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Data Article

All cholesterol-lowering interventions are expected to reduce stroke: Confirmatory data from IMPROVE-IT

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ABSTRACT

The relationship of cholesterol with stroke is much less clear than its relationship with myocardial infarction, thus confounding the interpretation of results with cholesterol-lowering trials (Di Napoli et al., 2002) [1], (De Caterina et al., 2010) [2]). IMPROVE-IT data ((Cannon et al. 2015) [3]), showing a 13.3% reduction in total cholesterol at one year in association with a hazard ratio (HR) of 0.86 for total stroke during the trial, are very closely aligned with the relative risk of 0.90 predicted based on the totality of lipid lowering interventions ((De Caterina et al., 2016) [4]). We here provide the data from the original trials used to construct this meta-analysis, with the now added additional data from IMPROVE-IT, well-fitting the previously found meta-regression line.

These data are important to predict stroke outcomes in currently ongoing trials now testing PCSK9 or cholesterol ester transfer protein inhibitors.

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Specifications Table

Subject area	<i>Biology/Medicine</i>
More specific subject area	<i>Lipid-lowering intervention trials in cardiovascular disease prevention</i>

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Type of data	<i>Table</i>
How data was acquired	<i>Literature data extraction</i>
Data format	<i>Raw</i>
Experimental factors	<i>No data pretreatment-calculation of percent reduction in stroke as a function of percent reduction in total cholesterol in each of the original source trials</i>
Experimental features	<i>Meta-regression now fitting the recently published IMPROVE-IT data into the meta-regression</i>
Data source location	<i>n/a</i>
Data accessibility	<i>Data are within this article</i>

Value of the data

- These data, as obtained through already published literature reinforce the idea that also reduction of stroke, contrary to what previously believed, can be explained by reduction in cholesterol (total cholesterol in this analysis), both in statin and non-statin trials.
 - Recently published data from IMPROVE-IT perfectly fit the regression line from other source data on such relationship.
 - These results now allow a prediction of the reduction in stroke in trials now testing the PCSK9 inhibitors and the cholesterol ester transfer protein (CETP) inhibitor anacetrapib.
-

1. Data

Data provided here are the characteristics of source trials used for the construction of the meta-regression of reduction in stroke as a function of reduction in total cholesterol.

2. Experimental design, materials and methods

We had previously carried out a meta-regression by using inverse variance weighted linear regression of the log RR for total stroke against the percent of TC reduction as the explanatory variable. Weights in each study were the reciprocals of the variances for the logarithm RR for stroke. The meta-regression had yielded the following equation:

$$\ln(\text{total stroke RR}) = 0.00518 - 0.00793 (\% \text{ TC reduction})$$

The regression coefficient for percent TC reduction was significantly different from zero ($p=0.0017$). This equation indicates that some benefit from cholesterol-lowering intervention on the risk of stroke can be expected when the percent reduction of serum cholesterol is $> 2-3\%$, the clinical benefit becoming statically significant when TC is reduced by $\sim 8\%$.

We have now compared the reduction in stroke observed in IMPROVE-IT [3] with that calculated from our previous meta-analysis of all lipid lowering interventions reporting effects on stroke, in all trials as previously reported and as shown in Table 1. IMPROVE-IT [3] has now shown that a 13.3% reduction in total cholesterol at one year was associated with a hazard ratio (HR) of 0.86 for total stroke during the trial. This result is very closely aligned with the relative risk of 0.90 predicted on the basis of the totality of lipid lowering interventions [2,5].

3. Original Source data

Table 1

Description of the trials selected – demographic characteristics.

TRIAL, [ref No], Year of publication	Design^a	Follow-up^b	Total patients	Total stroke	Fatal stroke	Non-fatal stroke	AGE (mean)	SMK (%)	DM (%)	HBP (%)	PMI (%)	PST (%)
Oslo [6–8],1966	D,op,SE	5	412	3	2	NA	56.0	64.6	10.0	–	100	–
MRC [9,10],1968	D,op,SE	4	393	2	2	0	–	82.5	0.0	13.0	100	–
LA [11],1969	D,b,PS	8	846	38	12	26	65.5	66.4	–	–	20.1	12.5
Newcastle [12],1971	F,b,SE	3.6	497	1	1	0	52.5	65.0	0.0	0.0	23.0	–
Scottish [13,14],1971	F,b,SE	3.4	717	5	5	0	52.1	56.6	0.0	–	72.9	–
VA [15],1974	F,b,SE	4.5	532	60	13	NA	–	–	23.5	64.5	–	16.0
CDP [16–19],1975	F O,b,SE	6.2	5011	161	34	NA	52.0	37.9	5.0	20.0	100.0	2.0
Dorr [20],1978	O,b,PS	1.9	1094	1	1	0	50.5	–	13.7	16.2	6.2	0.5
WHO [21–24],1980	F,b,PR	5.3	10627	NA	25	31	45.9	56.0	0.0	0.0	0.0	0.0
McCaughan [25],1981	O,b,PS	1	118	0	0	NA	49.8	44.6	–	–	33.9	–
LRC-CPPT [26],1984	O,b,PR	7.4	3806	35	4	NA	47.7	37.5	0.0	0.0	0.0	0.0
CLAS I [27,28],1987	O,b,SE	2	188	0	0	0	54.2	0.0	0.0	0.0	–	–
Helsinki [29,30],1987	F,b,PR	5	4081	10	10	0	47.3	36.2	2.6	14.0	0.0	–
Stockholm [31,32],1988	O,op,SE	5	555	11	6	5	59.8	67.3	3.3	36.0	100.0	–
Minnesota [33],1989	D,b,PR	1.1	9057	43	43	NA	48.0	–	–	–	–	–
FATS [34],1990	S O,b,SE	2.7	98	0	0	NA	47.3	23.9	0.0	34.7	43.6	–
POSCH [35–38],1990	B,op,SE	9.7	838	29	3	NA	51.0	35.0	0.1	0.0	100.0	0.0
EXCEL [39–41],1991	S,b,PS	0.9	8245	11	1	NA	55.8	18.3	1.1	39.6	–	3.9
Singh [42,43],1992	D,b,SE	1	406	3	3	0	51.3	35.4	18.0	22.0	100.0	–
Frick [44],1993	F,b,SE	5	628	2	2	0	48.6	38.8	–	–	9.0	–
MARS [45,46],1993	S,b,SE	2.2	270	3	0	NA	58.0	–	0.0	46.0	60.0	–
PMSG-CRP [47],1993	S,b,SE	0.5	1062	3	0	3	55.0	28.7	0.0	47.5	34.5	–
4 S [48–50],1994	S,b,SE	5.5	4444	132	26	NA	58.6	25.6	4.5	26.0	79.3	0.0
ACAPS [51],1994	S,b,PR	2.8	919	5	2	3	61.7	11.9	2.3	28.8	0.0	0.0
CCAIT [52],1994	S,b,SE	2	331	1	0	NA	53.0	27.0	14.0	37.0	54.0	18.0
LR [53],1994	S,b,SE	0.5	404	1	0	1	62.0	49.8	11.6	48.8	25.0	–
Lyon [54],1994	D,b,SE	2.3	605	3	0	3	53.5	6.2	–	0.0	100.0	–
MAAS [53],1994	S,b,SE	4	381	3	0	NA	55.3	23.9	0.0	–	54.3	–
PLAC-I [55–58],1994	S,b,SE	2.3	408	2	0	2	57.0	16.5	0.0	45.5	43.5	0.0
PLAC-II [57,59,60],1994	S,b,SE	3	151	4	1	NA	62.5	12.1	–	0.0	63.8	–
Regress [61,62],1994	S,b,SE	2	884	2	0	2	56.2	27.7	0.1	27.8	47.4	–
KAPS [63],1995	S,b,PS	3	447	6	1	5	57.4	26.2	2.5	33.1	7.6	–
CARE [64,65],1996	S,b,SE	5	4159	128	16	NA	59.0	21.0	14.5	42.5	100	–
WOSCOPS [66],1996	S,b,PR	4.9	6595	97	10	NA	55.2	44.0	1.0	15.5	0.0	0.0
CIS [67],1997	S,b,SE	2.3	254	0	0	0	49.3	84.3	0.0	–	–	–
LOCAT [68],1997	F,b,SE	2.5	395	0	0	0	59.2	–	0.0	40.0	55.2	–

Table 1 (continued)

TRIAL, [ref No], Year of publication	Design ^a	Follow-up ^b	Total patients	Total stroke	Fatal stroke	Non-fatal stroke	AGE (mean)	SMK (%)	DM (%)	HBP (%)	PMI (%)	PST (%)
PCABGT [69],1997	S,op,SE	4.3	1351	34	NA	NA	61.5	11.3	8.6	–	49.3	–
PREDICT [70],1997	S,b,SE	0.5	695	1	1	0	58.3	33.7	7.2	30.7	37.1	1.9
AFCAPS [71],1998	S,b,PR	5.2	6605	31	NA	NA	58.0	12.4	2.4	21.9	0.0	0.0
LIPID [72–74],1998	S,b,SE	6.1	9014	373	49	NA	61.5	9.6	8.7	41.7	63.8	4.1
Mas [75],1999	O,b,SE	0.5	437	1	NA	NA	58.0	32.7	17.8	82.2	–	3.9
GISSI P [76],2000	S,op,SE	1.9	4271	39	8	31	60.0	11.9	13.6	36.5	100.0	–
SCAT [77],2000	S,b,SE	4.0	460	11	9	NA	61.0	15.0	10.9	35.2	70.4	–
VA-HIT [78],2000	F,b,SE	5.1	2531	134	12	NA	64.0	20.5	24.5	57.0	61.0	–
BCAPS [79],2001	S,b,SE	3	793	8	NA	NA	61.8	30.8	3.0	12.1	–	–
BIP [80],2001	F,b,SE	6.2	3090	149	NA	NA	60.1	11.8	10.0	32.4	77.9	1.1
DAIS [81–83],2001	F,b,SE	3.3	418	12	NA	NA	56.8	14.8	100.0	51.4	–	–
HATS [84],2001	S,b,SE	3	160	4	0	4	53.0	24.0	16.0	49.0	55	–
ALLHAT-LLT [85],2002	S,op,PR	4.8	10355	440	109	NA	66.4	23.2	35.1	100.0	0.0	–
FAST [86],2002	S O,PR	2	246	0	0	0	66.1	59.3	22.8	41.5	–	–
GREACE [87],2002	S,op,SE	3	1600	26	1	NA	58.5	–	19.6	42.9	81.2	–
HPS [88,89],2002	S,b,SE	5	20536	1029	215	865	64.0	14.1	29.0	41.0	41.0	–
LEADER [90,91],2002	F,b,SE	4.6	1568	109	22	97	68.2	37.8	17.1	–	19.8	11.7
LIEM [92],2002	S,b,SE	1	540	3	3	0	60.5	–	–	–	100.0	–
LIPS [93],2002	S,b,SE	3.9	1677	3	3	NA	60.0	26.6	12.1	38.6	44.4	2.6
PROSPER [94],2002	S,b,PS	2.2	5804	266	36	235	75.4	26.8	10.7	61.9	13.4	–
ALERT [95,96],2003	S,b,PS	5.1	2102	104	31	NA	50.0	18.5	18.8	74.9	3.1	5.8
ASCOT-LLA [97],2003	S,b,PR	3.2	10305	210	NA	NA	63.0	32.7	24.6	100.0	0.0	–
Mohler [98],2003	S,b,SE	1	354	2	1	1	68.0	40.4	17.5	–	–	–
ALLIANCE [99],2004	S,b,SE	4.3	2442	74	NA	NA	61.2	19.5	22.1	–	57.8	6.6
ARBITER2 [100],2004	O,b,SE	1	167	1	NA	NA	67.5	10.2	27.5	74.9	49.7	–
BaeJH [101],2004	S,b,SE	6	205	2	0	2	60.0	41.5	29.8	48.3	12.2	–
CARDS [102],2004	S,b,PR	3.9	2838	60	6	50	62.0	22.2	100.0	83.8	0.0	0.0
PCS [103],2004	S,b,SE	5	120	7	NA	NA	59.6	67.5	17.5	59.2	–	–
4D [104,105],2005	S,b,SE	4	1255	103	40	65	65.7	8.6	100.0	–	17.6	–
FIELD [106,107],2005	F,b,SE	5	9795	333	NA	NA	62.2	9.4	100.0	56.6	5.0	3.5
Makuuchi [108],2005	S,op,SE	4.5	303	6	1	NA	58.9	41.9	33.3	51.5	62.0	–
Stone [109],2005	S,b,SE	1	300	2	NA	NA	–	0.0	16.0	63.6	39.3	–
ASPEN prim [110],2006	S,b,PR	4	1905	56	NA	NA	60.5	13.2	100.0	52.3	0.0	–
ASPEN sec [110],2006	S,b,SE	4	505	16	NA	NA	63.2	9.7	100.0	65.5	78.2	–
SPARCL [111],2006	S,b,SE	4.9	4731	576	65	527	62.7	19.2	16.7	61.9	30.9	69.1
WHI-DM [112],2006	D,o,PS	8.1	48835	1076	150	935	62.3	6.7	–	42.9	1.9	1.1
CORONA [120],2007	S,b,SE	2.7	5011	NA	67	197	73.0	8.6	29.5	63.4	59.9	12.4

ARISE [113],2008	O,b,SE	2	6144	54	0	64	65.0	13.5	37.0	72.0	72.0	-
CCSPS [114],2008	O,b,SE	4.5	4870	NA	25	NA	58.9	34.5	12.5	55.5	100.0	-
GISSI-HF [115],2008	S,b,SE	3.9	4574	148	67	86	68.0	14.1	26.1	54.3	-	4.5
JUPITER [116,117],2008	S,b,PR	1.9	17802	97	NA	88	66.0	15.8	0.0	57.3	0.0	0.0
OACIS lipid [118],2008	S,o,SE	0.7	353	2	NA	NA	63.2	57.4	31.7	747.6	100.0	7.3
IMPROVE-IT [119],2015	O,b,SE	6	18.144	641	NA	NA	64.0	33.0	27.2	61.5	21.0	NA

AGE mean age; **SMK** smoking status; **DM** diabetes mellitus; **HBP** high blood pressure; **PMI** previous myocardial infarction; **PST** previous stroke.

^a **DESIGN**: the first letter indicates the type of lipid lowering intervention (D: diet, S: statins, F: fibrates, O: other drugs, B: ileal bypass or other surgery); the second letter indicates the study design (op: open; b blind); the last letter indicates the clinical setting (PR: primary, SE: secondary, PS: primary and secondary)

^b **FOLLOW-UP** indicates mean duration (year), in its absence the maximum follow-up duration is indicated (*in italics*);

Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at <http://dx.doi.org/10.1016/j.dib.2016.04.059>.

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