatal and non-fatal events, and numbers in parentheses indicate the non-fatal events.

|| Adjusted for age, sex, race/ethnicity, urban-rural residence, statins use, number of antihypertensive medications, status of low-income subsidy, out of pocket medications payment/day, Charlson-Comorbidity-Index, and 10 chronic conditions at baseline.

Table S3. Adjusted Hazards Ratios for Risk of CVD, IHD, Stroke/TIA and Heart Failure Events, and Population Attributable Fraction Associated With Interval-Based Average PDC, Medicare 2008-2014 Cohort

Characteristics	Average Proportion Days Covered*			p-trend [†]	Adjusted PAF (95% CI) [‡]
	<40% (low adherence)	40% to 79% (intermediate adherence)	≥80% (high adherence)		
Number of Medicare beneficiaries and percent (%)	16 083 (10.3%)	78 954 (50.7%)	60 560 (38.9%)		
CVD					
Events [§]	7 188 (7 008)	29 086 (28 326)	10 924 (10 392)		
Total person years	70 363	387 862	340 396		
Crude incidence, per 1000 person years	102 (102 - 102)	75.0 (75.0 - 75.1)	32.1 (32.1 - 32.1)		
HR adjusted for age, sex, and race only (95% CI)	1.0	0.72 (0.70-0.74)	0.30 (0.29-0.31)	<0.001	
Fully-adjusted HR	1.0	0.77 (0.75-0.79)	0.34 (0.33-0.35)	<0.001	45.4 (44.2-46.5)
IHD					
IHD events [§]	4 013 (3 965)	16 072 (15 872)	5 906 (5 769)		
Total person years	76 644	411 024	347 513		
Crude incidence, per 1000 person years	52.4 (52.3 - 52.4)	39.1 (39.1-39.1)	17.0 (17.0 – 17.1)		
HR adjusted for age, sex, and race only (95% CI)	1.0	0.74 (0.71 - 0.77)	0.32 (0.30-0.33)	<0.001	
Fully-adjusted HR	1.0	0.78 (0.75 - 0.81)	0.35 (0.34-0.37)	<0.001	44.4 (42.9-46.0)
Stroke/TIA					
Stroke/TIA events [§]	1 106 (1 089)	4 103(4 006)	1 545(1 467)		
Total person years	87 538	451 129	359 355		
Crude incidence, per 1000 person years	12.6 (12.6-12.7)	9.1 (9.09- 9.10)	4.3 (4.29-4.31)		
HR adjusted for age, sex, and race only (95% CI)	1.0	0.73 (0.68-0.78)	0.34 (0.31-0.37)	<0.001	
Fully-adjusted HR	1.0	0.78 (0.73-0.83)	0.39 (0.36-0.42)	<0.001	40.9 (37.7- 44.0)
Heart failure					
Heart failure events [§]	1 511 (1 473)	5 939 (5 775)	2 268 (2 164)		
Total person years	84 486	440 454	35 6204		
Crude incidence, per 1000 person years	17.9 (17.9-17.9)	13.5 (13.5-13.5)	6.4 (6.36-6.38)		
HR adjusted for age, sex, and race only (95% CI)	1.0	0.78 (0.74-0.83)	0.38 (0.35- 0.4)	<0.001	

Fully-adjusted HR	1.0	0.86 (0.81-0.91)	0.44 (0.41-0.47)	<0.001	38.7 (36.1-41.4)
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Abbreviations: CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; IHD, ischemic heart disease; PAF, population attributable fraction; TIA, transient ischemic attack.

* For the calculation of the interval-based average PDC, it calculates PDC for each medication separately, then averages each individual PDC to get the overall PDC. For example, for beneficiaries taking two classes of antihypertensives, the interval-based PDC for each medication was calculated, and then two PDCs were averaged to get overall average PDC.

† P-value for trends across the categories of proportion days covered; all tests two-tailed.

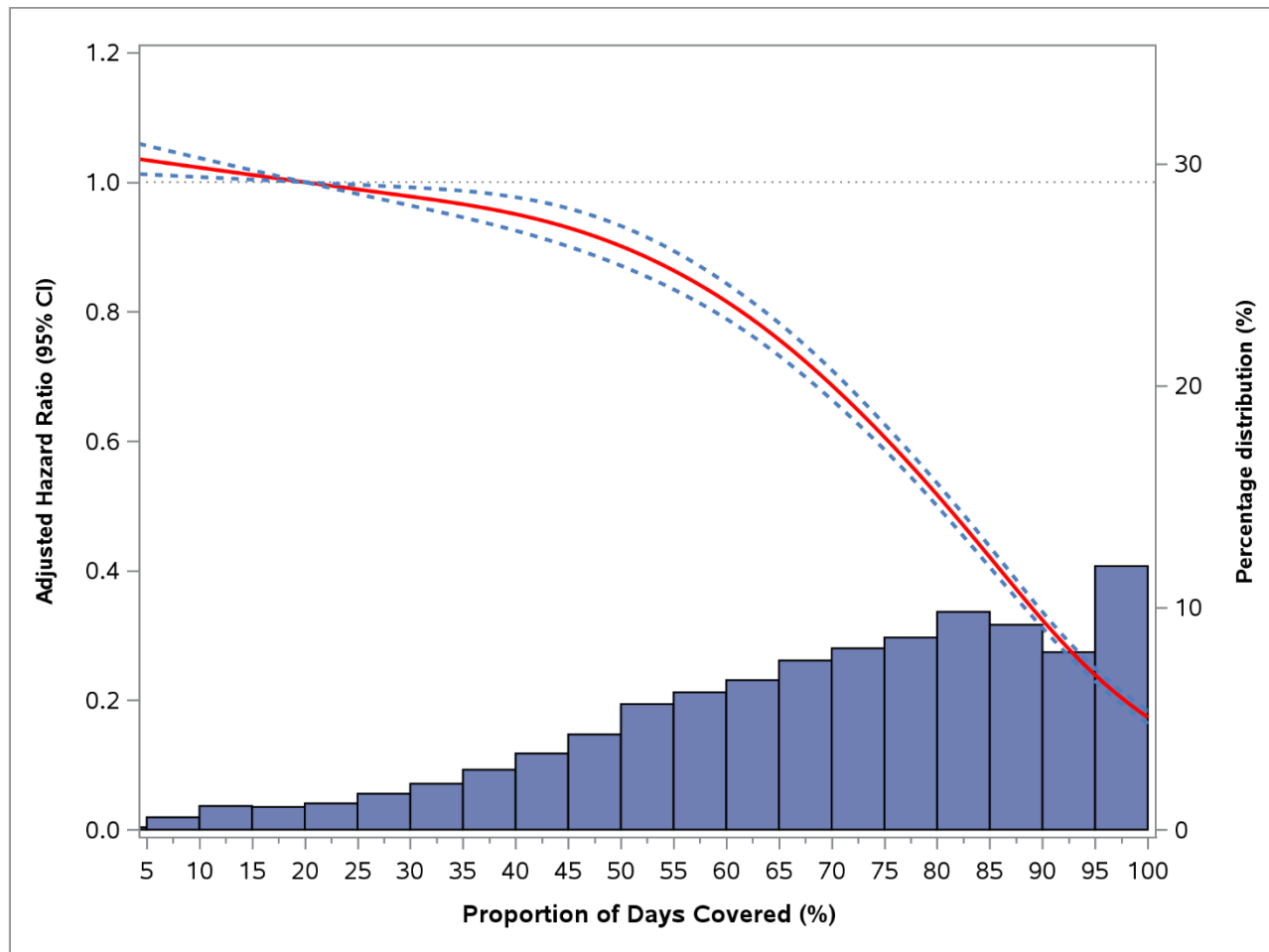
‡ PAF adjusted for age, sex, race/ethnicity, urban-rural residence, statins use, number of antihypertensive medications, status of low-income subsidy, out of pocket medications payment/day, Charlson-Comorbidity-Index, and 10 chronic conditions at baseline.

§ CVD events included both fatal and non-fatal events, and numbers in parentheses indicate the non-fatal events.

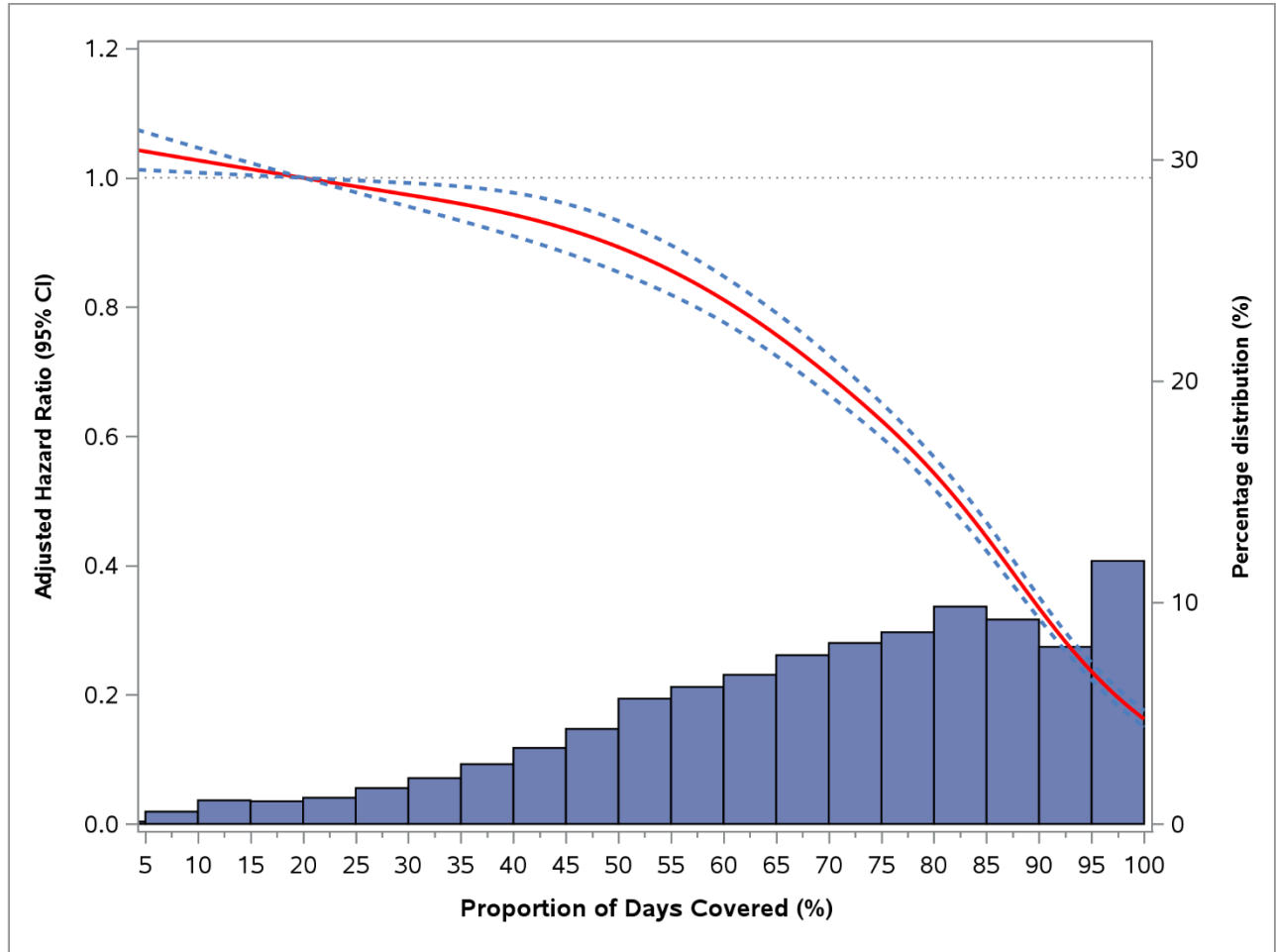
|| Adjusted for age, sex, race/ethnicity, urban-rural residence, statins use, number of antihypertensive medications, status of low-income subsidy, out of pocket medications payment/day, Charlson-Comorbidity-Index, and 10 chronic conditions at baseline.

Figure S1. Adjusted Hazard Ratios (95% CI) for CVD Events (**A**), IHD (**B**), Stroke/TIA (**C**) and Heart Failure Events (**D**) Associated With Interval-Based Average PDC, Medicare 2008-2014 Cohort. CVD indicates cardiovascular disease; IHD, ischemic heart disease; PDC, proportion days covered; TIA, transient ischemic attack.

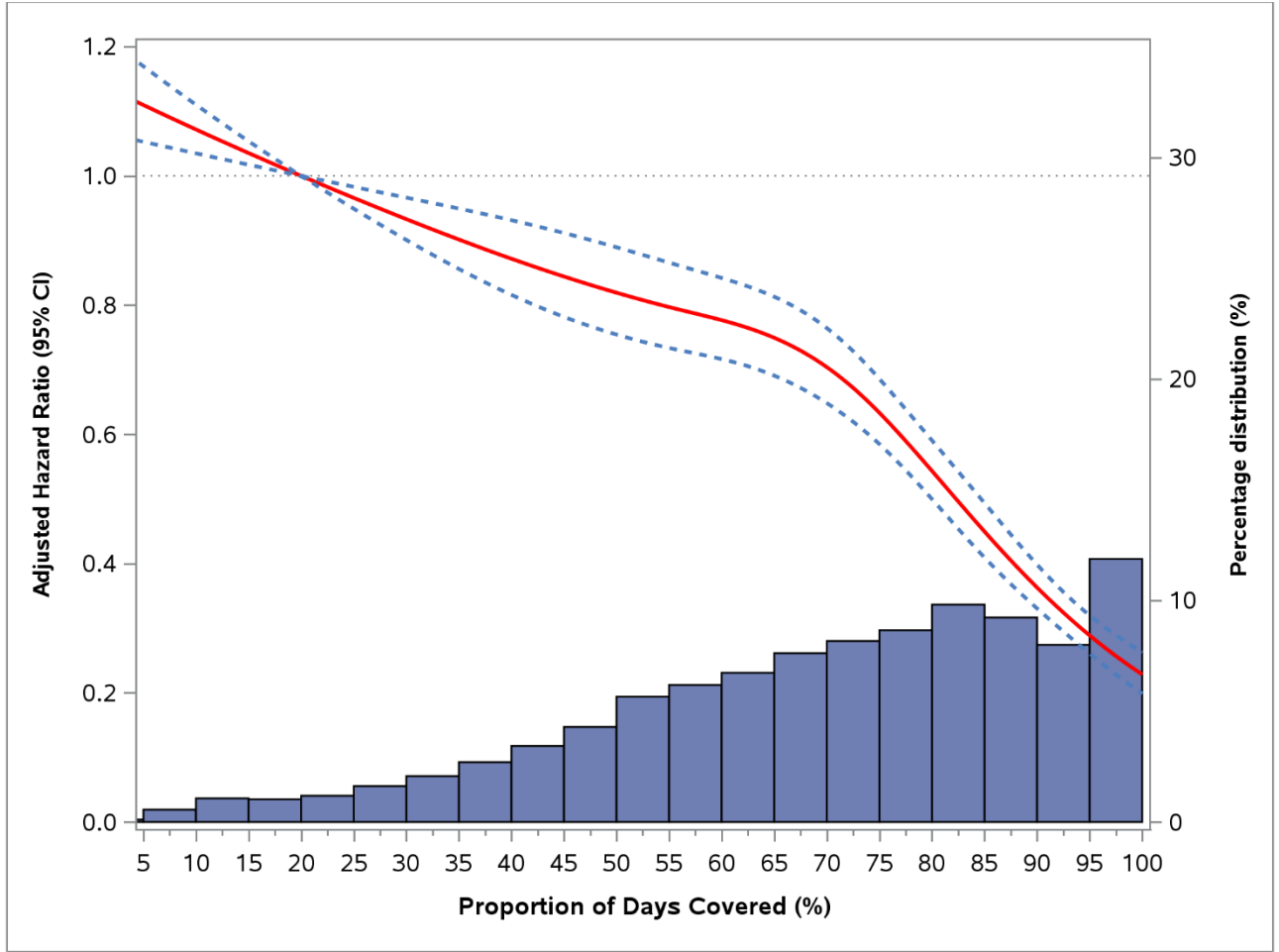
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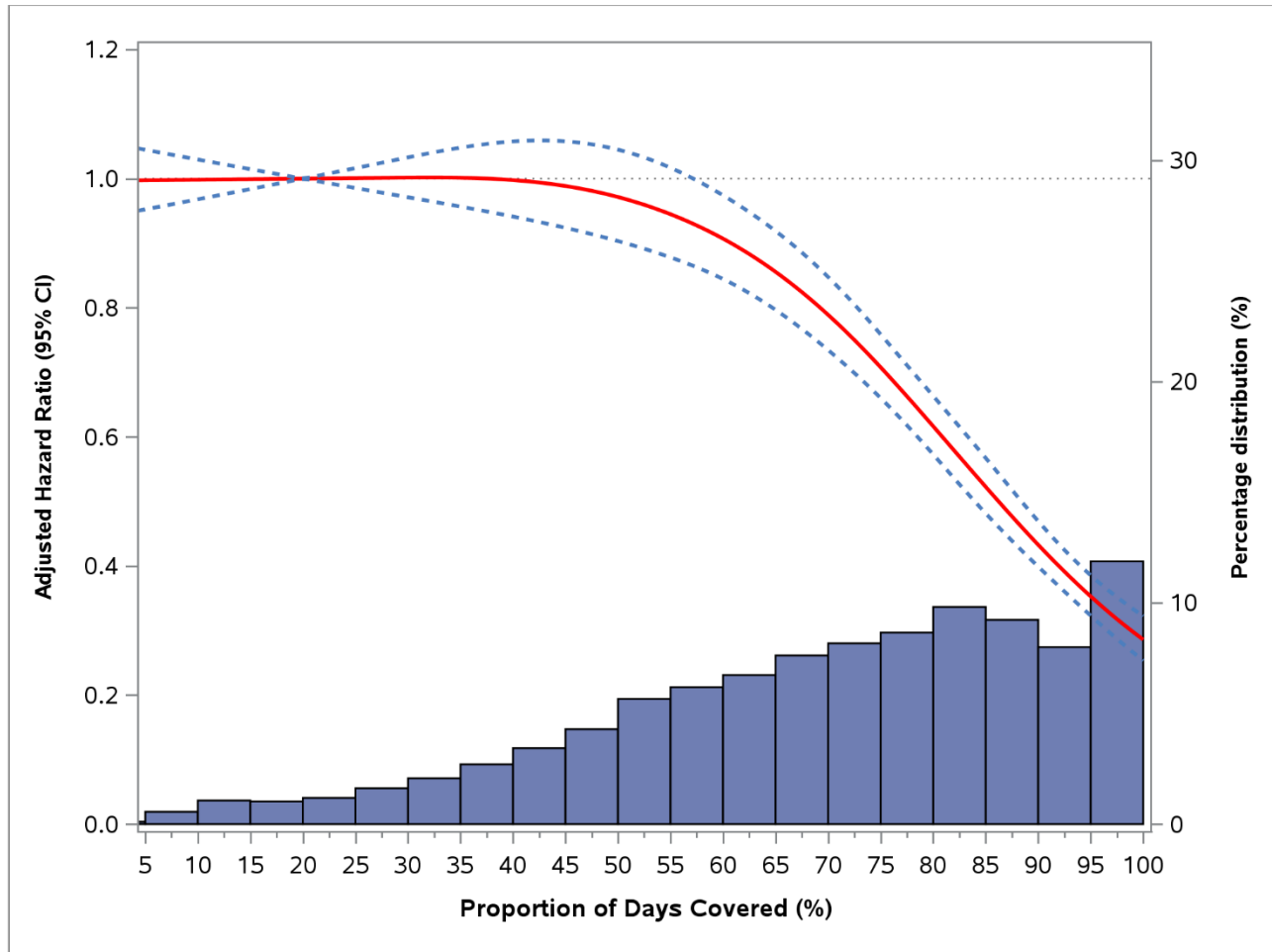
B



C



D



For the dose-response analyses of relationship between average PDC and CVD events, we used the 20th percentile PDC as the referent value (mid-value among beneficiaries with <40% PDC).