Associations of Hemostatic Variables with Cardiovascular Disease and Total Mortality: The Glasgow MONICA Study

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Introduction

Plasma levels of some hemostatic factors and activation markers have been associated with the risk of arterial cardiovascular diseases (CVDs): coronary heart disease (CHD), stroke, and peripheral arterial disease (PAD).1,2 Fibrinogen is associated with risks of CHD, stroke, and total mortality3 and may add to risk prediction scores for CVD risk.4,5 A meta-analysis has established significant, but
weaker, associations of plasma levels of von Willebrand factor (VWF), tissue plasminogen activator (t-PA) antigen, and the hemostatic activation marker fibrin-D-dimer with the risk of CHD. There is increasing evidence that these three markers are also associated with risks of stroke and PAD.

For other hemostatic factors, inhibitors, and activation markers, there are insufficient data to assess with confidence their associations with CVD or mortality. From the prospective Glasgow MONICA (Monitoring of Trends and Determinants of Cardiovascular Disease) study, we now report the associations with incident CVD (CHD and stroke), and with total mortality, of plasma levels of coagulation factors VII, VIII, and IX; coagulation activation markers prothrombin fragment 1 + 2 (F1 + 2), thrombin–antithrombin (TAT) complexes, and D-dimer; coagulation inhibitors antithrombin and protein C and protein S; activated partial thromboplastin time (aPTT), activated protein C (APC) resistance, and its common genetic determinant (the FV:R506Q mutation); and the fibrinolytic variables t-PA antigen and plasminogen activator inhibitor type 1 (PAI-1) activity.

Methods

Study Participants
The Glasgow MONICA study recruited random population samples of men and women aged 25 to 64 years in four phases: 1984–1987 (as part of the Scottish Heart Health Study); 1989; 1992 (aged 25–74 years); and 1995. Data were subsequently combined to form the Scottish Heart Health Extended Cohort Study (SHHEC), from which a car.

Results

Follow-up and End Point Definition
Individuals who gave written permission were followed up for cause-specific mortality through linkage with two national systems: death registrations and the record linkage database. The latter was also used to follow up, and trace back, hospitalizations. Records were obtained from 1981 to 2009. CVD end points were: deaths attributed to a cardiovascular cause (International Classification of Disease [ICD] 9 codes 390–459, ICD 10 codes 100–199); any hospital discharge diagnosis postrecruitment of CHD (ICD 9 codes 410–414, ICD 10 codes 120–125) or cerebrovascular disease (ICD 9 codes 430–438, ICD 10 G45, 160–169); or surgical codes for CABG or PTCA.

Hemostatic Variables
Blood was anticoagulated with 0.11 mol/L trisodium citrate (9:1 v/v) and centrifuged, and aliquots were stored at –80°C. Four hemostatic variables other than fibrinogen were studied in the 1989 survey:11 VWF was assayed using an in-house enzyme-linked immunoassay (ELISA) employing rabbit anti-human polyclonal antibodies, obtained from DAKO plc, High Wycombe, United Kingdom. t-PA antigen was measured with a commercial ELISA (Biopool AB, Umea, Sweden). PAI-1 activity was measured with a commercial kit (Kabi, Sweden). D-dimer was assayed by a commercial ELISA (Dimentest; Agen Biomedical, Parsippany, New Jersey, United States). Significant baseline correlations with demographic and cardiovascular risk factor variables on multivariable analyses for these variables were age and triglycerides.11

Ten other hemostatic variables were studied in the 1992 survey: coagulation factors VII, VIII, and IX, antithrombin and protein C and protein S activities, F1 + 2, TAT, aPTT, APC resistance, and the FV:R506Q mutation. Their assays, distributions, and correlations with baseline demographic and cardiovascular risk factor variables have been described.12–14

Statistical Methods
Data from the 1989 and 1992 MONICA cohorts were analyzed as two separate cohorts, reflecting the fact that different hemostatic variables were measured in the two baseline surveys. Cox proportional hazards models were used to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) for CVD, and total mortality, for each hemostatic variable. We predefined two models: model 1 was adjusted for age and sex only; model 2 was adjusted for the CVD risk factors also in the ASSIGN score: systolic blood pressure, serum total and high-density lipoprotein cholesterol, cigarettes smoked per day, diabetes status, family history of CHD, and the Scottish Index of Multiple Deprivation (SIMD) score. Analyses were conducted for a 1 standard deviation (SD) increase in level of each hemostatic variable; and for the highest third compared with the lowest third of its distribution. All statistical analyses were performed using R, version 2.15.3 (R Foundation for Statistical Computing, Vienna, Austria).

Results

1989 Survey: PAI-1, VWF, t-PA, D-dimer
Table 1 shows the baseline characteristics of participants in the second phase of the Glasgow MONICA study in 1989: baseline levels of PAI-1, VWF, D-dimer, and t-PA; and outcomes. During a median (interquartile interval) of 20.6 (20.5–20.8) years, 181 CVD events and 173 deaths occurred. Of 706 participants, citrated plasma aliquots were available, after routine measurement of plasma
fibrinogen, from 523 participants for assay of PAI-1. There-
after, as laboratory assays were developed sequentially for
VWF, D-dimer, and t-PA antigens, residual plasma aliquots
were sufficient for assay in 405, 384, and 382 participants,
respectively.

Table 2 shows the associations of these hemostatic
variables with the study outcomes, both as a 1 SD increase
in levels and as ratio of top third to bottom third of levels. PAI-1
and VWF showed no association with CVD or mortality after
full adjustment for ASSIGN variables. D-dimer and t-PA
showed associations with CVD and mortality after full adjust-
ment—HRs, top third versus bottom third: 2.34 (95% CI, 1.26–
4.35) and 2.81 (95% CI, 1.43–5.54); and per 1 SD increase: 1.16
(95% CI, 0.99–1.36) and 1.63 (95% CI, 1.35–1.96).

Table 1 Baseline summary statistics: 1989 MONICA survey

| Variable                                           | n      | Variable                                           | n  |
|----------------------------------------------------|--------|----------------------------------------------------|----|
| **Cardiovascular risk factors**                     |        |                                                    |    |
| Age (y), mean (SD)                                 | 706    | 48 (10)                                           |    |
| Male sex, %                                        | 353    | 50                                                |    |
| Systolic blood pressure (mm Hg), mean (SD)         | 706    | 132 (21)                                          |    |
| Total cholesterol (mmol/L), mean (SD)              | 706    | 5.9 (1.2)                                         |    |
| HDL cholesterol (mmol/L), mean (SD)                | 706    | 1.2 (0.3)                                         |    |
| Body mass index (kg/m²), mean (SD)                 | 705    | 26 (4)                                            |    |
| Current smokers, %                                 | 706    | 43                                                |    |
| Diabetes, %                                        | 706    | 3                                                 |    |
| Family history of CVD, %                           | 706    | 26                                                |    |
| SIMD, median (IQI), mean (SD)                      | 706    | 45 (24)                                           |    |
| **Hemostatic variables**                           |        |                                                    |    |
| PAI-1 activity (AU/mL), mean (SD)                  | 523    | 98.5 (46.5)                                        |    |
| VWF (IU/dL), median (IQI)                          | 405    | 91 (73–118)                                        |    |
| D-dimer (ng/mL), median (IQI)                      | 384    | 56 (37–78)                                        |    |
| t-PA antigen (ng/mL), median (IQI)                 | 382    | 3.9 (5.5–8.5)                                     |    |

Abbreviations: CVD, cardiovascular disease; HDL, high-density lipoprotein; IQI, interquartile interval; PAI-1, plasminogen activator inhibitor type 1; SD, standard deviation; t-PA, tissue plasminogen activator; VWF, von Willebrand factor.

Note: Decreasing number of available samples reflects decreasing availability of plasma aliquot.

Table 2 Associations with outcomes: 1989 MONICA survey

| Variable                                           | CVD                  | Total mortality               |
|----------------------------------------------------|----------------------|------------------------------|
|                                                    | Age and sex          | ASSIGN                       | Age and sex          | ASSIGN                       |
| HRs for a 1 SD increase in level                   |                      |                              |                      |
| PAI-1                                              | 1.18 (1.01–1.39)     | 1.07 (0.92–1.25)             | 1.12 (0.95–1.32)     | 1.06 (0.90–1.25)             |
| VWF                                                | 1.02 (0.85–1.23)     | 0.99 (0.83–1.18)             | 1.05 (0.88–1.25)     | 1.01 (0.84–1.20)             |
| D-dimer                                            | 1.18 (1.01–1.37)     | 1.17 (1.00–1.38)             | 1.18 (1.02–1.38)     | 1.16 (0.99–1.36)             |
| t-PA                                               | 1.30 (1.06–1.58)     | 1.17 (0.94–1.46)             | 1.62 (1.36–1.92)     | 1.63 (1.35–1.96)             |
| HRs for top third vs bottom third of distribution   |                      |                              |                      |
| PAI-1                                              | 1.08 (0.72–1.62)     | 0.95 (0.63–1.44)             | 1.20 (0.78–1.86)     | 1.11 (0.71–1.74)             |
| VWF                                                | 1.01 (0.62–1.65)     | 1.03 (0.63–1.69)             | 1.10 (0.67–1.80)     | 1.01 (0.61–1.66)             |
| D-dimer                                            | 1.28 (0.77–2.13)     | 1.39 (0.83–2.32)             | 2.26 (1.23–4.15)     | 2.34 (1.26–4.35)             |
| t-PA                                               | 1.49 (0.84–2.63)     | 1.09 (0.61–1.97)             | 3.20 (1.64–6.24)     | 2.81 (1.43–5.54)             |

Abbreviations: CVD, cardiovascular disease; HRs, hazard ratios; PAI-1, plasminogen activator inhibitor type 1; SD, standard deviation; t-PA, tissue plasminogen activator; VWF, von Willebrand factor.

Note: HRs and 95% confidence intervals for CVD and total mortality. Analyzed first for a 1 SD increase in hemostatic factor level and then for top third versus bottom third of distribution of level. Adjusted for age and sex and then also for ASSIGN risk variables (systolic blood pressure, serum total and high-density lipoprotein cholesterol, cigarettes smoked per day, diabetes status, family history of coronary heart disease, and the Scottish Index of Multiple Deprivation [SIMD] score).
1992 Survey: Factors VII, VIII, and IX, Antithrombin, Protein C, Protein S, F1 + 2, TAT, aPTT, APC Resistance, FV:R506Q Mutation

- Table 3 shows the baseline characteristics of participants in the third phase of the Glasgow MONICA study in 1992; baseline levels of coagulation factors, inhibitors, and activation markers; and outcomes. During a median (interquartile interval) of 17.5 (15.4–17.8) years, 381 CVD events and 401 deaths occurred. Of 1,324 participants, citrated plasma aliquots were available, after routine measurement of plasma fibrinogen, from 1,088 to 1,123 participants for assay of factors VII, VIII, IX, antithrombin, and protein C activities. Thereafter, as laboratory assays were developed sequentially for protein S, F1 + 2, and TAT antigens, residual plasma aliquots were sufficient for assay in 843 to 896 participants and then for aPTT and APC ratio in 709 to 715 participants.

- Table 4 shows the associations of these hemostatic variables with the study outcomes, both as a 1 SD increase in levels and as ratio of top third to bottom third of levels. Age- and sex-adjusted HRs for CVD, top third versus bottom third, were significant only for factor VIII (1.30; 95% CI, 1.06–1.58) and factor IX (1.18; 95% CI, 1.01–1.39); these HRs were attenuated by further adjustment for CVD risk factors, respectively, to 1.17 (95% CI, 0.94–1.46) and 1.07 (95% CI, 0.92–1.25). In contrast, factor VIII was strongly associated with total mortality after full risk factor adjustment: HRs, top third versus bottom third, 1.63 (95% CI, 1.35–1.96) and per 1 SD increase 1.14 (95% CI, 1.03–1.28). No other hemostatic variable measured in this survey was significantly associated with either CVD or with total mortality.

### Table 3 Baseline summary statistics: 1992 MONICA survey

| Variable                        | n     |              |
|---------------------------------|-------|--------------|
| **Cardiovascular risk factors** |       |              |
| Age (y), mean (SD)              | 1,324 | 51 (13)      |
| Male sex, %                     | 1,324 | 47           |
| Systolic blood pressure (mm Hg), mean (SD) | 1,324 | 133 (24)    |
| Total cholesterol (mmol/L), mean (SD) | 1,324 | 6.1 (1.2)  |
| HDL cholesterol (mmol/L), mean (SD) | 1,324 | 1.5 (0.4)  |
| Body mass index (kg/m²), mean (SD) | 1,313 | 26 (5)     |
| Current smokers, %              | 1,324 | 42           |
| Diabetes, %                     | 1,324 | 1            |
| Family history of CVD, %        | 1,324 | 28           |
| SIMD, median (IQR), mean (SD)   | 1,324 | 46 (24)      |
| **Hemostatic variables**        |       |              |
| Factor VII (IU/dL), mean (SD)   | 1,115 | 109.9 (24.3) |
| Factor VIII (IU/dL), mean (SD)  | 1,121 | 146.3 (50.0) |
| Factor IX (IU/dL), mean (SD)    | 1,113 | 131.4 (33.8) |
| Antithrombin (IU/dL), mean (SD) | 1,088 | 100.2 (12.9) |
| Protein C (IU/dL), mean (SD)    | 1,123 | 108.6 (31.9) |
| Protein S (%pool), mean (SD)    | 896   | 130.7 (29.4) |
| F1 + 2 (ng/mL), median (IQR)    | 887   | 2.12 (1.53–2.95) |
| TAT (ng/mL), median (IQR)       | 843   | 4.09 (2.73–7.36) |
| aPTT (s), mean (SD)             | 709   | 31.1 (4.3)   |
| APC ratio, mean (SD)            | 715   | 2.86 (0.54)  |
| Heterozygous FV:R506Q (%)       | 1293  | 2.5          |

Abbreviations: APC, activated protein C; aPTT, activated partial thromboplastin time; CVD, cardiovascular disease; F1 + 2, prothrombin fragment 1 + 2; HDL, high-density lipoprotein; IQR, interquartile interval; SD, standard deviation; TAT, thrombin–antithrombin.

Note: Decreasing number of available samples reflects decreasing availability of plasma aliquots.

### Discussion

In this study of the associations of plasma levels of 15 hemostatic variables with risks of CVD, and of total mortality, in two random population samples of men and women aged 30 to 74 years, age- and sex-adjusted HRs for CVD were significant for factor VIII, factor IX, D-dimer, and t-PA. Apart from D-dimer, these were attenuated by further adjustment for CVD risk factors. In contrast, factor VIII, D-dimer, and t-PA were strongly associated with total mortality after full risk factor adjustment.
Table 4  Associations with outcomes: 1992 MONICA survey

|                      | CVD |                  | Total mortality |                  |
|----------------------|-----|------------------|-----------------|------------------|
|                      | Adjustments |                  | Adjustments |                  |
|                      | Age and sex | ASSIGN score | Age and sex | ASSIGN score |
| HRs for a 1 SD increase in level (\(^\log\) transformed) |     |                  |                 |                 |
| Factor VII           | 1.12 (1.00–1.26) | 1.07 (0.95–1.21) | 1.09 (0.97–1.22) | 1.09 (0.97–1.23) |
| Factor VIII          | 1.10 (0.99–1.22) | 1.09 (0.97–1.22) | 1.13 (1.02–1.26) | 1.14 (1.03–1.28) |
| Factor IX            | 1.10 (0.98–1.22) | 1.02 (0.91–1.15) | 1.09 (0.98–1.21) | 1.06 (0.94–1.18) |
| Antithrombin         | 1.06 (0.95–1.18) | 1.10 (0.89–1.12) | 1.02 (0.92–1.14) | 1.00 (0.89–1.11) |
| Protein C            | 0.94 (0.84–1.05) | 0.92 (0.82–1.04) | 0.90 (0.81–1.01) | 0.91 (0.81–1.02) |
| Protein S            | 1.14 (1.00–1.30) | 1.06 (0.93–1.20) | 1.08 (0.95–1.23) | 1.03 (0.90–1.17) |
| F1 + 2\(^*\)         | 1.12 (0.99–1.27) | 1.09 (0.96–1.25) | 1.02 (0.90–1.15) | 1.02 (0.90–1.16) |
| TAT\(^*\)            | 1.04 (0.91–1.19) | 1.02 (0.89–1.17) | 0.96 (0.85–1.09) | 0.94 (0.82–1.07) |
| aPTT                 | 0.94 (0.81–1.09) | 0.92 (0.79–1.08) | 1.03 (0.90–1.18) | 1.03 (0.89–1.19) |
| APC ratio            | 0.97 (0.83–1.13) | 1.00 (0.86–1.16) | 0.98 (0.84–1.14) | 0.98 (0.84–1.14) |

| HRs for top third versus bottom third of distribution |     |                  |                 |                 |
| Factor VII           | 1.02 (0.85–1.23) | 0.99 (0.83–1.18) | 1.05 (0.88–1.25) | 1.01 (0.84–1.20) |
| Factor VIII          | 1.30 (1.06–1.58) | 1.17 (0.94–1.46) | 1.62 (1.36–1.92) | 1.63 (1.35–1.96) |
| Factor IX            | 1.18 (1.01–1.39) | 1.07 (0.92–1.25) | 1.12 (0.95–1.32) | 1.06 (0.90–1.25) |
| Antithrombin         | 1.25 (0.95–1.64) | 1.11 (0.84–1.47) | 1.19 (0.91–1.55) | 1.12 (0.85–1.48) |
| Protein C            | 0.84 (0.64–1.10) | 0.82 (0.62–1.08) | 0.82 (0.63–1.06) | 0.84 (0.64–1.10) |
| Protein S            | 1.18 (0.86–1.62) | 1.03 (0.75–1.41) | 1.17 (0.85–1.60) | 1.04 (0.75–1.43) |
| F1 + 2               | 1.37 (0.99–1.89) | 1.23 (0.89–1.71) | 1.15 (0.84–1.58) | 1.11 (0.81–1.52) |
| TAT                  | 0.96 (0.69–1.33) | 0.94 (0.68–1.31) | 0.86 (0.63–1.18) | 0.81 (0.59–1.12) |
| aPTT                 | 1.06 (0.74–1.52) | 0.98 (0.68–1.41) | 1.17 (0.82–1.66) | 1.16 (0.81–1.66) |
| APC ratio            | 0.94 (0.65–1.35) | 1.03 (0.70–1.49) | 0.95 (0.67–1.35) | 0.99 (0.69–1.42) |

Abbreviations: APC, activated protein C; aPTT, activated partial thromboplastin time; CVD, cardiovascular disease; F1 + 2, prothrombin fragment 1 + 2; HRs, hazard ratios; SD, standard deviation; TAT, thrombin–antithrombin.

Note: HRs and 95% confidence intervals for CVD and total mortality. Analyzed first for a 1 SD increase in hemostatic factor level and then for top third versus bottom third of distribution of level. Adjusted for age and sex and then also for ASSIGN risk variables (systolic blood pressure, serum total and high-density lipoprotein cholesterol, cigarettes smoked per day, diabetes status, family history of coronary heart disease, and the Scottish Index of Multiple Deprivation [SIMD] score). Log transformation was required for variable F1 + 2 and TAT, for calculation of HRs for a 1 SD increase in level (top half of Table 4).

Factor VII level was not associated with CVD or mortality in our study after risk factor adjustment. This is consistent with recent reviews of studies\(^2,15\) and with meta-analyses of functional mutations in the factor VII gene, which showed no associations with CHD.\(^{15,16}\)

The association of factor VIII level with CVD (HR, top to bottom third, 1.30; 95% CI, 1.06–1.58) was attenuated after risk factor adjustment. There is uncertainty in the literature on this association.\(^2,17–20\) We observed no significant association of its carrier protein, VWF, with CVD; a meta-analysis of the association of VWF level with CHD in 15 studies with 6,556 cases showed a significant association: HR per 1 SD, 1.16 (95% CI, 1.10–1.22).\(^6\) Plasma VWF, as its carrier protein, is correlated with plasma factor VIII.\(^17,18\)

Plasma factor VIII was associated with total mortality in our study, after risk factor adjustment (HR, 1.63; 95% CI, 1.35–1.96). This association has also been reported from the Multi-Ethnic Study of Atherosclerosis\(^19\) and the MEGA study,\(^20\) which suggested that environmental factors, such as chronic comorbidities and chronic inflammation, are at least in part responsible. While we did not observe an association of VWF with mortality in the present study, this association was found in the MEGA study.\(^20\)

Factor IX level was weakly associated with CVD after adjustment for age and sex (HR, top to bottom third, 1.18; 95% CI, 1.01–1.39) and attenuated after further adjustment for risk factors in the ASSIGN score (HR, 1.07; 95% CI, 0.92–1.25). As with factor VIII, there is uncertainty in the literature on this association.\(^2,27,28\) We did not observe an association of factor IX with mortality.

Among coagulation activation markers, F1 + 2 showed a borderline association with CHD when adjusted for age and sex, but no coagulation activation marker was associated with incident CVD after additional adjustment for risk.
factors. Studies of the associations of F1 + 2 and TAT complexes with risk of CVD are inconclusive. A meta-analysis found a significant association of D-dimer levels with CHD: HR, 1.23 (95% CI, 1.16–1.32; 18 studies with 6,799 cases).6

Among coagulation inhibitors, protein S showed a borderline association with CHD when adjusted for age and sex; but no coagulation inhibitor was associated with incident CVD after additional adjustment for age, sex, and risk factors in the ASSIGN score; nor with total mortality. The Atherosclerosis Risk in Communities (ARIC) study found a similar lack of association for antithrombin and protein C for CHD but found an increased risk of stroke for low protein C in longer-term follow-up. A meta-analysis confirmed increased risk of stroke for deficiencies of proteins C and S, but not of antithrombin. No increase in mortality has been reported in persons with deficiencies of coagulation inhibitors.6

aPTT was not associated with CHD in our study, as in the ARIC study. Neither APC resistance nor its major genetic determinant, the FV:R506Q mutation, was associated with CHD in our study; however, meta-analyses have shown significant associations of FV:R506Q with CHD and stroke.6 We observed a borderline association of FV:R506Q with total mortality, but this was not observed in a larger study.6

The fibrinolytic variables, tPA antigen and PAI-1 activity, did not show significant associations with incident CVD in our study. The association of tPA was, however, consistent with a meta-analysis of incident CHD (HR, 1.13; 95% CI, 1.06–1.21; 13 studies with 5,494 cases).6 The association of PAI-1 with incident CVD was consistent with that in another meta-analysis of its associations with CHD risk, which reported an HR for top third to bottom third of 0.98 (95% CI, 0.53–1.87).31

In contrast, t-PA was significantly associated with total mortality after adjustment for age, sex, and risk factors in the ASSIGN score (HR, top third to bottom third, 2.81; 95% CI, 1.43–5.54). This association was also observed in the PROSPER study cohort.23

Strengths of our study include that it is a large random sample of a general population of men and women aged 30 to 74 years, followed for up to 20 years for both CVD and total mortality. Also, the study assessed 15 hemostatic variables in a combined analysis, using well-calibrated laboratory assays, applying national or international standards, where available.12 We had a limited number of outcome events, which precluded reliable estimation of associations with stroke and CHD separately or of causes of mortality. We were also unable to look at changes in hemostatic variables over time, having only baseline values. Another limitation was the largely Scottish ethnic population, and hence results may not be generalizable to other populations, worldwide.

Conclusion

In this study, we found no compelling evidence of independent associations of hemostatic variables with CVD, suggesting that they may not add significantly to CVD risk stratification. We report that factor VIII, D-dimer, and t-PA were strongly associated with total mortality after full risk factor adjustment, but found no such association for other hemostatic variables. Further studies and meta-analyses are required to reliably assess the associations of the hemostatic variables we have studied with the risks of components of CVD, particularly stroke and CHD, and causes of mortality.

What Is Known about This Topic?

- Apart from fibrinogen, there are limited data on the associations of hemostatic factors with risks of CVD and total mortality.

What Does This Paper Add?

- Of 15 hemostatic variables assayed in a well-defined cohort followed for 17 years, factors VIII and IX were associated with risks of CVD after adjustment for age and sex; but these associations were attenuated after adjustment for CVD risk factors.
- Factor VIII, D-dimer, and t-PA were associated with total mortality after adjustment for age, sex, and CVD risk factors.

Authors’ Contributions

G. D. O. L., A. R., M. W., and H. T.-P. performed the study of hemostatic factors in the Glasgow MONICA study. S. A. E. P. and M. W. performed the analyses of follow-up data. G. D. O. L. drafted the manuscript, and all co-authors provided critical review.

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Conflict of Interest

M. W. is a consultant to Amgen, Kyowa, Kirin, and Freeline. G. D. O. L. is a consultant to Freeline. S. A. E. P., A. R., and H. T.-P. declare no conflicts of interest.

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