ATHEROSCLEROTIC VASCULAR EVENTS IN SYSTEMIC LUPUS ERYTHEMATOSUS – AN EVOLVING STORY

Running Head: AVE in SLE in decades

AUTHORS:

Murray B. Urowitz, MD, FRCPC, Professor of Medicine, University of Toronto, Senior Scientist, Krembil Research Institute, Director, Centre for Prognosis Studies in The Rheumatic Disease and University of Toronto Lupus Clinic, Toronto Western Hospital

Jiandong Su, MB, BSc, Biostatistician, Centre for Prognosis Studies in The Rheumatic Diseases, University of Toronto Lupus Clinic.

Dafna D. Gladman, MD, FRCPC, Professor of Medicine, University of Toronto, Senior Scientist, Krembil Research Institute, Deputy Director, Centre for Prognosis Studies in The Rheumatic Disease and University of Toronto Lupus Clinic, Toronto Western Hospital

AUTHORS' AFFILIATION:

The University of Toronto Lupus Clinic, Centre for Prognosis Studies in The Rheumatic Disease, Toronto Western Hospital

CORRESPONDING AUTHOR:

Murray B. Urowitz MD, FRCPC

Professor of Medicine, University of Toronto; Senior Scientist, Krembil Research Institute

Director, Centre for Prognosis Studies in The Rheumatic Diseases

Toronto Western Hospital, 399 Bathurst St. 1E-410B, Toronto, Ontario, M5T 2S8.

Tel: 416-603-5838 ; Fax: 416-603-9387; Email: m.urowitz@utoronto.ca

Word Count: 2038

ABSTRACT

Background: Atherosclerotic vascular events (AVEs) are a major cause of mortality and morbidity in systemic lupus erythematosus (SLE). We aimed to determine the impact of early recognition and therapy for both classic risk factors for AVE and for SLE on the burden of AVEs in lupus in recent decades.

Methods: Inception patients who entered the University of Toronto lupus Clinic between 1975 and 1987 followed to 1992 (Cohort 1) and between 1999 and 2011 followed to 2016 (Cohort 2) were studied. AVEs, attributed to atherosclerosis, and occurring during the 17 years were identified. Lupus disease activity and therapy as well as hypertension, hypercholesterolemia, hyperglycemia and smoking were assessed. Analysis included descriptive statistics on baseline characteristics, traditional risk factors over the follow up, outcome rates by each 100 person years; Kaplan-Meier cumulative AVE curves, as well as competing risk Cox models adjusted by Inverse Probability Weights (IPW).

Results: Of the 234 in Cohort 1, 26 patients (11%) had an AVE compared with 10 of 262 (3.8%) in Cohort 2. The rate per 100 patient-years of follow-up was 1.8 in Cohort 1 and 0.44 in Cohort 2 ($P < 0.0001$). Better control of all risk factors and disease activity were achieved in Cohort 2. There was a reduction of 60% in the risk for AVE in cohort 2.

Conclusion: The incidence of AVE in SLE in the modern era has declined in large part due to more effective management of classic coronary artery risk factors and of SLE.

INTRODUCTION

The description of the bimodal mortality pattern of systemic lupus erythematosus (SLE) highlighted the importance of premature atherosclerotic vascular events (AVE) as an important cause of late mortality in SLE[1]. Cardiovascular disease remains a major cause of death in SLE[2]. Furthermore, subsequent studies described the increased prevalence of AVE as a significant comorbidity in SLE [3-6]. Risk factors for accelerated atherosclerosis in SLE include both traditional risk factors (e.g. hypertension, hyperlipidemia, smoking and diabetes) as well as lupus related factors (e.g disease activity, damage) [3,7-10]. Current recommendations for monitoring for cardiovascular risk in SLE indicate that high quality evidence would recommend regular monitoring for hypertension, dyslipidemia, diabetes and smoking [11]. Subclinical atherosclerosis has also been documented in a significant proportion of patients with SLE[12-18], further emphasizing the importance of this comorbidity.

We aimed to determine the prevalence of AVEs in the current millennium compared to the prevalence in the 1970-80s and the impact of early recognition and newer therapy for both classic risk factors for AVE and for the treatment of SLE on the burden of atherosclerotic vascular events (AVE) in lupus in recent decades.

METHODS

SETTING

The Toronto Lupus Cohort was established in 1970 and has followed patients prospectively according to a standard protocol at 2-6 month intervals according to a standard protocol[19]. Disease activity is measured by the SLE disease activity index 2000 (SLEDAI-2K) [20]. Disease activity over time is measured by the adjusted mean SLEDAI-2K (AMS) [21]. The research program is approved

by the Research Ethics Board of University Health Network (REB# 11-0397-AE), and all patients have consented.

PATIENT SELECTION

Patients who entered the Lupus Clinic within 12 months of diagnosis without a prior AVE were included. The first cohort (Cohort 1) included patients who entered between 1975 and 1987, and followed until the end of 1992. The second cohort who entered between 1999 and 2011 was followed until the end of 2016.

OUTCOMES

AVE: AVEs that occurred within the first 17 years from enrolment were included. AVEs are collected prospectively in the data collection form according to the following definitions: (1) Myocardial infarction, defined as one of: definite electrocardiographic (ECG) abnormalities, typical symptoms with probable ECG abnormalities and abnormal enzymes (> 2X upper limit of normal); typical symptoms and abnormal enzymes. (2) Angina, defined as severe pain or discomfort over the upper or lower sternum or anterior left chest and left arm, of short duration, relieved by rest or vasodilators, and confirmed by a cardiologist. (3) Transient ischemic attack (TIA), defined as a brief episode of neurological dysfunction without residua. (4) Stroke, defined as an abrupt onset of neurological dysfunction resulting in neurological damage. (5) Congestive heart failure due to ischemic heart disease requiring treatment. In these cases either the evidence of atherosclerosis was present prior to entering our clinic and the first AVE in our clinic was congestive heart failure, or the patients presented with congestive heart failure and the atherosclerosis was identified in the course of investigation. All in the absence of active SLE. (6) Bradyarrhythmia due to ischemic heart disease requiring pacemaker insertion. Angioplasty and

coronary artery bypass surgery were not included as they only occurred after a previous diagnosis of an AVE. AVEs are recorded as being due to atherosclerosis and not related to active SLE based on SLE being inactive at the time of the event and/or typical atherosclerotic changes on angiogram or evidence of atherosclerosis elsewhere. Only the first AVE was included with its corresponding date defined as outcome date. For patients without AVE, their censoring dates were the last clinic visit or cutoff dates when they reached 17 years' of follow-up since first visit.

Disease Factors: Disease activity was measured by the AMS at 5 years. Use of corticosteroids ever, or average to first AVE or last clinic visit. Antimalarials and immunosuppressive therapy ever to the time of first AVE or last assessment.

Classic Risk Factors: The percent of time over the 17 years that patients had normal blood pressure (≤140/90 mmHg), normal total cholesterol (≤ 5.2mmol/L), normal blood sugar (≤ 7mmol/L) and the percent of time patients smoked was calculated.

Statistical Analysis

Baseline information was described by mean ± standard deviation / median (inter-quartile ranges) or counts (frequencies) for continuous and binary variables respectively, and tested using un-paired t-test, 2 sided Mann-Whitney test, Wilcoxon test or Chi Square test as appropriate. The unadjusted prevalence of AVE in the two cohorts was calculated by counts of patients with AVE divided by cohort sizes. The rate of AVE by per 100 person-years within the 17 years of follow-up was calculated. Kaplan-Meier survival curve was plotted without adjusting for any covariates.

Risk factors over the 17 years were calculated individually as outlined above.

To reveal the cohort effect after adjusting for confounding variables, inverse probability weights (IPW) were calculated from propensity scores derived from the logistic regression using all important baseline variables and risk factors, as well as summary variables over the follow up,

irrespective of their level of statistical significance. The confounding factors included: age sex, ethnicity, AMS in the first 5 years, SDI excluding cardiovascular events, use of steroids average steroid dose, use of antimalarial and immunosuppressives, percent of years with normal blood pressure, normal cholesterol, normal glucose, percent of years smoking.

Finally the IPW was entered as adjustment continuous covariate along with the cohort variable in a Cox proportional hazard model to establish the relationship between cohort effect and survival free of AVE. All-cause mortality was accounted as a competing risk**Error! Bookmark not defined.**[2]. The IPW adjusted hazard ratios with 95% confidence intervals and p values were reported, IPW adjusted survival curves were plotted[22]. All analyses were carried out in SAS 9.4 (SAS Institute Inc., Cary, NC, USA), $p<0.05$ was adapted as the significance of statistical difference.

RESULTS

Of the 826 patients in the inception cohort, 234 entered between 1975 and 1987 (Cohort 1) and were followed through the end of 1992. Two Hundred and sixty two patients entered between 1999 and 2011 (Cohort 2) and followed through the end of 2016 (Table 1). The two inception cohorts were similar in age, sex and disease activity. However, Cohort 1 had significantly more Caucasian patients while Cohort 2 had more Black, Chinese and Filipino patients. More patients in Cohort 2 were receiving corticosteroids (although the mean dose was similar), antimalarials, and immunosuppressive medications.

During the 17 years of follow-up interventions with respect to cardiovascular risk factors varied.

As can be seen in Table 2, patients in Cohort 1 received significantly less therapeutic interventions for cardiovascular risk factors and less aggressive therapeutic interventions for SLE than those in Cohort 2.

Twenty-six patients in Cohort 1 sustained an AVE (11%) compared to only 10 patients in Cohort 2 (3.8%) (P<0.001) (Table 3, Figure 1). As patient follow-up was different between the two cohorts, we calculated events per 100 patient-years of follow-up. That rate was 1.8 in Cohort 1 and 0.44 in Cohort 2 (P < 0.0001).

Table 3 shows while there was no difference in the time to event or age at first event, there were significant differences in the classic risk factors and in disease activity over the first 5 years of the disease course. Patients in Cohort 2 sustained normal blood pressure for a greater percent of the time than those in Cohort 1. They also spent a greater percent of time with normal blood sugar and cholesterol levels. Patients in Cohort 2 smoked significantly less than those in Cohort 1. Disease activity burden (as measured by the AMS) in the first 5 years of disease was lower in Cohort 2 than in Cohort 1. At the end of the 17 year follow-up 78% of the patients in Cohort 1 were alive compared with 94% of the patients in Cohort 2.

Because of the collinearity between risk factors and the cohort effect we did not do a multivariable analysis but rather used the IPW score derived from the propensity score to balance the non-comparability between the two cohorts. The cohort effect was determined through a competing risk Cox model weighted by IPW. As can be seen figure 2, the two cohorts are different with regards to the probability of being free from AVE, over the 17 years of follow-up. The hazard ratio from the IPW weighted model is 0.40 (95%CI: 0.23, 0.70) comparing Cohort 2 to Cohort 1 at any time, a reduction of risk of AVE of 60% (p = 0.0013).

DISCUSSION

The bimodal mortality pattern in patients with SLE highlighted the importance of AVE in SLE as a cause of death[1,23]. Subsequently we highlighted the contribution of AVE to the morbidity of patients with SLE[3]. Others have demonstrated the impact of AVE in young women with SLE as well as the economic burden on society[24,25].

Subclinical disease long before AVE clinical manifestations has been demonstrated in SLE patients using a variety of modalities including carotid ultrasound, cardiac perfusion studies, flow mediated dilatation, cardiac CT, and coronary angiography [10,13,16,17,26].

In this study we examined two inception cohorts within our SLE population, one entered in the 1970s and early 1980s, after the recognition of the importance of AVE in SLE, and a more recent cohort entered in the current millennium, when therapeutic approaches would have been significantly different. Our study demonstrated that Cohort 1 had significantly more AVEs over a 17 year period than Cohort 2. Our findings are in keeping with the declining incidence of myocardial infarction noted in the general population[27,28]. In a study of British men there was a decline of 3.8% per year in the incidence of coronary heart disease. In a mixed population study from Norway, there was an annual decrease of 4.3% in hospitalized acute myocardial infarctions. This has also been observed in the Framingham population study[29].

The therapeutic approaches used in the two eras of our cohorts were significantly different with less treatment of hypertension, hyperlipidemia, diabetes, and smoking cessation in terms of the traditional risk factors, in Cohort 1. In addition, patients in Cohort 2 were more often treated for their lupus with antimalarials and immunosuppressive medications. In order to assess the impact of the therapeutic intervention we calculated the percent of the time patients achieved normal risk factor levels and showed that patients in Cohort 2 had a longer time over the 17 years with normal

blood pressure, cholesterol, and glucose, and smoked less of the time than those in Cohort 1. In addition, the disease burden in the first 5 years of lupus was lower in Cohort 2 than in Cohort 1. As a consequence, survival was greater among the patients who entered in the later cohort.

To take into account these improvements in disease and risk factor management in patients in Cohort 2, we adjusted for these risk factors and outcomes and found that the hazard ratio for AVE was significantly reduced by 60% in Cohort 2 compared to Cohort 1. Thus the cohort effect is not entirely explained by the successful management of the risk factors and disease control. Similarly, in the British and Norwegian studies the treatment of risk factors accounted for only 46% of the decline in British men and 66% of the decline in the Norwegian population[27,28].

A major strength of our study is that the data have been collected prospectively according to a standard protocol and definitions which were set up initially. Information is entered when it is confirmed. Thus although this is a retrospective analysis, all data were collected systematically in real time. In our study the risk factors assessed included only some of the classic cardiac risk factors, as well as disease related factors and these did not entirely explain the cohort effect. We were unable to evaluate other important factors such as body mass index, degree of physical activity, novel lupus therapies, family history of AVE in first degree relatives, nor antiphospholipid levels, all of which were either not recorded or not yet available in the first cohort and which could contribute to the cohort effect noted.

These results provide an insight as to how physicians may improve outcomes due to AVEs in patients with SLE. Studies of subclinical coronary artery disease in patients with SLE have revealed that 23-35% of patients with no history of CAD have abnormal screening tests such as dual isotope myocardial perfusion imaging and flow mediated dilatation [2,12,30]. These findings would not have been discerned by the classic Framingham risk score[31,32] , but will now afford the

physician the knowledge to intensify therapy as indicated. Indeed a recent systematic review has stressed the importance of monitoring risk factors and disease activity on a regular basis to reduce the incidence of AVE in patients with SLE[33].

In conclusion, the incidence of AVE in SLE in the modern era has declined, in large part due to more effective management of classic coronary artery disease risk factors and better management of SLE. Further improvement may be anticipated with more aggressive screening and therapy of subclinical disease.

ACKNOWLEDGMENTS AND FINANCIAL SUPPORT

The University of Toronto lupus clinic has been supported by The Arthritis Society, Canadian Institutes of Health Research, University Health Network, the Rocca family, and the Bozzo Family.

DISCLOSURE STATEMENT

The authors declare that they do not have any potential conflicts of interests.

REFERENCES

1. Urowitz MB, Bookman AA, Koehler BE, Gordon DA, Smythe HA, Ogryzlo MA. The bimodal mortality pattern of systemic lupus erythematosus. Am J Med 1976;60:221-5.
2. Sheane BJ, Urowitz MB, Gladman DD. Atherosclerosis in Systemic Lupus Erythematosus – Epidemiology, Risk Factors, Subclinical Assessment and Future Study. Rheumatology Current Research 2013; S5

3. Urowitz MB, Ibañez D, Gladman DD. Atherosclerotic vascular events (AVE) in a single large lupus cohort: prevalence and risk factors. J Rheumatol 2007;34:70-5.
4. Manzi S, Meilahn EN, Rairie JE, et al. Age specific incidence rates of myocardial infarction and angina in women with systemic lupus erythematosus: Comparison with the Framingham Study. Am J Epidemiol 1997;145:408-5.
5. Petri M, Perez-Gutthann S, Spence D, Hochberg MC. Risk factors for coronary artery disease in patients with systemic lupus erythematosus. Am J Med 1992;93:513-9.
6. Urowitz MB, Gladman D, Ibañez, et al. for the Systemic Lupus International Collaborating Clinics. Atherosclerotic Vascular Events in a Multinational Inception Cohort of Systemic Lupus Erythematosus (SLE). Arthritis Care & Research 2010;62:881-7.
7. Goldberg RJ, Urowitz MB, Ibañez, Nikpour M, Gladman DD. Risk factors for development of coronary artery disease in women with systemic lupus erythematosus. J Rheumatol. 2009; 11:2454-61.
8. Tselios K, Gladman DD, Su J, Urowitz MB. Evolution over time of risk factors for atherosclerotic cardiovascular events in systemic lupus erythematosus: A long-term prospective study. J Rheumatol 2017;44:1841-9.
9. Nikpour M, Ibañez D, Gladman DD, Urowitz MB. Variability and Correlates of High Sensitivity C-reactive Protein in Systemic Lupus Erythematosus. Lupus 2009;18:966-73.
10. Nikpour M, Gladman DD, Ibañez D, Harvey PJ, Urowitz MB. Variability Over Time and Correlates of Cholesterol and Blood Pressure in Systemic Lupus Erythematosus: A Longitudinal Cohort Study. Arthritis Res Ther 2010;12:R125.

11. Keeling S, Alabdurubalnabi Z, Avina-Zubieta A, et al. Canadian Rheumatology Association (CRA) recommendations for the assessment and monitoring of systemic lupus erythematosus in Canada. J Rheumatol 2018;45:1426-39.
12. Bruce IN, Burns RJ, Gladman DD, Urowitz MB. Single photon emission computed tomography(SPECT) dual isotope myocardial perfusion imaging (DIMPI) in women with SLE. I. Prevalence and distribution of abnormalities. J Rheumatol 2000;27:2372-2377.
13. Nikpour M, Urowitz MB, Ibanez D, Gladman DD. Relationship between cardiac symptoms, myocardial perfusion defects and coronary angiography findings in systemic lupus erythematosus. Lupus 2011;30:299-304.
14. Ibañez D, Urowitz MB, Gladman DD. Adjusted mean systemic lupus erythematosus disease activity index -2K is a predictor of outcome in SLE. J Rheumatol 2005;32:824-827.
15. Henrota P, Foretb J, Barnetchea T, et al. Assessment of subclinical atherosclerosis in systemic lupus erythematosus: A systematic review and meta-analysis. Joint Bone Spine 2018;85:155–63.
16. Eder L, Gladman D, Ibañez D, Urowitz M. The correlation between carotid artery atherosclerosis and clinical ischemic heart disease in lupus patients. Lupus 2014;23:1142-8.
17. Lima DS, Sato EI, Lima VC, Miranda F Jr, Hatta FH. Brachial endothelial function is impaired in patients with systemic lupus erythematosus. J Rheumatol 2002;29:292-7.
18. Nikpour M, Gladman DD, Ibañez D, Bruce IN, Burns RJ, Urowitz MB. Myocardial perfusion imaging in assessing risk of coronary events in patients with systemic lupus erythematosus. J Rheumatol 2009;36:288-94.

19. Urowitz MB, Gladman DD. Contributions of observational cohort studies in systemic lupus erythematosus: the university of Toronto lupus clinic experience. Rheum Dis Clin North Am 2005; 31:211-21.

20. Gladman DD, Ibañez D, Urowitz MB. SLE Disease Activity Index 2000. J Rheumatol 2002;29:288-91.

21. Ibañez D, Urowitz MB, Gladman DD. Summarizing disease features over time: I. Adjusted mean SLEDAI derivation and application to an index of disease activity in lupus. J Rheumatol 2003; 30:1977-82.

22. Cole SR, Henan MA. Adjusted survival curves with inverse probability weights. Computer methods and Programs in Biomedicine 2004;75:45-9.

23. Urowitz MB, Gladman DD, Tom BDM, Ibanez D, Farewell VT. Changing pattern in mortality and disease outcomes for patients with systemic lupus erythematosus. J Rheumatol 2008;35:2152-8.

24. Thorburn CM, Ward MM. Hospitalizations for coronary artery disease among patients with systemic lupus erythematosus. Arthritis Rheum 2003;48:2519-23.

25. Smilowitz NR, Katz G, Buyon JP, Clancy RM, Berger JS. Systemic lupus erythematosus and the risk of perioperative major adverse cardiovascular events. J Thromb Thrombolysis 2018;45:13-7.

26. Asanuma Y, Oeser A, Shintani AK et al. Premature coronary-artery atherosclerosis in systemic lupus erythematosus. N Engl J Med 2003;349:2407-15.

27. Hardoon SL, Whincup PH, Lennon LT, Wannamethee SG, Capewell S, Morris RW. How much of the recent decline in the incidence of myocardial infarction in British men can be

explained by changes in cardiovascular risk factors? Evidence from a prospective population-based study. Circulation 2008;117:598-604.

28. Mannsverk J, Wilsgaard T, Mathiesen EB et al. Trends in Modifiable Risk Factors Are Associated With Declining Incidence of Hospitalized and Nonhospitalized Acute Coronary Heart Disease in a Population. Circulation 2016;133:74-81.
29. Voelker R. Framingham at 70: What We've Learned About Women and Heart Disease. JAMA 2018;319:2259-60.
30. Johnson S, Harvey P, Floras J, et al. Impaired brachial artery endothelium dependent flow mediated dilation in systemic lupus erythematosus: preliminary observations. Lupus 2004;13:590-3.
31. Esdaile JM, Abrahamowicz M, Grodzicky T,et al. Traditional Framingham risk factors fail to fully account for accelerated atherosclerosis in systemic lupus erythematosus. Arthritis Rheum 2001;44:2331-7.
32. Urowitz MB, Ibanez D, Su J, Gladman DD. Modified Framingham Risk Factor Score for Systemic Lupus Erythematosus. J Rheumatol 2016 43:875-9.
33. Tselios K, Sheane BJ, Gladman DD, Urowitz MB. Optimal Monitoring For Coronary Heart Disease Risk in Patients with Systemic Lupus Erythematosus: A Systematic Review. J Rheumatol 2016;43:54-65.

Table 1: PATIENT CHARACTERISTICS AT ENROLMENT			
Variable	Cohort 1 1975-1987	Cohort 2 1999-2011	P value
Number of patients	234	262	NA
Age at enrolment (years)	35.4±15.2	36.1±13.8	0.62
Sex Female	205 (87.6%)	232 (88.5%)	0.75
Ethnicity			< 0.001
Black	19 (8.1%)	52 (19.8%)	
Caucasian	199 (85.0%	135 (51.5%)	
Chinese	11 (4.7%)	31 (11.8%)	
Filipino	2 (0.9%)	16 (6.1%)	
Others	3 (1.3%)	28 (10.7%)	
Disease duration at enrolment months	2.9 ± 3.5	2.6 ± 3.0	0.31
SLEDAI-2K at enrolment	10.0 ± 9.0	9.8 ± 7.8	0.81
Nephritis	75 (32.1%)	71 (27.1%)	0.23
Vasculitis	33 (14.1%)	23 (8.8%)	0.06
Corticosteroids	114 (48.7%)	163 (62.2%)	0.003
Corticosteroid Dose (mg/day)	33.4 ± 28.7	30.6 ± 20.3	0.34
Antimalarials	44 (18.8%)	117 (44.7%)	< 0.001
Immunosuppressive	12 (5.1%)	61 (23.3%)	< 0.001
Hypertension	41 (17.5%)	70 (26.7%)	0.01
Hypercholesterolemia	70 (29.9%)	108 (41.2%)	0.009
Diabetes	2 (0.9%)	9 (3.4%)	0.05
Smoking	56 (24.1%)	37 (14.4%)	0.006
*SLEDAI-2K - Systemic Lupus Erythematosus Disease Activity Index 2000			

Table 2: INTERVENTION DURING THE FIRST 17 YEARS OF FOLLOW-UP

Intervention	Cohort 1 1975 – 1987	Cohort 2 1999 – 2011	P values
Number of patients	234	262	
Antihypertensive	29 (12.4%)	124 (47.3%)	0.0001
Lipid Lowering	4*(1.7%)	63 (24%)	<0.0001
Diabetes	11 (4.7%)	18 (6.9%)	0.30
Smoking	80 (34.2%)	54 (20.6%)	0.0007
Ever Treated with steroids	161 (68.8%)	214 (81.7%)	0.001
Average steroid dose (mg/d)	17.6 ± 14.6	12.3 ± 8.5	0.001
Ever treated with Antimalarials	114 (48.7%)	241 (92.0%)	0.001
Ever treated with Immunosuppressives	67 (28.6%)	178 (67.9%)	0.001

*earliest recorded use May 1986

Table 3: OUTCOMES			
Variable	Cohort 1 1975 – 1987	Cohort 2 1999 - 2011	P values
Number of patients	234	262	NA
Follow-up time (years)	6.6±4.8	8.3±4.7	< 0.001
Person-years of follow-up	1480.0	2288.0	
Outcomes			
Number of AVEs*	26 (11.1%)	10 (3.8%)	0.001
MI	7	3	
Angina	8	2	
CHF	8	1	
Bradyarrhythmia requiring pace maker	0	1	
Stroke	3	1	
TIA	0	3	
Years from enrolment to AVE	4.2±5.0	5.9±4.2	NS
Median age at first AVE	48.2	56.9	NS
Incidence of AVE per 100/patient years	1.8	0.44	< 0.001
Classic Risk Factors			
Percent years with Normal BP*	72.0%	86.7%	0.0001
Percent years with Normal Cholesterol	39.6%	72.3%	0.0001
Percent years with Normal glucose	84.8%	93.2%	0.0001
Percent of years Smoked	24.7%	11.3%	0.0001
Disease Related Factors			
AMS* within 5 years of enrolment	5.7±5.2	4.5±3.4	0.003
Alive at end of 17 years of follow-up	183 (78.2%)	247 (94.3%)	< 0.001
*AVEs – atherosclerotic vascular events, BP – blood pressure, AMS – adjusted mean SLEDAI-2K			

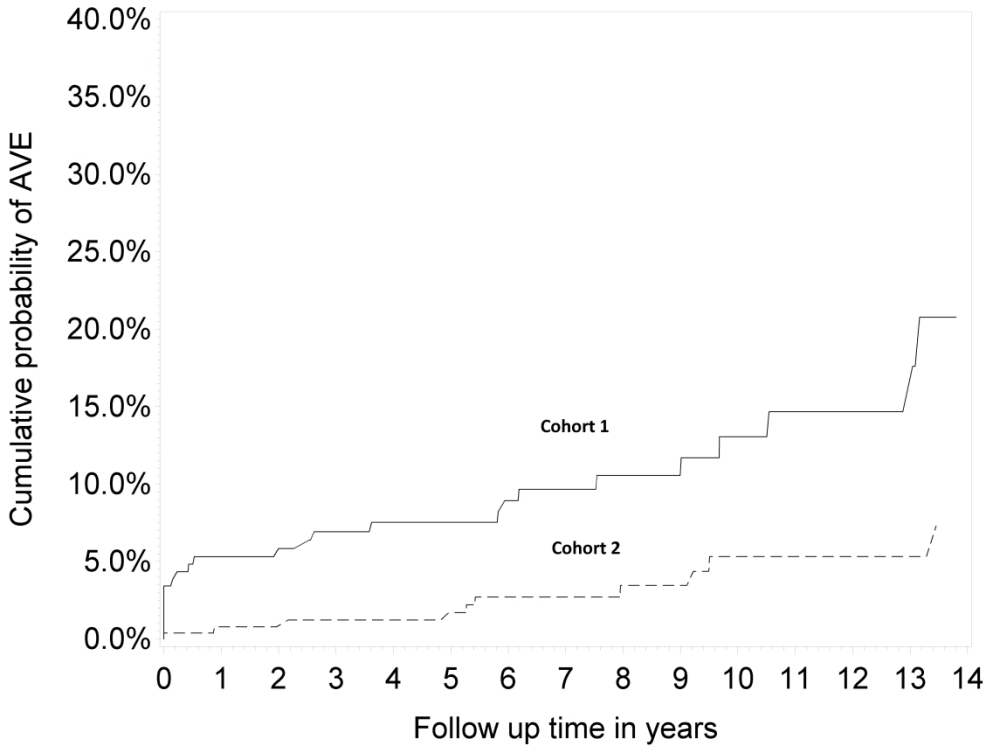

Figure 1: Kaplan-Meier cumulative probability of developing AVE in two cohorts, p = 0.0003 from Log-Rank test

1058x793mm (96 x 96 DPI)

Figure 2: The hazard ratio from IPW weighted model is 0.40 (95%CI: 0.23, 0.70) comparing later to early cohort, p = 0.0013

1270x940mm (96 x 96 DPI)