Human cytomegalovirus is the cause of human atherosclerosis

Ilija Barukčić[1]

[1] Internist, Horandstrasse, DE-26441 Jever, Germany

Cor respondence: Ilija Barukčić, Horandstrasse, DE-26441 Jever, Germany. Tel: 49-4466-333. E-mail: Barukcic@t-online.de

Received: December 31th, 2019; Accepted December 31th, 2019; Published: December 31th, 2019

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 uses 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 more a 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 value for HCMV

positivity was 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
Adam et 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
Blum et 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			
										X^2(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 3**).

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)	X^2(SINE|Bt)	X^2(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 of 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)	X^2(EXCL| At)	X^2(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				
										X^2(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 8**) 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*

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

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*

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

The meaning of the abbreviations a, b, c, d, n et cetera are explained by following 2 by 2-table (**Table 9**). 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	$\underline{A}$
	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 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 *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 = 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, Alioto, Serrano Garrote, & Ferrari Piquero, 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 not 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, 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 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.

Acknowledgements

The open source, independent and non-profit **Zotero Citation Manager** was used to create and manage references and bibliographies. The public domain software GnuPlot is used frequently, to draw some figures.

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.

Financial support and sponsorship

Nil.

References

Adam, E., Melnick, J. L., Probtsfield, J. L., Petrie, B. L., Burek, J., Bailey, K. R., … DeBakey, M. E. "High levels of cytomegalovirus antibody in patients requiring vascular surgery for atherosclerosis." *Lancet (London, England)* 1987; *2*:8554, 291–293 . [PMID: 2886763]

Adler, S. P., Hur, J. K., Wang, J. B., & Vetrovec, G. W. "Prior infection with cytomegalovirus is not a major risk factor for angiographically demonstrated coronary artery atherosclerosis." *The Journal of Infectious Diseases* 1998; *177*:1, 209–212 . [PMID: 9419190]

Al-Ghamdi, A. "Role of herpes simplex virus-1, cytomegalovirus and Epstein-Barr virus in atherosclerosis." *Pakistan Journal of Pharmaceutical Sciences* 2012; *25*:1, 89–97 . [PMID: 22186314]

Altannavch, T., Roubalová, K., Broz, J., Hrubá, D., & Anděl, M. "Serological markers of Chlamydia pneumoniae, cytomegalovirus and Helicobacter pylori infection in diabetic and non-diabetic patients with unstable angina pectoris." *Central European Journal of Public Health* 2003; *11*:2, 102–106 . [PMID: 12884557]

Androutsos, G., Vladimiros, L., & Diamantis, A. "John Hunter (1728-1793): founder of scientific surgery and precursor of oncology." *Journal of B.U.ON.: Official Journal of the Balkan Union of Oncology* 2007; *12*:3, 421–427 . [PMID: 17918302]

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, I. "Statins and death due to any cause – all doubts removed?" *International Journal of Current Science Research* 2019e; *5*:12, 1884–1911 .

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

Betjes, M. G. H., Litjens, N. H. R., & Zietse, R. "Seropositivity for cytomegalovirus in patients with end-stage renal disease is strongly associated with atherosclerotic disease." *Nephrology, Dialysis, Transplantation: Official Publication of the European Dialysis and Transplant Association - European Renal Association*

2007; *22*:11, 3298–3303 . doi: https://doi.org/10.1093/ndt/gfm348 [PMID: 17597084]

Bloemenkamp, D. G. M., Mali, W. P. T. M., Tanis, B. C., Rosendaal, F. R., van den Bosch, M. A. A. J., Kemmeren, J. M., … van der Graaf, Y. "Chlamydia pneumoniae, Helicobacter pylori and cytomegalovirus infections and the risk of peripheral arterial disease in young women." *Atherosclerosis* 2002; *163*:1, 149–156 . [PMID: 12048133]

Blum, A., Giladi, M., Weinberg, M., Kaplan, G., Pasternack, H., Laniado, S., & Miller, H. "High anti-cytomegalovirus (CMV) IgG antibody titer is associated with coronary artery disease and may predict post-coronary balloon angioplasty restenosis." *The American Journal of Cardiology* 1998; *81*:7, 866–868 . [PMID: 9555776]

Blum, A., Peleg, A., & Weinberg, M. "Anti-cytomegalovirus (CMV) IgG antibody titer in patients with risk factors to atherosclerosis." *Clinical and Experimental Medicine* 2003; *3*:3, 157–160 . doi: https://doi.org/10.1007/s10238-003-0019-7 [PMID: 14648230]

Cai, X., Cai, H., & Lu, D. "[Study on the correlation of between infection, inflammation and coronary artery disease]." *Zhonghua Liu Xing Bing Xue Za Zhi = Zhonghua Liuxingbingxue Zazhi* 2003; *24*:6, 503–507 . [PMID: 12848920]

Cannon, M. J., Schmid, D. S., & Hyde, T. B. "Review of cytomegalovirus seroprevalence and demographic characteristics associated with infection." *Reviews in Medical Virology* 2010; *20*:4, 202–213 . doi: https://doi.org/10.1002/rmv.655 [PMID: 20564615]

Chen, R., Xiong, S., Yang, Y., Fu, W., Wang, Y., & Ge, J. "The relationship between human cytomegalovirus infection and atherosclerosis development." *Molecular and Cellular Biochemistry* 2003; *249*:1–2, 91–96 . [PMID: 12956403]

Ciervo, A., Mancini, F., Sale, P., Russo, A., & Cassone, A. "Real-time polymerase chain reaction and laser capture microdissection: an efficient combination tool for Chlamydophila pneumoniae DNA quantification and localization of infection in atherosclerotic lesions." *International Journal of Immunopathology and Pharmacology* 2008; *21*:2, 421–428 . doi: https://doi.org/10.1177/039463200802100222 [PMID: 18547488]

Cottet, J., & Lenoir, M. "Deux mille ans d'étude historique des mots athérome, athéromatose, athérosclérose, artériosclérose: (Two thousand years of historical study on the words atheroma, atheromatosis, atherosclerosis, arteriosclerosis; Article in French)." *Bulletin de l'Academie Nationale de Medecine* 1992; *176*:9, 1385–1391 . [PMID: 1303293]

Courivaud, C., Bamoulid, J., Chalopin, J.-M., Gaiffe, E., Tiberghien, P., Saas, P., & Ducloux, D. "Cytomegalovirus exposure and cardiovascular disease in kidney transplant recipients." *The Journal of Infectious Diseases* 2013; *207*:10, 1569–1575 . doi: https://doi.org/10.1093/infdis/jit064 [PMID: 23417659]

Dolan, A., Cunningham, C., Hector, R. D., Hassan-Walker, A. F., Lee, L., Addison, C., … Davison, A. J. "Genetic content of wild-type human cytomegalovirus." *The Journal of General Virology* 2004; *85*:Pt 5, 1301–1312 . doi: https://doi.org/10.1099/vir.0.79888-0 [PMID: 15105547]

Elkind, M. S. V., Luna, J. M., Moon, Y. P., Boden-Albala, B., Liu, K. M., Spitalnik, S., … Paik, M. C. "Infectious burden and carotid plaque thickness: the northern Manhattan study." *Stroke* 2010; *41*:3, e117-122 . doi: https://doi.org/10.1161/STROKEAHA.109.571299 [PMCID: PMC2830875] [PMID: 20075350]

Eryol, N. K., Kiliç, H., Gül, A., Ozdogru, I., Inanç, T., Dogan, A., … Basar, E. "Are the high levels of cytomegalovirus antibodies a determinant in the development of coronary artery disease?" *International Heart Journal* 2005; *46*:2, 205–209 . [PMID: 15876804]

Espinola-Klein, C., Rupprecht, H.-J., Blankenberg, S., Bickel, C., Kopp, H., Victor, A., … Meyer, J. "Impact of infectious burden on progression of carotid atherosclerosis." *Stroke* 2002; *33*:11, 2581–2586 . [PMID: 12411646]

Gabrylewicz, B., Mazurek, U., Ochała, A., Sliupkas-Dyrda, E., Garbocz, P., Pyrlik, A., … Tendera, M. "Cytomegalovirus infection in acute myocardial infarction. Is there a causative relationship?" *Kardiologia Polska* 2003; *59*:10, 283–292 . [PMID: 14618212]

Gilbert, A., & Lion, G. "Artérites infectieuses expérimentales." *Comptes Rendus Hebdomadaires Des Séances et Mémoires de La Société de Biologie* 1889; *41*, 583–584 .

Gkrania-Klotsas, E., Langenberg, C., Sharp, S. J., Luben, R., Khaw, K.-T., & Wareham, N. J. "Higher

immunoglobulin G antibody levels against cytomegalovirus are associated with incident ischemic heart disease in the population-based EPIC-Norfolk cohort." *The Journal of Infectious Diseases* 2012; *206*:12, 1897–1903 . doi: https://doi.org/10.1093/infdis/jis620 [PMID: 23045624]

Gómez Valbuena, I., Alioto, D., Serrano Garrote, O., & Ferrari Piquero, J. M. "Use of leflunomide in a cytomegalovirus infection resistant: a report of a case. (Article in Spanish)." *Farmacia Hospitalaria: Organo Oficial De Expresion Cientifica De La Sociedad Espanola De Farmacia Hospitalaria* 2016; *40*:1, 52–54 . doi: https://doi.org/10.7399/fh.2016.40.1.10161 [PMID: 26882834]

González-Quijada, S., Mora-Simón, M. J., & Martin-Ezquerro, A. "Association between serological evidence of past Coxiella burnetii infection and atherosclerotic cardiovascular disease in elderly patients." *Clinical Microbiology and Infection: The Official Publication of the European Society of Clinical Microbiology and Infectious Diseases* 2014; *20*:9, 873–878 . doi: https://doi.org/10.1111/1469-0691.12541 [PMID: 24438335]

Grahame-Clarke, C., Chan, N. N., Andrew, D., Ridgway, G. L., Betteridge, D. J., Emery, V., … Vallance, P. "Human cytomegalovirus seropositivity is associated with impaired vascular function." *Circulation* 2003; *108*:6, 678–683 . doi: https://doi.org/10.1161/01.CIR.0000084505.54603.C7 [PMID: 12900349]

Gredmark, S., Jonasson, L., van Gosliga, D., Ernerudh, J., & Söderberg-Nauclér, C. "Active cytomegalovirus replication in patients with coronary disease." *Scandinavian Cardiovascular Journal : SCJ* 2007; *41*:4, 230–234 . doi: https://doi.org/10.1080/14017430701383755 [PMID: 17680510]

Hagiwara, N., Toyoda, K., Inoue, T., Shimada, H., Ibayashi, S., Iida, M., & Okada, Y. "Lack of association between infectious burden and carotid atherosclerosis in Japanese patients." *Journal of Stroke and Cerebrovascular Diseases : The Official Journal of National Stroke Association* 2007; *16*:4, 145–152 . doi: https://doi.org/10.1016/j.jstrokecerebrovasdis.2007.02.001 [PMID: 17689410]

Haller, A. von *Opuscula pathologica partim recusa partim inedita: quibus sectiones cadaverum morbosorum potissimum continentur. Accedunt experimenta de respiratione, quarta parte aucta.* 1755; Lausanne (Suisse): M.-M. Bousquet. Retrieved from https://www.zvab.com/buch-suchen/titel/opuscula-pathologica-partim/autor/haller/

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

Hodgson, J. *A Treatise on the Diseases of Arteries and Veins, Containing the Pathology and Treatment of Aneurisms and Wounded Arteries* 1815; London: Printed for Thomas Underwood. Retrieved from https://archive.org/details/b21299870

Horváth, R., Cerný, J., Benedík, J., Hökl, J., & Jelínková, I. "The possible role of human cytomegalovirus (HCMV) in the origin of atherosclerosis." *Journal of Clinical Virology : The Official Publication of the Pan American Society for Clinical Virology* 2000; *16*:1, 17–24 . [PMID: 10680737]

Huang, Z.-R., Yu, L.-P., Yang, X.-C., Zhang, F., Chen, Y.-R., Feng, F., … Cai, J. "Human cytomegalovirus linked to stroke in a Chinese population." *CNS Neuroscience & Therapeutics* 2012; *18*:6, 457–460 . doi: https://doi.org/10.1111/j.1755-5949.2012.00326.x [PMID: 22672297]

Huchard, H. "Les Causes de l'artério-sclérose et des cardiopathies artérielles, leur origine alimentaire et leur traitement préventif." *Revue Générale de Clinique et Thérapeutique. Journal Des Praticiens* 1891; 23 .

Hung, Y.-M., Lin, L., Chen, C.-M., Chiou, J.-Y., Wang, Y.-H., Wang, P. Y.-P., & Wei, J. C.-C. "The effect of anti-rheumatic medications for coronary artery diseases risk in patients with rheumatoid arthritis might be changed over time: A nationwide population-based cohort study." *PloS One* 2017; *12*:6, e0179081 . doi: https://doi.org/10.1371/journal.pone.0179081 [PMCID: PMC5489160] [PMID: 28658301]

Izadi, M., Fazel, M., Saadat, S. H., Nasseri, M. H., Ghasemi, M., Dabiri, H., … Taheri, S. "Cytomegalovirus localization in atherosclerotic plaques is associated with acute coronary syndromes: report of 105 patients." *Methodist DeBakey Cardiovascular Journal* 2012; *8*:2, 42–46 . [PMID: 22891128]

Jeong, S. J., Ku, N. S., Han, S. H., Choi, J. Y., Kim, C. O., Song, Y. G., & Kim, J. M. "Anti-cytomegalovirus antibody levels are associated with carotid atherosclerosis and inflammatory cytokine production in elderly Koreans." *Clinica Chimica Acta; International Journal of Clinical Chemistry* 2015; *445*, 65–69 . doi: https://doi.org/10.1016/j.cca.2015.03.015 [PMID: 25797894]

Jha, H. C., & Mittal, A. "Coronary artery disease patient's first degree relatives may be at higher risk for atherosclerosis." *International Journal of Cardiology* 2009; *135*:3, 408–409 . doi:

https://doi.org/10.1016/j.ijcard.2008.03.031

Jha, H. C., Prasad, J., & Mittal, A. “High immunoglobulin A seropositivity for combined Chlamydia pneumoniae, Helicobacter pylori infection, and high-sensitivity C-reactive protein in coronary artery disease patients in India can serve as atherosclerotic marker.” *Heart and Vessels* 2008; *23*:6, 390–396 . doi: https://doi.org/10.1007/s00380-008-1062-9 [PMID: 19037586]

John, G. T., Manivannan, J., Chandy, S., Peter, S., & Jacob, C. K. “Leflunomide therapy for cytomegalovirus disease in renal allograft recepients.” *Transplantation* 2004; *77*:9, 1460–1461 . doi: https://doi.org/10.1097/01.tp.0000122185.64004.89 [PMID: 15167608]

Kälvegren, H. *The Role of Chlamydia pneumoniae-induced Platelet Activation in Cardiovascular Disease. In vitro and In vivo Studies. Dissertation* 2007; Linköping (Sweden): Linköping University. Faculty of Health Sicences. Retrieved from http://liu.diva-portal.org/smash/get/diva2:23385/FULLTEXT01.pdf

Kawasaki, M., Arai, Y., Takayama, M., Hirata, T., Takayama, M., Abe, Y., … Hirose, N. “Carotid atherosclerosis, cytomegalovirus infection, and cognitive decline in the very old: a community-based prospective cohort study.” *Age (Dordrecht, Netherlands)* 2016; *38*:2, 29 . doi: https://doi.org/10.1007/s11357-016-9890-5 [PMCID: PMC5005896] [PMID: 26886582]

Kilic, A., Onguru, O., Tugcu, H., Kilic, S., Guney, C., & Bilge, Y. “Detection of cytomegalovirus and Helicobacter pylori DNA in arterial walls with grade III atherosclerosis by PCR.” *Polish Journal of Microbiology* 2006; *55*:4, 333–337 . [PMID: 17416070]

Knudsen, A., Kristoffersen, U., Panum, I., Hansen, Y., Skottrup, P., Hasbak, P., … Lebech, A.-M. “Coronary artery calcium and intima-media thickness are associated with level of cytomegalovirus immunoglobulin G in HIV-infected patients.” *HIV Medicine* 2019; *20*:1, 60–62 . doi: https://doi.org/10.1111/hiv.12672

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]

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

Kurkowska-Jastrzebska, I., Karlinski, M. A., Błazejewska-Hyzorek, B., Sarzynska-Dlugosz, I., Filipiak, K. J., & Czlonkowska, A. “Carotid intima media thickness and blood biomarkers of atherosclerosis in patients after stroke or myocardial infarction.” *Croatian Medical Journal* 2016; *57*:6, 548–557 . [PMCID: PMC5209935] [PMID: 28051279]

Laek, B., Szklo, M., McClelland, R. L., Ding, J., Tsai, M. Y., Bluemke, D. A., … Matsushita, K. “The prospective association of Chlamydia pneumoniae and four other pathogens with development of coronary artery calcium: the multi-ethnic study of atherosclerosis (MESA).” *Atherosclerosis* 2013; *230*:2, 268–274 . doi: https://doi.org/10.1016/j.atherosclerosis.2013.07.053 [PMCID: PMC3815605] [PMID: 24075755]

Latsios, G., Saetta, A., Michalopoulos, N. V., Agapitos, E., & Patsouris, E. “Detection of cytomegalovirus, Helicobacter pylori and Chlamydia pneumoniae DNA in carotid atherosclerotic plaques by the polymerase chain reaction.” *Acta Cardiologica* 2004; *59*:6, 652–657 . doi: https://doi.org/10.2143/AC.59.6.2005249 [PMID: 15636450]

Lebedeva, A. M., Shpektor, A. V., Vasilieva, E. Y., & Margolis, L. B. “Cytomegalovirus Infection in Cardiovascular Diseases.” *Biochemistry. Biokhimiia* 2018; *83*:12, 1437–1447 . doi: https://doi.org/10.1134/S0006297918120027 [PMID: 30878019]

Lee, Y.-L., Liu, C.-E., Cho, W.-L., Kuo, C.-L., Cheng, W.-L., Huang, C.-S., & Liu, C.-S. “Presence of cytomegalovirus DNA in leucocytes is associated with increased oxidative stress and subclinical atherosclerosis in healthy adults.” *Biomarkers: Biochemical Indicators of Exposure, Response, and Susceptibility to Chemicals* 2014; *19*:2, 109–113 . doi: https://doi.org/10.3109/1354750X.2013.877967 [PMID: 24446591]

Li, B., Xu, C., & Wang, Q. “The detection of the antibodies of human cytomegalovirus in the sera of patients with coronary heart disease. (Article in Chinese).” *Zhonghua Nei Ke Za Zhi* 1996; *35*:11, 741–743 . [PMID: 9592340]

Lidón, F., Padilla, S., García, J. A., Fernández, M., García, J., Ortiz de la Tabla, V., … Masiá, M. “Contribution of Human Herpesvirus 8 and Herpes Simplex Type 2 to Progression of Carotid Intima-Media Thickness in People Living With HIV.” *Open Forum Infectious Diseases* 2019; *6*:2, ofz041 . doi: https://doi.org/10.1093/ofid/ofz041 [PMCID: PMC6386804] [PMID: 30815506]

Lin, T.-M., Chen, W. -j, Chen, H.-Y., Wang, P.-W., & Eng, H.-L. “Increased incidence of cytomegalovirus but not Chlamydia pneumoniae in atherosclerotic lesions of arteries of lower extremities from patients with diabetes mellitus undergoing amputation.” *Journal of Clinical Pathology* 2003; *56*:6, 429–432 . [PMCID: PMC1769971] [PMID: 12783969]

Linton, M. F., Yancey, P. G., Davies, S. S., Jerome, W. G., Linton, E. F., Song, W. L., … Vickers, K. C. “The Role of Lipids and Lipoproteins in Atherosclerosis.” In K. R. Feingold, B. Anawalt, A. Boyce, G. Chrousos, K. Dungan, A. Grossman, … D. P. Wilson (Eds.), *Endotext* 2000; South Dartmouth (MA): MDText.com, Inc. Retrieved from http://www.ncbi.nlm.nih.gov/books/NBK343489/ [PMID: 26844337]

Liu, L., Tuo, H.-Z., Wang, R.-J., Yi, L., Wang, J.-W., & Wang, D.-X. “Human cytomegalovirus-IgM seropositivity is not associated with atherogenic alterations of lipid profiles and inflammatory status in ischemic stroke patients: a preliminary study.” *Neurological Research* 2011; *33*:5, 473–481 . doi: https://doi.org/10.1179/016164111X13007856084007 [PMID: 21669115]

Lobstein, F. *Traité d’anatomie pathologique* 1833; (Vols. 1–Volume 1) Paris: Levrault.

Loebe, M., Schüler, S., Spiegelsberger, S., Warnecke, H., Fleck, E., & Hetzer, R. “Cytomegalovirus infection and coronary sclerosis after heart transplantation (Article in German).” *Deutsche Medizinische Wochenschrift (1946)* 1990; *115*:34, 1266–1269 . doi: https://doi.org/10.1055/s-2008-1065151 [PMID: 2167829]

López de Atalaya, J., Cour, M. I., García, M. C., Ferro, A., & Perezagua, C. “[Absence of seroprevalence against cytomegalovirus and herpes simplex in a group of patients with coronary atherosclerosis].” *Anales De Medicina Interna (Madrid, Spain: 1984)* 1989; *6*:1, 53 . [PMID: 2562342]

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

Martínez-Rodríguez, J. E., Munné-Collado, J., Rasal, R., Cuadrado, E., Roig, L., Ois, A., … López-Botet, M. “Expansion of the NKG2C+ natural killer-cell subset is associated with high-risk carotid atherosclerotic plaques in seropositive patients for human cytomegalovirus.” *Arteriosclerosis, Thrombosis, and Vascular Biology* 2013; *33*:11, 2653–2659 . doi: https://doi.org/10.1161/ATVBAHA.113.302163 [PMID: 23968979]

Masclee, G. M. C., Straatman, H., Arfè, A., Castellsague, J., Garbe, E., Herings, R., … Sturkenboom, M. C. J. M. “Risk of acute myocardial infarction during use of individual NSAIDs: A nested case-control study from the SOS project.” *PloS One* 2018; *13*:11, e0204746 . doi: https://doi.org/10.1371/journal.pone.0204746 [PMCID: PMC6211656] [PMID: 30383755]

Masiá, M., Robledano, C., Ortiz de la Tabla, V., Antequera, P., López, N., & Gutiérrez, F. “Increased carotid intima-media thickness associated with antibody responses to varicella-zoster virus and cytomegalovirus in HIV-infected patients.” *PloS One* 2013; *8*:5, e64327 . doi: https://doi.org/10.1371/journal.pone.0064327 [PMCID: PMC3662719] [PMID: 23717597]

Melnick, J. L., Adam, E., & DeBakey, M. E. “Possible role of cytomegalovirus in atherogenesis.” *JAMA* 1990; *263*:16, 2204–2207 . [PMID: 2157078]

Melnick, J. L., Hu, C., Burek, J., Adam, E., & DeBakey, M. E. “Cytomegalovirus DNA in arterial walls of patients with atherosclerosis.” *Journal of Medical Virology* 1994; *42*:2, 170–174 . [PMID: 8158112]

Minick, C. R., Fabricant, C. G., Fabricant, J., & Litrenta, M. M. “Atheroarteriosclerosis induced by infection with a herpesvirus.” *The American Journal of Pathology* 1979; *96*:3, 673–706 . [PMCID: PMC2042405] [PMID: 382868]

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]

Mori, I., Kimura, Y., Naiki, H., Matsubara, R., Takeuchi, T., Yokochi, T., & Nishiyama, Y. “Reactivation of HSV-1 in the brain of patients with familial Alzheimer’s disease.” *Journal of Medical Virology* 2004; *73*:4, 605–611 . doi: https://doi.org/10.1002/jmv.20133 [PMID: 15221907]

Mundkur, L. A., Rao, V. S., Hebbagudi, S., Shanker, J., Shivanandan, H., Nagaraj, R. K., & Kakkar, V. V. “Pathogen burden, cytomegalovirus infection and inflammatory markers in the risk of premature coronary artery disease in individuals of Indian origin.” *Experimental and Clinical Cardiology* 2012; *17*:2, 63–68 . [PMCID: PMC3395457] [PMID: 22826649]

Musiani, M., Zerbini, M. L., Muscari, A., Puddu, G. M., Gentilomi, G., Gibellini, D., … La Placa, M. “Antibody

patterns against cytomegalovirus and Epstein-Barr virus in human atherosclerosis." *Microbiologica* 1990; *13*:1, 35–41 . [PMID: 2155375]

Mussi-Pinhata, M. M., Yamamoto, A. Y., Aragon, D. C., Duarte, G., Fowler, K. B., Boppana, S., & Britt, W. J. "Seroconversion for Cytomegalovirus Infection During Pregnancy and Fetal Infection in a Highly Seropositive Population: "The BraCHS Study."" *The Journal of Infectious Diseases* 2018; *218*:8, 1200–1204 . doi: https://doi.org/10.1093/infdis/jiy321 [PMCID: PMC6129109] [PMID: 29868783]

Nyberg, A., Skagius, E., Nilsson, I., Ljungh, A., & Henriksson, A. E. "Abdominal aortic aneurysm and cytomegalovirus infection." *Journal of Medical Virology* 2008; *80*:4, 667–669 . doi: https://doi.org/10.1002/jmv.21022 [PMID: 18297722]

Olson, N. C., Doyle, M. F., Jenny, N. S., Huber, S. A., Psaty, B. M., Kronmal, R. A., & Tracy, R. P. "Decreased naive and increased memory CD4(+) T cells are associated with subclinical atherosclerosis: the multi-ethnic study of atherosclerosis." *PloS One* 2013; *8*:8, e71498 . doi: https://doi.org/10.1371/journal.pone.0071498 [PMCID: PMC3751895] [PMID: 24009662]

Ossewaarde, J. M., Feskens, E. J., De Vries, A., Vallinga, C. E., & Kromhout, D. "Chlamydia pneumoniae is a risk factor for coronary heart disease in symptom-free elderly men, but Helicobacter pylori and cytomegalovirus are not." *Epidemiology and Infection* 1998; *120*:1, 93–99 . doi: https://doi.org/10.1017/s0950268897008303 [PMCID: PMC2809353] [PMID: 9528823]

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

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 .

Pesonen, E., El-Segaier, M., Persson, K., Puolakkainen, M., Sarna, S., Ohlin, H., & Pussinen, P. J. "Infections as a stimulus for coronary occlusion, obstruction, or acute coronary syndromes." *Therapeutic Advances in Cardiovascular Disease* 2009; *3*:6, 447–454 . doi: https://doi.org/10.1177/1753944709345598 [PMID: 19773293]

Pinar, A., Oç, M., Akyön, Y., Farsak, B., Koçyildirim, E., Us, D., … Böke, E. "[The presence of Chlamydophila pneumoniae, Helicobacter pylori and cytomegalovirus in human atherosclerosis detected by molecular and serological methods]." *Mikrobiyoloji Bulteni* 2004; *38*:3, 213–222 . [PMID: 15490840]

Priyanka, S., Kaarthikeyan, G., Nadathur, J. D., Mohanraj, A., & Kavarthapu, A. "Detection of cytomegalovirus, Epstein-Barr virus, and Torque Teno virus in subgingival and atheromatous plaques of cardiac patients with chronic periodontitis." *Journal of Indian Society of Periodontology* 2017; *21*:6, 456–460 . doi: https://doi.org/10.4103/jisp.jisp_205_17 [PMCID: PMC5846241] [PMID: 29551863]

Rabczyński, M., Fiodorenko-Dumas, Ż., Mastej, K., Dumas, I., Adamiec, R., & Paprocka-Borowicz, M. "A relationship between serological markers of chronic C. pneumoniae and CMV infection and hsp60 in patients with atherosclerotic carotid stenosis." *Acta Biochimica Polonica* 2015; *62*:1, 89–95 . [PMID: 25654359]

Rabczyński, M., Jakobsche, U., & Adamiec, R. "[Serological markers of chronic Chlamydia pneumoniae and cytomegalovirus (CMV) infection in patients with peripheral occlusive artery disease--an initial report]." *Przeglad Lekarski* 2007; *64*:6, 416–418 . [PMID: 18159850]

Radke, P. W., Merkelbach-Bruse, S., Messmer, B. J., Vom Dahl, J., Dörge, H., Naami, A., … Hanrath, P. "Infectious agents in coronary lesions obtained by endatherectomy: pattern of distribution, coinfection, and clinical findings." *Coronary Artery Disease* 2001; *12*:1, 1–6 . [PMID: 11211160]

Rajasekhar, D., Subramanyam, G., Latheef, S. A., Vanajakshamma, V., Srilatha, A., & Chaudhury, A. "Infectious aetiology in acute coronary syndromes." *Indian Journal of Medical Microbiology* 2002; *20*:2, 83–87 . [PMID: 17657038]

Reinhardt, B., Vaida, B., Voisard, R., Keller, L., Breul, J., Metzger, H., … Mertens, T. "Human cytomegalovirus infection in human renal arteries in vitro." *Journal of Virological Methods* 2003; *109*:1, 1–9 . doi: https://doi.org/10.1016/s0166-0934(03)00035-1 [PMID: 12668261]

Reszka, E., Jegier, B., Wasowicz, W., Lelonek, M., Banach, M., & Jaszewski, R. "Detection of infectious agents by polymerase chain reaction in human aortic wall." *Cardiovascular Pathology: The Official Journal of the Society for Cardiovascular Pathology* 2008; *17*:5, 297–302 . doi:

https://doi.org/10.1016/j.carpath.2007.11.002 [PMID: 18402822]

Ridker, P. M., Hennekens, C. H., Stampfer, M. J., & Wang, F. "Prospective study of herpes simplex virus, cytomegalovirus, and the risk of future myocardial infarction and stroke." *Circulation* 1998; *98*:25, 2796–2799 . doi: https://doi.org/10.1161/01.cir.98.25.2796 [PMID: 9860778]

Rothenbacher, D., Brenner, H., Hoffmeister, A., Mertens, T., Persson, K., & Koenig, W. "Relationship between infectious burden, systemic inflammatory response, and risk of stable coronary artery disease: role of confounding and reference group." *Atherosclerosis* 2003; *170*:2, 339–345 . doi: https://doi.org/10.1016/s0021-9150(03)00300-9 [PMID: 14612216]

Saetta, A., Fanourakis, G., Agapitos, E., & Davaris, P. S. "Atherosclerosis of the carotid artery: absence of evidence for CMV involvement in atheroma formation." *Cardiovascular Pathology : The Official Journal of the Society for Cardiovascular Pathology* 2000; *9*:3, 181–183 . [PMID: 10989318]

Safaie, N., Ghotaslou, R., & Montazer Ghaem, H. "Seroprevalence of cytomegalovirus in patients with and without coronary artery diseases at Madani Heart Center, Iran." *Acta Medica Iranica* 2010; *48*:6, 403–406 . [PMID: 21287482]

Sepúlveda, M. A., Moreu, J., Cantón, T., Pajin, F., & Rodríguez, L. "Prevalence of IgG antibodies against Cytomegalovirus in patients with angiographically demonstrated coronary atherosclerosis. [Article in Spanish]." *Enfermedades Infecciosas Y Microbiologia Clinica* 1999; *17*:8, 386–389 . [PMID: 10563085]

Shi, Y., & Tokunaga, O. "Chlamydia pneumoniae and multiple infections in the aorta contribute to atherosclerosis." *Pathology International* 2002; *52*:12, 755–763 . [PMID: 12588444]

Siennicka, J., Kruk, M., Przyłuski, J., & Krajewski, P. "Relationship between CMV infection and coronary heart disease." *Acta Microbiologica Polonica* 2001; *50*:2, 175–178 . [PMID: 11720313]

Simanek, A. M., Dowd, J. B., Pawelec, G., Melzer, D., Dutta, A., & Aiello, A. E. "Seropositivity to cytomegalovirus, inflammation, all-cause and cardiovascular disease-related mortality in the United States." *PloS One* 2011; *6*:2, e16103 . doi: https://doi.org/10.1371/journal.pone.0016103 [PMCID: PMC3040745] [PMID: 21379581]

Sinclair, J., & Sissons, P. "Latency and reactivation of human cytomegalovirus." *The Journal of General Virology* 2006; *87*:Pt 7, 1763–1779 . doi: https://doi.org/10.1099/vir.0.81891-0 [PMID: 16760381]

Skowronski, E. W., Mendoza, A., Smith, S. C., & Jaski, B. E. "Detection of cytomegalovirus in paraffin-embedded postmortem coronary artery specimens of heart transplant recipients by the polymerase chain reaction: implications of cytomegalovirus association with graft atherosclerosis." *The Journal of Heart and Lung Transplantation: The Official Publication of the International Society for Heart Transplantation* 1993; *12*:5, 717–723 . [PMID: 8241208]

Sorlie, P. D., Adam, E., Melnick, S. L., Folsom, A., Skelton, T., Chambless, L. E., … Melnick, J. L. "Cytomegalovirus/herpesvirus and carotid atherosclerosis: the ARIC Study." *Journal of Medical Virology* 1994; *42*:1, 33–37 . [PMID: 8308517]

Staras, S. A. S., Dollard, S. C., Radford, K. W., Flanders, W. D., Pass, R. F., & Cannon, M. J. "Seroprevalence of cytomegalovirus infection in the United States, 1988-1994." *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America* 2006; *43*:9, 1143–1151 . doi: https://doi.org/10.1086/508173 [PMID: 17029132]

Stern-Ginossar, N., Saleh, N., Goldberg, M. D., Prichard, M., Wolf, D. G., & Mandelboim, O. "Analysis of human cytomegalovirus-encoded microRNA activity during infection." *Journal of Virology* 2009; *83*:20, 10684–10693 . doi: https://doi.org/10.1128/JVI.01292-09 [PMCID: PMC2753100] [PMID: 19656885]

Suissa, S., Bernatsky, S., & Hudson, M. "Antirheumatic drug use and the risk of acute myocardial infarction." *Arthritis and Rheumatism* 2006; *55*:4, 531–536 . doi: https://doi.org/10.1002/art.22094 [PMID: 16874796]

Szklo, M., Ding, J., Tsai, M. Y., Cushman, M., Polak, J. F., Lima, J., … Sharrett, A. R. "Individual pathogens, pathogen burden and markers of subclinical atherosclerosis: the Multi-Ethnic Study of Atherosclerosis." *Journal of Cardiovascular Medicine (Hagerstown, Md.)* 2009; *10*:10, 747–751 . doi: https://doi.org/10.2459/JCM.0b013e32832cacab [PMCID: PMC2732746] [PMID: 19444130]

Tan, B. H. "Cytomegalovirus Treatment." *Current Treatment Options in Infectious Diseases* 2014; *6*:3, 256–270 . doi: https://doi.org/10.1007/s40506-014-0021-5 [PMCID: PMC4431713] [PMID: 25999800]

Tewari, R., Nijhawan, V., Mishra, M., Dudeja, P., & Salopal, T. "Prevalence of Helicobacter pylori,

cytomegalovirus, and Chlamydia pneumoniae immunoglobulin seropositivity in coronary artery disease patients and normal individuals in North Indian population." *Medical Journal, Armed Forces India* 2012; *68*:1, 53–57 . doi: https://doi.org/10.1016/S0377-1237(11)60121-4 [PMCID: PMC3862904] [PMID: 24623916]

Thöne, K., Kollhorst, B., & Schink, T. "Non-Steroidal Anti-Inflammatory Drug Use and the Risk of Acute Myocardial Infarction in the General German Population: A Nested Case-Control Study." *Drugs - Real World Outcomes* 2017; *4*:3, 127–137 . doi: https://doi.org/10.1007/s40801-017-0113-x [PMCID: PMC5567458] [PMID: 28676983]

Timóteo, A., Ferreira, J., Paixão, P., Aguiar, C., Teles, R., Cardoso, E., … Seabra-Gomes, R. "Serologic markers for cytomegalovirus in acute coronary syndromes." *Revista Portuguesa de Cardiologia : Orgao Oficial Da Sociedade Portuguesa de Cardiologia = Portuguese Journal of Cardiology : An Official Journal of the Portuguese Society of Cardiology* 2003; *22*:5, 619–631 . [PMID: 12940177]

Tracy, R. P., Doyle, M. F., Olson, N. C., Huber, S. A., Jenny, N. S., Sallam, R., … Kronmal, R. A. "T-helper type 1 bias in healthy people is associated with cytomegalovirus serology and atherosclerosis: the Multi-Ethnic Study of Atherosclerosis." *Journal of the American Heart Association* 2013; *2*:3, e000117 . doi: https://doi.org/10.1161/JAHA.113.000117 [PMCID: PMC3698770] [PMID: 23688675]

Tremolada, S., Delbue, S., Ferraresso, M., Carloni, C., Elia, F., Larocca, S., … Ferrante, P. "Search for genomic sequences of microbial agents in atherosclerotic plaques." *International Journal of Immunopathology and Pharmacology* 2011; *24*:1, 243–246 . doi: https://doi.org/10.1177/039463201102400130 [PMID: 21496409]

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

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

Visseren, F. L., Bouter, K. P., Pon, M. J., Hoekstra, J. B., Erkelens, D. W., & Diepersloot, R. J. "Patients with diabetes mellitus and atherosclerosis; a role for cytomegalovirus?" *Diabetes Research and Clinical Practice* 1997; *36*:1, 49–55 . doi: https://doi.org/10.1016/s0168-8227(97)00027-2 [PMID: 9187415]

Voorend, M., van der Ven, A. J. a. M., Kubat, B., Lodder, J., & Bruggeman, C. A. "Limited role for C. pneumoniae, CMV and HSV-1 in cerebral large and small vessel atherosclerosis." *The Open Neurology Journal* 2008; *2*, 39–44 . doi: https://doi.org/10.2174/1874205X00802010039 [PMCID: PMC2577934] [PMID: 19018307]

Waldman, W. J., Knight, D. A., Blinder, L., Shen, J., Lurain, N. S., Miller, D. M., … Chong, A. S. "Inhibition of cytomegalovirus in vitro and in vivo by the experimental immunosuppressive agent leflunomide." *Intervirology* 1999; *42*:5–6, 412–418 . doi: https://doi.org/10.1159/000053979 [PMID: 10702725]

Waldman, W. J., Knight, D. A., Lurain, N. S., Miller, D. M., Sedmak, D. D., Williams, J. W., & Chong, A. S. "Novel mechanism of inhibition of cytomegalovirus by the experimental immunosuppressive agent leflunomide." *Transplantation* 1999; *68*:6, 814–825 . doi: https://doi.org/10.1097/00007890-199909270-00014 [PMID: 10515382]

Watt, S., Aesch, B., Lanotte, P., Tranquart, F., & Quentin, R. "Viral and bacterial DNA in carotid atherosclerotic lesions." *European Journal of Clinical Microbiology & Infectious Diseases: Official Publication of the European Society of Clinical Microbiology* 2003; *22*:2, 99–105 . doi: https://doi.org/10.1007/s10096-002-0867-1 [PMID: 12627283]

Weekes, M. P., Tan, S. Y. L., Poole, E., Talbot, S., Antrobus, R., Smith, D. L., … Lehner, P. J. "Latency-associated degradation of the MRP1 drug transporter during latent human cytomegalovirus infection." *Science (New York, N.Y.)* 2013; *340*:6129, 199–202 . doi: https://doi.org/10.1126/science.1235047 [PMCID: PMC3683642] [PMID: 23580527]

Westphal, M., Lautenschlager, I., Backhaus, C., Loginov, R., Kundt, G., Oberender, H., … Steinhoff, G. "Cytomegalovirus and proliferative signals in the vascular wall of CABG patients." *The Thoracic and Cardiovascular Surgeon* 2006; *54*:4, 219–226 . doi: https://doi.org/10.1055/s-2006-923891 [PMID: 16755441]

Wills, M. R., Poole, E., Lau, B., Krishna, B., & Sinclair, J. H. "The immunology of human cytomegalovirus latency: could latent infection be cleared by novel immunotherapeutic strategies?" *Cellular & Molecular Immunology* 2015; *12*:2, 128–138 . doi: https://doi.org/10.1038/cmi.2014.75 [PMCID: PMC4654298] [PMID: 25132454]

Wilson, J. “An Instance of the Obliteration of the Vena Cava Inferior from Inflammation.” *Transactions of a Society for the Improvement of Medical and Chirurgical Knowledge* 1793; 65–8074 . Retrieved from https://archive.org/details/b21469763_0003/page/n5

Witherell, H. L., Smith, K. L., Friedman, G. D., Ley, C., Thom, D. H., Orentreich, N., … Parsonnet, J. “C-reactive protein, Helicobacter pylori, Chlamydia pneumoniae, cytomegalovirus and risk for myocardial infarction.” *Annals of Epidemiology* 2003; *13*:3, 170–177 . [PMID: 12604160]

Wu, L.-C., Leong, P.-Y., Yeo, K.-J., Li, T.-Y., Wang, Y.-H., Chiou, J.-Y., & Wei, J. C.-C. “Celecoxib and sulfasalazine had negative association with coronary artery diseases in patients with ankylosing spondylitis: A nation-wide, population-based case-control study.” *Medicine* 2016; *95*:36, e4792 . doi: https://doi.org/10.1097/MD.0000000000004792 [PMCID: PMC5023908] [PMID: 27603385]

Xenaki, E., Hassoulas, J., Apostolakis, S., Sourvinos, G., & Spandidos, D. A. “Detection of cytomegalovirus in atherosclerotic plaques and nonatherosclerotic arteries.” *Angiology* 2009; *60*:4, 504–508 . doi: https://doi.org/10.1177/0003319708322390 [PMID: 18818234]

Yamashiroya, H. M., Ghosh, L., Yang, R., & Robertson, A. L. “Herpesviridae in the coronary arteries and aorta of young trauma victims.” *The American Journal of Pathology* 1988; *130*:1, 71–79 . [PMCID: PMC1880556] [PMID: 2827495]

Yang, F.-J., Shu, K.-H., Chen, H.-Y., Chen, I.-Y., Lay, F.-Y., Chuang, Y.-F., … Chiu, Y.-L. “Anti-cytomegalovirus IgG antibody titer is positively associated with advanced T cell differentiation and coronary artery disease in end-stage renal disease.” *Immunity & Ageing* 2018; *15*:1 . doi: https://doi.org/10.1186/s12979-018-0120-0

Zhang, J., Liu, Y., Sun, H., Li, S., Xiong, H., Yang, Z., … Jiang, X. “High Human Cytomegalovirus IgG Level is Associated with Increased Incidence of Diabetic Atherosclerosis in Type 2 Diabetes Mellitus Patients.” *Medical Science Monitor: International Medical Journal of Experimental and Clinical Research* 2015; *21*, 4102–4110 . [PMCID: PMC4699628] [PMID: 26717490]

Zhu, J., Quyyumi, A. A., Norman, J. E., Csako, G., & Epstein, S. E. “Cytomegalovirus in the pathogenesis of atherosclerosis: the role of inflammation as reflected by elevated C-reactive protein levels.” *Journal of the American College of Cardiology* 1999; *34*:6, 1738–1743 . [PMID: 10577564]

Copyrights