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. An immediate statin therapy discontinuation should be considered.

Conclusions: Overwhelming evidence suggests that the risk potential harmful effects of statin therapy far outweigh any real or perceived benefit.

Keywords: ***Statins, death, causal relationship.***

1. Introduction

Influenced by Virchow's observation, 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 atherosclerosis, 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. 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. an 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 were 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 exclude death due to any cause 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

Trial name	Year	Drug	n	a	a+c	b	b+d	Caus. Rel. k	P Value (k)	p(EXCL)	P Value (EXCL)	X^2(EXCL|At)	X^2(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
X^2(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)	X^2(EXCL|At)	X^2(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 8**) 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*

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

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*

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

The meaning of the abbreviations a, b, c, d, n et cetera are explained by following 2 by 2-table (**Table 9**). 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 (risk factor)	Yes =+1	a	b	A
	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

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

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

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

Definition 4. Index of independence (IOI)

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

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

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

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

A variety of challenging issues is raised by an inappropriate study design. It should be noted that under these 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.

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

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

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

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

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

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

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

or alternatively as

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

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

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

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

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

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

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

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

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

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

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

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 (risk factor)	Yes =+1	a	b	A
	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	**$\underline{A}$=10**
	Total	**B=14**	$\underline{B}$=8	***n*=22**

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

$p(X = 10) = 0{,}043343653.$
$p(X < 10) = 0{,}952012384.$
$p(X \leq 10) = 0{,}995356037.$
$p(X > 10) = 0{,}004643963.$
$p(X \geq 10) = 0{,}047987616.$

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 deaths/1000 while the probability of dying in the year 2004 between ages 99–100 was about 266.786 deaths/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 deaths/1000. In other words, it is (6.799/1000)= c/n or n = (1000*c)/6.799. The value of d = n-a-b-c = n-c-c=(1000*c)/6.799)-c-c or d = c*((1000/6.799)-2). 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. STATIN STUDIES WHICH 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) = 0,442). 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. Thus far, 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. STATIN STUDIES WHICH 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 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**)." 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 exclude 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 would 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 control group potentially has 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 in detail completely 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.

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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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