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Von Willebrand Factor Plasma Levels Variability In Nonvalvular Atrial Fibrillation

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Abstract

Atrial Fibrillation (AF) is the most common cardiac arrhythmia of clinical significance; it increases the risk of mortality due to stroke. The mechanisms behind cerebral thromboembolism in AF are associated with a prothrombotic state, demonstrated by higher levels of von Willebrand Factor (vWF), a multimeric glycoprotein that plays a crucial role in platelet adhesion and aggregation and it has been proposed as a biomarker of endothelial dysfunction. Plasma vWF levels are elevated in patients with nonvalvular Atrial Fibrillation (NVAF) associated to the presence of cardiovascular risk factors. The variability in vWF plasma levels in healthy subjects has a wide distribution, but there is no description available of the variability in AF patients and among types of AF. The aim of this study was to determine the variability of vWF plasma concentrations in patients with NVAF, associated to cardiovascular risk factors. Search strategy included PubMed and Ovid. Keywords used were "Atrial Fibrillation" and "von Willebrand Factor". It includes original articles, with analysis of plasma vWF levels by ELISA, without acute stroke. Review articles and meta-analysis were excluded. Reviewed studies include 22 trials and 6542 patients with nonvalvular AF associated to cardiovascular disease risk factors: age, sex, hypertension, heart failure, diabetes mellitus, prior stroke, coronary artery disease. Variability in vWF plasma levels was wide, with minimum values of 77 IU/dl and maximum values of 245 IU/dl and a mean of 146 IU/dl. Age of patients ranged between 54 and 78 years, and the percentage of males ranged between 23% and 80%. According to type of AF vWF levels were as follows, in paroxysmal AF: 92-264 IU/dl; persistent AF: 76-234 IU/dl; permanent AF: 91-247 IU/dl. The variability in vWF plasma levels is affected by risk factors and the AF type, however vWF levels in AF patients are higher when compared with healthy subjects.

Introduction

Atrial Fibrillation

Atrial Fibrillation (AF) is the most common cardiac arrhythmia of clinical significance.[1] The presence of AF independently increases the risk of mortality and morbidity due to stroke and thromboembolism, congestive heart failure and impaired quality of life, resulting in high health-care cost and a public health burden.[2] AF is an epidemic disease, affecting 1% to 1.5% of the population in the developed world.[3] Approximately 2.3 million peo¬ple are currently diagnosed with AF in the United States and this number is expected to increase to 15.9 million by 2050.[4]

Risk factors for the development of AF include: increasing age, hypertension, myocardial infarction, heart failure, diastolic dysfunction, valvular heart disease, thyrotoxicosis, alcoholism, obesity and diabetes.[5-7] The term nonvalvular AF (NVAF) is restricted to cases in which the rhythm disturbance occurs in the absence of rheumatic mitral stenosis or a prosthetic heart valve.[8]

The prevalence of AF increases with advancing age.[9] The SAFE Study (Screening for Atrial Fibrillation in the Elderly) showed a prevalence of AF of 7.2 % in patients over 65 years and in those over 75 years old (10.3%).[10]

AF is classified into paroxysmal, persistent and permanent categories. It is designated paroxysmal AF when the arrhythmia episode terminates spontaneously within 7 days or by electrical/pharmacological cardioversion within 48 hours of its onset; AF is persistent when it is sustained beyond 7 days or terminated by electrical/pharmacological cardioversion after 48 hours of sustenance, it also includes cases of long-standing AF where AF has lasted for 12

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None.

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Table 1: Characteristics of participants and vWF levels in NVAF

Study		Participants			vWF levels (IU/dl)	
Author, year	Country	n	Age (years)	Man (%)	Mean	Range
Freynhofer et al. 2013 [41]	Austria	269	69	58	151	(89-212)
Roldan et al. 2011[42]	Spain	829	76	50	171	(131-230)*
Ammash et al. 2011 [43]	USA	414	63	75	157	(104-210)
Fu et al. 2011 [44]	China	90	54	70	117	(79-154)
Hou et al. 2010 [45]	China	26	65	58	132	(94-170)
Kalyoncu et al. 2009 [46]	Turkey	13	65	23	137	(102-190)*
Freestone et al. 2008 [47]	UK	52	71	73	122	(77-173)*
Freestone et al. 2008 [48]	UK	40	68	38	175	(113-237)
Freestone et al. 2007 [49]	UK	145	66	57	165	(85-245)
Varughese et al. 2007 [50]	UK	1235	70	74	145	(122-166)*
Heerringa et al. 2006 [51]	UK	162	78	51	144	(112-172)
Lip et al. 2005 [52]	UK	1321	70	70	144	(113-175)
Roldan et al. 2005 [53]	UK	200	72	51	143	(101-185)
Barber et al. 2004 [54]	UK	258	72	54	172	(142-211)*
Conway et al. 2004 [55]	UK	54	67	74	129	(103-155)*
Conway et al. 2003 [29]	UK	994	69	75	145	(114-176)
Conway et al. 2003 [56]	UK	162	78	51	144	(112-176)
Conway et al. 2002 [27]	UK	1321	70	71	145	(113-177)
Li-Saw-Hee et al. 2001 [57]	UK	78	65	65	132	(95-169)
Li-Saw-Hee et al. 2000 [58]	UK	61	64	72	143	(106-180)
Li-Saw-Hee et al. 2000 [59]	UK	52	68	80	137	(110-164)
Lip at al. 1995 [60]	UK	87	63	53	152	(108-198)*
Mean average			68	61	146	(106-188)

vWF: von Willebrand Factor; NVAF: nonvalvular Atrial Fibrillation; IU/dl: International Unit/deciliter; USA: United State of America; UK: United Kingdom.
vWF plasma levels are expressed as mean and range (minimum and maximum value). * Studies reported on a median (interquartile range).

months uninterruptedly; finally, the term permanent AF is applied to clinical AF when the attempts of restoration of sinus rhythm are not contemplated.[2]

AF occurring in the absence of structural heart disease, is called lone AF[2] and is considered a nosographic entity, when conditions such as hypertension, diabetes, hyperthyroidism, acute infections, recent cardiothoracic or abdominal surgery, and systemic inflammatory diseases, should be excluded.[11]

AF is associated with a prothrombotic (hypercoagulable) state and with an increased thromboembolic risk, by virtue of the Virchow's triad for thrombogenesis: endothelial or endocardial damage/dysfunction; abnormal blood stasis; and abnormal haemostasis, increased platelet activity, and fibrinolysis.[12]

The management of AF includes, reducing symptoms through rhythm or rate management, treating underlying medical conditions, concomitant cardiovascular disease and reducing the risk of stroke and thromboembolic events[13] with oral anticoagulation or aspirin.[14]

Atrial fibrillation confers a five-fold increased risk of stroke, and one in five of all strokes are attributed to this arrhythmia.[2] The mechanisms behind cerebral thrombo-embolism in AF are not completely understood, but it is well documented that AF is associated with a prothrombotic state, demonstrated by higher levels of von Willebrand Factor (vWF), when compared to healthy control subjects.[15, 16]

Von Willebrand Factor

von Willebrand factor (vWF) is a multimeric glycoprotein that plays a crucial role in platelet adhesion and aggregation, which are the main initial steps in haemostasis after vascular injury and also under conditions of high shear stress as it happens in lesions in the coronary arteries.[17] Recent studies have implicated vWF as a regulator of angiogenesis, smooth muscle cell proliferation, and interactions in the immune system. It is synthesized in endothelial cells and megakaryocytes as a propeptide. Following synthesis, vWF undergoes dimerization and further multimerization to finally be proteolized by ADAMTS 13 protease, into functional vWF multimers of varying size.[18, 19]

vWF has two main functions: this glycoprotein carries and protects factor VIII in circulation and mediates the initial platelet adhesion to the subendothelium, by linking to specific platelet membrane receptors: glycoprotein Ib-V-IX complex, facilitating platelet adhesion and glycoprotein αIIbβ3 mediating platelet aggregation at the site of injury, and consequently, activated coagulation.[18]

The mean vWF plasma level is 100 IU/dl, but the variability in the population is wide, with 95% of values between 50 IU/dl and 200 IU/dl.[20, 21]

Plasma vWF concentration is affected by the ABO blood group. O group individuals having plasma levels 25% lower than non-O (A, B and AB) subjects.[22] The mechanism by which ABO group determines vWF plasma levels has not been well established.[23]

Circulating plasma vWF, is almost exclusively synthesized, stored, and secreted by endothelial cells.[24] It has been proposed as a biomarker of endothelial damage/dysfunction as increased plasma

Table 2: Effect of risk factor in vWF levels in AF patients

Author, year	Risk Factor	vWF (IU/dl)			
		AF without RF		AF + RF	
		Mean	Range	Mean	Range
Kalyonku et al. 2009 [46]	HT	110	(50-394)	169	(67-390)
	DM	110	(50-390)	142	(67-390)
Heerringa et al. 2006 [51]	HT	145	(122-166)	149	(130-169)
Lip et al. 2005 [52]	HF	144	(113-175)	154	(125-183)
	HF	145	(115-175)	159	(128-190)
Conway et al. 2002 [27]	DM	145	(114-176)	159	(130-188)
	PS	145	(114-176)	154	(127-181)
	HT	144	(112-178)	149	(119-179)

vWF: von Willebrand Factor; AF: Atrial Fibrillation; IU/dl: International Unit/deciliter; RF: Risk Factor. HT: Hypertension, DM: Diabetes Mellitus; HF: Heart Failure; PS: Prior Stroke.
vWF plasma levels are expressed as mean and range (minimum and maximum value).

levels have been found in inflammatory and atherosclerotic vascular diseases.[25]

The availability of a useful index of endothelial dysfunction, may therefore have potential value, since the measurement of such a marker can be a non-invasive way of assisting in diagnosis as an indicator of disease progression and prognosis.[26]

Atrial Fibrillation And Stroke

Plasma vWF levels are elevated in patients with NVAF associated with endothelial dysfunction.[27, 28] Raised plasma levels of vWF are predictive of stroke and vascular events among patients with AF[29] and are associated with a poor prognosis. These levels in AF patients are not altered by warfarin and/or aspirin treatment.[30]

Multiple studies show increased plasma levels of vWF in patients with AF when compared with a control group; several studies associate this increase to the presence of cardiovascular risk factors. Finally, results have been reported on the levels of vWF according to the type of AF, however, there are no descriptions of the ranges of variation available.

Therefore, our hypothesis is that vWF plasma levels show variability in patients with NVAF and that this variability is influenced by risk factors and by AF type. The aim of the present study is to identify these ranges of variability in patients with AF.

Material And Methods

Study Selection

A search of the literature was conducted using electronic databases. Search strategy included: PubMed and Ovid. The keywords used were: "Atrial Fibrillation" and "von Willebrand Factor" (examination term of January 31, 2014).

A separate search for each keyword was realized. With the objective of providing reliability in the selection process of articles, two researchers were given the task of performing the process independently, afterwards their level of agreement was found.

Original articles were reviewed with experimental, quasi-experimental and observational designs, the articles must have been written in English, and followed methodological characteristics like: inclusion of patients with nonvalvular AF (NVAF), with description of associated risk factors, average age of the sample, percentage of male, analysis of plasma vWF levels by ELISA and report vWF concentrations in International Unit/deciliter (IU/dl), with presence or absence of a control group, without acute stroke or acute coronary syndrome, and provide statistical data for analysis and interpretation of results. Review articles and meta-analysis articles with incomplete methodological description or unclear data, were excluded.

Statistical Analysis

Continuous data are expressed as mean and interquartile range, while categorical variables are expressed as a percentage. Statistical analysis was performed using the program IBM® SPSS® Statistics 20 version.

Results

The combination of the keywords "Atrial Fibrillation" and "von Willebrand Factor" showed 97 results in Pub Med and 43 in OVID; only 22 articles met the selection criteria.

Sato et al.[31] was excluded because AF patients were enrolled with acute stroke; several studies were excluded because they reported their results in different international units: Alonso et al.,[32] Feng et al.[33] and Mondillo et al.[34] informed in percentage (%); Yip et al.[35] in g/ml; Marín et al.[36] on ng/ml; Kahn et al.[37] in μ/ml; Pinto et al.[38] on pg/ml. Kumagai et al.[39] and Fukuchi et al.[40] were not included because they presented results based on expression of vWF mRNA in the endocardium and by measuring vWF by endothelial cell Immunohistochemistry, respectively. The remaining articles did not show inclusion criteria and were excluded on the basis of title and abstract, for clearly not being related to clinical trials in AF.

Reviewed studies included 22 trials and 6542 patients with nonvalvular AF (NVAF), associated to cardiovascular disease risk factors. Table 1 shows general characteristics and levels of vWF in these studies. 16 studies showed a normal distribution and continuous data are expressed as mean ± standard deviation (SD), however, in Table 1, the value of the standard deviation is described as minimum value and maximum value (or range); the other 6 studies had a nonparametric distribution and vWF levels reported as a median (interquartile range).

Variability in vWF plasma levels in patients with NVAF was observed in Table 1, values of 77 IU/dl (minimum) to 245 IU/dl (maximum) were found; with a mean of 146 IU/dl. The age of patients ranged between 54 and 78 years, with a mean of 68 years and the percentage of males ranged between 23 - 80% with an average of 61%.

The study with the lowest vWF plasma levels was reported by Fu et al. 2011[44] with values of 117 IU/dl (79-154) for 90 participants from China, with an average age of 54 years old and 70% of male participants. The highest value was from Freestone et al. in 2008[47] with levels of 175 IU/dl (113-237) in 1321 patients from United Kingdom, 65 years of age and 38% males.

Table 3: Characteristics and vWF levels in AF patients with and without Warfarin

	n	Age (years)	Mean (%)	vWF (IU/dl)			
				No warfarin Tx		Warfarin Tx	
				Mean	Range	Mean	Range
Freestone et al 2007 [49]	30	68	50	155	(82-228)	151	(100-202)*
Li-Saw-Hee et al. 2000 [58]	23	64	75	144	(106-180)	148	(108-188)**
Barber et al. 2004 [54]	166	70	55	156	(124-196)	181	(50-218)
Lip et al. 1995 [60]	31	60	39	152	(108-198)	169	(118-227)
Freestone et al. 2008 [47]	31	71	73	122	(77-173)***	100	(68-171)

vWF: von Willebrand Factor; AF: Atrial Fibrillation; IU/dl: International Unit/deciliter; Tx: Treatment
vWF plasma levels are expressed as mean and range (minimum and maximum value)
* After at least 4 weeks of therapeutic anticoagulation. ** After 8 weeks of warfarin. *** Patients with and without warfarin.

Table 4: Characteristics and vWF levels in Lone AF

Publications	Participants					
Authors, year	Country	n	Age (years)	Man (%)	vWF (IU/dl)	
					Mean	Range
Fu et al. 2011 [44]	China	60	49	72	114	(79-147)
Freestone et al. 2007 [49]	UK	35	62	69	169	(84-254)
Conway et al. 2003 [56]	UK	66	76	94	139	(107-171)
Li-Saw-Hee et al. 2000 [58]	UK	16	69	69	149	(123-175)
Li-Saw-Hee et al. 2000 [59]	UK	16	68	80	136	(129-143)

vWF: von Willebrand Factor; IU/dl: International Units/ deciliter; UK: United Kingdom.
vWF plasma levels are expressed as mean and range (minimum and maximum value)

The reviewed studies include cities from three continents. However, most of research studies (86.4%) were performed in Europe. The United Kingdom is the country with the largest number of studies (72.7%); 9.1% of the studies were performed in Asia and the rest (4.5%) in North America.

Influence Of Risk Factors In Vwf Levels

Cardiovascular risk factors associated with AF in the reviewed studies included: hypertension (39%), heart failure (33%), coronary artery disease (24%), diabetes mellitus (15%), prior stroke (12%) and hyperlipidemia (8%).

Four studies described the effects of risk factors in vWF levels in AF patients (Table2). Kalyonku et al.[46] evidence the highest levels of vWF in patients with hypertension and diabetes compared with AF patients without the risk factor. Herringa et al.[51] and Lip et al.52 show the greatest vWF levels by effect of hypertension and heart failure, respectively. Finally, Conway et al.[27] describe the effect of 6 risk factors: heart failure, hypertension, diabetes, prior stroke, age and female sex. The influence of age and female sex in vWF levels were: patient >75 years 151 IU/dl (123-179) and ≤75 years 145 IU/dl (113-177); women 150 IU/dl (119-181) and men 145 IU/dl (114-176).

Differences of vWF concentrations in patients with and without warfarin treatment are showed in Table 3. Two studies had a longitudinal design and show vWF levels in AF patients before and after warfarin treatment: Freestone et al. 2007[49] and Li-Saw-Hee et al. 2000[58] showed the same variation of 4I U/dl in the mean value, after 4 and 8 weeks of treatment with warfarin, respectively.

Three studies show differences in vWF by comparing two groups of patients: AF with and without warfarin. Barber et al. in 2004[54] showed a difference of 25 IU/dl between their means: AF without warfarin group (n = 92, age 72 years, 52% men) and warfarin group (n = 166, Age 70 years, 50% men). Lip et al. 1995[58] described a difference of 17 IU/dl between the 2 groups: without warfarin (n = 37, age 73 years, 51% men) and warfarin (n = 31, age = 60, 39% male). And Finally, Freestone et al. 2008,[47] presented high levels of vWF in patients with warfarin therapy, but they don´t specify the differences between their groups.

Lone Atrial Fibrillation

The general characteristics and vWF plasma levels in Lone AF patients are shown in Table 4. In this group, 193 subjects with AF were included; 2 types of Lone AF were found: Lone AF (Fu et al. 2011) with patients <60 years of age (mean 49 years) where variability in plasma vWF concentrations ranged between 79 and 147 IU/dl, with a mean value of 114 IU/dl. More studies[49, 56, 58, 59] with Lone AF in patients >60 years of age (mean 69 years) had vWF levels ranged between 84 and 254 IU/dl, with an average of 148 IU/dl.

Types of Atrial Fibrillation

Table 5 summarizes the variability of vWF plasma levels in AF studies categorized into 3 types. These studies included a total of 658 participants. In Paroxysmal AF (47.6%) concentrations of vWF ranged between 92 to 264 IU/dl, with a mean of 141 IU/dl in patients 62 years old and 70% men; Persistent AF (30.7%) varied between 76 and 234 IU/dl with a mean of 137 IU/dl, 62 years and 70% men; finally in Permanent AF (21.7%) values rangedfrom 91 to 247 IU/dl with a mean of 162 IU/dl, mean age of 66 years and 61% of participants were male.

Control Groups

Studies that involved a control group are shown in Table 6; 2 types of subjects were found: healthy subjects (no AF and no risk factors) and patients with sinus rhythm matched (by age and gender, in terms of smoking status, body mass index, and systolic and diastolic blood pressure). Healthy patients (n=233) showed vWF plasma levels between 55 and 136 IU/dl with a mean of 95 IU/dl, age of 60 years and 70% men. And 371 participants with sinus rhythm matched had values of 54 to 176 IU/dl with a mean of 114 IU/dl, mean age of 64 years and 58% men.

Most of these studies were conducted in Europe (82%), mainly in the UK (73%) and the rest in Asia (18%).

Variability In Vwf

Table 7 summarizes the vWF plasma concentrations, shows the variability of these based on the different types of atrial fibrillation. The highest values were found in patients with Permanent AF (162 IU/dl) and the lowest (114 IU/dl) were found in Lone AF patients younger than 60 years. Healthy subjects showed the lowest vWF plasma levels (95 IU/dl).

Discussion

In this study, we show the variability of vWF plasma levels, as a marker of endothelial dysfunction in Atrial Fibrillation patients, and the influence of cardiovascular risk factors on these concentrations.

The endothelial damage or dysfunction may play an important role in the pathobiology of vascular outcome in diabetes, hypertension and heart failure. Shear stress at the vessel wall, affect endothelial cell integrity and function, leading to the secretion of vWF in these disorders.[46] Reviewed studies show there is an effect of hypertension, diabetes and heart failure in the increased vWF plasma levels, therefore, these are risk factors to be taken into consideration to measure the variability of vWF.

Increased vWF plasma levels are well recognized to be associated

Table 5: vWF plasma levels in participants of 3 categories of Atrial Fibrillation

Study	vWF (IU/dl)					
	Paroxysmal AF		Persistent AF		Permanent AF	
	Mean	Range	Mean	Range	Mean	Range
Scridon et al. 2013 [61]	107	(99-115)	125	(115-135)		
Ammash et al. 2011 [43]	148	(95-201)	160	(105-215)	174	(117-231)
Freestone et al. 2007 [49]	178	(92-264)	155	(76-234)	169	(91-247)
Li-Saw-Hee et al. 2001 [28]	130	(96-164)	106	(80-132)	143	(96-190)
Mean Average	141	(96-186)	137	(94-179)	162	(101-223)

vWF plasma levels are expressed as mean and range (minimum and maximum value)
vWF: von Willebrand Factor; AF: Atrial Fibrillation; IU/dl: International Units/deciliter.

Table 6: von Willebrand Factor levels in 2 types of Control Groups

Authors, year	Participants				Healthy* Control		Matched** Control	
	Country	n	Age (years)	Man (%)	vWF (IU/dl)			
					Mean	Range	Mean	Range
Scridon et al. 2013 [61]	France	17	55	76	87	(73-101)		
Fu et al. 2011 [44]	China	79	55	57	106	(76-136)		
Freestone et al. 2008 [47]	UK	117	68	73	81	(55-133)***		
Li-Saw-Hee et al. 2001 [57]	UK	20	63	75	105	(75-135)		
Hou et al. 2010 [45]	China	26	65	58			113	(76-150)
Freestone et al. 2008 [46]	UK	26	66	50			115	(54-176)
Freestone et al. 2007 [47]	UK	40	64	40			116	(57-175)
Conway et al. 2004 [55]	UK	41	67	61			125	(104-146)***
Li-Saw-Hee et al. 2001 [57]	UK	20	63	65			119	(76-162)
Li-Saw-Hee et al. 2000 [58]	UK	60	66	75			105	(75-135)
Lip et al. 1995 [60]	UK	158	59	56			105	(80-147)***
Mean Average		604	63	62	95	(75-126)	114	(75-156)

vWF: von Willebrand Factor; UK: United Kingdom. IU/dl: International Units/ deciliter
vWF plasma levels are expressed as mean and range (minimum and maximum value).
*Healthy control: patients with sinus rhythm without risk factors; ** Matched Control: patients with sinus rhythm (without AF) and matched for age and sex, in terms of smoking status, body mass index, and systolic and diastolic blood pressure. *** Studies reported on a median (interquartile range).

with ischemic cerebrovascular events,[26] which were verified in the study of Conway et al.,[27] where there was an increase of vWF in patients with prior stroke. Also age and female gender influence the levels of vWF as demonstrated in all studies reviewed: vWF levels were elevated in those studies involving elderly patients and with a higher percentage of women.

VWF levels in AF patients are not altered by warfarin treatment.[30] This is demonstrated in the results published by Freestone et al. 2007[49] and Li-Saw-Hee et al. 2000,[58] where vWF levels were very similar before and after treatment with warfarin (difference not statistically significant). Moreover, in studies where two groups were compared, Barber et al.,[54] Lip et al.[60] and Freestone et al.,[47] the differences in plasma levels were justifiable because both groups were not homogeneous (not matched in their risk factors) and this difference was not due to the use of warfarin.

Lone AF has not been defined consistently; many cardiologists have suggested that a major diagnosis of lone AF should be restricted to patients <60 years of age[11] in order to avoid the effect of age on the increased levels of vWF. Accordingly, Fu et al.[44] describe lower vWF levels (mean 114 IU/dl), in AF Lone patients with an average age of 49 years; nevertheless, several reports do not consider age younger than 60 to define Lone AF. According to this, studies by Freestone et al.,[49] Conway et al.[56] and Li-Saw-Hee et al.[58, 59] describe higher vWF levels (148 IU/dl) in patients whose average age was 69 years. All these studies support the idea that age is an important factor in the variability of vWF levels, consequently, it is important to take age factor into account when defining Lone AF.

Endothelial dysfunction exists whether AF is paroxysmal, persistent, or permanent,[28] but the differences in vWF levels among them, are unclear. Our review shows that there is in fact a difference between the 3 types of AF, with the highest levels found in patients with permanent AF, although this might be influenced by the older age found in patients included and a smaller amount of men; unlike paroxysmal AF and persistent AF studies.

Finally, the results showed in this analysis, have confirmed the presence of higher vWF levels in patients with AF compared with healthy control subjects in sinus rhythm. The mean plasma level of VWF in healthy subjects is 100 IU/dl, but the population distribution is broad, with 95% of values between 50 IU/dl and 200 IU/dl.[20, 21] Similar results were found in the reviewed studies: healthy patients had vWF levels between 55 and 136 IU/dl with a mean of 95 IU/dl.

Plasma vWF concentrations are strongly influenced by ABO blood group. Blood group O individuals have lower levels than non-O subjects;[22] although this issue is well described in the hemostasis field, none of the articles reviewed considered neither reported the blood group.

Limits and Features: Other factor that affect the variability on vWF levels, and which was not taken into account in the studies reviewed, was genetic determinant. Moreover, twin studies have demonstrated that 66% of all variations in plasma VWF are genetically determined.[62] Further studies are required in different populations, including Latin American countries.

Table 7: Variability in vWF levels in AF and Control Groups

	vWF (IU/dl)		
	Intervals (minimum - maximum values)	Mean Average	Range Average
NVAF* [27, 29, 41-60]	77 - 245	146	(106-188)
Lone AF** < 60 years [44]	79 – 147	114	(79-147)
Lone AF > 60 years [49, 56, 58, 59]	84 - 254	148	(111-186)
Paroxysmal AF [28, 43, 49, 61]	96 – 264	141	(96-186)
Persistent AF [28, 43, 49, 61]	76 – 234	137	(94-179)
Permanent AF [28, 43, 49]	91 – 247	162	(101-223)
Healthy Control*** [44, 47, 57, 61]	55 - 136	95	(70-126)
Matched Control**** [45, 48, 49, 55, 57,58, 60]	54 - 176	114	(75-156)

vWF: von Willebrand Factor; NVAF: nonvalvular Atrial Fibrillation; AF: atrial fibrillation.; IU/dl: International Units/deciliter.
vWF plasma levels are expressed as mean and range (minimum and maximum value).
*NVAF: AF + Risk Factors; ** Lone AF: AF without Risk Factors; ***Healthy control: patients whit sinus rhythm without risk factors; **** Matched Control: patients whit sinus rhythm (without AF) and matched for age and sex, in terms of smoking status, body mass index, and systolic and diastolic blood pressure.

Conclusion

The variability in vWF plasma levels found in the studies involving atrial fibrillation patients associated to cardiovascular risk factors ranged from 77 to 245 IU/dl, with a mean average of 146 IU/dl. Associated risk factors were: elderly age, female gender, hypertension, heart failure, diabetes, and prior stroke. Furthermore this variability in vWF plasma levels is affected by AF type: paroxysmal, persistent or permanent. And vWF levels in AF patients are higher compared with healthy subjects.

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