SUPPLEMENTAL MATERIAL

Supplemental material 1. Annual event rate abstraction

For each trial, we abstracted data for event numbers and annual event rates for nonfatal stroke, nonfatal MI, vascular death, and composite endpoint. For event numbers, if more than one outcome event occurred in one patient, only the first event was included. If the event number was duplicated across individual events, we first abstracted the numbers of nonfatal stroke, nonfatal MI, and composite endpoint, and then recalculated the numbers of vascular death. However, for the Women's Health Initiative (WHI) trial, the sum of fatal and nonfatal stroke events was less than all stroke events.[1] Therefore, we estimated the nonfatal stroke events by subtracting fatal stroke from all stroke. The annual event rates were abstracted if directly stated and otherwise derived from the event number and person-years of follow-up. The person-years were derived in following hierarchical order based on the available data: 1) person-years directly stated in the article, 2) derivation from displayed number of patients at risk in survival curves, and 3) number of patients multiplied by mean or median duration of follow-up years.

Reference

1. Writing Group for the Women's Health Initiative Investigators. Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women: Principal Results From the Women's Health Initiative Randomized Controlled Trial. *Jama*. 2002;288:321-333.

Supplemental material 2. DALY derivation for each vascular event

DALY lost due to vascular death at age of 60

DALY =YLL (YLD=0)

$YLL[r,K]=KCe^{rA}/(r+\beta)^2\{e^{-(r+\beta)(L+A)}[-(r+\beta)(L+A)-1]-e^{-(r+\beta)A}[-(r+\beta)A-1]\}+[(1-K)/r](1-e^{-rL})$

K: age-weighting modulation factor (K=1 or 0), β: parameter from age weighting function (β =0.04 or 0), r: discount rate (r=0.03 or 0), C: constant (C=0.1658), A: age of death, L: life expectancy of general population at age A

For YLL[3,1]:

K=1, r=0.03, β =0.04, A=60

L: life expectancy of 60 year-old person without cardiovascular disease (CVD) from the Framingham Heart Study (FHS) cohort: Men, 20; Women, 24.5; ***average: 22.25***

YLL[3,1] = 11.59

DALY[3,1] for vascular death at age of 60 = 11.59

DALY lost for stroke survivor at age of 60 (Figure 1)

$YLD[r,K]=DWKCe^{rAv}/(r+\beta)^2\{e^{-(r+\beta)(Ld+Av)}[-(r+\beta)(L_d+A_v)-1]-e^{-(r+\beta)Av}[-(r+\beta)A_v-1]\}+[(1-K)/r](1-e^{-rLd})$

DW: disability weight, K: age-weighting modulation factor (K=1 or 0), β: parameter from age weighting function (β =0.04 or 0), r: discount rate (r=0.03 or 0), C: constant (C=0.1658), A_v: age at vascular event, L_d: duration of disability after vascular event (=life expectancy of a survivor after vascular event at age Av)

For YLD[3,1]:

DW=0.266 (from the WHO-GBDP), K=1, r=0.03, β=0.04, A_v=60

L_d: life expectancy of 60 year-old person with stroke from the FHS cohort, L_d=8.90

YLD[3,1]=1.69

$YLL[r,K]=KCe^{rA}/(r+\beta)^2\{e^{-(r+\beta)(L+A)}[-(r+\beta)(L+A)-1]-e^{-(r+\beta)A}[-(r+\beta)A-1]\}+[(1-K)/r](1-e^{-rL})$

K: age-weighting modulation factor (K=1 or 0), β: parameter from age weighting function (β =0.04 or 0), r: discount rate (r=0.03 or 0), C: constant (C=0.1658), A: age of death, L: life expectancy of general population at age A

For YLL[3,1]:

K=1, r=0.03, β =0.04, A=68.9

L: life expectancy of 68.9 year-old general population from US life table 2004 for white, L=16.36

The life expectancy of 68.9 year-old general population was not provided in the FHS article. Since the life expectancy of FHS population are quite close to US white population, we employed the life expectancy of this age from US white population life tables.

YLL[3,1] at age of 68.9 = 7.75

YLL[3,1] at age of 60 = (YLL[3,1] at age of 68.9) x e^{rxLd} = 7.75x$e^{0.03x8.90}$ = 5.94

Finally, DALY[3,1] = YLL + YLD = 5.94 + 1.69 = 7.63

DALY lost for MI survivor (Figure 1)

For YLD[3,1]:

DW=0.037 (from frequency- and density-weighting), K=1, r=0.03, β =0.04, A_v=60

L_d: life expectancy of 60 year-old person with MI from the FHS cohort, L_d=11.2

YLD[3,1]=0.28

For YLL[3,1]:

K=1, r=0.03, β =0.04, A=71.2

L: life expectancy of 71.2 year-old general population from US life table 2004 for white, L=14.62

The life expectancy of 71.2 year-old general population was not provided in the FHS article. Since the life expectancy of FHS population are quite close to US white population, we employed the life expectancy of this age from US white population life tables.

YLL[3,1] at age of 71.2 = 6.80

YLL[3,1] at age of 60 = (YLL[3,1] at age of 71.2) x e^{rxLd} = 7.75x$e^{0.03x11.2}$ = 4.86

Finally, DALY[3,1] = YLL + YLD = 4.86 + 0.28 = 5.14

Supplemental material 3. NNT to save one DALY and one event by each trial treatment

We converted the each vascular event rates into DALYs lost per 100 person-years. By comparing the DALYs lost between active arm and control arm, we generated the DALYs saved by each trial treatment for a 100 person-years, and calculated NNTs.

The following table is an example of our derivation from the European Atrial Fibrillation Trial (EAFT).[1]

	Anticoagulation	Placebo
Event number		
Nonfatal stroke	18	47
Nonfatal MI	2	5
Vascular death	22	11
Composite outcome	42	63
Follow-up person-year	507	405
Event rate per 100 person-year		
Nonfatal stroke	3.55	11.60
Nonfatal MI	0.39	1.23
Vascular death	4.34	2.72
Composite outcome	8.28	15.56
DALYs lost per 100 person-year		
Nonfatal stroke	27.09 (= 3.55 X 7.63)	88.55 (= 3.55 X 7.63)
Nonfatal MI	2.03 (= 0.39 X 5.14)	6.35 (= 1.23 X 5.14)
Vascular death	50.29 (= 4.34 X 11.59)	31.48 (= 2.72 X 11.59)
Composite outcome	79.41	126.37

The DALYs saved from anticoagulation treatment for a 100 person-years were 61.46 for nonfatal stroke, 4.32 for nonfatal MI, -18.81 for vascular death, and 46.96 for the composite outcome.

For nonfatal stroke, the NNT_{event} can be derived from the following calculation: 100/(11.6-3.55)=12.4. NNT_{DALY} can be calculated as follows: 100/(88.55-27.09)=1.6.

Supplemental material 4. Hypothetical model trials assumption and age-weighting and future discounting

Hypothetical model trials assumption

In order to further illustrate the perspectives afforded by DALY analysis, we also generated six model trials demonstrating two different patterns of treatment effect in three different populations. The treatment effect patterns studied were an intervention effective for stroke prevention but ineffective for MI prevention and an intervention effective for MI prevention but ineffective for stroke prevention. The model populations were: 1) patients at equal risk for stroke or MI, 2) stroke-prone patients at higher stroke risk than MI, and 3) MI-prone patients at higher MI risk than stroke. In these six models (two treatment effect patterns crossed with three model populations), we assessed the treatment effect on DALYs for a sample size of 4000 person-years in each arm. Relative risk reductions were set at 40% on the endpoints for which the treatment was effective and nil for the ineffective endpoints.

For the trials of patients (the average age set to 60) at equal risk for stroke and MI, the annual event rates of control arms were assumed to be 5% for stroke, 5% for MI, and 8% for the composite endpoint. Case fatality rates of 20% were chosen for both stroke and MI, and other vascular death rate was set to 0.5% annually. These assumed control arm event rates were based on data from the systematic review of published stroke prevention trials.[1] It is widely recognized that stroke prevalent age is higher than that of MI. Therefore, for population at unequal risk for stroke and MI, the average age was set at 60 for the stroke-prone population and 50 for the MI-prone population. For the stroke-prone population, annual event rates of control arms were assumed to be 5% for stroke and 2.5% for MI. For the MI-prone population, annual event rates of control arms were assumed to be 2.5% for stroke and 5% for MI.

Based on these assumptions, we generated the tabular outcome events, and then derived NNT_{event} and NNT_{DALY} for each hypothetical trials.

Future discounting and age-weighting

The future discounting is a standard health policy modeling assumption that values a year of healthy life lost in the future less than a year of healthy life lost in the immediate present. The age-weighting reflects another assumption that assigns different values to different years of life, higher in young adult ages than in infancy or old ages. As in the WHO-GBDP, we employed an annual 3% of discount rate (r=0.03) and age-weighting (K=1, β=0.04) for the primary DALY analysis (DALY[3,1]).

However, there have been some ethical criticisms on applying discount rate and age-weighting: DALY[3,1].[2] For this reason, the 2000 WHO-GBDP also provided DALY with 3% discounting and non age-weighting: DALY[3,0], and DALY without both discounting and age-weighting: DALY[0,0], in addition to the standard DALY[3,1].[3] To explore the effect of removing

these assumptions, for the hypothetical trials, we also calculated additional sets of DALYs, in which the age-weighting was not employed (DALY[3,0]) or both were not employed (DALY[0,0]).

References

1. Hong KS, Yegiaian S, Lee M, Saver JL. Declining Stroke Recurrence Rates in Secondary Prevention Trials over the Past 50 Years and Consequences for Current Trial Design. *2010 International Stroke Conference (abstract)*.
2. Murray CJ. Rethinking DALYs. *In The Global Burden of Disease, ed. C. J. L. Murray and A. D. Lopez, Vol. 1 of Global Burden of Disease and Injury Series. Cambridge, MA: Harvard University Press.*; 1996:1-98.
3. WHO. The global burden of disease 2000: Version 2 methods and results (http://www.who.int/healthinfo/paper50.pdf). Accessed 10/28/2009.

Supplemental material 5. Included published trials

Secondary Stroke Prevention Trials

European Atrial Fibrillation (EAFT)[1]

North American Symptomatic Carotid Endarterectomy (NASCET)[2]

European Stroke Prevention Study-2 (ESPS-2)[3]

Perindopril Protection Against Recurrent Stroke Study (PROGRESS)[4]

European/Australasian Stroke Prevention in Reversible Ischaemia Trial (ESPRIT)[5]

Ticlopidine Aspirin Stroke Study (TASS)[6]

Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL)[7]

Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) stroke subgroup[8]

United Kingdom Transient Ischaemic Attack (UK-TIA)[9, 10]

Women's Estrogen for Stroke Trial (WEST)[11]

Warfarin-Aspirin Symptomatic Intracranial Disease (WASID)[12]

Secondary Coronary Heart Disease Prevention Trials

Clopidogrel in Unstable angina to prevent Recurrent Events (CURE)[13]

Prasugrel Thrombolysis in Myocardial Infarction (TRITON-TIMI 38)[14]

Cholesterol and Recurrent Events (CARE)[15]

Treating to New Targets (TNT)[16]

Primary Prevention Trials

Heart Outcomes Prevention Evaluation (HOPE)[17]

Study on Cognition and Prognosis in the Elderly (SCOPE)[18]

Women's Health Initiative (WHI)[19]

References for included trials

1. Secondary prevention in non-rheumatic atrial fibrillation after transient ischaemic attack or minor stroke. EAFT (European Atrial Fibrillation Trial) Study Group. *Lancet*. 1993;342:1255-1262.
2. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. North American Symptomatic Carotid Endarterectomy Trial Collaborators. *N Engl J Med*. 1991;325:445-453.
3. Diener HC, Cunha L, Forbes C, Sivenius J, Smets P, Lowenthal A. European Stroke Prevention Study. 2. Dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. *J Neurol Sci*. 1996;143:1-13.
4. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack. *Lancet*. 2001;358:1033-1041.

5. Halkes PH, van Gijn J, Kappelle LJ, Koudstaal PJ, Algra A. Aspirin plus dipyridamole versus aspirin alone after cerebral ischaemia of arterial origin (ESPRIT): randomised controlled trial. *Lancet*. 2006;367:1665-1673.
6. Hass WK, Easton JD, Adams HP, Jr., Pryse-Phillips W, Molony BA, Anderson S, Kamm B. A randomized trial comparing ticlopidine hydrochloride with aspirin for the prevention of stroke in high-risk patients. Ticlopidine Aspirin Stroke Study Group. *N Engl J Med*. 1989;321:501-507.
7. Amarenco P, Bogousslavsky J, Callahan A, 3rd, Goldstein LB, Hennerici M, Rudolph AE, Sillesen H, Simunovic L, Szarek M, Welch KM, Zivin JA. High-dose atorvastatin after stroke or transient ischemic attack. *N Engl J Med*. 2006;355:549-559.
8. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). CAPRIE Steering Committee. *Lancet*. 1996;348:1329-1339.
9. United Kingdom transient ischaemic attack (UK-TIA) aspirin trial: interim results. UK-TIA Study Group. *Br Med J (Clin Res Ed)*. 1988;296:316-320.
10. Farrell B, Godwin J, Richards S, Warlow C. The United Kingdom transient ischaemic attack (UK-TIA) aspirin trial: final results. *J Neurol Neurosurg Psychiatry*. 1991;54:1044-1054.
11. Viscoli CM, Brass LM, Kernan WN, Sarrel PM, Suissa S, Horwitz RI. A Clinical Trial of Estrogen-Replacement Therapy after Ischemic Stroke. *N Engl J Med*. 2001;345:1243-1249.
12. Chimowitz MI, Lynn MJ, Howlett-Smith H, Stern BJ, Hertzberg VS, Frankel MR, Levine SR, Chaturvedi S, Kasner SE, Benesch CG, Sila CA, Jovin TG, Romano JG. Comparison of warfarin and aspirin for symptomatic intracranial arterial stenosis. *N Engl J Med*. 2005;352:1305-1316.
13. The Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators. Effects of Clopidogrel in Addition to Aspirin in Patients with Acute Coronary Syndromes without ST-Segment Elevation. *N Engl J Med*. 2001;345:494-502.
14. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, Neumann FJ, Ardissino D, De Servi S, Murphy SA, Riesmeyer J, Weerakkody G, Gibson CM, Antman EM. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2007;357:2001-2015.
15. Sacks FM, Pfeffer MA, Moye LA, Rouleau JL, Rutherford JD, Cole TG, Brown L, Warnica JW, Arnold JM, Wun CC, Davis BR, Braunwald E. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. *N Engl J Med*. 1996;335:1001-1009.
16. LaRosa JC, Grundy SM, Waters DD, Shear C, Barter P, Fruchart J-C, Gotto AM, Greten H, Kastelein JJP, Shepherd J, Wenger NK, the Treating to New Targets Investigators. Intensive Lipid Lowering with Atorvastatin in Patients with Stable Coronary Disease. *N Engl J Med*. 2005;352:1425-1435.

17. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. *N Engl J Med*. 2000;342:145-153.
18. Lithell H, Hansson L, Skoog I, Elmfeldt D, Hofman A, Olofsson B, Trenkwalder P, Zanchetti A. ; SCOPE Study Group. The Study on Cognition and Prognosis in the Elderly (SCOPE): principal results of a randomized double-blind intervention trial. *Journal of Hypertension*. 2003;21:875-886.
19. Writing Group for the Women's Health Initiative Investigators. Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women: Principal Results From the Women's Health Initiative Randomized Controlled Trial. *Jama*. 2002;288:321-333.

Supplemental Table 1. Ranks of treatment effect of included trials for composite endpoint

Rank	Conventional approach	DALY approach		
		Age 60	Age 50	Age 70
1	EAFT	EAFT	EAFT	EAFT
2	NASCET	NASCET	NASCET	NASCET
3	CURE	CURE	CURE	CURE
4	TRITON-TIMI 38	ESPS-2	ESPS-2	ESPS-2
5	ESPS-2	TRITON-TIMI 38	PROGRESS	TRITON-TIMI 38
6	PROGRESS	PROGRESS	TRITON-TIMI 38	PROGRESS
7	ESPRIT	ESPRIT	ESPRIT	ESPRIT
8	CARE	HOPE	HOPE	HOPE
9	HOPE	CARE	CARE	CARE
10	TASS	TASS	TASS	TASS
11	SPARCL	SPARCL	SPARCL	SPARCL
12	TNT	CAPRIE_Stroke	CAPRIE_Stroke	TNT
13	UK-TIA	TNT	TNT	CAPRIE_Stroke
14	CAPRIE_Stroke	UK-TIA	UK-TIA	UK-TIA
15	SCOPE	SCOPE	SCOPE	SCOPE
16	WASID	WHI	WHI	WHI
17	WHI	WEST	WEST	WEST
18	WEST	WASID	WASID	WASID

Supplemental Table 2. Sensitivity analyses varing the assumption of age of onset to ages 50 and 70

For age of onset at 50, DALYs[3,1] saved for 100 patient-years and NNT for saving one DALY[3,1] and preventing one event

	Composite endpoint			Nonfatal stroke			Nonfatal MI			Vascular death		
	DALY saved	NNT for one DALY	NNT for one event	DALY saved	NNT for one DALY	NNT for one event	DALY saved	NNT for one DALY	NNT for one event	DALY saved	NNT for one DALY	NNT for one event
Stroke trials												
EAFT	62.89	1.6	13.8	84.49	1.2	12.4	5.65	17.7	119.0	-27.25	-3.7	-61.6
NASCET	52.23	1.9	21.6	42.32	2.4	24.8	NR	NR	NR	9.91	10.1	169.4
ESPS-2	15.96	6.3	67.1	15.61	6.4	67.2	-0.20	-495.4	-3334.4	0.55	183.2	3079.6
PROGRESS	12.02	8.3	71.4	9.27	10.8	113.1	2.04	49.0	330.1	0.71	140.5	2358.3
ESPRIT	11.97	8.4	104.3	5.38	18.6	194.9	0.60	166.5	1120.6	5.99	16.7	280.4
TASS	8.01	12.5	129.0	8.34	12.0	125.9	NR	NR	NR	-0.33	-303.9	-5103.1
SPARCL	6.04	16.5	142.3	3.36	29.7	311.9	2.50	40.0	269.3	0.18	550.0	9233.6
CAPRIE_Str	5.71	17.5	179.2	4.86	20.6	215.9	0.50	201.5	1356.1	0.35	281.8	4731.6
UK-TIA	3.85	25.9	177.5	5.41	18.5	193.7	1.57	63.6	427.8	-3.13	-31.9	-535.9
WEST	-8.04	-12.4	-208.6	2.88	34.7	364.3	-1.16	-85.9	-577.8	-9.75	-10.3	-172.2
WASID	-10.32	-9.69	-4538.8	21.15	4.73	49.6	-1.84	-54.3	-365.4	-29.62	-3.4	-56.7
CHD trials												
CURE	29.31	3.4	31.8	3.78	26.5	277.7	14.18	7.1	47.5	11.36	8.8	147.8
TRITON-TIMI 38	11.93	8.4	54.1	0.01	8702.0	91284.0	12.77	7.8	52.7	-0.85	-117.8	-1977.8
CARE	9.19	10.9	111.5	3.02	33.1	346.9	2.71	36.9	248.3	3.45	29.0	486.5
TNT	5.65	17.7	177.3	1.56	64.0	671.3	1.93	51.9	349.0	2.16	46.3	778.1
Primary prevention trials												
HOPE	10.91	9.2	120.3	2.14	46.6	489.2	1.18	84.9	571.1	7.59	13.2	221.3
SCOPE	3.80	26.3	351.3	2.63	38.0	399.0	-0.40	-247.9	-1668.4	1.58	63.4	1064.0
WHI	-1.52	-66.0	-627.8	-0.83	-121.2	-1270.6	-0.44	-225.5	-1517.4	-0.25	-405.9	-6814.6

For age of onset at 70, DALYs[3,1] saved for 100 patient-years and NNT for saving one DALY[3,1] and preventing one event

	Composite endpoint			Nonfatal stroke			Nonfatal MI			Vascular death		
	DALY saved	NNT for one DALY	NNT for one event	DALY saved	NNT for one DALY	NNT for one event	DALY saved	NNT for one DALY	NNT for one event	DALY saved	NNT for one DALY	NNT for one event
Stroke trials												
EAFT	32.24	3.1	13.8	40.76	2.5	12.4	3.23	30.9	119	-11.75	-8.5	-61.6
NASCET	24.69	4.1	21.6	20.41	4.9	24.8	NR	NR	NR	4.27	23.4	169.4
ESPS-2	7.65	13.1	67.1	7.53	13.3	67.2	-0.12	-866.1	-3334.4	0.24	425.4	3079.6
PROGRESS	5.95	16.8	71.4	4.47	22.4	113.1	1.17	85.7	330.1	0.31	325.7	2358.3
ESPRIT	5.52	18.1	104.3	2.60	38.5	194.9	0.34	291.1	1120.6	2.58	38.7	280.4
TASS	3.88	25.8	129	4.02	24.9	125.8	NR	NR	NR	-0.14	-704.8	-5103.1
SPARCL	3.13	31.9	142.3	1.62	61.6	311.9	1.43	69.9	269.3	0.08	1275.4	9233.6
CAPRIE_Str	2.78	36.0	179.2	2.34	42.7	215.9	0.28	352.2	1356.1	0.15	653.5	4731.6
UK-TIA	2.16	46.3	177.5	2.61	38.3	193.7	0.90	111.1	427.8	-1.35	-74.0	-535.9
WEST	-3.48	-28.7	-208.6	1.39	72.0	364.3	-0.67	-150.1	-577.8	-4.20	-23.8	-172.2
WASID	-3.63	-27.6	-4538.8	10.20	9.8	49.6	-1.05	-94.9	-365.4	-12.77	-7.8	-56.7
CHD trials												
CURE	14.83	6.7	31.8	1.82	54.9	277.7	8.11	12.3	47.5	4.90	20.4	147.8
TRITON-TIMI 38	6.94	14.4	54.1	0.01	18040.3	91284	7.30	13.7	52.7	-0.37	-273.2	-1977.8
CARE	4.50	22.2	111.5	1.46	68.6	346.9	1.55	64.5	248.3	1.49	67.2	486.5
TNT	2.79	35.9	177.3	0.75	132.7	671.3	1.10	90.7	349	0.93	107.5	778.1
Primary prevention trials												
HOPE	4.98	20.1	120.3	1.03	96.7	489.2	0.67	148.3	571.1	3.27	30.6	221.3
SCOPE	1.72	58.2	351.3	1.27	78.8	399	-0.23	-433.4	-1668.4	0.68	147.0	1064
WHI	-0.76	-131.9	-627.8	-0.40	-251.1	-1270.6	-0.25	-394.1	-1517.4	-0.11	-941.2	-6814.6

Supplemental Table 3. DALY analysis for subsequent vascular events

	YLD to nonfatal MI	YLD to nonfatal stroke	YLL to premature death	DALY
Nonfatal MI at 60, nonfatal stroke at 65, and death at 70	0.26 (for 10 years from age of 60)	0.93 (for 5 years from age of 65)	7.24	8.43
Nonfatal stroke at 60, nonfatal MI at 65, and death at 70	0.13 (for 5 years from age of 65)	1.85 (for 10 years from age of 60)	7.24	9.22
Nonfatal MI at 60, and death at 70	0.26 (for 10 years from age of 60)		7.24	7.50
Nonfatal stroke at 60, and death at 70		1.85 (for 10 years from age of 60)	7.24	9.09
Nonfatal MI at 60, and death at 65	0.15 (for 5 years from age of 60)		9.36	9.51
Nonfatal stroke at 60, and death at 65		1.05 (for 5 years from age of 60)	9.36	10.41

For a patient who has an MI at age 60, and then a stroke at 65, and then die at 70, the DALY lost of this patient would be the sum of the YLD lost to nonfatal MI for 10 years (as he will have post-MI disability until death even after the subsequent stroke), YLD to nonfatal stroke for 5 years, and YLL due to premature death at 70.

The life expectancies for general population at 60, 65 and 70 were assumed to be 22.5, 18.93, and 15.35 years. The life expectancies at 60 and 70 were derived from the data of Framingham study and that at 65 were derived from the extrapolation of these two values. Although, in the main analysis, the DALYs lost for nonfatal stroke and nonfatal MI at 60 were calculated from the assumption of the life expectancy at 60 for stroke survivors as 8.9 years and for MI survivors as 11.2 years based on Framingham study observation, here we assume that patients with nonfatal event without subsequent events will die at 65 or 70 for convenient comparison.

When compared to the DALY lost values for nonfatal MI (5.14) and nonfatal stroke (7.63) at 60 provided in table 2 of the manuscript, those for nonfatal MI at 60 and death at 70 (7.50) and nonfatal stroke at 60 and death at 70 (9.09) in the above table are magnified. This difference is mainly caused by whether future discounting for death event was applied or not. In our main analysis, we were to derive the DALY lost value for the vascular event at 60. In this case, since the death is the future event for patients with nonfatal event, the DALY lost of the future death needs to be discounted (annual discount rate of 3%).[1] However, in this supplemental analysis, as we are to demonstrate how the DALY metric incorporates the subsequent events, we do not apply the future discounting assuming that we prospectively capture the subsequent events.

Reference

1. Fox-Rushby JA, Hanson K. Calculating and presenting disability adjusted life years (DALYs) in cost-effectiveness analysis. *Health Policy and Planning*. 2001;16:326-331.