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Human cytomegalovirus is the cause of human atherosclerosis

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Abstract

Objective: Human cytomegalovirus (HCMV) infection has been supposed to play an important role in the pathogenesis of human atherosclerosis (AS). Although many authors proved the presence of viral DNA in arterial wall tissue, the role of HCMV in the origin and progress of atherosclerosis still remains unclear and no definite consensus has been reached. Whether HCMV may be involved in the development of AS has not yet been established.

Methods: The purpose of this study was to investigate whether HCMV and AS are causally related. The conditio sine qua non method, the conditio per quam method, the causal relationship and other methods were used to re-analyzed the data available.

Results: HCMV is a necessary condition of AS. HCMV is a sufficient condition of AS. There is a highly significant cause effect between a HCMV infection and AS. This review and meta-analysis results provide striking evidence that a HCMV infection and AS are causally connected.

Conclusions: In conclusion, a HCMV infection is the cause of AS.

Keywords: *Human cytomegalovirus, atherosclerosis, causal relationship.*

1. Introduction

Atherosclerosis is as old as human (Kälvegren, 2007) mankind itself while the term *atheroma* has been coined by *Celsius* (Cottet & Lenoir, 1992) more than two thousands of years ago. However, it was especially *Lobstein* (Lobstein, 1833) who defined in 1833 the word *atheromatosis*. In 1904, Félix Jacob *Marchand* (1846 – 1928) renamed the word "atheroma" by the word "atherosclerosis" (Marchand, 1904, pp. 23–59). The historical roots of a scientific

understanding of atherosclerosis can already be found in pre-modern and medieval age. Historically, it was *Albrecht von Haller* who described in 1755 atherosclerosis as a degenerative (Haller, 1755) process observed in the intima of arteries (Haller, 1755) while *John Hunter* (1728–1793), the famous Scottish physician and the "*Founder of Scientific Surgery*" (Androutsos, Vladimiros, & Diamantis, 2007) observed already in 1793 that inflammation (Wilson, 1793) of the internal surface of veins is common. In the following, the British surgeon *Joseph Hodgson* famous for his 1815 monograph (Hodgson, 1815) was of the opinion that inflammation (Hodgson, 1815) was the underlying cause of atheromatous arteries. The inflammatory theory of atherosclerosis was advocated in 1856 by the prominent German pathologist *Rudolf Virchow* too who writes about "*die acute Entzüdung der Arterien*" (Virchow, 1856) proposing an *'infiltration' theory of atherosclerosis* claiming that atherosclerosis is a chronic inflammatory disease of the intima of an artery. In point of fact, it is notable that since the 19th century several authors postulated that the development of atherosclerotic plaques and their rupture is determined by an inflammation (Huchard, 1891) caused by infection (Gilbert & Lion, 1889). In the following, several different infectious agents have been implicated in the etiology of atherosclerosis including C. pneumoniae, H. pylori and other and the development and progression has kept growing and includes several viral infections too. Minick et al. (Minick, Fabricant, Fabricant, & Litrenta, 1979) performed an experimental study in 1979, while contaminating birds by a herpesvirus. The birds developed typical atherosclerosis. Among all human herpesviruses (HHV), especially human herpesvirus 5 (HHV-5) or **human cytomegalovirus** has been linked with the development of atherosclerosis. The HCMV infection is relatively common among women of reproductive age, the seroprevalence is ranging from 45 to 100% (Cannon, Schmid, & Hyde, 2010) while the worldwide HCMV seroprevalence (Mussi-Pinhata et al., 2018) shows a substantial geographic variation. In point of fact, the overall seroprevalence rate of HCMV increases gradually from 36.3% in 6-11-year-olds to 90.8% in those aged > or =80 years (Staras et al., 2006), while the seroprevalence among women of reproductive age is about 45–100%. Increasing arguments supports a direct link between HCMV infection and cardiovascular disorders, stroke et cetera and are documented by evaluation of anti- HCMV antibodies, PCR analysis and other studies.

Mounting but to some extent still conflicting (Ridker, Hennekens, Stampfer, & Wang, 1998) evidence strongly indicates (Simanek et al., 2011) the implication of persistent HCMV infection with several health-related changes including atherosclerosis. Findings indicate that even relatively young asymptomatic individuals seropositive for CMV have abnormal endothelial dysfunction (Grahame-Clarke et al., 2003). However, contradictory results have also been reported too and a more detailed review and meta-analysis is needed before the final verdict on this exciting question can be presented and the more popular "the lipid hypothesis" (I. Barukčić, 2019e; Linton et al., 2000) of arteriosclerosis became, the less the infection hypothesis of arteriosclerosis became important over time. To date, atherosclerosis is the most frequent reason of deaths in Western countries and equally an important problem of the contemporary medicine. However, despite the long history of investigation, a cause or the cause of atherosclerosis remains largely unknown.

2. Material and Methods

HCMV is a double-stranded DNA virus of the β-herpesvirus family genome and persists in certain human host cells for life after primary infection (Dolan et al., 2004), HCMV is never cleared by human host. Reactivation and latency are defining characteristics of HCMV infection. A reactivation from latency (Sinclair & Sissons, 2006) even in non-immunocompromised individuals can results in serious disease. HCMV IgG indicates HCMV positivity or latency while changes of HCMV IgG during HCMV latency might point to recent or frequent HCMV reactivation. Reactivations or superinfections may result in higher titers of HCMV immunoglobulin G (IgG) antibodies but of increased levels of pro-inflammatory markers too. HCMV-specific IgG is used as an indicator for long-term HCMV infection. HCMV IgG titers are measured while using different kits. The cutoff values for HCMV positivity were different. The sensitivity and specificity of these kits is different which might have impact on the results achieved.

2.1. Material

2.1.1. Search Strategy

In general, for the questions addressed in this paper, the electronic database PubMed was searched for appropriate studies conducted in any country which investigated the relationship between HCMV and AS i. e. sero-epidemiologically or by polymerase chain reaction (PCR) et cetera. The search in PubMed was performed while using some medical key words like "cytomegalovirus and atherosclerosis". Those articles were considered for a re-view where data were available without significant access barrier. Additionally, the reference list of identified articles was used as a potential source of articles appropriate for this study.

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

1. Identification of records	Size	Total
Records identified by searching in the databases		
PubMed	561	
Lipid Studies	44	
Immune-suppressive Drug studies	3	
		608
2. Clean-up of search (Screening)		
Records removed after verifying duplication, excluded by title, excluded due to other reasons		449
3. Eligibility		
Articles evaluated for eligibility		159
Articles excluded for various reasons	113	
4. Included		
Articles included in the meta-analysis		46

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

2.1.2. HCMV IgG-Studies considered for re-analysis

The following CMV IgG sero-epidemiological studies (Adam et al., 1987; Adler, Hur, Wang, & Vetrovec, 1998; Blum, Peleg, & Weinberg, 2003; Gabrylewicz et al., 2003; González-Quijada, Mora-Simón, & Martin-Ezquerro, 2014; Huang et al., 2012; Kurkowska-Jastrzebska et al., 2016; Li, Xu, & Wang, 1996; Loebe et al., 1990; Mundkur et al., 2012; Ossewaarde, Feskens, De Vries, Vallinga, & Kromhout, 1998; Pesonen et al., 2009; Ridker et al., 1998; Safaie, Ghotaslou, & Montazer Ghaem, 2010; Sepúlveda, Moreu, Cantón,

Pajin, & Rodríguez, 1999; Timóteo et al., 2003; Yang et al., 2018; Zhang et al., 2015; Zhu, Quyyumi, Norman, Csako, & Epstein, 1999) as presented by **Table 2** were considered for meta-analysis.

Table 2. ***Without*** **HCMV IgG sero-positivity** ***no*** **AS.**

Study	Year	n	a	a+c	b	b+d	k	P Value (k)	p(SINE)	P Value (SINE)	X²(SINE|Bt)	p (IOI) + P(IOU)	p(IOU)	p(IOI)
Kurkowska-Jastrzębska et al.	2016	195	114	116	73	79	**0,145**	0,041	0,990	0,010	0,034	0,918	0,554	0,364
Adamet al.	1987	314	141	157	116	157	**0,207**	0,000	0,949	0,050	1,631	0,637	0,318	0,318
Izadi et al.	2012	105	30	33	60	72	**0,101**	0,151	0,971	0,028	0,273	0,714	0,171	0,543
Izadi et al.	2012	105	30	33	60	72	**0,101**	0,151	0,971	0,028	0,273	0,714	0,171	0,543
Mundkur et al.	2012	866	425	433	422	433	**0,024**	0,145	0,991	0,009	0,148	0,956	0,478	0,478
Huang et al.	2012	400	197	200	195	200	**0,036**	0,220	0,993	0,007	0,045	0,960	0,480	0,480
Safaie et al.	2010	157	94	113	28	44	**0,211**	0,006	0,879	0,114	3,195	0,554	0,497	0,057
Gabrylewicz et al.	2003	158	94	110	15	48	**0,539**	0,000	0,899	0,096	2,327	0,392	0,386	0,006
Blumet al.	2003	91	57	60	25	31	**0,228**	0,032	0,967	0,032	0,150	0,802	0,560	0,242
Timóteo et al.	2003	90	57	60	24	30	**0,236**	0,029	0,967	0,033	0,150	0,800	0,567	0,233
Li et al.	1996	186	101	106	68	80	**0,177**	0,012	0,973	0,027	0,236	0,817	0,478	0,339
Loebe et al.	1990	50	20	26	6	24	**0,519**	0,000	0,880	0,113	1,385	0,040	0,040	0,000
	Total	**2717**	1360	1447	1092	1270			0,968	0,024	**9,846**	0,692	0,392	0,300

Alpha =	0,05	
D. f. =	12	
X²(Critical) =	**21,0261**	
P Value (right-tail) =		0,6295

The study design of the most studies was very inappropriate thus that the result of the re-analysis can be biased. The only study design which was convincing was the study design of Leobe et al. with p (IOI) + p(IOU) = 0,040. Only studies with a **p(IOI) < 0.367** were able to provide evidence of a significant cause effect relationship.

2.1.3. HCMV IgG-Studies not considered for re-analysis

It was not possible to consider several CMV IgG sero-epidemiological studies (Al-Ghamdi, 2012; Altannavch, Roubalová, Broz, Hrubá, & Anděl, 2003; Betjes, Litjens, & Zietse, 2007;

Bloemenkamp et al., 2002; Blum et al., 1998; Cai, Cai, & Lu, 2003; Elkind et al., 2010; Eryol et al., 2005; Espinola-Klein et al., 2002; Gkrania-Klotsas et al., 2012; Grahame-Clarke et al., 2003; Gredmark, Jonasson, van Gosliga, Ernerudh, & Söderberg-Nauclér, 2007; Jeong et al., 2015; Jha & Mittal, 2009; Jha, Prasad, & Mittal, 2008; Kawasaki et al., 2016; Knudsen et al., 2019; Laek et al., 2013; Lidón et al., 2019; Liu et al., 2011; Loebe et al., 1990; López de Atalaya, Cour, García, Ferro, & Perezagua, 1989; Martínez-Rodríguez et al., 2013; Masiá et al., 2013; Musiani et al., 1990; Olson et al., 2013; Rabczyński et al., 2015; Rabczyński, Jakobsche, & Adamiec, 2007; Rajasekhar et al., 2002; Rothenbacher et al., 2003; Siennicka, Kruk, Przyłuski, & Krajewski, 2001; Simanek et al., 2011; Sorlie et al., 1994; Szklo et al., 2009; Tewari, Nijhawan, Mishra, Dudeja, & Salopal, 2012; Tracy et al., 2013; Visseren et al., 1997; Voorend, van der Ven, Kubat, Lodder, & Bruggeman, 2008; Witherell et al., 2003; Zhang et al., 2015) for meta-analysis due to various reasons (data access barriers, data are self-contradictory et cetera).

2.1.4. HCMV is a sufficient condition of AS

Polymerase chain reaction (PCR) and other different HCVM DNA based studies where considered for a re-analysis. The PCR methodology itself is not completely free of any errors and it is not possible to exclude any imponderability due to PCR. HCMV DNA must be purified from a specimen with different quality while using a certain kit. Manufacturer's protocol does not guarantee a PCR specify and sensitivity of 100 %. HCMV DNA must be amplified by PCR using different (forward and reverse) HCMV primers selected from a certain region of the CMV genome (**Table 3**).

Table 3. HCMV (PCR DNA) is a sufficient condition of AS

Study	Year	n	a	a+c	b	b+d	k	P Value (k)	p(IMP)	P Value (IMP)	X^2(IMP| At)	X^2(IMP|Bt)	p(IOU)	p(IOI)
Cao et al.	2017	40	21	25	2	15	0,692	0,000	0,950	0,049	0,174	0,267	0,200	0,050
Wang et al.	2016	32	14	15	0	17	0,939	0,000	1,000	0,000	0,000	0,000	0,094	0,031
Beyaz et al.	2019	36	12	19	0	17	0,669	0,000	1,000	0,000	0,000	0,000	0,139	0,194
Izadi et al.	2012	87	37	48	18	39	0,319	0,002	0,793	0,187	5,891	8,308	0,184	0,080

Yi et al.	2008	55	21	35	6	20	0,289	0,024	0,891	0,103	1,333	1,800	0,127	0,145
Ibrahim et al.	2005	96	5	48	0	48	0,234	0,028	1,000	0,000	0,000	0,000	0,448	0,448
Heybar et al.	2015	110	8	55	2	55	0,190	0,039	0,982	0,018	0,400	0,073	0,409	0,409
Izadi et al.	2014	60	9	30	1	30	0,358	0,006	0,983	0,017	0,100	0,033	0,333	0,333
Yi et al.	2008	55	21	35	6	20	0,289	0,024	0,891	0,103	1,333	1,800	0,127	0,145
Bayram et al.	2011	60	3	30	0	30	0,229	0,119	1,000	0,000	0,000	0,000	0,450	0,450
Imbronito et al.	2010	78	28	30	0	48	0,947	0,000	1,000	0,000	0,000	0,000	0,256	0,026
Gred.-Russ et al.	2009	25	21	22	0	3	0,846	0,002	1,000	0,000	0,000	0,000	0,720	0,040
Reszka et al.	2008	60	22	40	10	20	0,047	0,202	0,833	0,154	3,125	5,000	0,200	0,133
Westphal et al.	2006	116	52	68	0	48	0,757	0,000	1,000	0,000	0,000	0,000	0,034	0,138
Shi et al.	2002	33	4	10	1	23	0,457	0,020	0,970	0,030	0,200	0,043	0,545	0,152
Hu et al.	2001	90	51	60	2	30	0,750	0,000	0,978	0,022	0,075	0,133	0,256	0,078
Hendrix et al.	1990	64	27	30	18	34	0,405	0,001	0,719	0,245	7,200	9,529	0,172	0,234
Lin et al.	2003	224	64	200	2	24	0,161	0,008	0,991	0,009	0,061	0,167	0,188	0,598
Radke et al.	2001	101	16	53	0	48	0,413	0,000	1,000	0,000	0,000	0,000	0,317	0,366
Horváth et al.	2000	331	185	244	0	87	0,672	0,000	1,000	0,000	0,000	0,000	0,296	0,178
Chiu et al.	1997	96	27	76	0	20	0,321	0,001	1,000	0,000	0,000	0,000	0,073	0,510
Chen et al.	1995	47	13	32	1	15	0,346	0,015	0,979	0,021	0,071	0,067	0,021	0,383
	Total	**1896**	661	1205	69	691			0,964	0,036	**19,964**	**27,220**	0,254	0,233
									Alpha =	0,05				
									D. f. =	22				
									X²(Critical) =	**33,9244**				
									P Value (right-tail) =		0,5853	0,2030		

2.1.5. HCMV is a necessary condition of AS

Ten HCMV PCR DNA studies were able to provide evidence of a conditio sine qua non relationship between HCMV and AS (**Table 4**).

Table 4. HCMV (PCR DNA) is a necessary condition of AS

Study	Year	n	a	a+c	b	b+d	k	P Value (k)	p(SINE)	P Value (SINE)	X²(SINE|Bt)	X²(SINE|At)	p(IOU)	p(IOI)
Cao et al.	2017	40	21	25	2	15	0,692	0,000	0,900	0,095	0,640	0,941	0,200	0,050
Wang et al.	2016	32	14	15	**0**	**17**	0,939	0,000	0,969	0,031	0,067	0,056	0,094	0,031
Beyaz et al.	2019	36	12	19	0	17	0,669	0,000	0,806	0,177	2,579	2,042	0,139	0,194
Izadi et al.	2012	87	37	48	18	39	0,319	0,002	0,874	0,119	2,521	3,781	0,184	0,080
Imbronito et al.	2010	78	28	30	**0**	**48**	0,947	0,000	0,974	0,025	0,133	0,080	0,256	0,026
Gred.-Russ et al.	2009	25	21	22	0	3	0,846	0,002	0,960	0,039	0,045	0,250	0,720	0,040
Westphal et al.	2006	116	52	68	**0**	**48**	0,757	0,000	0,862	0,129	3,765	4,000	0,034	0,138

Shi et al.	2002	33	4	10	1	23	0,457	0,020	0,818	0,166	3,600	1,286	0,545	0,152
Hu et al.	2001	90	51	60	2	30	0,750	0,000	0,900	0,095	1,350	2,189	0,256	0,078
Hendrix et al.	1990	64	27	30	18	34	0,405	0,001	0,953	0,046	0,300	0,474	0,172	0,234
	Total	**601**	267	327	41	274			0,900	0,593	**15,000**	**15,098**	0,260	0,102

Alpha =	0,05		
D. f. =	10		
X^2(Critical) =	**18,3070**		
P Value (right-tail) =		**0,1321**	**0,1285**

The studies of Wang et al., Imbronito et al. and Westphal et al. did not provide an appropriate control group. Still, the calculation of the Chi-square statistics was possible, a fair study design provided. The following PCR and other HCMV DNA studies (Chen et al., 2003; Ciervo, Mancini, Sale, Russo, & Cassone, 2008; Courivaud et al., 2013; Hagiwara et al., 2007; Horváth, Cerný, Benedík, Hökl, & Jelínková, 2000; Huang et al., 2012; Izadi et al., 2012; Kilic et al., 2006; Latsios, Saetta, Michalopoulos, Agapitos, & Patsouris, 2004; Lebedeva, Shpektor, Vasilieva, & Margolis, 2018; Lee et al., 2014; Lin, Chen, Chen, Wang, & Eng, 2003; Melnick, Adam, & DeBakey, 1990; Melnick, Hu, Burek, Adam, & DeBakey, 1994; Nyberg, Skagius, Nilsson, Ljungh, & Henriksson, 2008; Pinar et al., 2004; Priyanka, Kaarthikeyan, Nadathur, Mohanraj, & Kavarthapu, 2017; Radke et al., 2001; Reinhardt et al., 2003; Reszka et al., 2008; Saetta, Fanourakis, Agapitos, & Davaris, 2000; Shi & Tokunaga, 2002; Skowronski, Mendoza, Smith, & Jaski, 1993; Tremolada et al., 2011; Watt, Aesch, Lanotte, Tranquart, & Quentin, 2003; Westphal et al., 2006; Xenaki, Hassoulas, Apostolakis, Sourvinos, & Spandidos, 2009; Yamashiroya, Ghosh, Yang, & Robertson, 1988) were not considered for further analysis due to several reasons.

2.1.6. Statins and AS

The statin drug studies were not able to establish evidence of the lipid hypothesis beyond all doubt (I. Barukčić, 2019e).

2.1.6. Drugs and AS

Under the assumption that atherosclerosis of coronary arteries (CAD) is an inflammatory process, an ‘immunosuppressive’ or ‘immunomodifying’ therapy in patients treated with

'immunosuppressive' or modifying medication and other drugs should decrease the number of new cardio-vascular events (CAD incidence). It was possible to identify view studies (Hung et al., 2017; Suissa, Bernatsky, & Hudson, 2006; Wu et al., 2016) which investigated the relationship between intake of putative immunosuppressive drugs and cardio-vascular events.

Table 5. Drugs and cardio-vacular events

Study name	Year	Drug	N	CVD and drug	CVD total	No CVD and drug	No CVD total	Causal relationship k	P Value (k)	p(EXCL)	P Value (EXCL)	X²(EXCL| At)	X²(EXCL|Bt)	p(IOU)	p(IOI)
Wu et al.	2016	**Etoricoxib**	4112	11	346	264	3766	-0,04257	0,00139	0,99732	0,00267	0,44000	0,34971	0,84898	0,01727
Hung et al.	2017	**Etoricoxib**	6260	12	1253	144	5007	-0,04924	0,00001	0,99808	0,00192	0,92308	0,11492	0,77492	0,17524
Hung et al.	2017	**Etanercept**	6260	2	1253	54	5007	-0,03905	0,00034	0,99968	0,00032	0,07143	0,00319	0,79089	0,19121
Suissa et al.	2006	**Leflunomide**	6138	6	558	194	5580	-0,03888	0,00038	0,99902	0,00098	0,18000	0,06452	0,87651	0,05833
		Total	**22770**	31	3410	656	19360			0,9986	0,0014	1,6145	0,5323	0,8228	0,1105
										Alpha =	0,05				
										D. f. =	4				
										X²(Critical) =	9,4877				

A study design which aims to investigate an **exclusion relationship** should assure conditions where **p(IOI) = 0** or as near to zero as possible. Especially Wu et al. and Suissa et al. assured appropriate conditions but Hung et al. only to some extent too. The etoricoxib analysis of Thöne et al. (Thöne, Kollhorst, & Schink, 2017) and of Masclee et al. (Masclee et al., 2018) was not considered for a re-analysis.

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 6**) may show the relationships in more details.

Table 6. 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*

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

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*

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

The meaning of the abbreviations a, b, c, d, n et cetera are explained by following 2 by 2-table (**Table 7**). The relationships are valid even under conditions where n = 1.

Table 7. 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	A
	Total	B	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 study design for single risk factors or conditions)

Assuming the *necessary* condition (I. Barukčić, 2018d, 1989, 1997, 2017, 2018a, 2018b, 2019d; K. Barukčić & Barukčić, 2016, 2016) relationship (**conditio sine qua non**) is given in the population (a + b + d = n), it has to be that **c = 0** or

$$\begin{aligned} B - a &\equiv n - A - d = c = 0 \\ A + B &\equiv n + a - d \\ \frac{A + B}{n} &\equiv \left(\frac{n}{n}\right) + \left(\frac{+a - d}{n}\right) \\ \left(\frac{A + B}{n}\right) - 1 &\equiv \left(\frac{+a - d}{n}\right) \\ \left(\frac{A + B}{n}\right) - 1 &\equiv \left(\frac{+a - d}{n}\right) = IOU \end{aligned} \tag{4}$$

A study design which assures an index of unfairness as near as possible to **IOU = 0** or **a=d** is appropriate enough to recognize a single risk factor or a *single* condition like conditio sine qua

non or conditio per quam but is not appropriate enough to recognize an exclusion (I. Barukčić, 2019e) relationship.

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) is defined *at every single event* (I. Barukčić, 2016a, 2018b, 2018a, 2019d; K. Barukčić & Barukčić, 2016; K. Barukčić, Barukčić, & Barukčić, 2018) , *at every single Bernoulli trial (Uspensky, 1937, p. 45) t* and was used to proof the data for a causal relationship while the significance was tested by *the hypergeometric distribution* (HGD) and sometimes by the chi-square distribution (Karl Pearson, 1900) too. The *conditio sine qua non* (I. Barukčić, 2018d, 1989, 1997, 2017, 2018a, 2018b, 2019d; K. Barukčić & Barukčić, 2016, 2016) relationship (SINE) was used to proof the hypothesis, *without* (I. Barukčić, 2019e) HCMV infection *no* AS. The *conditio per quam* (I. Barukčić, 2018d, 1989, 1997, 2017, 2018a, 2018b, 2019d; K. Barukčić & Barukčić, 2016, 2016) relationship (IMP) was used to proof the hypothesis, *if* (I. Barukčić, 2019e) HCMV infection *then* AS. The *necessary and sufficient condition* (I. Barukčić, 2018d, 1989, 1997, 2017, 2018a, 2018b, 2019d; K. Barukčić & Barukčić, 2016, 2016) relationship (SINE) can be used to proof the hypothesis, (*without* HCMV infection *no* AS) **and** (*if* HCMV infection *then* AS). 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. WITHOUT HCMV IGG SERO-POSITIVITY NO AS

CLAIM.

Null-Hypothesis: HCMV IgG sero-positivity is a necessary condition of AS.

Alternative Hypothesis: HCMV IgG sero-positivity is not a necessary condition of AS.

PROOF.

In toto, 12 studies with a sample size of n = 2717 (**Table 2**) were considered for a re-analysis of a conditio sine qua non relationship between HCMV and AS based on HCMV IgG serology. The study design was not highly appropriate (Mean (IOU) = 0,392; Mean (IOI) = 0,300). In this context, the data analyzed could be of very limited use. However, the average conditio sine qua non relationship between HCMV and AS was p(SINE) = 0,968. The X^2 calculated was determined as X^2(Calculated) = 9,846 while the X^2 critical (degrees of freedom = 12; Alpha = 0,05) was found to be X^2(Critical) = 21,0261. Since X^2(Calculated) < X^2(Critical) it was not possible to refute the null-hypothesis. Thus far, we refute the alternative hypothesis and accept the null-hypothesis: HCMV IgG sero-positivity is a necessary condition of AS. In other words, *without* HCMV IgG sero-positivity *no* AS.

QUOD ERAT DEMONSTRANDUM.

THEOREM 2. WITHOUT HCMV PCR DNA POSITIVITY NO AS

CLAIM.

Null-Hypothesis: HCMV PCR DNA positivity is a necessary condition of AS.

Alternative Hypothesis: HCMV PCR DNA positivity is not a necessary condition of AS.

PROOF.

In toto, 10 HCMV PCR DNA studies (**Table 4**) were considered for a re-analysis of a conditio sine qua non relationship between HCMV and AS based on the detection of HCMV DNA in vessels or plaques but not in serum or plasma. The study design was more or less appropriate (Mean (IOU) = 0,26; Mean (IOI) = 0,102). In this context, the data analyzed were of use even if the average conditio sine qua non relationship between HCMV and AS was p(SINE) = 0,90. The X^2 calculated was determined as X^2(Calculated 1) = 15,0 and X^2(Calculated 2) = 15,098 while the X^2 critical (degrees of freedom = 10; Alpha = 0,05) was found to be X^2(Critical) = 18,307. Since X^2(Calculated) < X^2(Critical) it was not possible to refute the null-hypothesis. Thus far, we refute the alternative hypothesis and accept the null-hypothesis: HCMV PCR DNA positivity is a necessary condition of AS. In other words, according to the HCMV PCR DNA studies analyzed, *without* HCMV PCR DNA positivity *no* AS.

QUOD ERAT DEMONSTRANDUM.

THEOREM 3. IF HCMV PCR DNA POSITIVITY THEN AS

CLAIM.

Null-Hypothesis: HCMV PCR DNA positivity is a sufficient condition of AS.

Alternative Hypothesis: HCMV PCR DNA positivity is not a sufficient condition of AS.

PROOF.

In toto, 22 HCMV PCR DNA studies presented by **Table 3** provided evidence of a sufficient condition relationship between HCMV and AS. The study design was more or less appropriate (Mean (IOU) = 0,254; Mean (IOI) = 0,233) while the sample size of all HCMV PCR DNA studies analyzed was n = 1896. In this context, the data analyzed were of use even if the average conditio per quam relationship between HCMV and AS was only p(SINE) = 0,964. The X^2 calculated was determined as X^2(Calculated 1) = 19,964 and as X^2(Calculated 2) = 27,220 while the X^2 critical (degrees of freedom = 22; Alpha = 0,05) was found to be X^2(Critical) = 33,9244. Since X^2(Calculated) < X^2(Critical) it was not possible to refute the null-hypothesis. Thus far, we refute the alternative hypothesis and accept the null-hypothesis: HCMV PCR DNA positivity is a sufficient condition of AS. In other words, according to the HCMV PCR DNA studies analyzed, *if* HCMV PCR DNA positivity *then* AS.

QUOD ERAT DEMONSTRANDUM.

THEOREM 4. HCMV IS THE CAUSE OF AS

The evidence is increasing that HCMV is suspected to initiate and/or to stimulate the process of atherosclerosis too. **Thus far, an anti-HCMV drug usage (leflunomide, etoricoxib, etanercept, betahistine (a strong antagonist of the histamine H3 receptor and a weak agonist of the histamine H1 receptor)) could be associated with significantly decreased incidence of atherosclerotic events and would provide some evidence of the infectious etiology of AS**. Especially the dose dependent antiviral activity of leflunomide (N- (4'- trifluoromethylphenyl)- 5- methylisoxazole- 4- carboxamide) against HCMV, an inhibitor of protein kinase activity and pyrimidine synthesis, is known since years (Waldman, Knight, Blinder, et al., 1999; Waldman, Knight, Lurain, et al., 1999). Leflunomide does not to inhibit *viral DNA synthesis*, but seems to interfere with *virion assembly*. Meanwhile, there are

reports of efficacy of leflunomide in humans (John, Manivannan, Chandy, Peter, & Jacob, 2004) with HCMV disease too. Gómez Valbuena et al. (Gómez Valbuena, Alioto, Serrano Garrote, & Ferrari Piquero, 2016) administered a patient an initial **leflunomide regimen of 100 mg of leflunomide daily for the first five days, followed by 20 mg every 12 hours**. After fifteen days of treatment the HCMV viral load had fallen and became undetectable in one month. In the following (four months of treatment) the patient remained with undetectable viral load without having any adverse effect associated with it. To date, a drug-resistant CMV (Tan, 2014) is still a therapeutic challenge. However, even if it has been well confirmed that MicroRNA S25-1 (miR-US25-1) is encoded (Stern-Ginossar et al., 2009) by HCMV to control the life cycle of the virus, today's ability to chemotherapeutically target specific aspects of the HCMV virus life cycle are very limited. In point of fact, single studies provided some indirect evidence, that new and attractive possibilities (Weekes et al., 2013; Wills, Poole, Lau, Krishna, & Sinclair, 2015) in this context should be considered.

CLAIM.

Null-Hypothesis: HCMV is not the cause of AS ($k = 0$) due to drug studies.

Alternative Hypothesis: HCMV is the cause of AS ($k \neq 0$) due to drug studies.

PROOF.

View single drug studies (Etoricoxib, Etanercept, Leflunomide) presented by **Table 5** provided some evidence of the infectious hypothesis of atherosclerosis. In this context, it is necessary to point especially to the study of the Suissa et al. group. The study group of Suissa et al. (Suissa et al., 2006) investigated the risk of acute myocardial infarction (AMI) with respect to the use of Leflunomide, a disease-modifying antirheumatic drugs (DMARD) and other medications commonly used in rheumatoid arthritis (RA) and found that acute myocardial infarction rate significantly decreased with the use of any DMARD. The sample size of this study was n = 6138, the index of independence was IOI = 0,05833. The data published by Suissa et al. were appropriate enough to be analyzed for an exclusion relationship. The causal relationship was found to be negative (k = -0,03888; P Value (k) = 0,00038). The exclusion relationship between the use of Leflunomide and acute myocardial infarction was highly significant (p (EXCl) = 0,99902; P Value (I. Barukčić, 2019f) = 0,00098) while the X^2 calculated of the exclusion

relationship (**Table 5**) was determined as X^2(Calculated 1) = 0,18000 or as X^2(Calculated 2) = 0,06452 while the X^2 critical (degrees of freedom = 1; Alpha = 0,05) was found to be X^2(Critical) = 3,84145882. Since X^2(Calculated) < X^2(Critical) it was not possible to refute the null-hypothesis. Thus far, we refute the alternative hypothesis and accept the null-hypothesis: **Leflunomide excludes acute myocardial infarction** according the data published by the Suissa et al. group. However, as already discussed previously in greater detail, Leflunomide itself is highly effective against HCMV (Gómez Valbuena et al., 2016). Conclusion. The drug studies support the hypothesis that **HCMV is the cause of AS**.

QUOD ERAT DEMONSTRANDUM.

THEOREM 5. HCMV IS THE CAUSE OF AS

CLAIM.

Null-Hypothesis: HCMV is <u>not</u> the cause of AS ($k = 0$).

Alternative Hypothesis: HCMV is the cause of AS ($k \neq 0$).

PROOF.

The most of the HCMV PCR DNA studies as presented by **Table 3 and Table 4** provided a striking evidence of a positive causal relationship between HCMV PCR DNA positivity and AS. The P Value of the causal relationship was calculated by the hypergeometric distribution. As demonstrated by **Table 3 and Table 4**, **HCMV is the cause of AS**.

QUOD ERAT DEMONSTRANDUM.

4. Discussion

The lipid hypothesis in the pathogenesis of atherosclerosis (Konstantinov & Jankovic, 2013) is meanwhile more or less refuted (I. Barukčić, 2019e). The results of the HCMV studies re-analyzed in this publication are consistent and do provide convincing evidence of a causal relationship between a HCMV infection and AS. However, it is quite appropriate to remind again that several different IgG (Al-Ghamdi, 2012; Altannavch, Roubalová, Broz, Hrubá, & Anděl, 2003; Betjes, Litjens, & Zietse, 2007; Bloemenkamp et al., 2002; Blum et al., 1998; Cai, Cai, & Lu, 2003; Elkind et al., 2010; Eryol et al., 2005; Espinola-Klein et al., 2002;

Gkrania-Klotsas et al., 2012; Grahame-Clarke et al., 2003; Gredmark, Jonasson, van Gosliga, Ernerudh, & Söderberg-Nauclér, 2007; Jeong et al., 2015; Jha & Mittal, 2009; Jha, Prasad, & Mittal, 2008; Kawasaki et al., 2016; Knudsen et al., 2019; Laek et al., 2013; Lidón et al., 2019; Liu et al., 2011; Loebe et al., 1990; López de Atalaya, Cour, García, Ferro, & Perezagua, 1989; Martínez-Rodríguez et al., 2013; Masiá et al., 2013; Musiani et al., 1990; Olson et al., 2013; Rabczyński et al., 2015; Rabczyński, Jakobsche, & Adamiec, 2007; Rajasekhar et al., 2002; Rothenbacher et al., 2003; Siennicka, Kruk, Przyłuski, & Krajewski, 2001; Simanek et al., 2011; Sorlie et al., 1994; Szklo et al., 2009; Tewari, Nijhawan, Mishra, Dudeja, & Salopal, 2012; Tracy et al., 2013; Visseren et al., 1997; Voorend, van der Ven, Kubat, Lodder, & Bruggeman, 2008; Witherell et al., 2003; Zhang et al., 2015) and PCR DNA studies (Chen et al., 2003; Ciervo, Mancini, Sale, Russo, & Cassone, 2008; Courivaud et al., 2013; Hagiwara et al., 2007; Horváth, Cerný, Benedík, Hökl, & Jelínková, 2000; Huang et al., 2012; Izadi et al., 2012; Kilic et al., 2006; Latsios, Saetta, Michalopoulos, Agapitos, & Patsouris, 2004; Lebedeva, Shpektor, Vasilieva, & Margolis, 2018; Lee et al., 2014; Lin, Chen, Chen, Wang, & Eng, 2003; Melnick, Adam, & DeBakey, 1990; Melnick, Hu, Burek, Adam, & DeBakey, 1994; Nyberg, Skagius, Nilsson, Ljungh, & Henriksson, 2008; Pinar et al., 2004; Priyanka, Kaarthikeyan, Nadathur, Mohanraj, & Kavarthapu, 2017; Radke et al., 2001; Reinhardt et al., 2003; Reszka et al., 2008; Saetta, Fanourakis, Agapitos, & Davaris, 2000; Shi & Tokunaga, 2002; Skowronski, Mendoza, Smith, & Jaski, 1993; Tremolada et al., 2011; Watt, Aesch, Lanotte, Tranquart, & Quentin,2003; Westphal et al., 2006; Xenaki, Hassoulas, Apostolakis, Sourvinos, & Spandidos, 2009; Yamashiroya, Ghosh, Yang, & Robertson, 1988) have not been considered for re-analysis which can but need not to be a source of bias. Therefore better designed studies using more effective assays, study design and methods are needed to resolve this important issue ultimately.

5. Conclusion

This study provides important insights into the mechanisms of HCMV with atherosclerosis. In conclusion, **without** a HCMV infection **no** atherosclerosis (AMI, CHD, Stroke, abdominal aortic aneurysm et cetera). Besides of some limitations of the present study, the facts presented

encourage us unless the contrary is proven to conclude that **human cytomegalovirus is the cause of atherosclerosis**. The underlying pathophysiological mechanism linking HCMV with atherosclerosis is yet to be determined in greater detail.

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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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