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Statins and death due to any cause – all doubts removed ?

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Abstract

Objective: To date, it is quite common to claim that some patient groups benefit from statin therapy in both primary and secondary prevention of cardiovascular disease while equally the use of higher-intensity statin therapies is emphasized. In this Review, the efficacy of statin therapy in light of the study data available is explored.

Methods: All in all, 40 studies with a sample size of n = 88388 were re-analyzed. The exclusion relationship was used to test the null-hypothesis: a certain statin does exclude death due to any cause. The causal relationship k was used to test the data for causality. The level of significance was set to Alpha = 0,05.

Results: The data of the studies reanalyzed provide convincing evidence that statins unfortunately do not exclude death due to any cause. Overwhelming evidence suggests that the risk of harmful effects of statin therapy far outweigh any real or perceived benefit.

Conclusions: An immediate statin therapy discontinuation should be considered.

Keywords: *Statins, death, causal relationship.*

1. Introduction

Influenced by Virchow's observation (Virchow, 1856), the Russian scientist *Alexander I. Ignatowski* (1875-1955), father of *the lipid hypothesis in the pathogenesis of atherosclerosis* (Konstantinov & Jankovic, 2013), was the first of many researchers who assumed that cholesterol is involved in the development of arteriosclerosis. To test this hypothesis,

Ignatowski fed rabbits a high-cholesterol diet of egg yolk and milk. The rabbits developed atherosclerosis and Ignatowski concluded to have confirmed (Ignatowski, 1908) his own lipid hypothesis of *arteriosclerosis* (Marchand, 1904), often referred to as one of the greatest (Dock, 1958) discoveries of the 20th century. However, rabbits are herbivores and usually do not eat food like cholesterol of animal origin. Furthermore, due to historical (Craig, Macauley, Weller, & Wirth, 1957; Ho, 2008; Ribbert, 1904) reasons, Ignatowski was not able to consider whether rabbits where Cytomegalvirus positive or negative in this context and whether the results were pure coincidence (*cum hoc ergo propter hoc logical fallacy*). In 1910, Adolf Windaus (Windaus, 1910) published that atheromatous lesions contained more free cholesterol and esterified cholesterol compared to normal arterial wall. The role of cholesterol in the development of atherosclerosis (Konstantinov, Mejevoi, & Anichkov, 2006) was suggested by experiments of *Nikolai N. Anichkov* (1885–1964) *and Chalatow* (Anitschkow & Chlatow, 1913). As a result, the atherosclerotic scientific research was directed to the lipids and cholesterol. On June 16, 1948, the U.S. President Harry Truman signed the U. S. National Heart Act (Mahmood, Levy, Vasan, & Wang, 2014) and enabled the Framingham Heart Study. The dominance of the lipid theory of atherosclerosis was reinforced especially by Ancel Benjamin Keys (1904 – 2004), an U. S. American physiologist, who hypothesized a relationship between cholesterol levels and cardiovascular disease. In the following, Michael S. Brown and Joseph L. Goldstein discovered the LDL receptor (Brown & Goldstein, 1976) and were jointly awarded "*The Nobel Prize in Physiology or Medicine 1985*" for their discoveries concerning the regulation of cholesterol metabolism. Brown and Goldstein published that acetylated low-density lipoprotein (LDL) and not native LDL was responsible for foam cell formation of macrophages (Goldstein & Brown, 1977) followed by Daniel Steinberg (Steinberg, Parthasarathy, Carew, Khoo, & Witztum, 1989) and his group who demonstrated that oxidized LDL (oxLDL) induces foam cell formation of macrophages. Meanwhile, atherosclerosis is considered by many authors to consist largely of the accumulation of low-density lipoprotein (LDL) cholesterol (Ross, 1999) within the artery wall. No wonder that the sale of statins in the United States in 2005 were estimated at US$18.7 billion (Taylor, Huffman, & Ebrahim, 2013). Meanwhile especially Simvastatin is indexed by the *World Health Organization's List of*

Essential Medicines (WHO, 2019) while atorvastatin became in 2003 the best-selling pharmaceutical (Simons, 2003) in history of mankind. Historically, *Mevastatin* was the first member of the statin class of drugs and firstly discovered by the Japanese biochemist Akira Endō (A. Endo, Kuroda, & Tsujita, 1976; Akira Endo, Kuroda, & Tanzawa, 2004) in 1976. Statins or cholinesterase inhibitors (CSE) such as atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin and other which block 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase are widely used for the prevention of all-cause mortality, major vascular events, and revascularizations and for lowering the blood cholesterol level but exhibit **antimicrobial effects** (Ting, Whitaker, & Albandar, 2016) **against** various microorganisms including **human cytomegalovirus** too. Statins are able to *inhibit the cholesterol/isoprenoid pathway* (Rothwell et al., 2009) and block the infection (Heaton & Randall, 2011) of many enveloped viruses. The antiviral activity of statins (Shrivastava-Ranjan et al., 2018) against human cytomegalovirus (HCMV), a risk factor in the pathogenesis of atherosclerosis is comparable to ganciclovir (Ponroy, Taveira, Mueller, & Millard, 2015). To the best of our knowledge, pro-inflammatory markers, especially high-sensitivity C-reactive protein (hs-CRP), are established predictors of cardiovascular morbidity and mortality and there are notable differences between statins. Rosuvastatin when compared with atorvastatin (Kumar, Shah, Kumar, Kumar, & Memon, 2019) had better impact on the reduction of pro-inflammatory markers, especially hs-CRP. However, the physiology of statins has not been investigated in detail in this publication. Due to the results of several statin studies which investigated the relationship between the use of statins and death due to any cause, statins are used regularly in the prevention of major atherosclerotic events. However, several systematic reviews and meta-analysis (Mills et al., 2011; Zhong et al., 2017) of statin studies reported differences or even no evidence for the benefit of the efficacy of statin therapy on all-cause mortality (Ray et al., 2010). Thus far and despite the long history of the use of statins, the medical value of these drugs remains largely unknown.

2. Material and Methods

2.1. Material

2.1.1. Search Strategy

In general, for the questions addressed in this paper, the reference list of some review articles was searched for appropriate articles.

Table 1. ***The article selection process of the studies analyzed***

1. Identification of records	Size	Total
Records identified by searching in the databases		
Zhong et al., 2017	67	
Mills et al., 2011	58	
Ray et al., 2010	36	
		161
2. Clean-up of search (Screening)		
Records removed after verifying duplication, excluded by title, excluded due to other reasons		117
3. Eligibility		
Articles evaluated for eligibility		44
Articles excluded for various reasons	4	
4. Included		
Articles included in the meta-analysis		40

Adopted from PRISMA 2009 (Moher, Liberati, Tetzlaff, & Altman, 2009).

2.1.2. Statins and AS

Several different statin studies (3T et al., 2003; 4S, 1994; AFCAPS/TexCAPS et al., 1998; ALLIANCE, Koren, Hunninghake, & ALLIANCE Investigators, 2004; ALPS-AMI et al., 2015; APTCA et al., 2004; ASPEN, Knopp, d'Emden, Smilde, & Pocock, 2006; ATHEROMA et al., 2005; CARE et al., 1996; CCAIT et al., 1994; CENTAURUS et al., 2010; CORONA et al., 2007; FACS et al., 2010; FLORIDA et al., 2002; GISSI-HF et al., 2008; GISSP-P, 2000; GREACE et al., 2002; IDEAL et al., 2005; LIPID, 1998; LIPS et al., 2002; LRTS et al., 1994; LUNAR et al., 2012; MAAS, 1994; MARS et al., 1993; MIRACL et al., 2001; OACIS-LIPID et al., 2008; PACT et al., 2004; PCABG et al., 2005; PCS et al., 2004; PEARL et al., 2013; PLAC I et al., 1995; PLAC-II et al., 1995; PREDICT et al., 1997; PROSPER et al., 2002; PROVE IT-TIMI et al., 2004; REGRESS et al., 1995; REVERSAL et al., 2004; SAGE et al., 2007; SATURN et al., 2011; SCAT et al., 2000; SPACE ROCKET et al., 2009; SPARCL et al., 2006; VASBA et al., 2005; WOSCOPS I et al., 1995) investigated the relationship between the use of statins and death due to any cause. The studies CARE 1996, TREAT TO TARGET 2003, APTCA 2004 and SATURN 2011, provided none or inappropriate data and were not

re-analyzed. Single CSE studies which do not exclude death due to any cause for sure are presented by **Table 2**. Single statin studies which do not exclude death due to any cause are presented by **Table 3**. However, the data are still very self-contradictory. In the following, the contradictions as associated with the data of the statin studies are marked by red color. The green color indicates a favorable condition.

Table 2. Single CSE studies which do not exclude death due to any cause for sure

Trial name	Year	Drug	n	a	a+c	b	b+d	Caus. Rel. k	P Value (k)	p(EXCL)	P Value (EXCL)	X²(EXCL|At)	X²(EXCL|Bt)	p(IOI)
SAGE	2007	Atorvastatin	891	6	24	440	867	-0,083	0,010	0,993	0,007	0,081	1,500	0,474
PROVE														
IT-TIMI	2004	Atorvastatin	4162	46	112	2053	4050	-0,031	0,028	0,989	0,011	1,008	18,893	0,477
GREACE	2002	Atorvastatin	1600	23	63	777	1537	-0,055	0,019	0,986	0,014	0,661	8,397	0,461
4S	1994	Simvastatin	4444	182	438	2039	4006	-0,056	0,000	0,959	0,040	14,914	75,626	0,401
WOSCOPS	1995	Pravastatin	6595	106	241	3196	6354	-0,024	0,031	0,984	0,016	3,403	46,622	0,464
LIPID	1998	Pravastatin	9014	498	1131	4014	7883	-0,046	0,000	0,945	0,054	54,965	219,279	**0,375**
		Total	**26706**	**861**	**2009**	**12519**	**24697**			0,968	0,032	75,032	370,316	0,442

Alpha = 0,05

D. f. = 6

X²(Critical) = **12,592**

Table 3. Single CSE studies which do not exclude death due to any cause

Trial name	Year	Drug	N	a	a+c	b	b+d	Causal relat. k	P Value k(HGD)	P (EXCL)	P Value (EXCL)	X²(EXCL|At)	X²(EXCL|Bt)	p(IOI)
REVERSAL	**2004**	**Atorvastatin**	**654**	**1**	**2**	**326**	**652**	**0,0000**	**0,7504**	**0,9985**	**0,0015**	**0,0031**	**0,5000**	**0,4969**
LUNAR	2012	Atorvastatin	829	2	6	404	823	-0,0267	0,3627	0,9976	**0,0024**	0,0099	0,6667	0,4825
VASBA	2005	Atorvastatin	199	1	1	95	198	0,0736	1,0000	0,9950	**0,0050**	0,0104	1,0000	0,4774
MIRACL	2001	Atorvastatin	3086	64	132	1474	2954	-0,0057	0,4096	0,9793	**0,0205**	2,6632	31,0303	0,4556
IDEAL	2005	Atorvastatin	8888	366	740	4073	8148	-0,0029	0,4064	0,9588	**0,0403**	30,1771	181,0216	0,4162
SPARCL	2006	Atorvastatin	4731	216	427	2149	4304	0,0038	0,6213	0,9543	**0,0446**	19,7277	109,2646	0,4096
ALLIANCE	2004	Atorvastatin	2442	121	248	1096	2194	-0,0070	0,3896	0,9505	**0,0483**	12,0304	59,0363	0,3968
ASPEN–sec.	2006	Atorvastatin	505	26	53	226	452	-0,0058	0,5061	0,9485	0,0502	2,6825	12,7547	0,3941
MAAS	**1994**	**Simvastatin**	**381**	**4**	**15**	**189**	**366**	**-0,0971**	**0,0500**	**0,9895**	**0,0104**	**0,0829**	**1,0667**	**0,4672**
SCAT	2000	Simvastatin	460	13	19	217	441	0,0765	0,9709	0,9717	**0,0279**	0,7348	8,8947	0,4587
FACS	**2010**	**Fluvastatin**	**156**	**1**	**5**	**77**	**151**	**-0,1092**	**0,1834**	**0,9936**	**0,0064**	**0,0128**	**0,2000**	**0,4680**
FLORIDA	2002	Fluvastatin	540	7	18	258	522	-0,0378	0,2622	0,9870	**0,0129**	0,1849	2,7222	0,4574
LIPS	2002	Fluvastatin	1677	36	85	808	1592	-0,0369	0,0809	0,9785	**0,0212**	1,5356	15,2471	0,4526

ATHEROMA	**2005**	**Pravastatin**	**373**	**1**	**3**	**185**	**370**	**-0,0298**	**0,5020**	**0,9973**	**0,0027**	**0,0054**	**0,3333**	**0,4906**
REGRESS	1995	Pravastatin	884	5	12	445	872	-0,0217	0,3620	0,9943	**0,0056**	0,0556	2,0833	0,4955
PREDICT	1997	Pravastatin	695	4	5	343	690	0,0512	0,9694	0,9942	**0,0057**	0,0461	3,2000	0,4921
PACT	2004	Pravastatin	3408	24	61	1686	3347	-0,0293	0,0569	0,9930	**0,0070**	0,3368	9,4426	0,4839
OACIS-LIPID	2009	Pravastatin	353	3	5	173	348	0,0243	0,8161	0,9915	**0,0085**	0,0511	1,8000	0,4844
PLAC-I	1995	Pravastatin	408	4	10	202	398	-0,0333	0,3633	0,9902	**0,0098**	0,0777	1,6000	0,4804
GISSP-P	2000	Pravastatin	4271	72	160	2066	4111	-0,0200	0,1105	0,9831	**0,0167**	2,4247	32,4000	0,4631
PCABG	2005	Pravastatin	303	6	17	146	286	-0,0725	0,1557	0,9802	**0,0196**	0,2368	2,1177	0,4455
PLAC-II	1995	Pravastatin	151	3	8	72	143	-0,0576	0,3669	0,9801	**0,0197**	0,1200	1,1250	0,4437
ALPS-AMI	2015	Pravastatin	525	14	23	247	502	0,0478	0,9049	0,9733	**0,0263**	0,7510	8,5217	0,4533
PCS	2004	Pravastatin	120	5	8	49	112	0,0940	0,9189	0,9583	**0,0408**	0,4630	3,1250	0,3833
PROSPER – Sec	2002	Pravastatin	5804	298	604	2593	5200	-0,0032	0,4198	0,9487	0,0501	30,7174	147,0265	0,3940
CCAIT	**1994**	**Lovastatin**	**331**	**2**	**4**	**163**	**327**	**0,0003**	**0,6909**	**0,9940**	**0,0060**	**0,0242**	**1,0000**	**0,4864**
LRTS	1994	Lovastatin	404	3	4	200	400	0,0495	0,9372	0,9926	**0,0074**	0,0443	2,2500	0,4926
MARS	1993	Lovastatin	247	2	3	121	244	0,0374	0,8780	0,9919	**0,0081**	0,0325	1,3333	0,4858
AFCAPS/TexCAPS	1998	Lovastatin	6605	80	157	3224	6448	0,0029	0,6245	0,9879	**0,0120**	1,9371	40,7643	0,4765
CENTAURUS	**2010**	**Rosuvastatin**	**829**	**2**	**6**	**404**	**823**	**-0,0267**	**0,3627**	**0,9976**	**0,0024**	**0,0099**	**0,6667**	**0,4825**
SPACE ROCKET	2009	Rosuvastatin	1263	11	27	622	1236	-0,0277	0,2149	0,9913	**0,0087**	0,1912	4,4815	0,4798
GISSI-HF	2008	Rosuvastatin	4574	657	1301	1628	3273	0,0069	0,6901	0,8564	0,1338	188,9055	331,7825	0,2151
CORONA	2007	Rosuvastatin	5011	728	1487	1786	3524	-0,0158	0,1393	0,8547	0,1352	210,8131	356,4116	0,2050
PEARL	**2013**	**Pitavastatin**	**577**	**27**	**64**	**262**	**513**	**-0,0558**	**0,1135**	**0,9532**	**0,0457**	**2,5225**	**11,3906**	**0,3900**
		Total	**61684**	**2809**	**5720**	**28009**	**55964**			0,9545	0,0445	**509,6209**	**1386,2606**	0,4428
										Alpha =	0,05			
										D. f. =	34			
										X^2(Critical) =	48,6024			

2.2. Methods

2.2.1. Definitions

Definition 1. (The 2x2 Table)

Karl Pearson (K. Pearson, 1904) introduced in 1904 the notion of a contingency table (I. Barukčić, 2019a, 2019d) or two by two table. Especially the relationships between Bernoulli (i. e. Binomial) distributed random variables can be examined by contingency tables. Thus far, let a Bernoulli distributed random variable A_t occur/exist et cetera with the probability $p(A_t)$ at the Bernoulli trial (period of time) t. Furthermore, let another Bernoulli distributed random variable B_t occur/exist et cetera with the probability $p(B_t)$ at the same Bernoulli trial (period of time) t. Let $p(a_t)= p(A_t \cap B_t)$ denote the joint probability distribution of A_t and B_t at the same Bernoulli trial (period of time) t. The following table (**Table 4**) may show the relationships in more details.

Table 4. The probabitlities of a contingency table

		Conditioned B		
		Yes = +1	**No = +0**	**Total**
Condition A	Yes =+1	$p(a_t)$	$p(b_t)$	$p(A_t)$
	No = +0	$p(c_t)$	$p(d_t)$	$p(\underline{A}_t)$
	Total	$p(B_t)$	$p(\underline{B}_t)$	**1**

In this context, it is *per definitionem*

$$\begin{array}{rcccc} p(A_t) & \equiv & p(a_t)+p(b_t) & = & 1-p(\underline{A}_t) \\ p(B_t) & \equiv & p(a_t)+p(c_t) & = & 1-p(\underline{B}_t) \\ p(a_t) & \equiv & p(A_t \cap B_t) & = & 1-p(b_t)-p(c_t)-p(d_t) \\ +1 & \equiv & p(A_t)+p(\underline{A}_t) & = & p(B_t)+p(\underline{B}_t) \\ +1 & \equiv & p(a_t)+p(b_t) & + & p(c_t)+p(d_t) \\ p(B_t)+p(\Lambda_t) & \equiv & p(A_t) & = & 1-p(\underline{B}_t)+p(\Lambda_t) \\ p(\underline{A}_t) & = & 1-\left(1-p(\underline{B}_t)+p(\Lambda_t)\right) & = & p(\underline{B}_t)-p(\Lambda_t) \\ p(\Lambda_t) & = & p(A_t)-p(B_t) & = & p(b_t)-p(c_t) \\ p(b_t)+p(c_t) & = & \left(2\times p(c_t)\right)+p(\Lambda_t) & = & 1-p(a_t)-p(d_t) \end{array} \quad (1)$$

while +1 may denote *the normalized sample space* of A_t and B_t. Under circumstances were *the probability of an event is* ***constant*** *from trial to trial* (i. e. Binomial distribution), the relationships above simplifies. It is *per definitionem*

$$\begin{array}{rcccc} A & \equiv & n\times p(a_t)+n\times p(b_t) & = & n\times p(A_t) \\ B & \equiv & n\times p(a_t)+n\times p(c_t) & = & n\times p(B_t) \\ a & \equiv & n\times p(a_t) & = & n\times p(A_t \cap B_t) \\ b & \equiv & n\times p(b_t) & & \\ c & \equiv & n\times p(c_t) & & \\ d & \equiv & n\times p(d_t) & & \\ a & \equiv & A-b & = & B-c \\ d & \equiv & \underline{B}-b & = & \underline{A}-c \\ n & \equiv & n\times p(a_t)+n\times p(b_t) & + & n\times p(c_t)+n\times p(d_t) \\ n & \equiv & n\times p(A_t)+n\times p(\underline{A}_t) & = & n\times p(B_t)+n\times p(\underline{B}_t) \end{array} \quad (2)$$

The meaning of the abbreviations a, b, c, d, n et cetera are explained by following 2 by 2-table (**Table 5**). The relationships are valid even under conditions where n = 1.

Table 5. The sample space of a contingency table

		Conditioned B (Outcome)		
		Yes = +1	**No = +0**	**Total**
Condition A	Yes =+1	a	B	A
(risk factor)	No = +0	c	D	$\underline{A}$
	Total	B	$\underline{B}$	*n*

Definition 2. (Index of unfairness)

The index of unfairness (IOU) is defined (I. Barukčić, 2019c) as

$$IOU \equiv \left(\left(\frac{A + B}{n}\right) - 1\right) \tag{3}$$

The range of A is $0 \leq A \leq n$, while the range of B is $0 \leq B \leq n$. A study design based on A=B=0 leads to an index of unfairness of IOU = (((0+0)/n)-1) = -1. A study design which demands that A=B=n leads to an index of unfairness of IOU = (((n+n)/n)-1) = +1. In particular, the range of the index of unfairness is [-1;+1].

Definition 3. (The probability of an index of unfairness)

The probability of an index of unfairness p(IOU) is defined as

$$p(IOU) \equiv Absolute\left(\left(\frac{A + B}{n}\right) - 1\right) \tag{4}$$

Definition 4. Index of independence (IOI)

The index of independence (IOI) is defined (I. Barukčić, 2019b) as

$$IOI \equiv \left(\left(\frac{A + \underline{B}}{n}\right) - 1\right) \tag{5}$$

Remark.

A **study design** should ensure appropriate conditions where a cause effect, positive or negative, can be detected for sure. Under optimal conditions, it is necessary to detect from the data at the same time a necessary condition and a sufficient condition. Mathematically, it is that

$$\begin{array}{ccccc} \boldsymbol{Necessary\ condition} & = & \boldsymbol{Sufficient\ condition} & & \\ & or & & & \\ a + b + d & = & a + c + d & = & n \end{array} \tag{6}$$

Simplifying equation, under these assumptions it is

$$\begin{array}{ccccc} \boldsymbol{b} & = & \boldsymbol{c} & & \\ a + b & = & a + c & & \\ A & = & B & = & n - \underline{B} \end{array} \tag{7}$$

In other words, the detection of a *positive* causal relationships in sample data demands a study design which assures as much as possible the condition IOI = 0 or

$$\begin{aligned} A \quad + \underline{B} \quad &= \quad n \\ \frac{A \quad + \underline{B}}{n} \quad &= \quad 1 \\ \left(\left(\frac{A \quad + \underline{B}}{n}\right)\right) - 1 \quad &= \quad 0 \\ IOI \quad = \quad \left(\left(\frac{A \quad + \underline{B}}{n}\right)\right) - 1 \quad &= \quad 0 \end{aligned} \tag{8}$$

However, a study design which ensures the condition **b = c** enables the recognition of a *negative cause effect relationship* too. The exclusion relationship is defined as

$$\begin{aligned} & & b + c + d \quad &= \quad b + c + d \\ & & c + \underline{B} \quad &= \quad b + \underline{A} \\ It \quad is: & & \boldsymbol{c} \quad &= \quad \boldsymbol{b} \\ & & c + \underline{B} \quad &= \quad c + \underline{A} \\ & & & or \\ & & \underline{B} \quad &= \quad \underline{A} \\ & & & or \\ & & \underline{B} \quad &= \quad n - A \\ & & A \quad + \underline{B} \quad &= \quad n \\ & & \frac{A \quad + \underline{B}}{n} \quad &= \quad 1 \\ & & \left(\left(\frac{A \quad + \underline{B}}{n}\right)\right) - 1 \quad &= \quad 0 \\ IOI \quad = & & \left(\left(\frac{A \quad + \underline{B}}{n}\right)\right) - 1 \quad &= \quad 0 \end{aligned} \tag{9}$$

A variety of challenging issues is raised by an inappropriate study design. It should be noted that under inappropriate circumstances it is often difficult or even impossible to analyze data for causal relationships. As it is almost impossible to identify studies published which meet the requirement **b = c** or **IOI = 0** additional assumptions and great care is necessary when study data are analyzed for causal relationships.

Definition 5. (The probability of an index of independence)

The probability of an index of independence p(IOI) is defined (I. Barukčić, 2019b) as

$$p(IOI) \equiv Absolute\left(\left(\frac{A \quad + \underline{B}}{n}\right) - 1\right) \tag{10}$$

Definition 6. Sufficient Condition (Conditio per Quam)

The *sufficient* condition (I. Barukčić, 2018d, 1989, 1997, 2017, 2018a, 2018b, 2019d; K. Barukčić & Barukčić, 2016, 2016) relationship (***conditio per quam***) of a population is defined (I. Barukčić, 2019a, 2019d) as

$$\begin{aligned} p(A_t \rightarrow B_t) &\equiv \frac{(a\ ) + (c\ ) + (d\ )}{n} = 1 \\ &\equiv p(a_t) + p(c_t) + p(d_t) \\ &\equiv p(B_t) + p(d_t) \\ &\equiv p(a_t) + p(\underline{A}_t) \\ &\equiv +1. \end{aligned} \tag{11}$$

and is used to prove the hypothesis: *if* A_t *then* B_t or is taken to express that *the occurrence of an event* A_t *is a sufficient condition for existence or occurrence of an event* B_t. Sufficient and necessary conditions are converse relations (I. Barukčić, 2019a, 2019d).

Definition 7. The X² Test of Goodness of Fit of a Sufficient Condition

The chi-square value of a conditio per quam relationship is derived (I. Barukčić, 2019a, 2019d) as

$$X^2\left((A \quad \rightarrow B\ )|A\ \right) \equiv \frac{\left((b\ ) - (1/2)\right)^2}{A} + 0 = 0 \tag{12}$$

or alternatively as

$$X^2\left((A \quad \rightarrow B\ )|\underline{B}\ \right) \equiv \frac{\left((b\ ) - (1/2)\right)^2}{\underline{B}} + 0 = 0 \tag{13}$$

Definition 8. Necessary Condition (Conditio Sine Qua Non)

The mathematical formula of the *necessary* condition (I. Barukčić, 2018d, 1989, 1997, 2017, 2018a, 2018b, 2019d; K. Barukčić & Barukčić, 2016, 2016) relationship (**conditio sine qua non**) of a population is defined (I. Barukčić, 2019a, 2019d) as

$$\begin{aligned} p(A_t \leftarrow B_t) &\equiv \frac{(a\ ) + (b\ ) + (d\ )}{n} = 1 \\ &\equiv p(a_t) + p(b_t) + p(d_t) \\ &\equiv p(A_t) + p(d_t) \\ &\equiv p(a_t) + p(\underline{B_t}) = p(a_t) + \left(1 - p(B_t)\right) \\ &\equiv +1. \end{aligned} \tag{14}$$

and was to test the null-hypothesis *without* A_t *no* B_t.

Definition 9. The X^2 Test of Goodness of Fit of a Necessary Condition

The chi-square value of a *conditio sine qua non* distribution (I. Barukčić, 2019a, 2019d) before changes to

$$X^2\left((A \leftarrow B)|B\right) \equiv \frac{\left((c\ ) - (1/2)\right)^2}{B} + 0 = 0 \tag{15}$$

Depending upon the study design, another alternative and equivalent method to calculate the chi-square value of a *conditio sine qua non* distribution (while using *the continuity correction (Yates, 1934)*) is defined as

$$X^2\left((A \leftarrow B)|\underline{A}\right) \equiv \frac{\left((c\ ) - (1/2)\right)^2}{\underline{A}} + 0 = 0 \tag{16}$$

Definition 10. Exclusion (A_t Excludes B_t and Vice Versa Relationship)

The mathematical formula of the *exclusion* (I. Barukčić, 2018d, 1989, 1997, 2017, 2018a, 2018b, 2019d; K. Barukčić & Barukčić, 2016, 2016) relationship (A_t excludes B_t and vice versa) of a population is defined (I. Barukčić, 2019a, 2019d) as

$$\begin{aligned} p(A_t\,|B_t\,) &\equiv \frac{(b\;)+(c\;)+(d\;)}{n}=1 \\ &\equiv p(b_t\,)+p(c_t\,)+p(d_t\,) \\ &\equiv p(b_t\,)+p(\underline{A}_t\,)=p(b_t\,)+\left(1-p(A_t\,)\right) \\ &\equiv p(c_t\,)+p(\underline{B}_t\,)=p(c_t\,)+\left(1-p(B_t\,)\right) \\ &\equiv +1. \end{aligned} \tag{17}$$

and used to prove the hypothesis: A_t *excludes* B_t and vice versa.

Definition 11. The X² Test of Goodness of Fit of the Exclusion Relationship

The chi square value with degree of freedom 2-1=1of the exclusion relationship with a *continuity correction* can be calculated (I. Barukčić, 2019a, 2019d) as

$$X^2\left((A\;\;|B\;\;)|A\;\right) \equiv \frac{\left((a\;)-(1/2)\right)^2}{A}+0=0 \tag{18}$$

Another equivalent method to calculate the chi-square value of a *conditio sine qua non* distribution is defined (I. Barukčić, 2019a, 2019d) as

$$X^2\left((A\;\;|B\;\;)|B\;\right) \equiv \frac{\left((a\;)-(1/2)\right)^2}{B}+0=0 \tag{19}$$

In particular, the chi square Goodness of Fit Test of the exclusion relationship provides evidence how well observed data compare with the expected theoretical distribution of an exclusion relationship (I. Barukčić, 2019a, 2019d).

Definition 12. Independence

In the case of independence (Kolmogoroff, 1933; Moivre, 1718, p. 7) of A_t and B_t it is generally valid that

$$p(A_t\;\cap B_t\,) \equiv p(A_t\,)\times p(B_t\,) \tag{20}$$

Definition 13. The Mathematical Formula of the Causal Relationship k

The causal relationship k (I. Barukčić, 2016a, 2018b, 2018a, 2019d; K. Barukčić & Barukčić, 2016; K. Barukčić, Barukčić, & Barukčić, 2018) is defined *at every single event, at every single Bernoulli trial (Uspensky, 1937, p. 45) t*, as

$$k(A_t, B_t) \equiv \frac{p(A_t \cap B_t) - (p(A_t) \times p(B_t))}{\sqrt[2]{p(A_t) \times (1 - p(A_t)) \times p(B_t) \times (1 - p(B_t))}} \quad (21)$$

where A_t denotes the cause and B_t denotes the effect. The significance of causal relationship k is tested while using several methods.

Definition 14. The 95% Confidence Interval of the Causal Relationship k

The approximate 95% interval for the causal relationship k can be estimated by the formula

$$\left\{ k(A_t, B_t) - \sqrt[2]{\frac{5}{n}} \;;\; k(A_t, B_t) + \sqrt[2]{\frac{5}{n}} \right\} \quad (22)$$

Definition 15. The P Value according to hypergeometric distribution

To date statistics relies heavily and too much on large-sample approximations instead of developing exact inferential methods especially for contingency tables. However, approximations or even different statistics used possess the potential to give quite different and sometimes contradictory results, even for very large samples.

Table 6. The sample space of a hypergeometric distribution

		Conditioned B (Outcome)		
		Yes = +1	**No = +0**	**Total**
Condition A	Yes =+1	a	b	A
(risk factor)	No = +0	c	d	$\underline{A}$
	Total	B	$\underline{B}$	*n*

where a+c = B, b+d = $\underline{B}$, a+b = A, c+d=$\underline{A}$ and a+b+c+d = n. The probability mass function of the hypergeometric distribution (Gonin, 1936; Huygens & van Schooten, 1657; Karl Pearson, 1899), denoted as p(X = a), is a defined as

$$p(X = a) \equiv \frac{\binom{a+b}{a} \times \binom{c+d}{c}}{\binom{n}{a+c}} \equiv \frac{\binom{A}{a} \times \binom{n-A}{B-a}}{\binom{n}{B}} \equiv \frac{\binom{B}{a} \times \binom{n-B}{A-a}}{\binom{n}{A}} \quad (23)$$

where **n** is the sample/population size, **A** is the number of success in the sample/population, B is the number of draws (i.e. quantity drawn in each trial), **a** is the number of observed successes.

The one-sided left-tailed P Value is calculated as

$$p(X \leq a) \equiv \sum_{t=0}^{t=a} \frac{\binom{A}{t} \times \binom{n-A}{B-t}}{\binom{n}{B}} \equiv \sum_{t=0}^{t=a} \frac{\binom{B}{t} \times \binom{n-B}{A-t}}{\binom{n}{A}} \quad (24)$$

The null hypothesis of Fisher's exact test (R. A. Fisher, 1922, 1935; Ronald A. Fisher, 1925) is that A and B does not affect each other and are independent each other. Thus far, the one-sided left-tailed P Value is of use to test whether A and B are dependent of each other and may negatively affect each other. In case of an exclusion relationship we expect that A and B negatively affect each other and the one-sided left-tailed P Value could be used. The one-sided right-tailed P Value is calculated as

$$p(X \geq a) \equiv 1 - \sum_{t=0}^{t=(a-1)} \frac{\binom{A}{t} \times \binom{n-A}{B-t}}{\binom{n}{B}} \equiv 1 - \sum_{t=0}^{t=(a-1)} \frac{\binom{B}{t} \times \binom{n-B}{A-t}}{\binom{n}{A}} \quad (25)$$

The one-sided right-tailed P Value is useful to test whether A and B are dependent of each other and may positively affect each other. In case of a conditio sine qua non relationship, a conditio per quam relationship et cetera, we expect that A and B positively affect each other and the one-sided right-tailed P Value could be used. A *P Value < significance level Alpha* indicates that the null hypothesis can be rejected and forces us to accept that A and B are not independent of each other. **Example.**

Table 7. The probabilities of a hypergeometric distribution

		Conditioned B (Outcome)		
		Yes = +1	**No = +0**	**Total**
Condition A	Yes =+1	**a=10**	b=2	**A=12**
(risk factor)	No = +0	**c=4**	d=6	**A=10**
	Total	**B=14**	B=8	***n*=22**

The probabilities of the hypergeometric distribution as calculated by Excel ® are as follows.

p(X = 10) = 0,043343653.
p(X < 10) = 0,952012384.
p(X ≤ 10) = 0,995356037.
p(X > 10) = 0,004643963.
p(X ≥ 10) = 0,047987616.

Very often, Ronald Aylmer Fisher's exact test (R. A. Fisher, 1922, 1935; Ronald A. Fisher, 1925) is applied when sample sizes are small although the same is valid for all sample sizes. Methods of forming two-sided p-values (Agresti, 1992; Davis, 1986; Gibbons & Pratt, 1975) in Fisher's exact test were discussed by several authors.

Definition 16. The fictive placebo groups

The death toll of young children under the age of 1 compared to older inhabitants differs. In developed countries like USA, the probability of dying in the year 2004 between ages 0 to 1 was about 6.799 per 1000 while the probability of dying in the year 2004 between ages 99–100 was about 266.786 per 1000 (Arias, 2007). Such data are of use to construct a fictive control group. For example, the probability of dying between ages 0–1 in the year 2004 was 6.799 per 1000. In other words, it is (6.799/1000)= c/n or n = (1000*c)/6.799. Theoretically, such a *placebo* group can be administered a suitable amount of healthy and fresh water (placebo). To assure fair test conditions for causal analysis, an p(IOI)=0 as much as possible should be assured.

2.2.2. Data analysis

The causal relationship k (I. Barukčić, 1989, 1997, 2016a, 2016b, 2017, 2018a, 2019d; K. Barukčić & Barukčić, 2016; Hessen, 1928; Korch, 1965) was used to proof the data for a causal relationship while the significance of the causal relationship was tested by *the hypergeometric distribution* (HGD) and sometimes by the chi-square distribution (Karl Pearson, 1900) too. The *exclusion* (I. Barukčić, 2018d, 1989, 1997, 2017, 2018a, 2018b, 2019d; K. Barukčić & Barukčić, 2016, 2016) relationship (EXCL) was used to proof the hypothesis, the use of statins excludes death due to any cause and vice versa. The index of unfairness (I. Barukčić, 2019c) and the index of independence (I. Barukčić, 2019b) was used to control publication bias. All statistical analyses were performed with Microsoft® Excel® for Mac® version 16.2 (181208) software (© 2018, Microsoft GmbH, Munich, Germany). The level of significance was set to 0.05.

3. Results

THEOREM 1. STATINS DO NOT EXCLUDE DEATH DUE TO ANY CAUSE I

CLAIM.

Null-Hypothesis: Statins do exclude death due to any cause.

Alternative Hypothesis: Statins do not exclude death due to any cause.

PROOF.

The statin studies (**Table 2**) analyzed were able to provide evidence of a significant negative cause effect relationship while the study design was very inappropriate (p(IOI) = 0,442). The only study which assured to some extent reliable conditions was the 1998 Pravastatin LIPID study with a sample size n = 9014 and provided **a significant negative causal relationship**. However, under these to some extent appropriate experimental conditions, the exclusion relationship (EXCL) was not significant (**P Value = 0,054**; X^2(EXCL Calculated 1) = 54,965; X^2(Calculated 2) = 219,279; p(IOI) = 0,375). Thus far, even studies which documented a significant negative causal relationship between statins and death due to any cause (**Table 2**) **failed to provide evidence of significant exclusion relationship between statins and death due to any cause beyond any reasonable doubt**. In other words, since X^2(Critical) < X^2(Calculated) we reject the null-hypothesis and accept the alternative hypothesis. **Statins do not exclude death due to any cause** (Alpha = 0,05; Degrees of freedom = 6; X^2(Critical) =12,592; X^2(Calculated 1) = 75,032; X^2(Calculated 2) = 370,316; p(IOI) = 0,442).

QUOD ERAT DEMONSTRANDUM.

THEOREM 2. STATINS DO NOT EXCLUDE DEATH DUE TO ANY CAUSE II

CLAIM.

Null-Hypothesis: Statins do exclude death due to any cause.

Alternative Hypothesis: Statins do not exclude death due to any cause.

PROOF.

The majority of the statin studies (**Table 3**) do not exclude death due to any cause. In this context, the study design of the **atorvastatin** studies presented by **Table 3** was very inappropriate and very unfair. The study design of the **fluvastatin** studies was very unfair too.

The LISP study provided self-contradictory data. The **pravastatin** studies PREDICT, OACIS-LIPID, ALPS-AMI and PCS provided self -contradictory data too. None of the pravastatin studies including PACT, WOSCOPS and GISSP-P were able to provide evidence of **a significant negative causal relationship** and equally of a non-self-contradictory significant exclusion relationship (based on *the chi square distribution*). However, whether does it make sense to use the Chi-square distribution for greater sample size to test for statistical significance may stay an open question. The study design of these studies was very inappropriate. Using an alternative method to calculate the P Value of the exclusion relationship of the studies presented by **Table 3**, all the studies but ASPEN –sec., PROSPER –Sec., GISSI-HF and CORONA provided evidence of *a significant exclusion relationship and but not of a significant negative cause effect relationship*. The **lovastatin** studies CCAIT, LRTS, MARS and AFCAPS/TexCAPS provided self -contradictory data because $k > +0$. The causal relationship k is positive but not significant (P Value left tailed one sided). At the same time the exclusion relationship is more or less significant too. *Mathematically, a (significant) positive causal relationship excludes at the same time a significant exclusion relationship*. Furthermore, the study design of the lovastatin studies was very inappropriate and the data published are completely worthless in this respect. The drug lovastatin appears to be very dangerous and is of none or of a very restricted value. The **rosuvastatin** studies CENTAURUS and SPACE ROCKET provided none evidence of a significant negative cause effect relationship while the study design of both studies was very problematic ($p(IOU) > 0,25$). In contrast to these two rosuvastatin studies, the study design of the GISSI-HF and of the CORONA study was the only study design of rosuvastatin statin studies presented in this publication which was to some extent acceptable ($p(IOI) < 0,25$). However, in circumstances such as those ($p(IOI) < 0,25$) and based on the subsequent ex post evaluation and calculations above, **any positive effect of the statins (i.e. rosuvastatin) collapsed completely**. The GISSI-HF study provided evidence of a *positive* cause effect relationship. The GISSI-HF study, the CORONA study and the LIPID study were the only of all statin studies presented which provided to some extent an acceptable study design. However, under these conditions, neither pravastatin (LIPID Study) nor rosuvastatin (GISSI-HF study, CORONA study) did exclude death due to any cause

significantly. In toto, X^2(Critical) < X^2(Calculated) and we reject the null-hypothesis and accept the alternative hypothesis. **Statins do not exclude death due to any cause** (Alpha = 0,05; Degrees of freedom = 34; X^2(Critical) = 48,6024; X^2(Calculated 1) = 509,6209; X^2(Calculated 2) = 1386,2606; p(IOI) = 0,4428).

QUOD ERAT DEMONSTRANDUM.

4. Discussion

To date, atherosclerosis as the primary pathologic process in coronary artery disease (CAD) or cardiovascular disease (CVD), carotid artery disease, stroke, abdominal aortic aneurysm, and peripheral vascular disease is assumed to be determined by conventional risk factors like high blood pressure, cigarette smoking, obesity, diabetes mellitus and especially by high blood lipids. In particular, the lipid theory of atherosclerosis became by time the dominant theory of atherosclerosis. However, conventional risk factors for CAD are not able fully to account for the risk of atherosclerosis which implicates that the lipid theory of atherosclerosis is not a closed book. Especially **young CAD patients** often do **not** have any of these **conventional risk factors for CAD** but suffer from CAD (Goyal, Kalek, Chaudhry, Chauhan, & Shah, 2007). The *Framingham Heart Study*, worldwide among the longest running and most expensive endeavors in U.S. American health history, was founded in 1948 to examine among other and once and for all whether the lipid theory of atherosclerosis is true or not. Unfortunately, and contrary to expectation, the Framingham Heart Study, has *refuted the lipid hypothesis of atherosclerosis*. "After age 50 years **there is no increased overall mortality with either high or low serum cholesterol levels**. There is a direct association between falling cholesterol levels over the first 14 years and mortality over the following 18 years (11% overall and 14% **CVD death rate increase per 1 mg/dL per year drop in cholesterol levels**)." (Anderson, Castelli, & Levy, 1987). Tuikkala et al. (Tuikkala et al., 2010) investigated the association between serum total cholesterol and all-cause mortality in elderly individuals and discovered that **individuals with low serum total cholesterol have a lower survival rate than individuals with an elevated cholesterol** level independently of concomitant diseases or health status. Cabrera et al. (Cabrera, de Andrade, & Dip, 2012) documented by a 12-year follow-up cohort

study with 800 people (60-85 years old) a **higher mortality among older adults with low total cholesterol**. In contrast to the lipid hypothesis of atherosclerosis, the ***mortality*** according to Cabrera et al. showed a **positive association with low total cholesterol** and *a negative association with high total cholesterol and high LDL-cholesterol*. Several systematic reviews and meta-analysis of statin treatment for prevention of cardiovascular events provided very contradictory (Ravnskov et al., 2018; Silverman et al., 2016; Zhong et al., 2017) results. The study design and especially the placebo groups of the CSE inhibitor lipid studies re-analyzed appears to be highly biased and excellent for masking and adulterating the true properties of CSE inhibitors. To test whether CSE inhibitors are of any use at all, it is necessary to exclude bias as much as possible. In this context, a *p(IOI) = 0* is required or at least a p(IOI) < 0.25. The average p(IOI) of the CSE inhibitor lipid studies re-analyzed was p(IOI) = 0,432. However, if we take the data of the statin studies as they are, only the SAGE study provided some non-contradictory evidence that atorvastatin excludes death due to any cause. The one-sided left tails P-Value of the atorvastatin SAGE study calculated due to hypergeometric distribution was P Value = 0,01030 (p(IOI)=0,474). The 4S, WOSCOPS, GREACE, PROVE IT-TIMI studies provided some contradictory evidence that statins exclude death due to any cause. The Pravastatin LIPID study impressed by an p(IOI) = 0,375 in the positive and a sample size n=9014 (**Table 2**). In general, small trials are believed to be more biased than studies with larger sample size. However, even the very large LIPID study (n=9014) provided no significant evidence of a negative cause effect relationship between pravastatin and death due to any cause because the exclusion relationship was not significant. In toto, the lipid studies lead to contradictory findings and conclusions. It cannot be assumed with certainty that the differences observed and reported do really represent true differences, it is much more probable that the results of the most lipid studies are determined by significant bias. To put it in an exaggerated nutshell, the positive conclusions drawn from the CSE inhibitor lipid studies are very unsure and it is highly probably that the same are completely worthless. **The lipid studies used an inappropriate placebo group**. Theoretically, testing the **verum group** of the statins **against a fictive placebo group of newborn children** who were administered a suitable amount of fresh water daily while a p(IOI) = 0 was assured as much as possible, all studies analyzed could

support the hypothesis, **without** CSE inhibitor intake **no** death of individuals *within the sample investigated*. By looking at conclusion drawn from the current lipid studies data, it is that the views rely on radically inappropriate placebo groups. Questions about the correct study design need not be conclusively settled here. However, due to the result of this study, it is necessary and plausible to hypothesize whether an inappropriate study design or an insufficient verum or placebo group potentially had a distortionary influence on the positive effects as ascribed today to statins. In the light of the issue to be addressed, it seems perfectly natural to consider the possibility that the picture of statins as extremely successful drugs does not fit with realty. The issue of statins is not conclusively clarified scientifically and there is great doubt about any value of these drugs at all and of its significance in CAD risk assessment. Clearly, there are a lot of arguments which justify such a scientific attitude. To further worsen the already damaged confidence into the CSE inhibitors, an incorrect analytical approach of any research investigation at worst may completely invalidate results of a study and their associated conclusions. In order to produce valid results, it is not appropriate to compare *a bad rogue* to *an even worse rogue* (Altman, 1980) as it was the case by the most of the lipid studies presented in this publication. In the light of this publication and for safety reasons people should consider to stop at once any intake of the CSE inhibitors until reliable, publicly completely in detail available studies with an acceptable study design are published while the authorities are called to take action to stop the prescription of these drugs immediately.

5. Conclusion

The results of the lipid studies re-analyzed are consistent and provide convincing evidence against the further use of CSE inhibitors until better designed studies are publicly available.

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Author Contributions

The author confirms being the sole contributor of this work and has approved it for publication.

Conflict of Interest Statement

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. There are no conflict of interest exists according to the guidelines of the International Committee of Medical Journal Editors.

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References

3T, S., Olsson, A. G., Eriksson, M., Johnson, O., Kjellström, T., Lanke, J., … Wiklund, O. "A 52-week, multicenter, randomized, parallel-group, double-blind, double-dummy study to assess the efficacy of atorvastatin and simvastatin in reaching low-density lipoprotein cholesterol and triglyceride targets: the treat-to-target (3T) study." *Clinical Therapeutics* 2003; *25*:1, 119–138 . [PMID: 12637115]

4S, S. "Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S)." *Lancet (London, England)* 1994; *344*:8934, 1383–1389 . [PMID: 7968073]

AFCAPS/TexCAPS, S., Downs, J. R., Clearfield, M., Weis, S., Whitney, E., Shapiro, D. R., … Gotto, A. M. "Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study." *JAMA* 1998; *279*:20, 1615–1622 . doi: https://doi.org/10.1001/jama.279.20.1615 [PMID: 9613910]

Agresti, A. "A Survey of Exact Inference for Contingency Tables." *Statistical Science* 1992; *7*:1, 131–153 . doi: https://doi.org/10.1214/ss/1177011454

ALLIANCE, S., Koren, M. J., Hunninghake, D. B., & ALLIANCE Investigators "Clinical outcomes in managed-care patients with coronary heart disease treated aggressively in lipid-lowering disease management clinics: the alliance study." *Journal of the American College of Cardiology* 2004; *44*:9, 1772–1779 . doi: https://doi.org/10.1016/j.jacc.2004.07.053 [PMID: 15519006]

ALPS-AMI, S., Izawa, A., Kashima, Y., Miura, T., Ebisawa, S., Kitabayashi, H., … ALPS-AMI Investigators "Assessment of lipophilic vs. hydrophilic statin therapy in acute myocardial infarction – ALPS-AMI study." *Circulation Journal: Official Journal of the Japanese Circulation Society* 2015; *79*:1, 161–168 . doi: https://doi.org/10.1253/circj.CJ-14-0877 [PMID: 25392071]

Altman, D. G. "Statistics and ethics in medical research. Misuse of statistics is unethical." *British Medical Journal* 1980; *281*:6249, 1182–1184 . doi: https://doi.org/10.1136/bmj.281.6249.1182 [PMCID: PMC1714517] [PMID: 7427629]

Anderson, K. M., Castelli, W. P., & Levy, D. "Cholesterol and mortality. 30 years of follow-up from the Framingham study." *JAMA* 1987; *257*:16, 2176–2180 . doi: https://doi.org/10.1001/jama.1987.03390160062027 [PMID: 3560398]

Anitschkow, N., & Chlatow, S. "Über experimentelle Cholesterin-Steatose und ihre Bedeutung für die Entstehung einiger pathologischer Prozesse." *Zentralblatt Für Allgemeine Pathologie Und Pathologische Anatomie* 1913; *24*, 1–9 .

APTCA, S., Bae, J.-H., Bassenge, E., Kim, K.-Y., Synn, Y.-C., Park, K.-R., & Schwemmer, M. "Effects of low-dose atorvastatin on vascular responses in patients undergoing percutaneous coronary intervention with stenting." *Journal of Cardiovascular Pharmacology and Therapeutics* 2004; *9*:3, 185–192 . doi: https://doi.org/10.1177/107424840400900306 [PMID: 15378139]

Arias, E. "United States Life Tables, 2004." *National Vital Statistics Reports* 2007; *56*:9, 40 .

ASPEN, S., Knopp, R. H., d'Emden, M., Smilde, J. G., & Pocock, S. J. "Efficacy and safety of atorvastatin in the prevention of cardiovascular end points in subjects with type 2 diabetes: the Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in non-insulin-dependent diabetes mellitus (ASPEN)." *Diabetes Care* 2006; *29*:7, 1478–1485 . doi: https://doi.org/10.2337/dc05-2415 [PMID: 16801565]

ATHEROMA, S., Yokoi, H., Nobuyoshi, M., Mitsudo, K., Kawaguchi, A., Yamamoto, A., & ATHEROMA Study Investigators "Three-year follow-up results of angiographic intervention trial using an HMG-CoA reductase inhibitor to evaluate retardation of obstructive multiple atheroma (ATHEROMA) study." *Circulation Journal: Official Journal of the Japanese Circulation Society* 2005; *69*:8, 875–883 . [PMID: 16041153]

Barukčić, I. "Human Papillomavirus—The Cause of Human Cervical Cancer." *Journal of Biosciences and Medicines* 2018d; *06*:04, 106–125 . doi: https://doi.org/10.4236/jbm.2018.64009

Barukčić, I. *Die Kausalität* 1989; (1. Aufl.) Hamburg: Wiss.-Verl.

Barukčić, I. *Die Kausalität* 1997; (2., völlig überarb. Aufl.) Wilhelmshaven: Scientia.

Barukčić, I. "The Mathematical Formula of the Causal Relationship k." *International Journal of Applied Physics and Mathematics* 2016a; *6*:2, 45–65 . doi: https://doi.org/10.17706/ijapm.2016.6.2.45-65

Barukčić, I. "Unified Field Theory." *Journal of Applied Mathematics and Physics* 2016b; *04*:08, 1379–1438 . doi: https://doi.org/10.4236/jamp.2016.48147

Barukčić, I. *Die Kausalität* 2017; (Reprint of first Edition 1989.) Norderstedt: Books on Demand.

Barukčić, I. "Epstein-barr virus is the cause of multiple sclerosis." *International Journal of Current Medical and Pharmaceutical Research* 2018a; *4*:9 (A), 3674–3682 . doi: https://doi.org/10.24327/23956429.ijcmpr20180538

Barukčić, I. "Helicobacter Pylori is the Cause of Gastric Cancer." *Modern Health Science* 2018b; *1*:1, 43–50 . doi: https://doi.org/10.30560/mhs.v1n1p43

Barukčić, I. "Human papillomavirus is the cause of human prostate cancer." *Journal of Drug Delivery and Therapeutics* 2019a; *9*:4-s, 577–588 . doi: https://doi.org/10.22270/jddt.v9i4-s.3385

Barukčić, I. "Index of Independence." *Modern Health Science* 2019b; *2*:2, 1–25 . doi: https://doi.org/10.30560/mhs.v2n2p1

Barukčić, I. "Index of Unfairness." *Modern Health Science* 2019c; *2*:1, p22 . doi: https://doi.org/10.30560/mhs.v2n1p22

Barukčić, I. "Smoking of tobacco is the cause of human lung cancer." *Journal of Drug Delivery and Therapeutics* 2019d; *9*:1-s, 148–160 . doi: https://doi.org/10.22270/jddt.v9i1-s.2273

Barukčić, K., & Barukčić, I. "Epstein Barr Virus—The Cause of Multiple Sclerosis." *Journal of Applied Mathematics and Physics* 2016; *04*:06, 1042–1053 . doi: https://doi.org/10.4236/jamp.2016.46109

Barukčić, K., Barukčić, J. P., & Barukčić, I. "Epstein-Barr virus is the cause of rheumatoid arthritis." *Romanian Journal of Rheumatology* 2018; *27*:4, 148–163 . Retrieved from https://view.publitas.com/amph/rjr_2018_4_art-02/page/1

Brown, M. S., & Goldstein, J. L. "Receptor-mediated control of cholesterol metabolism." *Science (New York, N.Y.)* 1976; *191*:4223, 150–154 . doi: https://doi.org/10.1126/science.174194 [PMID: 174194]

Cabrera, M. A. S., de Andrade, S. M., & Dip, R. M. "Lipids and all-cause mortality among older adults: a 12-year follow-up study." *TheScientificWorldJournal* 2012; *2012*, 930139 . doi: https://doi.org/10.1100/2012/930139 [PMCID: PMC3361290] [PMID: 22666169]

CARE, S., Sacks, F. M., Pfeffer, M. A., Moye, L. A., Rouleau, J. L., Rutherford, J. D., … Braunwald, E. "The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators." *The New England Journal of Medicine* 1996; *335*:14, 1001–1009 . doi: https://doi.org/10.1056/NEJM199610033351401 [PMID: 8801446]

CCAIT, S., Waters, D., Higginson, L., Gladstone, P., Kimball, B., Le May, M., … Lespérance, J. "Effects of monotherapy with an HMG-CoA reductase inhibitor on the progression of coronary atherosclerosis as assessed by serial quantitative arteriography. The Canadian Coronary Atherosclerosis Intervention Trial." *Circulation* 1994; *89*:3, 959–968 . [PMID: 8124836]

CENTAURUS, S., Lablanche, J.-M., Leone, A., Merkely, B., Morais, J., Alonso, J., … CENTAURUS investigators "Comparison of the efficacy of rosuvastatin versus atorvastatin in reducing apolipoprotein B/apolipoprotein A-1 ratio in patients with acute coronary syndrome: results of the CENTAURUS study." *Archives of Cardiovascular Diseases* 2010; *103*:3, 160–169 . doi: https://doi.org/10.1016/j.acvd.2010.01.005 [PMID: 20417447]

CORONA, S., Kjekshus, J., Apetrei, E., Barrios, V., Böhm, M., Cleland, J. G. F., … CORONA Group "Rosuvastatin in older patients with systolic heart failure." *The New England Journal of Medicine* 2007; *357*:22, 2248–2261 . doi: https://doi.org/10.1056/NEJMoa0706201 [PMID: 17984166]

Craig, J. M., Macauley, J. C., Weller, T. H., & Wirth, P. "Isolation of intranuclear inclusion producing agents from infants with illnesses resembling cytomegalic inclusion disease." *Proceedings of the Society for Experimental Biology and Medicine. Society for Experimental Biology and Medicine (New York, N.Y.)* 1957; *94*:1, 4–12 . doi: https://doi.org/10.3181/00379727-94-22841 [PMID: 13400856]

Davis, L. J. "Exact Tests for 2 × 2 Contingency Tables." *The American Statistician* 1986; *40*:2, 139–141 . doi: https://doi.org/10.1080/00031305.1986.10475377

Dock, W. "Research in arteriosclerosis; the first fifty years." *Annals of Internal Medicine* 1958; *49*:3, 699–705 . doi: https://doi.org/10.7326/0003-4819-49-3-699 [PMID: 13571855]

Endo, A., Kuroda, M., & Tsujita, Y. "ML-236A, ML-236B, and ML-236C, new inhibitors of cholesterogenesis produced by Penicillium citrinium." *The Journal of Antibiotics* 1976; *29*:12, 1346–1348 . doi: https://doi.org/10.7164/antibiotics.29.1346 [PMID: 1010803]

Endo, Akira, Kuroda, M., & Tanzawa, K. "Competitive inhibition of 3-hydroxy-3-methylglutaryl coenzyme A reductase by ML-236A and ML-236B fungal metabolites, having hypocholesterolemic activity. 1976." *Atherosclerosis. Supplements* 2004; *5*:3, 39–42 . doi: https://doi.org/10.1016/j.atherosclerosissup.2004.08.021 [PMID: 15531273]

FACS, S., Ostadal, P., Alan, D., Vejvoda, J., Kukacka, J., Macek, M., … Cepova, J. "Fluvastatin in the first-line therapy of acute coronary syndrome: results of the multicenter, randomized, double-blind, placebo-controlled trial (the FACS-trial)." *Trials* 2010; *11*, 61 . doi: https://doi.org/10.1186/1745-6215-11-61 [PMCID: PMC2886041] [PMID: 20500832]

Fisher, R. A. "On the Interpretation of χ 2 from Contingency Tables, and the Calculation of P." *Journal of the Royal Statistical Society* 1922; *85*:1, 87 . doi: https://doi.org/10.2307/2340521

Fisher, R. A. "The Logic of Inductive Inference." *Journal of the Royal Statistical Society* 1935; *98*:1, 39 . doi: https://doi.org/10.2307/2342435

Fisher, Ronald A. *Statistical Methods for Research Workers* 1925; Edinburgh: Oliver and Boyd. Retrieved from http://www.haghish.com/resources/materials/Statistical_Methods_for_Research_Workers.pdf

FLORIDA, S., Liem, A. H., van Boven, A. J., Veeger, N. J. G. M., Withagen, A. J., Robles de Medina, R. M., … FLuvastatin On Risk Diminishment after Acute myocardial infarction study group "Effect of fluvastatin on ischaemia following acute myocardial infarction: a randomized trial." *European Heart Journal* 2002; *23*:24, 1931–1937 . doi: https://doi.org/10.1053/euhj.2002.3291 [PMID: 12473255]

Gibbons, J. D., & Pratt, J. W. "P-values: Interpretation and Methodology." *The American Statistician* 1975; *29*:1, 20–25 . doi: https://doi.org/10.1080/00031305.1975.10479106

GISSI-HF, S., Tavazzi, L., Maggioni, A. P., Marchioli, R., Barlera, S., Franzosi, M. G., … Gissi-HF Investigators "Effect of rosuvastatin in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial." *Lancet (London, England)* 2008; *372*:9645, 1231–1239 . doi: https://doi.org/10.1016/S0140-6736(08)61240-4 [PMID: 18757089]

GISSP-P, S. "Results of the low-dose (20 mg) pravastatin GISSI Prevenzione trial in 4271 patients with recent myocardial infarction: do stopped trials contribute to overall knowledge? GISSI Prevenzione Investigators (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico)." *Italian Heart Journal: Official Journal of the Italian Federation of Cardiology* 2000; *1*:12, 810–820 . [PMID: 11302109]

Goldstein, J. L., & Brown, M. S. "The low-density lipoprotein pathway and its relation to atherosclerosis." *Annual Review of Biochemistry* 1977; *46*, 897–930 . doi: https://doi.org/10.1146/annurev.bi.46.070177.004341 [PMID: 197883]

Gonin, H. T. "XIV. The use of factorial moments in the treatment of the hypergeometric distribution and in tests for regression." *The London, Edinburgh, and Dublin Philosophical Magazine and Journal of Science* 1936; *21*:139, 215–226 . doi: https://doi.org/10.1080/14786443608561573

Goyal, P., Kalek, S. C., Chaudhry, R., Chauhan, S., & Shah, N. "Association of common chronic infections with coronary artery disease in patients without any conventional risk factors." *The Indian Journal of Medical Research* 2007; *125*:2, 129–136 . [PMID: 17431281]

GREACE, S., Athyros, V. G., Papageorgiou, A. A., Mercouris, B. R., Athyrou, V. V., Symeonidis, A. N., … Kontopoulos, A. G. "Treatment with atorvastatin to the National Cholesterol Educational Program goal versus "usual" care in secondary coronary heart disease prevention. The GREek Atorvastatin and Coronary-heart-disease Evaluation (GREACE) study." *Current Medical Research and Opinion* 2002; *18*:4, 220–228 . doi: https://doi.org/10.1185/030079902125000787 [PMID: 12201623]

Heaton, N. S., & Randall, G. "Multifaceted roles for lipids in viral infection." *Trends in Microbiology* 2011; *19*:7, 368–375 . doi: https://doi.org/10.1016/j.tim.2011.03.007 [PMCID: PMC3130080] [PMID: 21530270]

Hessen, J. *Das Kausalprinzip* 1928; Augsburg: Filser.

Ho, M. "The history of cytomegalovirus and its diseases." *Medical Microbiology and Immunology* 2008; *197*:2, 65–73 . doi: https://doi.org/10.1007/s00430-007-0066-x [PMID: 18087722]

Huygens, C. (1629-1695), & van Schooten, F. (1615-1660) *De ratiociniis in ludo alae: In: Exercitationum mathematicarum liber primus [- quintus]* 1657; Lugdunum Batavorum (Leiden, The Netherlands): ex officina Johannis Elsevirii. doi: https://doi.org/10.3931/e-rara-8813

IDEAL, S., Pedersen, T. R., Faergeman, O., Kastelein, J. J. P., Olsson, A. G., Tikkanen, M. J., … Incremental Decrease in End Points Through Aggressive Lipid Lowering (IDEAL) Study Group "High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction: the IDEAL study: a randomized controlled trial." *JAMA* 2005; *294*:19, 2437–2445 . doi: https://doi.org/10.1001/jama.294.19.2437 [PMID: 16287954]

Ignatowski, A. I. "Influence de la nourriture animale sur l'organisme des lapins: (Influence of animal foods on the rabbit organism)." *Archives Medecine Experimentale Anatomie Pathologiques* 1908; *20*, 1–20 .

Kolmogoroff, A. *Grundbegriffe der Wahrscheinlichkeitsrechnung* 1933; Berlin, Heidelberg: Springer Berlin Heidelberg. doi: https://doi.org/10.1007/978-3-642-49888-6

Konstantinov, I. E., & Jankovic, G. M. "Alexander I. Ignatowski: a pioneer in the study of atherosclerosis." *Texas Heart Institute Journal* 2013; *40*:3, 246–249 . [PMID: 23914012]

Konstantinov, I. E., Mejevoi, N., & Anichkov, N. M. "Nikolai N. Anichkov and His Theory of Atherosclerosis." *Texas Heart Institute Journal* 2006; *33*:4, 417–423 . Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1764970/ [PMCID: PMC1764970] [PMID: 17215962]

Korch, H. *Das Problem der Kausalität* 1965; Berlin: Dt. Verlag der Wissenschaften.

Kumar, B., Shah, M. A. A., Kumar, R., Kumar, J., & Memon, A. "Comparison of Atorvastatin and Rosuvastatin in Reduction of Inflammatory Biomarkers in Patients with Acute Coronary Syndrome." *Cureus* 2019; *11*:6, e4898 . doi: https://doi.org/10.7759/cureus.4898 [PMCID: PMC6689481] [PMID: 31423377]

LIPID, S. "Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels." *The New England Journal of Medicine* 1998; *339*:19, 1349–1357 . doi: https://doi.org/10.1056/NEJM199811053391902 [PMID: 9841303]

LIPS, S., Serruys, P. W. J. C., de Feyter, P., Macaya, C., Kokott, N., Puel, J., … Lescol Intervention Prevention Study (LIPS) Investigators "Fluvastatin for prevention of cardiac events following successful first percutaneous coronary intervention: a randomized controlled trial (LISP)." *JAMA* 2002; *287*:24, 3215–3222 . [PMID: 12076217]

LRTS, S., Weintraub, W. S., Boccuzzi, S. J., Klein, J. L., Kosinski, A. S., King, S. B., … DeMaio, S. J. "Lack of effect of lovastatin on restenosis after coronary angioplasty. Lovastatin Restenosis Trial Study Group." *The New England Journal of Medicine* 1994; *331*:20, 1331–1337 . doi:

https://doi.org/10.1056/NEJM199411173312002 [PMID: 7935702]

LUNAR, S., Pitt, B., Loscalzo, J., Monyak, J., Miller, E., & Raichlen, J. "Comparison of lipid-modifying efficacy of rosuvastatin versus atorvastatin in patients with acute coronary syndrome (from the LUNAR study)." *The American Journal of Cardiology* 2012; *109*:9, 1239–1246 . doi: https://doi.org/10.1016/j.amjcard.2011.12.015 [PMID: 22360820]

MAAS, S. "Effect of simvastatin on coronary atheroma: the Multicentre Anti-Atheroma Study (MAAS)." *Lancet (London, England)* 1994; *344*:8923, 633–638 . [PMID: 7864934]

Mahmood, S. S., Levy, D., Vasan, R. S., & Wang, T. J. "The Framingham Heart Study and the Epidemiology of Cardiovascular Diseases: A Historical Perspective." *Lancet* 2014; *383*:9921, 999–1008 . doi: https://doi.org/10.1016/S0140-6736(13)61752-3 [PMCID: PMC4159698] [PMID: 24084292]

Marchand, F. J. *Über Arteriosklerose. In: Verhandlungen des Kongress für Innere Medizin. Einundzwanzigster Kongress. Gehalten zu Leipzig, vom 18.-21. April 1904* 1904; Wiesbaden: Verlag von J. F. Bergmann. Retrieved from http://archive.org/details/verhandlungen12medigoog

MARS, S., Blankenhorn, D. H., Azen, S. P., Kramsch, D. M., Mack, W. J., Cashin-Hemphill, L., … Hirsch, L. J. "Coronary angiographic changes with lovastatin therapy. The Monitored Atherosclerosis Regression Study (MARS)." *Annals of Internal Medicine* 1993; *119*:10, 969–976 . [PMID: 8214993]

Mills, E. J., O'Regan, C., Eyawo, O., Wu, P., Mills, F., Berwanger, O., & Briel, M. "Intensive statin therapy compared with moderate dosing for prevention of cardiovascular events: a meta-analysis of >40 000 patients." *European Heart Journal* 2011; *32*:11, 1409–1415 . doi: https://doi.org/10.1093/eurheartj/ehr035

MIRACL, S., Schwartz, G. G., Olsson, A. G., Ezekowitz, M. D., Ganz, P., Oliver, M. F., … Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) Study Investigators "Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes: the MIRACL study: a randomized controlled trial." *JAMA* 2001; *285*:13, 1711–1718 . [PMID: 11277825]

Moher, D., Liberati, A., Tetzlaff, J., & Altman, D. G. "Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement." *Annals of Internal Medicine* 2009; *151*:4, 264–964 . [PMID: 19622511]

Moivre, A. de [1667-1754] *The Doctrine of Chances or a Method of Calculating the Probability of Events in Play* 1718; London: printed by W. Pearson for the author. doi: https://doi.org/10.3931/e-rara-10420

OACIS-LIPID, S., Sato, H., Kinjo, K., Ito, H., Hirayama, A., Nanto, S., … Osaka Acute Coronary Insufficiency Study (OACIS)-LIPID Study Investigators "Effect of early use of low-dose pravastatin on major adverse cardiac events in patients with acute myocardial infarction: the OACIS-LIPID Study." *Circulation Journal: Official Journal of the Japanese Circulation Society* 2008; *72*:1, 17–22 . [PMID: 18159093]

PACT, S., Thompson, P. L., Meredith, I., Amerena, J., Campbell, T. J., Sloman, J. G., … Pravastatin in Acute Coronary Treatment (PACT) Investigators "Effect of pravastatin compared with placebo initiated within 24 hours of onset of acute myocardial infarction or unstable angina: the Pravastatin in Acute Coronary Treatment (PACT) trial." *American Heart Journal* 2004; *148*:1, e2 . doi: https://doi.org/10.1016/j.ahj.2003.10.052 [PMID: 15215811]

PCABG, S., Makuuchi, H., Furuse, A., Endo, M., Nakamura, H., Daida, H., … Yasui, H. "Effect of pravastatin on progression of coronary atherosclerosis in patients after coronary artery bypass surgery." *Circulation Journal: Official Journal of the Japanese Circulation Society* 2005; *69*:6, 636–643 . [PMID: 15914938]

PCS, S., Nakagawa, T., Kobayashi, T., Awata, N., Sato, S., Reiber, J. H. C., … Shibata, N. "Randomized, controlled trial of secondary prevention of coronary sclerosis in normocholesterolemic patients using pravastatin: final 5-year angiographic follow-up of the Prevention of Coronary Sclerosis (PCS) study." *International Journal of Cardiology* 2004; *97*:1, 107–114 . doi: https://doi.org/10.1016/j.ijcard.2003.11.002 [PMID: 15336816]

PEARL, S., Takano, H., Mizuma, H., Kuwabara, Y., Sato, Y., Shindo, S., … PEARL Study Investigators "Effects of pitavastatin in Japanese patients with chronic heart failure: the Pitavastatin Heart Failure Study (PEARL Study)." *Circulation Journal: Official Journal of the Japanese Circulation Society* 2013; *77*:4, 917–925 . [PMID: 23502990]

Pearson, K. *On the theory of contingency and its relation to association and normal correlation* 1904; London: Dulau and Co.

Pearson, Karl "XV. On certain properties of the hypergeometrical series, and on the fitting of such series to observation polygons in the theory of chance." *The London, Edinburgh, and Dublin Philosophical Magazine and Journal of Science* 1899; *47*:285, 236–246 . doi: https://doi.org/10.1080/14786449908621253

Pearson, Karl "X. On the criterion that a given system of deviations from the probable in the case of a correlated system of variables is such that it can be reasonably supposed to have arisen from random sampling." *The London, Edinburgh, and Dublin Philosophical Magazine and Journal of Science* 1900; *50*:302, 157–175 .

PLAC I, T., Pitt, B., Mancini, G. B., Ellis, S. G., Rosman, H. S., Park, J. S., & McGovern, M. E. "Pravastatin limitation of atherosclerosis in the coronary arteries (PLAC I): reduction in atherosclerosis progression and clinical events. PLAC I investigation." *Journal of the American College of Cardiology* 1995; *26*:5, 1133–1139 . [PMID: 7594023]

PLAC-II, S., Crouse, J. R., Byington, R. P., Bond, M. G., Espeland, M. A., Craven, T. E., … Furberg, C. D. "Pravastatin, Lipids, and Atherosclerosis in the Carotid Arteries (PLAC-II)." *The American Journal of Cardiology* 1995; *75*:7, 455–459 . [PMID: 7863988]

Ponroy, N., Taveira, A., Mueller, N. J., & Millard, A.-L. "Statins demonstrate a broad anti-cytomegalovirus activity in vitro in ganciclovir-susceptible and resistant strains." *Journal of Medical Virology* 2015; *87*:1, 141–153 . doi: https://doi.org/10.1002/jmv.23998 [PMID: 24976258]

PREDICT, S., Bertrand, M. E., McFadden, E. P., Fruchart, J. C., Van Belle, E., Commeau, P., … Lablanche, J. M. "Effect of pravastatin on angiographic restenosis after coronary balloon angioplasty. The PREDICT Trial Investigators. Prevention of Restenosis by Elisor after Transluminal Coronary Angioplasty." *Journal of the American College of Cardiology* 1997; *30*:4, 863–869 . [PMID: 9316510]

PROSPER, S., Shepherd, J., Blauw, G. J., Murphy, M. B., Bollen, E. L. E. M., Buckley, B. M., … PROSPER study group. PROspective Study of Pravastatin in the Elderly at Risk "Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial." *Lancet (London, England)* 2002; *360*:9346, 1623–1630 . doi: https://doi.org/10.1016/s0140-6736(02)11600-x [PMID: 12457784]

PROVE IT-TIMI, S., Cannon, C. P., Braunwald, E., McCabe, C. H., Rader, D. J., Rouleau, J. L., … Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 Investigators "Intensive versus moderate lipid lowering with statins after acute coronary syndromes." *The New England Journal of Medicine* 2004; *350*:15, 1495–1504 . doi: https://doi.org/10.1056/NEJMoa040583 [PMID: 15007110]

Ravnskov, U., de Lorgeril, M., Diamond, D. M., Hama, R., Hamazaki, T., Hammarskjöld, B., … Sundberg, R. "LDL-C does not cause cardiovascular disease: a comprehensive review of the current literature." *Expert Review of Clinical Pharmacology* 2018; *11*:10, 959–970 . doi: https://doi.org/10.1080/17512433.2018.1519391 [PMID: 30198808]

Ray, K. K., Seshasai, S. R. K., Erqou, S., Sever, P., Jukema, J. W., Ford, I., & Sattar, N. "Statins and all-cause mortality in high-risk primary prevention: a meta-analysis of 11 randomized controlled trials involving 65,229 participants." *Archives of Internal Medicine* 2010; *170*:12, 1024–1031 . doi: https://doi.org/10.1001/archinternmed.2010.182 [PMID: 20585067]

REGRESS, S., Jukema, J. W., Bruschke, A. V., van Boven, A. J., Reiber, J. H., Bal, E. T., … Lie, K. I. "Effects of lipid lowering by pravastatin on progression and regression of coronary artery disease in symptomatic men with normal to moderately elevated serum cholesterol levels. The Regression Growth Evaluation Statin Study (REGRESS)." *Circulation* 1995; *91*:10, 2528–2540 . [PMID: 7743614]

REVERSAL, S., Nissen, S. E., Tuzcu, E. M., Schoenhagen, P., Brown, B. G., Ganz, P., … REVERSAL Investigators "Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis: a randomized controlled trial." *JAMA* 2004; *291*:9, 1071–1080 . doi: https://doi.org/10.1001/jama.291.9.1071 [PMID: 14996776]

Ribbert, H. "Über protozoenartige Zellen in der Niere eines syphilitischen Neugeborenen und in der Parotis von Kindern." *Zentralblatt Für Allgemeine Pathologie Und Pathologische Anatomie* 1904; *15*, 945–948 .

Ross, R. "Atherosclerosis — An Inflammatory Disease." *New England Journal of Medicine* 1999; *340*:2, 115–126 . doi: https://doi.org/10.1056/NEJM199901143400207 [PMID: 9887164]

Rothwell, C., Lebreton, A., Young Ng, C., Lim, J. Y. H., Liu, W., Vasudevan, S., … Gaither, L. A. "Cholesterol biosynthesis modulation regulates dengue viral replication." *Virology* 2009; *389*:1–2, 8–19 . doi:

https://doi.org/10.1016/j.virol.2009.03.025 [PMID: 19419745]

SAGE, S., Deedwania, P., Stone, P. H., Bairey Merz, C. N., Cosin-Aguilar, J., Koylan, N., … Tzivoni, D. "Effects of intensive versus moderate lipid-lowering therapy on myocardial ischemia in older patients with coronary heart disease: results of the Study Assessing Goals in the Elderly (SAGE)." *Circulation* 2007; *115*:6, 700–707 . doi: https://doi.org/10.1161/CIRCULATIONAHA.106.654756 [PMID: 17283260]

SATURN, S., Nicholls, S. J., Ballantyne, C. M., Barter, P. J., Chapman, M. J., Erbel, R. M., … Nissen, S. E. "Effect of two intensive statin regimens on progression of coronary disease." *The New England Journal of Medicine* 2011; *365*:22, 2078–2087 . doi: https://doi.org/10.1056/NEJMoa1110874 [PMID: 22085316]

SCAT, S., Teo, K. K., Burton, J. R., Buller, C. E., Plante, S., Catellier, D., … Montague, T. J. "Long-term effects of cholesterol lowering and angiotensin-converting enzyme inhibition on coronary atherosclerosis: The Simvastatin/Enalapril Coronary Atherosclerosis Trial (SCAT)." *Circulation* 2000; *102*:15, 1748–1754 . [PMID: 11023927]

Shrivastava-Ranjan, P., Flint, M., Bergeron, É., McElroy, A. K., Chatterjee, P., Albariño, C. G., … Spiropoulou, C. F. "Statins Suppress Ebola Virus Infectivity by Interfering with Glycoprotein Processing." *MBio* 2018; *9*:3 . doi: https://doi.org/10.1128/mBio.00660-18 [PMCID: PMC5930306] [PMID: 29717011]

Silverman, M. G., Ference, B. A., Im, K., Wiviott, S. D., Giugliano, R. P., Grundy, S. M., … Sabatine, M. S. "Association Between Lowering LDL-C and Cardiovascular Risk Reduction Among Different Therapeutic Interventions: A Systematic Review and Meta-analysis." *JAMA* 2016; *316*:12, 1289–1297 . doi: https://doi.org/10.1001/jama.2016.13985 [PMID: 27673306]

Simons, J. "The $10 billion pill." *Fortune* 2003; *147*:1, 58–62, 66, 68 . [PMID: 12602122]

SPACE ROCKET, S., Hall, A. S., Jackson, B. M., Farrin, A. J., Efthymiou, M., Barth, J. H., … SPACE ROCKET Trial Group "A randomized, controlled trial of simvastatin versus rosuvastatin in patients with acute myocardial infarction: the Secondary Prevention of Acute Coronary Events--Reduction of Cholesterol to Key European Targets Trial." *European Journal of Cardiovascular Prevention and Rehabilitation: Official Journal of the European Society of Cardiology, Working Groups on Epidemiology & Prevention and Cardiac Rehabilitation and Exercise Physiology* 2009; *16*:6, 712–721 . doi: https://doi.org/10.1097/HJR.0b013e3283316ce8 [PMID: 19745745]

SPARCL, S., Amarenco, P., Bogousslavsky, J., Callahan, A., Goldstein, L. B., Hennerici, M., … Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Investigators "High-dose atorvastatin after stroke or transient ischemic attack." *The New England Journal of Medicine* 2006; *355*:6, 549–559 . doi: https://doi.org/10.1056/NEJMoa061894 [PMID: 16899775]

Steinberg, D., Parthasarathy, S., Carew, T. E., Khoo, J. C., & Witztum, J. L. "Beyond cholesterol. Modifications of low-density lipoprotein that increase its atherogenicity." *The New England Journal of Medicine* 1989; *320*:14, 915–924 . doi: https://doi.org/10.1056/NEJM198904063201407 [PMID: 2648148]

Taylor, F. C., Huffman, M., & Ebrahim, S. "Statin therapy for primary prevention of cardiovascular disease." *JAMA* 2013; *310*:22, 2451–2452 . doi: https://doi.org/10.1001/jama.2013.281348 [PMID: 24276813]

Ting, M., Whitaker, E. J., & Albandar, J. M. "Systematic review of the in vitro effects of statins on oral and perioral microorganisms." *European Journal of Oral Sciences* 2016; *124*:1, 4–10 . doi: https://doi.org/10.1111/eos.12239 [PMID: 26718458]

Tuikkala, P., Hartikainen, S., Korhonen, M. J., Lavikainen, P., Kettunen, R., Sulkava, R., & Enlund, H. "Serum total cholesterol levels and all-cause mortality in a home-dwelling elderly population: a six-year follow-up." *Scandinavian Journal of Primary Health Care* 2010; *28*:2, 121–127 . doi: https://doi.org/10.3109/02813432.2010.487371 [PMCID: PMC3442317] [PMID: 20470020]

Uspensky, J. v. *Introduction To Mathematical Probability* 1937; New York (USA): McGraw-Hill Company.

VASBA, S., Stone, P. H., Lloyd-Jones, D. M., Kinlay, S., Frei, B., Carlson, W., … Vascular Basis Study Group "Effect of intensive lipid lowering, with or without antioxidant vitamins, compared with moderate lipid lowering on myocardial ischemia in patients with stable coronary artery disease: the Vascular Basis for the Treatment of Myocardial Ischemia Study." *Circulation* 2005; *111*:14, 1747–1755 . doi: https://doi.org/10.1161/01.CIR.0000160866.90148.76 [PMID: 15809368]

Virchow, R. L. K. *Gesammelte Abhandlungen zur Wissenschaftlichen Medicin* 1856; Frankfurt am Main: Meidinger Sohn & Comp. Retrieved from https://archive.org/details/b21462161

WHO “Model list of essential medicines.” *World Health Organization* 2019; *21*, 65 . Retrieved from https://apps.who.int/iris/handle/10665/325771

Windaus, A. “Über den Gehalt normaler und atheromatöser Aorten an Cholesterin und Cholesterinestern.” *Hoppe-Seyler´s Zeitschrift Für Physiologische Chemie* 1910; *67*:2, 174–176 . doi: https://doi.org/10.1515/bchm2.1910.67.2.174

WOSCOPS I, S., Shepherd, J., Cobbe, S. M., Ford, I., Isles, C. G., Lorimer, A. R., … Packard, C. J. “Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group.” *The New England Journal of Medicine* 1995; *333*:20, 1301–1307 . doi: https://doi.org/10.1056/NEJM199511163332001 [PMID: 7566020]

Yates, F. “Contingency Tables Involving Small Numbers and the χ 2 Test.” *The Journal of the Royal Statistical Society (Supplement)* 1934; *1*:2, 217 . doi: https://doi.org/10.2307/2983604

Zhong, P., Wu, D., Ye, X., Wu, Y., Li, T., Tong, S., & Liu, X. “Secondary prevention of major cerebrovascular events with seven different statins: a multi-treatment meta-analysis.” *Drug Design, Development and Therapy* 2017; *11*, 2517–2526 . doi: https://doi.org/10.2147/DDDT.S135785 [PMCID: PMC5587089] [PMID: 28919704]