The incidence and risk factors for new onset atrial fibrillation in the PROSPER study*.

Peter W. Macfarlane[1], Heather Murray[2], Naveed Sattar[1], David Stott[1], Ian Ford[2], Brendan Buckley[3], J. Wouter Jukema[4], Rudi G.J. Westendorp[5], J. Shepherd[1].

1. Institute of Cardiovascular and Medical Sciences, University of Glasgow.
2. Robertson Centre for Biostatistics, University of Glasgow
3. College of Medicine and Health, University College Cork
4. Cardiology, Leiden University Medical Centre
5. Gerontology and Geriatrics, Leiden University Medical Centre

* The study was supported by a scientific grant from Bristol Myers Squibb.

Corresponding author:

Professor Peter W. Macfarlane
Electrocardiology
Level 1, QEB,
Royal Infirmary,
10 Alexandra Parade,
Glasgow G31 2ER

peter.w.macfarlane@clinmed.gla.ac.uk

Tel: (44) 141 552 8464
Fax: (44) 141 552 6114

ABSTRACT

Introduction

Atrial fibrillation/flutter (AF) is the most common arrhythmia in older people. It associates with reduced exercise capacity, increased risk of stroke, and mortality. We aimed to determine retrospectively whether pravastatin reduces the incidence of AF and whether any electrocardiographic measures or clinical conditions might be risk factors for its development.

Methods and Results

The PROspective Study of Pravastatin in the Elderly at Risk (PROSPER) was a randomised, double-blind controlled trial that recruited 5,804 individuals aged 70-82 years with a history of, or risk factors for, vascular disease. 2,891 were allocated to pravastatin and 2,913 to placebo; mean follow-up was 3.2 years. ECGs, which were recorded at baseline, annually thereafter and at run out, were processed by computer and reviewed manually.

264/2912 (9.1%) of the placebo group and 283/2888 (9.8%) of the pravastatin treated group developed AF [HR 1.08 (0.92,1.28), p=0.35)]. Multivariate analysis showed that PR and QTc intervals, age, left ventricular hypertrophy and ST-T abnormalities were related to development of AF after adjustment for many variables including alcohol consumption, which itself was univariately predictive of developing AF. Previous myocardial infarction on the ECG was not a risk factor. A history of vascular disease was strongly linked with developing AF but not diabetes and hypertension.

Conclusion

Pravastatin does not reduce the incidence of AF in older people at risk of vascular disease, at least in the short-medium term. Risk factors for AF include older age, prolongation of PR or QTc intervals, left ventricular hypertrophy and ST-T abnormalities on the ECG.

Key words: Atrial fibrillation, ECG, statins, risk factors

Introduction.

Atrial fibrillation / flutter (AF) is the most common cardiac arrhythmia and its prevalence varies from 0.1% in individuals under 55 years of age to 9% in individuals over 80 years of age (1). AF is well known to be a risk factor for stroke and indeed all cause mortality (2). In the recent QRISK2 study, atrial fibrillation conferred the highest risk of a future cardiovascular endpoint (3). QRISK is a cardiovascular disease risk calculator, based on a database of anonymised UK primary care patients. With an aging population, and a consequent increase in the absolute numbers of individuals having AF, any therapy that might prevent the development of AF would be potentially of significant benefit.

Very recently, it has been suggested that N-terminal pro-brain natriuretic peptide (NT-proBNP) is an excellent predictor of atrial fibrillation even after adjustment for other known risk factors (4). A different approach was adopted by Framingham Heart Study investigators who recently reported (5) on the development of a risk score for atrial fibrillation. This involved various constitutional factors, systolic blood pressure, clinically significant heart failure and PR interval among others.

If AF could be reliably predicted, the question arises as to what treatment might be started. In this connection, there is conflicting evidence on the effects of statin therapy. On the one hand, statin therapy has recently been reported as being of no value in preventing atrial fibrillation, e.g. in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) (6) while on the other hand, in selected situations, statins have been found to be beneficial in preventing AF, e.g. in patients with coronary artery disease [7] and after cardiac surgery (8). This may be related to one of the pleiotropic effects of statins, namely being an anti-inflammatory (9) and hence anti-arrhythmic agent (10). However, one recent meta analysis suggested that further trials are required to assess the effects of statins on atrial fibrillation (11).

The Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) aimed to determine whether treatment with pravastatin reduces the risk of cardiovascular and cerebrovascular events in elderly subjects with vascular disease or at high risk of developing vascular disease (12).

The study showed (13) that pravastatin reduced the incidence of the primary endpoint of coronary death, non fatal myocardial infarction and fatal or non fatal stroke [HR 0.85 (0.74-0.97) p=0.014]. These effects were mainly due to a reduced incidence of coronary heart disease death and non-fatal myocardial infarction, with no reduction seen in stroke risk.

In this further retrospective analysis of the PROSPER dataset, we aimed to determine whether pravastatin reduces the incidence of AF and to elucidate risk factors for the development of this arrhythmia. This study laid emphasis on electrocardiographic measures of risk but it also reviewed baseline data to determine if any clinical risk factors could be identified. .

Methods

The Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) recruited 5,504 individuals between the ages of 70-82 years with a history of risk factors or established vascular disease (13). New York Heart Association (NYHA) class III/IV heart failure was an exclusion criterion. 2,891 were allocated to pravastatin 40mg daily and 2,913 to placebo in a double-blind randomised controlled parallel group trial; mean follow-up was 3.2 years. The study cohort was recruited from the Netherlands, Scotland and Southern Ireland.

ECGs were recorded at baseline, annually thereafter and at run out in all participants in the study. It was a requirement for entry that individuals should not have AF or flutter. ECG recordings were made

using a Burdick Eclipse 850i electrocardiograph and digital data was transmitted from the various recording sites to the ECG Core Lab in Glasgow Royal Infirmary. All ECGs were interpreted using the same software (14) which provided an interpretation, produced Minnesota Codes (15) and also made numerous measurements including the QT interval. A corrected QT interval was also available and the first preference was to use the Hodges Formula (16) for QT correction, namely:-

$QTc = QT + 1.75 (\text{heart rate} - 60)$.

All ECG measurements used in the study were derived from the baseline ECGs in order to obtain data that could be assessed for predictive value. Information about AF was obtained from annual ECG measurements since all baseline ECGs exhibited sinus rhythm.

All the ECGs were reviewed so that if rhythm were to be incorrectly reported by the automated system, the corrected interpretation was inserted into the system and the relevant Minnesota Code corrected also. Incident AF was defined as any ECG after baseline showing atrial fibrillation or flutter. Only the first occurrence of the arrhythmia was counted in each individual. In a few cases, AF was first recorded as part of an adverse event. In such cases, the time of this event was used to derive duration for time to onset models.

The Minnesota Codes were used to categorise previous myocardial infarction into strongly likely (based on Code 1-1), probably present (codes 1-2) or possibly present (codes 1-3).

Lipoprotein profiles were measured at the Core Lab in the CDC Certified Biochemistry Core Lab in Glasgow Royal Infirmary.

Statistical analysis

Summary statistics are reported in the Tables as the mean (standard deviation [SD]) for continuous variables and number (%) for categorical variables. Positively skewed variables (triglycerides) were log transformed. Baseline characteristics and baseline ECG variables were compared between participants who did and did not develop AF during the study using the unpaired two-sample t-test for continuous variables and the chi-squared test for categorical variables. The effect of pravastatin on development of AF was investigated by the Kaplan-Meier method and statistical significance assessed by the log-rank test. Associations between baseline ECG characteristics and development of AF were examined using Cox proportional hazards models, adjusting for randomized treatment and baseline covariates (age, sex, country, diabetes, use of anti-hypertension medication, smoking, systolic and diastolic blood pressure, low density lipoprotein (LDL) and high density lipoprotein (HDL) cholesterol, triglycerides, body mass index, alcohol consumption, history of coronary disease, history of cerebrovascular disease, history of peripheral arterial disease and heart rate). Validity of the proportional hazards assumption was assessed by testing the significance of interaction terms between ECG variables and the logarithm of time as a time dependent covariate. Results are reported, where appropriate, as hazard ratios with 95% confidence intervals and corresponding p-value. For continuous ECG variables (such as heart rate), the stated hazard ratio (HR) represents an increase of approximately 1 SD and for categorical variables, such as definite left ventricular hypertrophy (LVH), a change from No to Yes. A p-value of <0.05 was considered statistically significant.

Results

A total of 547 (9.4%) subjects developed AF (521 persons) or atrial flutter (26 persons) during the course of the study. Four individuals appeared to have AF on entry and had to be excluded from the analysis. Figure 1 shows that pravastatin had no effect on the cumulative incidence of AF. 264/2912

(9.1%) of the placebo group and 283/2888 (9.8%) of the pravastatin treated group developed AF [HR 1.08 (0.92-1.28) p=0.35].

Table 1 compares the baseline characteristics of those who did and those did not develop AF during the course of the study. It can be seen that in those who developed AF, age was on average about 7 months older, total and LDL cholesterol was marginally though statistically significantly lower, subjects were more likely to be male and were more likely to have a history of any vascular disease compared to those who did not develop AF. Alcohol consumption was very significantly higher in those who developed AF. Diabetes, hypertension (implying an individual was on treatment) and previous stroke/transient ischemic attack (TIA) were not risk factors for the development of AF - nor was being a current smoker (p=0.057). Table 2 lists the baseline anti-hypertensive medications for the statin treated and the placebo groups, separately and together. Additional adjustments were made for treatment with an ACE inhibitor and for each other blood pressure lowering treatment with no difference in the results.

With respect to some specific ECG findings, Table 3 shows a similar comparison between the two groups. QRS duration, corrected and uncorrected QT interval, as well as PR interval were statistically significantly longer in the group that developed AF. Interestingly, the P wave duration was also significantly longer in this group but the mean difference between groups of 2 ms is of no clinical significance.

The association between baseline characteristics and the risk of AF is shown in Table 4. The risks are shown for individual measures using different models. The first adjusted for treatment allocation only, the second adjusted in addition for age, sex, country, diabetes, alcohol consumption etc while the third

adjusted for vascular disease and heart rate in addition. Table 4 shows that age, corrected QT interval and PR interval were all strongly associated with increased risk of developing AF.

Other electrocardiographic markers of previous myocardial infarction and LVH were also studied. Table 4 shows that, although each of the three categories of myocardial infarction was strongly associated with the development of AF using the unadjusted model, the link disappeared after adjustment for other factors, as previously described.

Minnesota codes were also used to definite, probable and possible LVH. Evidence of very high QRS voltage plus ST-T changes defined definite LVH, less high though abnormal QRS voltage plus ST-T changes defined probable LVH while very high voltage only defined possible LVH. In all cases, as shown in Table 3, there was a significant relationship between the presence of LVH and the risk of AF. This was particularly true for definite or probable LVH where there was over a twofold increase in risk of developing AF in subjects in these categories.

ST-T changes based on Minnesota Codes 4-1 to 4-3 and 5-1 to 5-3 were also assessed independently of QRS voltage. Marked changes, i.e. 5-1 or 5-2 as well as 4-1 or 4-2 conferred a significantly increased risk of AF of approximately 70% (see Table 3). Even what might be termed minor ST-T changes, namely the presence of minimal ST depression (4-3) and T wave flattening or inversion (5-3) conferred an increased risk of 29% though this was not statistically significant.

Discussion

This study has shown that the administration of pravastatin 40mg per diem had no effect ($p = 0.35$) on the prevention of AF in an elderly group of individuals aged over 70 years who were followed for a mean of 3.2 years. It might be suggested that the treatment period was not long enough to show any

benefit but Figure 1 demonstrates that at the end of 3 years, there was a very similar incidence of AF in the treated and untreated groups with no suggestion of a trend in favour of either group that might have continued to significance in a longer study. Although there have been differing outcomes in the use of statins to prevent AF, this study is one of the largest of its kind in an age group where the incidence of AF is relatively high. Indeed, the study again showed that age itself is a significant risk factor for AF despite the narrow age range of those in the study cohort.

Although pravastatin reduced the risk of coronary events over a 3.2 year period, the time-span may not have been sufficient for the downstream consequences of cardiac damage, such as atrial fibrillation, to become evident. Alternatively it could be that pravastatin genuinely does not give protection against new onset AF, which in many older patients is likely to be a multifactorial arrhythmia, not due to ischaemic heart disease alone (17).

It might be argued that a different statin might have produced a different result but the only way that such a hypothesis could be tested would be to have run a much larger, and perhaps longer, trial with participants randomized to different statins to determine if there was any difference in incident AF.

Approximately 9% of this age group developed AF in a three year period in an almost linear fashion which suggests that the annual incidence of AF is approximately 3% per annum in the over 70 age group. This emphasizes the treatment burden that will arise as the number of individuals in this age group increases in the coming years.

Results are based on a single 10 second ECG recording made at an annual trial review and all ECGs were carefully reviewed centrally in the ECG core lab at Glasgow Royal Infirmary to ensure consistency of interpretation. Paroxysmal AF may have been grossly under-diagnosed from an annual

ECG but the converse of the 10 sec recording being obtained at the time of a paroxysm is much more unlikely.

It was not unexpected that increased P wave duration might be linked to the development of AF as this has been noted previously particularly using the signal averaged ECG (18). It could be argued that the increased P duration is due to the increased time for atrial activation to occur in what might be an overstretched left atrium. However, the clinical utility of this finding is limited in the context of a very small difference of 2 ms between the mean P values in each group. The result might imply that if serial ECGs were to be recorded in individuals and P wave duration tracked, some trend in P duration might be noted but the accuracy of automated P wave duration is not high with acceptable errors being the order of 20 ms (19). Furthermore, in the multivariate analysis, the contribution of the P wave was not significant.

In contrast, increased PR interval and QTc interval were linked with the development of AF. The link with PR interval confirms what was recently noted in the Framingham study cohort (5) and also in a group of cross country skiers (20) but to the best of our knowledge, the association of increasing QT interval with the development of AF has not previously been reported. The respective mean differences of approximately 5ms in PR interval and 7ms in QTc interval between those who do and those who do not develop AF are again of little clinical value but the 27% and 21% increase in risk associated with an increased PR and QTc suggest that more notice should be taken of ECGs showing an abnormal PR interval and/or abnormal QTc in this age group. A prolonged QTc has for some time been associated with arrhythmogenesis and, for example, sudden death in an elderly population (21) but AF is not generally regarded as being linked with this phenomenon.

LVH with ST-T changes has previously been linked with an adverse prognosis. In the Framingham study, ECG LVH carried a risk as great as previous myocardial infarction (22). An increased P terminal force (amplitude x duration of the negative component of P in V1) is in itself used as a criterion for LVH (23). Thus, LVH is linked with left atrial enlargement and hence a propensity to develop AF.

Marked ST-T changes were also linked to AF but in turn they can be linked to LVH and/or ischemic heart disease both of which would be regarded as precursors of AF.

It is important to note that those ECG measures regarded as risk factors for AF emerged after allowance for other factors that were also strongly implicated in the development of AF, namely age, alcohol consumption, and a history of vascular disease.

It might be conjectured that those with definite LVH, prolonged PR interval > 0.20ms and QTc > 0.46ms would be at high risk of developing AF but there were only two such individuals who met these criteria so there was no possibility of testing this simple model in a meaningful way.

There were some limitations to the study. First of all, the relatively short mean duration of 3.2 years follow up may have mitigated against pravastatin having an effect on the development of AF. It might also be that in this age group, structural changes in the myocardium are the main risk factor which cannot be influenced by any drug therapy.

Because of the design structure of the trial, the recruitment of more subjects with hypertension, history of smoking and diabetes, (and more women) into the low risk primary prevention group could have

potentially been misleading in terms of the significance or non-significance of univariate comparisons, and hence they were corrected for in the analysis.

In conclusion, this study has shown that the use of pravastatin in an elderly population at risk of developing AF did not have any effect on the incidence of this arrhythmia, at least in the short term.

Conflict of Interest

None declared.

REFERENCES

1. Go AS, Hylek EM, Phillips KA, Chang YC, Henault LE, Selby JV, Singer DE. Prevalence of Diagnosed Atrial Fibrillation in Adults. National Implications for Rhythm Management and Stroke Prevention: the AnTicoagulation and Risk Factors In Atrial Fibrillation (ATRIA) Study. J Amer Med Assoc 2001;**285**:2370-5.

2. Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB; Levy D. Impact of atrial fibrillation on the risk of death. The Framingham Heart Study. Circulation 1998;**98**:946-952.

3. Hippisley-Cox J, Coupland C, Vinogradova Y, Robson J, Sheikh A, Brindle, P. Predicting cardiovascular risk in England and Wales: prospective derivation and validation of QRISK2. BMJ 2008;336:1475-82

4 Patton KK, Ellinor PT, Heckbert SR, Christenson RH, DeFilippi C, Gottdiener JS, et al. N-terminal pro-B-type natriuretic peptide is a major predictor for the development of atrial fibrillation. Circulation 2009;120:1768-74

5. Schnabel RB, Sullivan LM, Levy D, Pencina MJ, Massaro JM, D'Agostino RB Sr, et al. Development of a risk score for atrial fibrillation (Framingham Heart Study): a community-based cohort study. Lancet 2009:373:739-45

6. Haywood LJ, Ford CE, Crow RS, Davis BR, Massie BM, Einhorn PT, et al. ALLHAT Collaborative Research Group. Atrial fibrillation at baseline and during follow up in ALLHAT (Antihypertensive and lipid lowering treatment to prevent heart attack trial). JACC 2009;54:2023-31

7. Young-Xu Y, Jabbour S, Goldberg R, Blatt CM, Graboys T, Bilchik B, et al. Usefulness of statin drugs in protecting against atrial fibrillation in patients with coronary artery disease. Am J Cardiol 2003;92:1379-1383

8. Liakopoulos OJ, Choi YH, Kuhn EW, Wittwer T, Borys M, Madershahian N, et al. Statins for prevention of atrial fibrillation after cardiac surgery: a systematic literature review. J Thorac Cardiovasc Surg 2009;138:678-86

9. Palaniswamy C, Selvaraj DR, Selvaraj T, Sukhija R. Mechanisms underlying pleiotropic effecrs of statins. Am J Therapeutics 2010;17:75-78

10. Thambidorai SK, Anand K, Mooss AN, Esterbrooks DJ, Mohiuddin SM. Hydroxymethylglutaryl Coenzyme A Inhibitors (Statins) and Arrhythmias: Systematic Review and Meta-Analysis. The Internet Journal of Cardiology. 2009;6(2).

11. Liu T, Korantzopolous P, li G, Li J. Statin use and development of atrial fibrillation: a systematic review and meta analysis of randomized clinical trials and observational studies. Int J Cardiology 2008;126:160-70

12. Shepherd J, Blauw GJ, Murphy MB, Cobbe SM, Bollen EL, Buckley BM, et al. The Design of a Prospective Study of Pravastatin in the Elderly at risk (PROSPER). Am J. Cardiol, 1999; **84**: 1192-1197.

13. Shepherd J, Blauw GJ, Murphy MB, Bollen EL, Buckley BM, Cobbe SM, et al on behalf of the PROSPER study group. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. Lancet, 2002; **360**: 1623-1630.

14. Macfarlane, P.W, Devine, B, Clark, E. The University of Glasgow (Uni-G) ECG Analysis Program. *Computers in Cardiology*, 2005; **32**: 451-4.

15. Macfarlane, P.W. Latif, S. Automated serial ECG comparison based on the Minnesota code. *J Electrocardiol*. 1996; **29**(Suppl): 29-34.

16. Luo, S. Michler, K. Johnston, P. Macfarlane, P.W. A comparison of Commonly used QT Correction formulae: The effect of Heart rate on the QTc of Normal ECGs. *J. Electrocardiol*. 2004; **37**(Suppl): 81-90.

17. Benjamin EJ, Chen PS, Bild DE, Mascette AM, Albert CM, Alonso A et al. Prevention of atrial fibrillation: report from a National Heart, Lung, and Blood Institute workshop. Circulation 2009; **119**:606-618.

18. Dorbala S, Steinberg JS. Signal averaging of the P wave. In: W. Zareba, P. Maison-Blanche, E.H. Locati (eds). Non invasive Electrocardiology in Clinical Practice. Futura, Armonk NY. 2001 pp31-47

19. International Standard IEC 60601-2-51. Medical electrical equipment – Part 2-51: Particular requirements for safety, including essential performance, of recording and analyzing single channel and multichannel electrocardiographs. International Electrotechnical Commission, Geneva 2003.

20. Grimso J, Grundvold I, MaehlumS, Arnesen H.
High prevalence of atrial fibrillation in long term endurance cross-country skiers: echocardiographic findings and possible predictors – a 28-30 years follow-up study.
Eur J Cardiovasc Prev Rehabilitation 2010;17:100-5

21. Straus SM, Kors JA, De Bruin ML, van der Hooft CS, Hofman A, Heeringa J, et al. Prolonged QTc interval and risk of sudden cardiac death in a population of older adults. *J Am Coll Cardiol* 2006; **47**: 362-7.

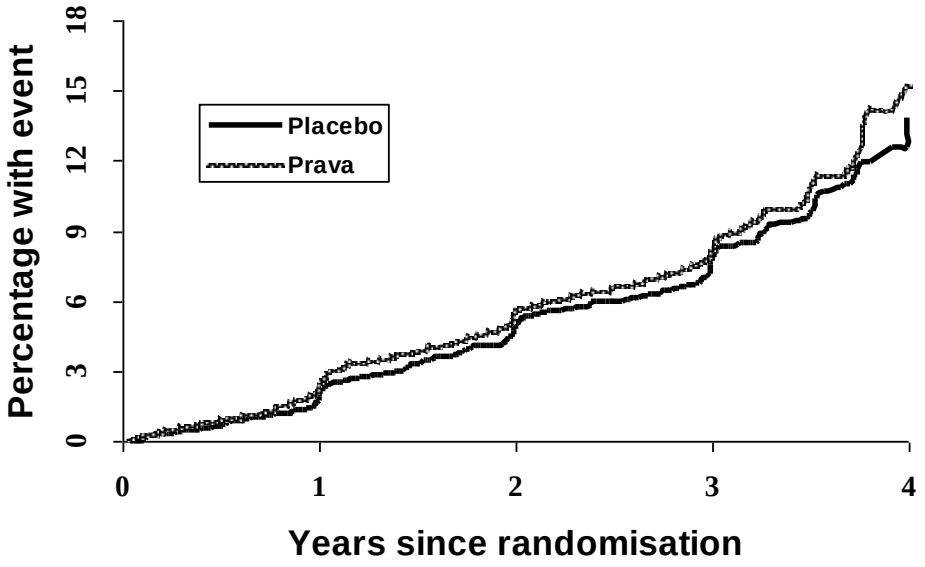
22. Kannel WB. Left ventricular hypertrophy as a risk factor in arterial hypertension. Eur Heart J 1992;13 (Supplement D):82-8

23. Romhilt DW, Estes EH Jr. A point score system for the ECG diagnosis of left ventricular hypertrophy. Am Heart J 1968;75:752-8

LEGEND

Figure 1. Cumulative incidence of Atrial Fibrillation in subjects allocated to Pravastatin compared to placebo. There was no significant difference between treatment groups [log-rank p = 0.35, HR 1.08 (0.92-1.28)].

Figure 1.



Numbers at risk:

Placebo	2912	2790	2623	2199	45
Pravastatin	2888	2762	2583	2190	33

Table

Table 1. Comparison of baseline characteristics in PROSPER subjects who developed atrial fibrillation/flutter (AF) versus those who did not develop this arrhythmia.

	AF (n=547)	No AF (n=5253)	P-value
Continuous variables, mean(SD)			
Age (years)	75.9 (3.5)	75.3 (3.3)	<0.0001
Body mass index (kg/m^2)	27.2 (4.3)	26.8 (4.2)	0.038
Systolic blood pressure (mmHg)	155.8 (22.1)	154.5 (21.8)	0.19
Diastolic blood pressure (mmHg)	83.5 (12.0)	83.8 (11.4)	0.52
Total cholesterol (mmol/l)	5.56 (0.89)	5.69 (0.91)	0.0014
HDL cholesterol (mmol/l)	1.27 (0.35)	1.28 (0.35)	0.42
LDL cholesterol (mmol/l)	3.69 (0.82)	3.80 (0.80)	0.0015
Triglycerides (mmol/l)*	1.39 (1.56)	1.41 (1.51)	0.41
Alcohol units per week	6.90 (12.2)	5.04 (8.93)	<0.0001
Categorical variables, n (%)			
Male	318 (58.1)	2483 (47.3)	<0.0001
Smoking			0.090
Never	184 (33.6)	1783 (33.9)	
Current smoker	128 (23.4)	1429 (27.2)	
Ex smoker	235 (43.0)	2041 (38.9)	
Country			0.090
Scotland	228 (41.7)	2291 (43.6)	
Ireland	228 (41.7)	1953 (37.2)	
Netherlands	91 (16.6)	1009 (19.2)	
History of:			
Diabetes	63 (11.5)	559 (10.6)	0.53
Hypertension	354 (64.7)	3234 (61.6)	0.15
Coronary disease	204 (37.3)	1641 (31.2)	0.0038
Peripheral arterial disease	76 (13.9)	573 (10.9)	0.035
Stroke or TIA	68 (12.4)	580 (11.0)	0.33
Any vascular disease	286 (52.3)	261 (47.7)	<0.0001

TIA: transient ischemic attack.
All available data used.
P-values for continuous variables are from two-sample t-test and for categorical variables from chi-squared test.
* Values are geometric means (SD) calculated from the log-transformed distribution.

Table 2. Baseline anti-hypertensive medications for the PROSPER cohort split by treatment allocation, and for the group as a whole.

Medication at baseline	**Placebo (n=2912)**	**Pravastatin (n=2888)**	**Both groups (n=5800)**
ACE-inhibitors	469 (16.1%)	480 (16.6%)	949 (16.4%)
Diuretic	1183 (40.6%)	1171 (40.5%)	2354 (40.6%)
All receptor antagonists	48 (1.6%)	68 (2.4%)	116 (2.0%)
Beta Blocker	764 (26.2%)	737 (25.5%)	1501 (25.9%)
Calcium Channel blocker	704 (24.2%)	754 (26.1%)	1458 (25.1%)
Other antihypertensive	122 (4.2%)	115 (4.0%)	237 (4.1%)

Table 3. Comparison of baseline ECG measurements in PROSPER subjects who developed atrial fibrillation/flutter (AF) versus those who did not develop this arrhythmia.

		AF		No AF	P-value
Continuous variables (N, mean (SD))					
Heart rate (bpm)	540	65.8 (12.0)	5140	66.4 (11.6)	0.29
QRS duration (ms)	540	97.5 (19.6)	5139	94.5 (19.0)	0.0005
QT interval (ms)	540	420.2 (39.8)	5140	411.9 (37.1)	<0.0001
QTc interval (ms)	540	430.4 (28.8)	5140	423.0 (27.1)	<0.0001
PR interval (ms)	513	169.4 (30.7)	5038	164.2 (27.7)	<0.0001
P wave duration (ms)	507	111.2 (19.5)	4956	109.6 (16.0)	0.028
Continuous variables (N, n (%))					
Previous Myocardial Infarction					
Strong evidence (Minnesota code 1-1-x)	540	49 (9.1)	5140	330 (6.4)	0.019
Less Strong evidence (Minnesota codes 1-1-x or 1-2-x)	540	76 (14.1)	5140	526 (10.2)	0.0058
Weak evidence (Minnesota codes 1-1-x or 1-2-x or 1-3-x)	540	123 (22.8)	5140	942 (18.3)	0.012
Left ventricular hypertrophy (LVH)					
(a) Definite LVH	540	22 (4.1)	5140	95 (1.8)	0.0005
(b) Probable LVH	540	27 (5.0)	5140	111 (2.2)	<0.0001
(c) Possible LVH	540	87 (16.1)	5140	622 (12.1)	0.0073
Non Specific ST changes					
Minnesota code 5-1	540	1 (0.2)	5140	28 (0.5)	0.52*
Minnesota code 5-1 plus (any code 4)	540	1 (0.2)	5140	28 (0.5)	0.52*
Minnesota code 5-1 or 5-2	540	91 (16.8)	5140	531 (10.3)	<0.0001
Minnesota code (5-1 or 5-2) plus (any code 4)	540	81 (15.0)	5140	475 (9.2)	<0.0001
Minnesota code 4-1 or 4-2	540	70 (13.0)	5140	381 (7.4)	<0.0001
Minnesota code 4-3 plus code 5-3	540	56 (10.4)	5140	418 (8.1)	0.074

P-values for continuous variables are from two-sample t-test and for categorical variables from chi-squared test.
* Fisher Exact Test.
(a) Minnesota Codes 3-1 plus (4-1 or 4-2 lateral) plus (5-1 or 5-2 lateral).
(b) (a) or Minnesota Codes 3-3 plus (4-1 or 4-2 lateral) plus (5-1 or 5-2 lateral).
(c) (a) or (b) or Minnesota Codes 3-1.

Table 4. Association between baseline age, heart rate and ECG characteristics, and risk of incident atrial fibrillation/flutter

	Model 1*		Model 2†		Model 3‡	
	Hazard Ratio (95% CI)	P-value	Hazard Ratio (95% CI)	P-value	Hazard Ratio (95% CI)	P-value
Continuous variables						
Age (5 years)	1.35 (1.20, 1.53)	<0.0001	1.38 (1.22, 1.57)	<0.0001	1.38 (1.21, 1.57)	<0.0001
Heart rate (10 bpm)	0.98 (0.91, 1.05)	0.98	1.00 (0.92, 1.07)	0.90	0.99 (0.92, 1.07)	0.82
QRS duration (20ms)	1.17 (1.08,1.27)	<0.0001	1.05(0.97, 1.15)	0.23	1.07 (0.98, 1.16)	0.14
QT interval (40ms)	1.24 (1.14, 1.35)	<0.0001	1.20 (1.10, 1.31)	<0.0001	1.41 (1.25, 1.58)	<0.0001
QTc interval (30 ms)	1.31 (1.20, 1.42)	<0.0001	1.27 (1.16, 1.38)	<0.0001	1.21 (1.11, 1.32)	<0.0001
PR interval (30ms)	1.19 (1.09, 1.30),	<0.0001	1.11 (1.01, 1.21)	0.027	1.29 (1.18, 1.41)	<0.0001
P wave duration (20ms)	1.14 (1.02, 1.27)	0.022	1.07 (0.96, 1.19)	0.26	1.08 (0.96, 1.20)	0.20
Categorical variables						
Previous MI						
Strong evidence (Minnesota code 1-1-x)	1.51 (1.12, 2.02)	0.0061	1.12 (0.82, 1.52)	0.49	1.22 (0.90, 1.65)	0.19
Less Strong evidence (Minnesota codes 1-1-x or 1-2-x)	1.46 (1.15, 1.86)	0.0021	1.13 (0.87, 1.46)	0.37	1.23 (0.58, 1.58)	0.11
Weak evidence (Minnesota codes 1-1-x or 1-2-x or 1-3-x)	1.33 (1.09, 1.63)	0.0055	1.09 (0.88, 1.35)	0.43	1.17 (0.95, 1.44)	0.14
LVH						
(a) Definite LVH	2.20 (1.44, 3.37)	0.0003	2.05 (1.33, 3.15)	0.0011	2.13 (1.38, 3.28)	0.0006
(b) Probable LVH	2.33 (1.58, 3.44)	<0.0001	2.14 (1.45, 3.17)	0.0001	2.21 (1.49, 3.28)	<0.0001
(c) Possible LVH	1.35 (1.08, 1.70)	0.010	1.29 (1.02, 1.63)	0.033	1.30 (1.03, 1.64)	0.028
Non Specific ST changes						
Minnesota code 5-1	0.34 (0.05, 2.43)	0.28	0.40 (0.06, 2.87)	0.37	0.39 (0.05, 2.76)	0.34
Minnesota code 5-1 plus (any code 4)	0.34 (0.05, 2.43)	0.28	0.40 (0.06, 2.87)	0.37	0.39 (0.05, 2.76)	0.34
Minnesota code 5-1 or 5-2	1.76 (1.41, 2.21)	<0.0001	1.62 (1.28, 2.04)	<0.0001	1.69 (1.34, 2.13)	<0.0001
Minnesota code (5-1 or 5-2) plus (any code 4)	1.72 (1.36, 2.18)	<0.0001	1.58 (1.24, 2.00)	0.0002	1.64 (1.29, 2.09)	0.0001
Minnesota code 4-1 or 4-2	1.85 (1.44, 2.38)	<0.0001	1.68 (1.30, 2.16)	<0.0001	1.70 (1.32, 2.20)	<0.0001
Minnesota code 4-3 plus code 5-3	1.34 (1.01, 1.76)	0.040	1.33 (1.00, 1.76)	0.047	1.35 (1.02, 1.78)	0.037

Hazard ratios and confidence intervals are for increases of units specified in brackets for continuous measures, i.e. for age increase of 5 years.

*Adjusted for treatment allocation only.

†Adjusted for treatment allocation, age, sex, country, diabetes, use of anti-hypertension medication, smoking, systolic and diastolic blood pressure, LDL and HDL cholesterol, triglycerides, body mass index and alcohol consumption.

‡ In addition adjusted for history of coronary disease, history of cerebrovascular disease, history of peripheral arterial disease and heart rate.

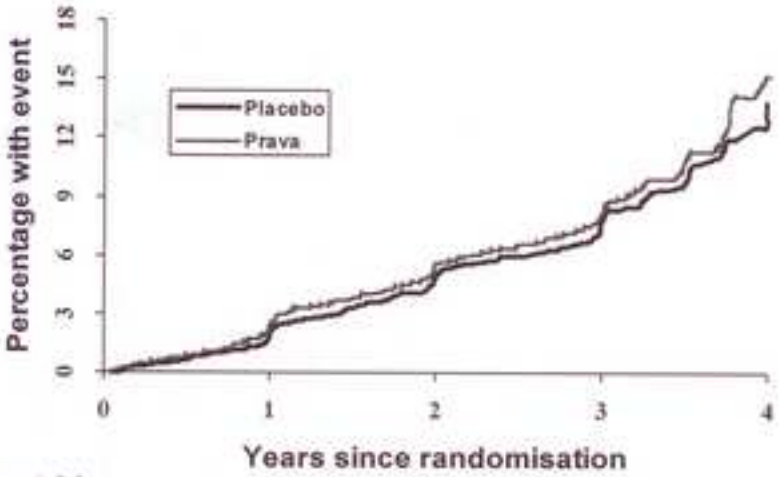
(a) Minnesota Codes 3-1 plus (4-1 or 4-2 lateral) plus (5-1 or 5-2 lateral).

(b) (a) or Minnesota Codes 3-3 plus (4-1 or 4-2 lateral) plus (5-1 or 5-2 lateral).

(c) (a) or (b) or Minnesota Codes 3-1.

Figure

Click here to download high resolution image



Numbers at risk:					
Placebo	2912	2790	2623	2199	45
Pravastatin	2888	2762	2583	2190	33

Letter

University of Glasgow

Charity number SC004401

Peter W. Macfarlane, DSc, FRCP (Glasg) FESC FRSE
Emeritus Professor

5th January, 2011

Professor John Camm,
Editor,
Europace.

Dear John,

EUPC-D-10-00526

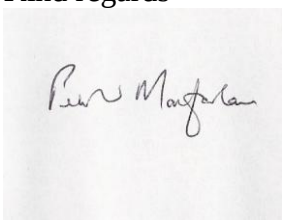
Happy New Year!

Many thanks f or dealing with the revised version of the AF in PROSPER paper so quickly. Scotland partially returned to work this morning and I therefore checked with Ian Ford who is of course very happy to include the additional sentence as requested. Indeed, he had already crafted this sentence in responding to the first set of referees' comments.

The system is not asking me for an abstract which should have been retained unchanged in any event. I hope this is not a problem.

I hope the paper can now be accepted and I look forward to seeing it published in due course.

Kind regards



Peter Macfarlane

Institute of Cardiovascular and Medical Sciences
Electrocardiology Section, Level 1, QEB
Royal Infirmary, 10 Alexandra Parade, Glasgow. G31 2ER.
Office Telephone: 0141-211-5082 *Direct Line*: 0141-211-4724
Private fax: 0141-552-6114 *E-mail*: peter.macfarlane@glasgow.ac.uk