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Sanofi-aventis/BMS P2	Interpretation of CAPRIE data: - design of trial not powered for subgroup analysis or for individual endpoints so caution required - MVD patients at higher risk of subsequent events so guidance on their management is required	The AG fully acknowledges the points raised with respect to the CAPRIE trial. However, it represents a unique evidential resource for considering the risks applying to patients with MVD, and for informing options for their management. We took the view that no case for or against giving particular attention to MVD patients could be made without exploring these data at a subgroup level, albeit with cautionary caveats. To do this it was necessary to identify the MVD patients within the three CAPRIE groups, using a straightforward objective definition of MVD. A natural corollary of separating MVD patients as a distinct group is the redefinition of the remaining non-MVD patients as three mutually exclusive subgroups.
Sanofi-aventis/BMS P2-3	The results of this study (PRoFESS) whilst unexpected, are extremely informative, yet seem to have been dismissed in the Assessment Report. .....although the pre-specified non-inferiority test was not achieved. In this, the largest stroke study evaluating antiplatelets for secondary prevention, it appears that MRD-ASA and clopidogrel are broadly comparable in terms of their efficacy. Importantly and seemingly under-represented in the Assessment Report are the relevance of the safety data from the PRoFESS study. In section 5.2.2 of the Assessment Group report, under adverse events for PRoFESS, discontinuation and headache were mentioned but notably absent are the increased rate of major haemorrhagic event for MRD-ASA compared with clopidogrel (HR 1.15, 95% confidence interval 1.00-1.32) as well as intracranial haemorrhage (HR 1.42, 95% confidence interval 1.11-1.83). Whilst included in Table 5-7, there is no reference to this important safety data elsewhere. The most recent American and European stroke guidelines include clopidogrel and MRD-ASA as equivalent options and after the PRoFESS trial, experts consider the two regimens to be at least equivalent. In our opinion, the PRoFESS study is a recent and important study that highlights the similarity in efficacy between clopidogrel and MRD-ASA but also distinguishes between the two antiplatelet regimens in terms of safety. On this basis we maintain our assertion that clopidogrel should be considered a first-line alternative to MRD-ASA in patients with ischaemic stroke.	The AG agrees that the statistically significantly different safety outcomes (major haemorrhagic event and intracranial haemorrhage) in favour of clopidogrel should have been discussed in the text of the AG. The AG will include relevant text in the AG report during the editing process before publication.
Sanofi-aventis/BMS P3/4	The trials informing the MTC in the Assessment Group report are limited to CAPRIE, PRoFESS, ESPS2 and ESPRIT. These trials were used to estimate the relative efficacy of the relevant treatments in a population with a previous stroke. Five main endpoints were estimated, namely stroke, MI, vascular death, all-cause death and bleedings. For the other populations (patients with MI, PAD or MVD) no MTC was	The MATCH and CHARISMA trials were not included in the AG's literature review as these trials included comparators that were not specified in the scope for the appraisal; the combination of clopidogrel plus ASA is not licensed in the patient

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	conducted. Two randomized controlled trials estimating the recurrence of atherothrombotic events in a secondary prevention population were not included in the MTC despite the fact that these trials provide new evidence since the original Technology Appraisal (TA90) in 2004 and can further extend the data available for clopidogrel (nb. the CAPRIE trial dates from 1996). The MATCH trial (N=3800 per arm) was designed to assess the relative efficacy and safety of clopidogrel alone (with placebo) against clopidogrel plus aspirin in reducing vascular ischeamic events in patients with recent TIA or ischaemic stroke at a high risk of a recurring atherothrombotic event. The inclusion of the CHARISMA trial, linking the combination of aspirin and clopidogrel with aspirin alone, would have closed the circle of evidence between clopidogrel and aspirin allowing the coherence in the network to be assessed. More than one third of patients in CHARISMA (N=7800 per arm, with previous stroke or TIA N=2730 per arm) suffered a previous stroke or TIA. The lack of inclusion of these data also resulted in loss of precision in the MTC results as the addition of over 17,000 patients would have resulted in a much stronger evidence base for the comparison of clopidogrel versus aspirin. Comparing the sanofi-aventis/BMS MTC results with the results of the MTC from the Assessment Group results in the following observations: i) the ranking of the odds ratios for clopidogrel and MRD+ASA versus ASA alone were the same in both MTCs; ii) for all endpoints the confidence intervals obtained by the Assessment Group were between 50% and 300% wider than the CIs obtained in our own MTC, reflecting (1) the omission of MATCH and CHARISMA in the network, and (2) the split of the stroke events into two separate stroke endpoints estimated with a subset of available trials each; iii) many confidence intervals in the MTC from the Assessment Group were overlapping “1” indicating no significant differences between the treatments and aspirin, which was not the case in our own MTC (e.g. the endpoints stroke and MI).	population under evaluation. After much discussion, the AG decided to also exclude these trials from the indirect comparison exercise undertaken. However, the AG notes that excluding these trials does not change the ranking of the interventions; their inclusion only strengthens confidence in the results generated. The AG has checked the methods used by the manufacturer and will commend the values from the manufacturers indirect comparison to the AC.
Sanofi-aventis/BMS P4	We have noted that the stroke endpoint was divided into “first ischaemic stroke” and “any recurrent stroke”. We would like to note that all patients in this ‘stroke’ cohort had already had a stroke therefore the estimated endpoints are actually “first recurrent stroke” and “second recurrent stroke”. The distinction, in respect to treatment effects, between the second and third stroke is likely to be less important than the distinction between first and second stroke.	Yes the AG agrees that “first IS” could also be labelled as “first recurrent stroke”. It is worth noting that there was a lack of comparative data across the trials and the AG attempted to make best use of available data. The AG acknowledges that the results of the indirect analysis should be interpreted with caution and that attention should be paid to the caveats stated in the AG report.
Sanofi-aventis/BMS	The trials informing the “first recurrent stroke” were CAPRIE, ESPRIT and PRoFESS whereas the trials informing the “second recurrent stroke” were ESPS2 and	It was important and necessary to divide the evidence base for ischaemic stroke into two

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P4	PRoFESS. The evidence base was divided over these two endpoints which is highly unusual1 2 3 , and results in small trials (ESPS2 N=1650 per arm and ESPRIT N=1360 per arm) playing a key role in the chain of evidence whereas a large trial (CAPRIE N=3200 per arm) is not used in all analyses.	categories; analyses were performed separately for 'first IS' and 'any recurrent stroke' due to differences in the definitions of stroke used by the trials. Evidence from the CAPRIE trial was not included in the indirect analysis for 'any recurrent stroke' since this specific outcome was not reported.
Sanofi-aventis/BMS P4	This is even more surprising as data on second and third stroke were requested by the Assessment Group, and submitted by SA/BMS, but were not used in this analysis; there is therefore no limitation to the inclusion of CAPRIE data in the "second recurrent stroke" endpoint. The splitting up of the evidence base resulted in a loss of power, wide confidence intervals and loss of statistical significance. For clopidogrel this analysis moreover suggested that clopidogrel is more efficacious in preventing the third stroke than it is in preventing the second stroke – which is in contradiction to its SmPC. Finally we noted that in the "second recurrent stroke" endpoint a mix of ischaemic and haemorrhagic strokes were used	The AG requested this information for use in the development of the economic model. The AG comments that there was no comparable data from the other trials to allow use of the additional CAPRIE data in the indirect analysis.
	We would like to seek some clarifications from the Assessment Group about their model structure: The NICE reference case stipulates that head-to-head clinical trials should be used where available and that a MTC should be conducted when indirect evidence is available in addition to head-to-head clinical trials. The commonly accepted method is to apply these treatment effects to a baseline risk model, preferably coming from a real-world dataset rather than from the reference arm of a clinical trial. Could the Assessment Group explain how their MTC results have been used to inform their cost-effectiveness model, as the assessment report is unclear in this regard; it would appear that the MTC is not used?	The scope of the appraisal as well as the SA/BMS submission led to designing the model to allow separate consideration of MVD as a distinct population. To achieve this we decided to employ 4 mutually exclusive populations based on redefinition of the CAPRIE data set. This proved effective in clearly characterising patient groups with quite different risk profiles. However, these new groups did not generally correspond with any of the cohorts featured in the other studies in the MTC. In this case simple direct application of MTC hazard ratios would have been inappropriate and inaccurate, and involved strong implicit assumptions which may not have been supportable.
Sanofi-aventis/BMS P5	Breaking up randomization should be avoided and it is uncommon to use event rates from single arms of different trials and compare them directly without making any adjustments for baseline characteristics, trial design, and perhaps in this case also year of trial publication. On p67 of the Assessment report, the Assessment Group mentions that "the trials were disparate in terms of their design, patient populations,	The baseline risks are defined by the clopidogrel arm of the CAPRIE trial for each population, with the CAPRIE ASA arm used to define ASA risks. PRoFESS is used as the secondary source for the IS only population as described below. Other

[1] The York Assessment Report 2004 For the original TA 90
[2] Stroke Prevention – Insights from Incoherence. Kent and Thaler, NEJM Editorial 2008:359
[3] MTC SA/BMS submission dossier Oct 2009

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	interventions and definition/reporting of outcomes which means it is difficult to compare outcomes across the trials ..." It seems unlikely, that the Assessment Group has simply taken selected arms from selected trials and compared them against each other. We would like to ask the Assessment Group how they modelled a baseline risk (which is reference treatment) and which steps have been taken by the Assessment Group to estimate the efficacy of the other comparators compared to that reference treatment?	studies (ESPS-2, ESPRIT and ATTC) are used to include risks for MRD and 'no treatment' by indirect comparison. See Appendix 10 for details. Risk modifiers were derived primarily from analysis of PRoFESS data supplemented by CAPRIE results.
	It seems that aspirin and clopidogrel data from CAPRIE have been pooled on repeated occasions and a single risk model is applied for both treatments based on lack of evidence of consistent differences (e.g. p200 for ischaemic stroke endpoint in the MI and PAD populations, p202 for MI endpoint in stroke patients). PRoFESS also included data on ischaemic stroke for clopidogrel, but surprisingly the data on clopidogrel patients in PRoFESS (N= 10,151) were ignored and only (older) CAPRIE data were used to inform the event rates for clopidogrel. This selection of data sources to calculate a treatment's event rates seems arbitrary and has not been justified in the report	Since the definition of subgroups is specific to the CAPRIE trial, it was necessary to use CAPRIE as the primary source of data for calibrating risk and fatality profiles. For comparisons in the IS only population, indirect comparison with PRoFESS was used, validated by observed comparability of clopidogrel arms in the two trials. This pragmatic approach does not undervalue PRoFESS data, but is driven by the initial decision to redefine population on the basis of the CAPRIE categories to allow evaluation of MVD patients as a coherent group. In the case of subgroup analysis it is important to apply the 'rule of parsimony' to avoid introducing large and unreasonable apparent parameter differences which may be generated by random sampling fluctuations alone. This involves the exercise of modeller's judgement, and leads to pooling of arms in cases where sample sizes are small and no consistent long-term risk patterns are present in the available data. This approach is necessarily conservative in potentially reducing the extent of differences in efficacy between treatments.
	The Assessment Group's de novo economic model is centred on treatment sequences. It is unclear what type of event triggers a switch in drug treatment (refer to p116 § 3 "the current preventive medication is updated if necessary"). Please can the Assessment Group clarify if the occurrence of an atherothrombotic event is the basis for a change medication, or whether a treatment switch is only driven by the all-cause discontinuation data? If this is the latter, then we observe that the discontinuation rates based on randomized clinical trials may be unrealistic	All-cause discontinuation rates are used. We acknowledge that these may not be equivalent to those in long-term clinical practice, but were obliged to make use of the only data available. However, it is likely that discontinuations due to early drug reactions should be reasonably accurate. Long-term persistence with secondary prevention medications is a matter of debate and research (e.g. anti-hypertensives, statins, etc.)
	With regards to discontinuation rates (p117) we noted that exponential survival curves were estimated to model duration of treatment. For MRD+ASA these were based on	A judgement was made that the comparison between clopidogrel and MRD+ASA was of primary

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	PRoFESS and ESPRIT whereas for clopidogrel they were only based on PRoFESS, excluding CAPRIE from the dataset. Discontinuation data were however published for CAPRIE.	importance to the appraisal, and to preserve comparability (i.e. avoid breaking randomization) PRoFESS discontinuation data was adopted as the source for these drugs. Comparison of the MRD+ASA arms of ESPRIT and PRoFESS yielded closely similar trends, and therefore ESPRIT was used as the link to incorporate ASA into the analysis. A comparison of the clopidogrel arms of CAPRIE and PRoFESS shows close similarity of trends as far as at least 2 years. The only mismatch lies between the ASA arms of CAPRIE and ESPRIT, where discontinuations in ESPRIT are considerably lower than in CAPRIE. However, this disparity was considered much less significant to economic comparisons between clopidogrel and MRD+ASA, since ASA in generally the final 3rd-line treatment stage to the other drugs.
	In the Results section we noted that, for the stroke population, in most scenarios the costs, life years and QALYs of all the treatment sequences including clopidogrel or ASA+MRD are very similar. ICERs are generally very low and we would be cautious in recommending specific treatment sequences including clopidogrel or ASA+MRD over one another. This is also apparent in the plots of the cost-effectiveness frontiers; for example in the cost-effectiveness plane for stroke patients, the point estimates for each strategy are very close. Limited probabilistic sensitivity analyses were conducted. If the Assessment Group had undertaken and plotted the simulations onto a cost-effectiveness plane, overlapping "clouds" surrounding each point estimate would have resulted suggesting that there are no significant differences between the treatment sequences in terms of cost-effectiveness.	This is a valid point, which we think should be emphasised to the Appraisal Committee.
	The observation of small differences in cost-effectiveness between clopidogrel and ASA+MRD is supported by the conclusions from the clinical section stating that the two treatments are comparable in preventing atherothrombotic events in a stroke population (p55-57). At a comparable cost per year (£132.62 for clopidogrel (tariff price) and £94.78 for MRD+ASA) one might reasonably expect to obtain similar cost-effectiveness results. In addition, safety and compliance issues associated with MRD should raise clopidogrel as a valuable alternative to MRD in this subgroup. Of note, in April 2010 roughly less than 3% of prescriptions written were for branded clopidogrel (Plavix)4 5 and roughly less than 13% of prescriptions were dispensed as	Agreed

[4] TNS Scriptcount data April 2010

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	branded clopidogrel (Plavix)10 6. Therefore the scenarios using the branded price of clopidogrel are less relevant than those using the new tariff price.	
Sanofi-aventis/BMS P6	We were also surprised to see the inclusion of the previous TA 90 (treatment with the combination of aspirin and MRD for 2 years after an ischaemic stroke) in the model as this is uncommon and this is the guidance currently under review. Building an older version of this guidance into the model structure would seem counter-intuitive. The original TA 90 cost-effectiveness model compared different scenarios looking at lifetime treatment but also 2 years treatment with clopidogrel or MRD+ASA followed by lifetime of ASA. Would it be possible to clarify whether the inclusion of TA 90 is applied to patients e.g. "clopidogrel– ASA– nothing". If a patient on this treatment regimen is allocated the following time on treatment: "clopidogrel: 3 years – ASA: 2 years – nothing: 10 years" and this patient experiences a stroke after spending 1 year in the model, will this patient then have 1 year on clopidogrel, followed by 2 years on MRD + ASA, followed by 2 years on ASA, followed by 10 years on no treatment? In addition would it be possible to clarify how the TA 90 feature is applied in patients with a history of MI, PAD and MVD? MRD should be used with caution in patients with severe CAD, including unstable angina or recent MI, left ventricular flow obstruction.	The inclusion of this feature is designed to allow the Appraisal Committee to consider scenarios in which the existing guidance is used as the 'current treatment' against which other treatments should be compared. However, making the transition from the previous short-term 'single-event' analysis to a long-term staged treatment strategy is difficult in terms a structuring a model. The compromise adopted involves overlaying TA90 periods of up to 2 years onto the long-term randomly generated pattern of periods spent on treatment 1, treatment 2 and treatment 3. This means that when the TA90 feature is active a non-fatal IS event triggers an immediate switch to MRD+ASA. At the end of 2 years, the patient reverts to the point on their long-term treatment pattern that they would have reached had the IS event not occurred. This is clearly only an approximation to the impact of TA90, but allows the relative impact of TA90 in the long-term to be considered.
Sanofi-aventis/BMS P7	The REACH data were available separately for year 1, 2 and 3 and the year 3 data were used as the basis for modelling constant event probabilities up to the end of the time horizon of our model. The Assessment Group commented that "extrapolating these transition probabilities for the remainder of the time horizon ... is an unreliable basis for long-term projection since close to the end of the trial patient numbers and the number of events are much reduced. As a consequence estimated incidence rates are very volatile and should not be relied on to drive the major part of the model calculations." We would like to highlight that the REACH dataset was very large and patient attrition rates low, resulting in sufficient numbers of patients and events in year 3 to provide estimated baseline event risks with small confidence intervals. The table below displays the sample size for the "nonfatal stroke" endpoint in REACH for the different populations and the accompanying graph displays the confidence intervals around the point estimates. We do agree with the Assessment Group that using end-of-trial data (e.g. from CAPRIE or PRoFESS) would have resulted in patient numbers being too low and very volatile, and as a consequence unrepresentative for estimating	The interpretation of reported registry data results is always difficult, and presents serious problems when attempting to use these data to populate a model. The AG critique gave only a brief pointer to some of these problems. We can indicate other specifics which led us to eschew REACH as a primary source of parameter values for our model: - REACH publications provide only very limited event rates (non-fatal MI, non-fatal stroke, and vascular death) which are not clearly defined (e.g. how is a non-fatal event followed by a fatal event counted, how are multiple non-fatal events in the same period counted?) - it is not apparent how these events can be extrapolated to other events for modelling purposes

[5] CSD Patient Data April 2010
[6] IMS BPI April 2010

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	further events, but we do not believe this is the case with the REACH dataset. The REACH registry was however, the preferred source of baseline data for aspirin in our model due to its size and time horizon, whilst CAPRIE was used only to calculate relative treatment effects (mean duration of follow-up 1.9 years and N=19185). The Assessment Group commented that in REACH "only" 67% of patients were taking aspirin monotherapy and secondly that the MVD patients were identified as patients with risk factors of cardiovascular disease. We recognise that 100% aspirin use would have been the preferred data, however the 33% of patients not on aspirin monotherapy, were either on a combination of aspirin with another antiplatelet agent, or on another single antiplatelet agent	(e.g. how to separate ischaemic from haemorrhagic strokes, how to separate STEMI from non-STEMI MIs, how to separate fatal MIs from fatal strokes and other vascular fatal events) - there were problems over the integrity of some year 2 results (the sample sizes of two patient groups increase between year 1 and and year 2 calling the reliability of these unpublished results into question) - it is unlikely that the event rates include any corrections for in-period drop-outs or for competing risks - the three period risk figures provided for each event are insufficient to establish that the year 3 results represent a long-term stable level of risk since in no case is the year 3 figure even approximately equal to the year 2 figure. Taken together with the heterogeneity of anti-platelet therapies within the registry data, we concluded that though REACH is a useful confirmatory source for broad patterns of risk developing over time, they were too vulnerable to these uncertainties to inform the baseline for calibrating the whole model. Instead we opted to focus on CAPRIE, using the redefined four patient groups as the basis for calibrating both clopidogrel and ASA effectiveness to ensure consistency of definition and interpretation throughout.
	The Assessment Group also commented on page 111 that "none of the effectiveness results used in their [sanofi-aventis/BMS] modelling of cost effectiveness are directly derived from publications from the CAPRIE trial". We would like to highlight that we presented five separate efficacy analyses: 2 analyses based on an MTC (including the CAPRIE trial) with direct reference to published data, 1 analysis based the PRoFESS trial, 1 analysis based on the CAPRIE publication and 1 analysis based on post-hoc data from CAPRIE, therefore this criticism is unfounded	The AG acknowledges that, as written, this sentence is clumsy. The AG was referring only to data used to model cost effectiveness in the MVD population. The AG's intention was to point out that the definition of MVD in the post hoc publication (self reported history of IS/MI before the qualifying event) was not the same as the definition used throughout the sanofi-aventis/BMS MS (disease in more than one vascular bed).
	Finally, in our submission we used the price for clopidogrel hydrogen sulphate (Plavix) of October 2009. The tariff price for clopidogrel has only recently changed to £10.90. Including this lower price into our cost-effectiveness model would result in clopidogrel being dominant compared to aspirin in stroke patients and MVD patients, and with an	Noted.

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	ICER of around £2,000 for MI and PAD patients. Compared to the combination of MRD+ASA in stroke patients, clopidogrel would have an ICER of under £500/QALY and therefore clopidogrel should be considered as an alternative to MRD-ASA in this subgroup.	
BI	In relation to tables 6.38 - 6.41 (pages 131-134) it would be useful to clarify in the accompanying text the definitions for the different incremental analyses carried out (referred to as column headings in the tables as "incremental analysis 1", "incremental analysis 2" and "incremental analysis vs. 3")	These are progressive analyses moving from point to point on the efficiency frontier. If the referees consider it necessary we can amend the text for publication in the HTA monograph to clarify this approach.
BI	Using the assessment group health economics model, cost effectiveness analyses have been reported which estimate ICERs with and without the application of TA90 guidance as it relates to limiting the use with IS / TIA patients of modified release dypyridamole plus aspirin to 2 years or allowing life time use (eg. in tables 6.38 - 6.41 (pages 131-134)); the relevance of this information is useful for decision making to determine whether limiting use to 2 years or not is the more cost effective option and its consideration would be valuably included in the relevant section of the discussion of the results (ie. pages 160 and 163) and in the executive summary (pages 17 and 21)	The application of TA90 guidance here is superimposed on the underlying long-term treatment strategy, i.e. it applies only for the 2 years following a non-fatal IS event, after which the previous treatment resumes (which could also be MRDP). A general examination of time-limited treatment would require additional model runs imposing limits on treatment duration of elements of the treatment strategy.
Diabetes UK	Diabetes UK is seeking clarification regarding whether it was possible to examine the evidence base specifically with regard to people with diabetes. While we recognise that this was not formally identified within the scope, people with diabetes formed an identified subgroup within the four trials examined by the Assessment Group, and as identified at the submission stage, people with diabetes are considered a high risk group, as once they have established CVD they are at increased risk of further occlusive vascular events. A review of this evidence could impact upon the conclusions of the Assessment Group with regard to people with diabetes specifically. Whereas the Assessment Group report considers intolerances to medications, contraindications also form an important part of decision making. Some contraindications that may be of particular relevance for people with diabetes were highlighted at the submission stage. Ultimately decisions about the most optimal antiplatelet therapy will need to be tailored to individual clinical need, suitability and choice, and consider safety, contraindications, efficacy, risks, benefits and quality of life considerations.	Although in general patients with diabetes were found to have higher event risks, there was no significant evidence of interactions between diabetes and treatment for any of the efficacy outcomes for either of the main trials (CAPRIE and PRoFESS). Therefore there was no basis for using diabetes as a criterion for a separate subgroup. Separate subgroup results were not presented for diabetes in either trial report.
British Association of Stroke Physicians	I note that a comparison with aspirin and clopidogrel (as assessed in the CHARISMA and MATCH studies) has not been undertaken	Clopidogrel +ASA is outside the scope of the appraisal.
	I assume on P13 that the assessors are referring to clopidogrel alone, and not clopidogrel and modified-release dipyridamole in combination (as I am not aware myself of a study that has undertaken an assessment of these two agents in	Correct

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	combination)	
	I think it would be useful for a definition of aspirin and modified-release dipyridamole intolerance to be provided	Noted. The AG report includes the contraindications to ASA, MRD and clopidogrel as stated in the Summary of Product Characteristics.
	There is no consideration on the duration of treatment despite the fact that the previous guidance recommended the use of aspirin and modified release dipyridamole in combination for only two years before reverting to aspirin monotherapy, and given that longer term follow up is now available from more recent studies	We have recently modelled long-term use of clopidogrel and MRD+ASA when limited to a maximum duration of 4 years (longest follow-up time available), but with unlimited use of ASA. This indicates that ASA becomes the preferred first-line treatment for all four populations, followed by clopidogrel (2nd line) and MRD+ASA (third-line). We did not have time to investigate a full range of different durations. It is questionable whether a truly long-term head-to-head trial will ever be carried out, and in practice it is likely that unlimited treatment duration will become the norm. The hazard trends all indicate that risks remain stable in the medium-term, so the results are likely to be valid for up to 10 years at least.
	There also should be some consideration to the time of commencement of treatment, ie acute vs secondary prevention, particularly given the recent publication of the EARLY trial	The EARLY trial aimed to investigate whether MRDP can be initiated within the first 7 days post stroke. It showed no significant differences between early and late initiation. So it has no impact on our analysis (post-acute long-term prevention).
	I note that 'bleeding' is defined in terms of efficacy on pgs 59 and 60. This seems strange as I would consider this more likely ' harm' than efficacy	Minor terminology