Acute Coronary Syndromes

Consultation on draft guideline - Stakeholder comments table

Friday, 14th February 2020 – Friday, 27th March 2020 & Wednesday, 17th June 2020 – Wednesday, 2nd July 2020

Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
AstraZeneca	Economic Analysis Report	009	016 – 026	Concern: Dual antiplatelet therapy (DAPT) discontinuation in the CE model is considerably underestimated. It is assumed that patients only discontinue prematurely if they die. This serves to significantly overestimate drug costs, leading to ticagrelor being deemed not cost-effective vs. prasugrel for STEMI-PCI patients in scenario 1 (unduly). In the PLATO trial, the mean days on study drug was 240 days for ticagrelor and 245 days for clopidogrel (Nikolic, 2012). However, under the current approach to discontinuation, the CE model inherently assumes that STEMI-PCI patients accrue a mean of 342 days ticagrelor drug cost or 337 days clopidogrel drug cost and UA/NSTEMI-PCI patients 354 days ticagrelor or 352 days clopidogrel. This is very unrealistic, as patients discontinue antiplatelets before 1 year for a variety of reasons other than death, including incidence of bleeding, stroke, need for major surgery, need for oral anticoagulation and drug intolerance (Boggon, 2011; Winter, 2019; Zeymer, 2018; Claeys, 2017). Prasugrel drug costs are likely to be overestimated for the same reason. An evidence-based approach is needed to ensure that drug costs are not overestimated. We suggest employing in the model mean days of study drug from the PLATO trial, since this is a large RCT of 12 months follow-up that also provides much of the weight to the 1 year pairwise M-As for ticagrelor + ASA vs. clopidogrel + ASA, as used in the CE model. An assumption may be needed for prasugrel, given median duration of therapy in TRITON-TIMI 38 was 14.5 months (Wiviott, 2007), which exceeds the antiplatelet treatment phase of the CE model), in which case it would be reasonable to assume that prasugrel days of therapy are equal to that of ticagrelor.	Thank you for your comment. This was not originally included in the model as in the committee's experience continuation with DAPT treatment is high in practice. An additional adjustment for discontinuation has now been incorporated into the model. In the base case it is now assumed that people who are alive at 1 year receive an average of 328 days DAPT. This was estimated from data reported for ISAR-REACT-5 about the number of people who discontinued and their average days on treatment. The committee agreed that this was most likely to reflect current real-world usage as it is a recent pragmatic trial and was consistent with their experience based on local data. Sensitivity analyses were also included using greater reductions such as that reported in PLATO. However, the committee highlighted that PLATO seemed likely to be an underestimate of real-world days on treatment as 12 months treatment was not mandated and participants could discontinue at 6 or 9 months if the target number of primary events had been reached. Updated model results incorporating this and other changes were discussed by the committee and it was agreed that the DAPT recommendations should not change due to these. The model methods and results, and the committee discussion have been updated in the relevant guideline documents.

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				We request the implications of the overestimation of drug costs be discussed by the guideline development group since, like the double counting of early treatment effects, this issue appears to be pivotal to the outcome of the scenario 1 cost-effectiveness analysis for STEMI-PCI patients. Detailed Comments: The CE model assumes that everyone alive will continue to take dual antiplatelet therapy (DAPT) (i.e. incur drug costs) until 1 year. This assumption is unrealistic and at odds with the evidence. Studies show that patients with acute coronary syndromes discontinue antiplatelet therapies before 1 year for a variety of reasons other than death, including incidence of bleeding, stroke, need for major surgery, need for oral anticoagulation and drug intolerance (Boggon, 2011; Winter, 2019; Zeymer, 2018; Claeys, 2017). Consequently, drug costs in the model are overestimated by a significant amount. Based on the intervention costs as presented in Table 51 of the Economic Analysis report (p.64), we calculate that the model is inherently assuming mean numbers of treatment days as shown at Table 1, with our having accounted for loading dose, time to death, prasugrel 5mg/10mg dose split and timing of prasugrel initiation in UA/NSTEMI patients. Table 1: Scenario 1 mean treatment days as assumed in the CE model (intention-to-treat basis) Population | Clopidogrel + ASA | Ticagrelor + ASA | Prasugrel + ASA	

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STEMI-PCI	337 days	342 days	340 days
UA/NSTEMI-PCI	352 days	354 days	353 days

To avoid a bias in the model, the source(s) used to inform relative treatment effects would ideally also be used to inform the number of days drug therapy for costing purposes. Three key studies provide the majority of the weight to the 1 year pairwise M-As: PLATO, TRITON-TIMI 38 and ISAR REACT-5. In TRITON-TIMI 38 the treatment period exceeded the 12 months treatment period considered by the CE model (Wiviott, 2007), as such it is not appropriate for use in this context. ISAR REACT-5 was followed-up at 12 months, however data reporting mean treatment days does not appear to be available (Schüpke, 2019). In the PLATO trial, follow-up was conducted at 12 months. The mean number of days on study drug were 240 days for ticagrelor and 245 days for clopidogrel (Nikolic, 2012).

We suggest employing in the model mean days of study drug from the PLATO trial, since this is a large RCT of 12 months follow-up that also provides much of the weight to the 1 year pairwise M-As for ticagrelor + ASA vs. clopidogrel + ASA, as used in the model.

Findings of the PLATO trial do not appear to be at odds with UK clinical practice. A UK real world evidence study of MI patients treated with clopidogrel found that the adjusted odds of still being prescribed clopidogrel at 12 months was 0.54 (95% CI, 0.52–0.56) in STEMI patients and 0.53 (95% CI, 0.51–0.55) in

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				NSTEMI patients (Boggon, 2012). Mean days of treatment is not reported however, the cumulative discontinuation curves over time for STEMI and NSTEMI patients are approximately linear, indicating a high number of lost treatment days over the 12 months (intention-to-treat basis). We have not been able to identify a source that would inform mean treatment days for prasugrel under 12 months follow-up and therefore we propose that an assumption is made for prasugrel, such that it is set equal to ticagrelor. AstraZeneca requests that the implications on recommendations of the overestimation of drug costs be discussed by the guideline development group since, like the double counting of early treatment effects, this issue appears to be pivotal to the outcome of the scenario 1 cost-effectiveness analysis for STEMI-PCI patients. <u>References</u> Boggon R, van Staa TP, Timmis A, Hemingway H, Ray KK, Begg A, et al. *Eur Heart J*. 2011 Oct 1;32(19):2376-86. Claeys MJ, Beauloye C, Pourbaix S, Sinnaeve PR, Rewinder Study Group. *Eur Heart J–CVP*. 2017 Oct 1;3(4):189-97. Nikolic E, Janzon M, Hauch O, Wallentin L, Henriksson M. *Eur Heart J*. 2013;34: 220–8. 10.1093/eurheartj/ehs149 Schüpke S, Neumann FJ, Menichelli M, Mayer K, Bernlochner I, Wöhrle J, et al. *N* Engl J Med. 2019. 17;381:1524-1534 Winter MP, von Lewinski D, Wallner M, Prüller F, Kolesnik E, Hengstenberg C, et al. *Sci Rep*. 2019 Jun 3;9(1):1-9 Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, et al. *N Engl J Med*. 2007. 15;357:2001-15	

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				Zeymer U, Cully M, Hochadel M. *Eur Heart J–CVP.* 2018 Oct 1;4(4):205-10.	
AstraZeneca	Economic Analysis Report	009	030	**Only Scenario 1 should be used to inform decision-making. Under scenarios 2 and 3, relative treatment effects for ticagrelor + ASA vs. prasugrel + ASA are informed by the ISAR-REACT 5 study (Schüpke, 2019).** **Findings of the ISAR-REACT 5 study are inconsistent with the findings of pivotal PLATO (Wallentin, 2009) and TRITON-TIMI 38 (Wiviott, 2007) phase 3 studies for ticagrelor and prasugrel respectively, as described above.** For example, the pivotal phase 3 trial PLATO demonstrated that ticagrelor reduced all-cause mortality: HR, 0.78, [0.69-0.89] vs. clopidogrel (Wallentin, 2009) which is consistent with the finding in the meta-analysis OR 0.77 [0.68 to 0.88] proposed by the Committee (scenario 1). When results from the pragmatic ISAR-REACT 5 study are included in scenario 2, the indirect comparison indicates that ticagrelor instead increase all-cause mortality vs. clopidogrel OR of 1.24 (CI 0.86 - 1.79) which clearly contradict the findings of a reduction in all-cause mortality in the pivotal phase 3 PLATO trial and which can be found in EU SmPC 5.1. Numerous editorials and review articles by experts in the field expressly warn against over-interpretation of the ISAR-REACT 5 study. We refer the reader to comment 2 for further information. <u>References</u> Schüpke S, Neumann FJ, Menichelli M, Mayer K, Bernlochner I, Wöhrle J, et al. *N Engl J Med*. 2019. 17;381:1524-1534 Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, et al. *N Engl J Med*. 2009. 10;361:1045-57 Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo	Thank you for your comment. The use of scenario 1 only effectively means disregarding ISAR-REACT 5 completely. Although the study is imperfect, the committee did not believe it is sufficiently flawed that they could disregard it, as it is the largest available direct comparison of prasugrel and ticagrelor. The committee discussed this issue in detail during guideline development and came to the view that the evidence directly comparing ticagrelor and prasugrel provided the best evidence to address the uncertainty between these treatment options in particular in the STEMI population. As described in the committee discussion of the evidence the committee acknowledge that practice for UA/NSTEMI in ISAR-REACT-5 is not representative of all people with UA/NSTEMI in the UK as time to angiography and so PCI is often longer. This uncertainty was therefore factored into the decision making with regard to the UA/NSTEMI population.

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				W, Gottlieb S, et al. *N Engl J Med*. 2007. 15;357:2001-15	
AstraZeneca	Economic Analysis Report	031	012 – 018	Concern: The approach taken when applying relative treatment effects to the cost-effectiveness (CE) model double counts 0-30 days treatment effects. Since 'early' treatment effect is most pronounced for prasugrel, this double counting serves to bias the number of QALYs accrued in favour of prasugrel, leading to ticagrelor being deemed not cost-effective vs. prasugrel for STEMI-PCI patients in scenario 1 (unduly), with a deterministic incremental cost-effectiveness ratio (ICER) of £21,665. The committee notes the approach taken as being a limitation but did not consider it to be a substantial issue. AstraZeneca strongly believes this to be a substantial issue. An alternative and less compromised approach, which ensures that relative treatment effects as accrued in the CE model at 1-year mirror those of the pairwise meta-analyses for 1-year outcomes, renders ticagrelor highly cost-effective for STEMI-PCI patients in scenario 1 (deterministic ICER £7,493), meriting a 'prasugrel or ticagrelor' recommendation in this population. We request this double counting issue be rectified (and implications on recommendations discussed) and provide suggestions on how to go about this. Detailed Comments: To inform this response AstraZeneca requested and received a copy of the CE model. Within this response we have run some alternative scenarios and in doing so we refer to deterministic analysis only. Ideally, we would have run these analyses probabilistically, however, the COVID-19 outbreak brought about additional time pressures which meant this was not possible. In	Thank you for your comment. When the model was initially developed (before the publication of ISAR-REACT 5) incorporation of 30-day data was considered essential by the committee as the studies that directly compared ticagrelor and prasugrel only had 30-day outcomes and this was considered the key new evidence in this area (6 studies [PRAGUE18, RAPID I, RAPID II, Alexopoulous 2012, Bonello 2015 and Laine 2014], total n = 1698). This was the primary reason the model was structured with the first year split into 0 to 30 days and 31 days to 1 year. The approach taken was considered the best way to take account of the full body of evidence including that which directly compared ticagrelor and prasugrel, although it did mean that the events generated by the model would not necessarily be consistent with the studies that did have 1 year outcomes. This approach was maintained when ISAR-REACT 5 was incorporated following publication late in development. This approach has been reconsidered and it was agreed that a more conservative approach was to ensure the model generated relative event numbers consistent with the 1 year relative treatment effects being used in that scenario. While this puts less weight on the studies with only 30 day outcomes, it reflects the key large studies in this area (when all scenarios of the analysis are considered) including one that directly compared ticagrelor and prasugrel (ISAR-REACT 5). The 30-day relative-treatment data was still incorporated but now just impacts the timing of events in the first year. The approach taken was considered preferable to the suggestions made as it

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				comparing results from the probabilistic analyses as presented in the Economic analysis report (p.57 onwards) to results of the deterministic analyses as presented in the CE model, the two appear very similar, so this seems appropriate. We have also made reference to some of the ICERs as presented in the Economic Analysis report, which are probabilistically derived. So, for each ICER we quote, we have made it clear whether it is deterministic or probabilistic. The issue at hand stems from the structure of the CE model and the lack of availability of treatment effects data to populate a model of that structure. The decision tree component of the model considers the first year (the antiplatelet treatment period) and is segmented into two sub-periods; 0 to 30 days, 31 days to 1 year. Treatment effects for the 0 to 30 days sub-period are informed by the network meta-analysis, whereas under scenario 1, relative treatment effects for the 31 days to 1-year sub-period are informed by the pairwise meta-analyses for ticagrelor + ASA vs. clopidogrel + ASA and prasugrel + ASA vs. clopidogrel + ASA. Here we focus commentary on the 'mortality' endpoint of the CE model, given that mortality is the key driver of cost-effectiveness. However, the same principle applies to other endpoints of the CE model. We refer the reader to the fact that the pairwise meta-analysis (M-A) for prasugrel + ASA vs. clopidogrel + ASA for the endpoint of all-cause mortality at 1 year finds the rate ratio to be 1.00 (95% CI 0.83, 1.20) (Evidence Review A – Antiplatelet Therapy,	allowed incorporation of more of the evidence base. Revised methods are described in the model report in section 2.3.3. Updated model results incorporating this and other changes were discussed by the committee and it was agreed that the DAPT recommendations should not change due to these. The model methods and results, and the committee discussion have been updated in the relevant guideline documents.

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				p.265). In other words, cumulatively at 1 year, the pairwise M-A finds there to be no treatment effect on mortality for prasugrel + ASA vs. clopidogrel + ASA. The CE model should reflect this but it does not; in STEMI-PCI patients, the decision tree accrues 925 life years (LY) per 1,000 patients for clopidogrel + ASA but 935 LYs for prasugrel + ASA. Similarly, in UA/NSTEMI-PCI patients, it accrues 966 LYs for clopidogrel + ASA but 969 LYs for prasugrel + ASA (CE model, Decision Tree [population] sheets, cells D5, D7), i.e. there is a substantial mortality treatment effect in favour of prasugrel + ASA. This disparity between 1-year treatment effects in the CE model and in the pairwise M-A stems from the way in which relative treatment effects are applied to the model. Owing to the lack of data from trials that would allow for subtraction of 30 days events from 1-year events, 1-year outcomes from the pairwise M-As are applied to the 31 days to 1-year sub-period of the CE model. However, this approach serves to double count early treatment effects and the CE model is extremely sensitive to this double counting. To illustrate, from a starting position of the scenario 1 base case, if we apply an odds ratio (OR) of 1.00 for mortality for prasugrel + ASA vs. clopidogrel + ASA to the 0 to 30 days period of the CE model, so as to accurately reflect 1 year relative mortality from the pairwise M-A (given an OR of 1.00 is also being applied to the 31 days to 1 year sub-period) and in doing so achieve parity in LYs accrued at one year (925 LYs for each treatment), then the deterministic ICER for ticagrelor + ASA vs. prasugrel + ASA in STEMI-PCI patients moves from £21,665 (not cost-effective) to £8,949 (highly cost-effective). Of course, it	

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				is not appropriate to amend the treatment effect for a single endpoint (mortality) only, we do so here just to illustrate the level of sensitivity. We recognise that an aim of the current CE model structure is to capture early treatment effects at the time when baseline risk is at its highest. However, such a model structure should only be employed if it can be populated with accordingly structured data. For the 31 days to 1-year period of the model, it is noted that *"Ideally 30 day events would have been removed from the 1-year events and treatment effects recalculated however this was not possible in many cases as trials did not necessarily report both 30 day and 1-year outcomes. If was therefore agreed that 1 year relative treatment effects would be used"*. In other words, a model structure has been chosen but appropriate data is not available to populate it. It is also stated that: *"The committee noted this limitation regarding the relative treatment effects but did not consider this to be a substantial issue".* AstraZeneca strongly believes this to be a substantial issue and asks the guideline development group to address this concern and consider onward implications on recommendations. We agree that data is not available that would allow for subtraction of 30 days events from 1-year events. We therefore see two options that would alleviate the double counting of treatment effects issue. Each has its pros and cons but both	

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				represent a better approach than the approach currently employed in the model. Option 1. Retain the current CE model structure and apply the pairwise M-A relative treatment effects at 1 year to both the 31 days to 1 year and the 0 to 30 days sub-periods of the model, for all endpoints The main benefit of this approach is that it ensures that relative treatment effects in the CE model at 1 year mirror the findings of the 1 year pairwise M-As, thus ensuring that patients exit the decision tree and enter the long-term Markov model having received the correct relative treatment effects. This protects the integrity of the model for the phase during which the great majority of QALYs are accrued. An additional benefit is that it is a quick and easy change to employ. A downside of this approach is that it creates an inaccuracy in the CE model at 30 days, relative to the findings of the 30 days pairwise M-As. It also assumes that the ORs are constant over time which one generally wouldn't expect unless there is no treatment effect. However, in terms of the model as a whole, it is much more important that the post 30 days period of the lifetime model is correct, than the first 30 days, as the great majority of QALYs are accrued post 30 days, despite the high baseline risk of events in the first 30 days. Using the scenario 1 base case for STEMI-PCI patients to illustrate, for a cohort of 1,000 patients, just 55 QALYs are accrued for prasugrel + ASA in the first 30 days of the model (CE model, Decision Tree STEMI sheet, cell F92) and 6,509 QALYs are accrued over lifetime (CE model,	

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				Markov STEMI sheet, cell BS94). This means 6,454 QALYs (99.2%) are accrued in the post 30 days period. Table 2 provides deterministic results for the approach whereby the pairwise M-A relative treatment effects at 1 year are applied to both the 31 days to 1 year and the 0 to 30 days sub-periods of the model, for all endpoints. Table 2: Scenario 1 deterministic results for STEMI-PCI patients where pairwise M-A relative treatment effects at 1 year are applied to both the 31 days to 1 year and the 0 to 30 days sub-periods of the model *STEMI* / Total costs / Total costs disc / Total LYs / Total QALYs / Total QALYs disc / Incr. cost / Incr. QALY / ICER / Extendedly dominated? / Incr. cost / Incr. QALY / ICER Clopidogrel £23,094 £17,351 13.05 8.29 6.423 Prasugrel £23,210 £17,446 13.07 8.30 6.434 £95 0.01 £8,837 Extendedly dominated Ticagrelor £24,419 £18,492 13.36 8.49 6.575 £1,045 0.14 £7,391 £1,141 0.15 £7,493 Under incremental analysis, prasugrel (+ASA) is not deemed cost-effective because of extended dominance, meaning clopidogrel (+ASA) is deemed the comparator for ticagrelor (+ASA). The deterministic ICER for ticagrelor (+ASA) becomes £7,493. Thus ticagrelor (+ASA) becomes the cost-effective choice under scenario 1 in STEMI-PCI patients (previously prasugrel [+ASA]). We request that the implications of this analysis upon guideline recommendations be discussed by the guideline development group.	

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				For completeness, at **Error! Reference source not found.** we report the equivalent findings for the UA/NSTEMI-PCI population. Although the double counting of early treatments effects issue is also relevant for this population, it is not pivotal to the outcome of the scenario 1 cost-effectiveness analysis, in the same way that it is for STEMI-PCI patients. Table 3: Scenario 1 deterministic results for UA/NSTEMI-PCI patients where pairwise M-A relative treatment effects at 1 year are applied to both the 31 days to 1 year and the 0 to 30 days sub-periods of the model *UA/NSTEMI* / Total costs / Total costs disc / Total LYs / Total QALYs / Total QALYs disc / Incr. cost / Incr. QALY / ICER / Extendedly dominated? / Incr. cost / Incr. QALY / ICER Clopidogrel £19,349 £14,865 12.95 8.210 6.44 Prasugrel £19,449 £14,959 12.97 8.222 6.45 £95 0.01 £12,188 Extendedly dominated Ticagrelor £20,312 £15,750 13.12 8.319 6.52 £791 0.08 £10,405 £886 0.08 £10,570 Under incremental analysis, prasugrel (+ASA) is not deemed cost-effective because of extended dominance, meaning clopidogrel (+ASA) becomes the comparator for ticagrelor (+ASA). The deterministic ICER for ticagrelor (+ASA) becomes £10,570. Thus ticagrelor (+ASA) remains the cost-effective choice under scenario 1 for UA/NSTEMI-PCI patients. Option 2. Amend the CE model structure such that the decision tree considers 0 days to 1 year as a single time period. Apply the 1 year pairwise M-A relative treatment effects for all endpoints. Amend	

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				other model inputs (baseline risks, costs, etc) accordingly. The resultant structure represents a very well-established approach to CE modelling for acute coronary syndromes (NICE TAs 236, 317). Its main advantage is that relative treatment effects (and other) data is readily available in the appropriate format. In terms of disadvantages such a model structure would not allow for the capture of early treatment effects of prasugrel and it would take additional work to adapt the current model in this manner (although not a significant amount). We have not attempted to adapt the CE model in this manner but have attempted a proxy for it, by amending the 31 days to 1 year baseline risks to reflect the 1 year probabilities of events (CE model, D1 Baseline risks sheet, appropriate cells in column C). Thereafter we amended the QALYs for 0 to 30 days to become zero (CE model, Decision Tree STEMI sheet, appropriate cells in column F). QALYs for 31 days to 1 year were adjusted by setting all of the fractions 335/365 to 365/365 in relevant cells in column K. To change the intervention costs for 0 to 30 days the days treated were set to 0 instead of 30 in column G, thus keeping the cost for the loading dose. Similarly, intervention costs for 31 to 1 year were adjusted by setting the days treated to 365 instead of 335 for non-fatal states, and 182.5 instead of 167.5 for fatal states in column L. The same adjustments were made for the sheet Decision Tree UANSTEMI except for the prasugrel intervention cost for 31 days to 1 year. There the days treated were set to 365-S_UANSTEMI_angio_days."	

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				Table 4 provides scenario 1 deterministic results for STEMI-PCI patients. Table 4: Scenario 1 deterministic results for STEMI-PCI patients under an approach that acts as a proxy for amending the decision tree to consider 0 days to 1 year as a single time period *STEMI* / Total costs / Total costs disc / Total LYs / Total QALYs / Total QALYs disc / Incr. cost / Incr. QALY / ICER / Extendedly dominated? / Incr. cost / Incr. QALY / ICER Clopidogrel £28,356 £21,334 12.75 8.01 6.253 Prasugrel £28,523 £21,465 12.76 8.02 6.261 £131 0.01 £16,739 Extendedly dominated Ticagrelor £29,905 £22,642 13.04 8.19 6.392 £1,177 0.13 £8,992 £1,308 0.14 £9,429 Under incremental analysis, prasugrel (+ASA) is not deemed cost-effective because of extended dominance, meaning clopidogrel (+ASA) is deemed the comparator for ticagrelor (+ASA). The deterministic ICER for ticagrelor (+ASA) becomes £9,429. Thus ticagrelor (+ASA) becomes the cost-effective choice under scenario 1 in STEMI-PCI patients (previously prasugrel [+ASA]). We request that the implications of this analysis upon guideline recommendations be discussed by the guideline development group. For completeness, at Table 5 we report the equivalent findings for the UA/NSTEMI-PCI population. Although the double counting of early treatments effects issue is also relevant for this population, it is not pivotal to the outcome of the scenario 1 cost-effectiveness analysis, in the same way that it is for STEMI-PCI	

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<tr><td></td><td></td><td></td><td></td><td>patients.

Table 5: Scenario 1 deterministic results for NSTEMI-PCI patients under an approach that acts as a proxy for amending the decision tree to consider 0 days to 1 year as a single time period

<table>
<tr><th>UA/NSTEMI</th><th>Total costs</th><th>Total costs disc</th><th>Total LYs</th><th>Total QALYs</th><th>Total QALYs disc</th><th>Incr. cost</th><th>Incr. QALY</th><th>ICER</th></tr>
<tr><td>Clopidogrel</td><td>£31,794</td><td>£23,925</td><td>12.72</td><td>7.876</td><td>6.22</td><td></td><td></td><td></td></tr>
<tr><td>Prasugrel</td><td>£31,921</td><td>£24,029</td><td>12.74</td><td>7.885</td><td>6.22</td><td>£104</td><td>0.01</td><td>£15,566</td></tr>
<tr><td>Ticagrelor</td><td>£33,164</td><td>£25,120</td><td>12.89</td><td>7.974</td><td>6.29</td><td>£1,092</td><td>0.07</td><td>£15,842</td></tr>
</table>

Under incremental analysis, prasugrel (+ASA) is cost-effective vs. clopidogrel (+ASA) and becomes the comparator for ticagrelor (+ASA). The deterministic ICER for ticagrelor (+ASA) is £15,842. Thus ticagrelor (+ASA) remains the cost-effective choice under scenario 1 for UA/NSTEMI-PCI patients.

References
National Institute for Health and Care Excellence. Ticagrelor for the treatment of acute coronary syndromes, TA 236. https://www.nice.org.uk/guidance/ta236
National Institute for Health and Care Excellence. Prasugrel with percutaneous coronary intervention for treating acute coronary syndromes, TA 317. https://www.nice.org.uk/guidance/ta317</td><td></td></tr>
<tr><td>Bayer PLC</td><td>Economic</td><td>047</td><td>025</td><td>The hazard ratio for mortality reported from the ATLAS TIMI-51</td><td>Thank you for your comment. This has been corrected in the</td></tr>
</table>

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	analysis report			trial is incorrect. This is reported in the Economic analysis report as 0.83 when the actual published value is 0.68 (0.53-0.87) for death from any cause and 0.66 (0.51-0.86) for CV death [Mega et al. Rivaroxaban in Patients with a Recent Acute Coronary Syndrome. N Engl J Med. 2012 Jan 5;366(1):9-19. doi: 10.1056/NEJMoa1112277. Epub 2011 Nov 13.] Bayer request that this is changed for factual accuracy but also we ask that a check is made to ensure this is reflected in the economic modelling and the results generated.	model. Updated model results incorporating this and other changes were discussed by the committee and it was agreed that the DAPT recommendations should not change due to these. The model methods and results, and the committee discussion have been updated in the relevant guideline documents.
Bayer PLC	Economic analysis report	089	006 - 007	The economic analysis report recognises a limitation in the one-year decision tree of assuming that the probabilities 31 days to 1 year were independent of events experienced 0 to 30 days. This is indeed a limitation and in the model supporting TA335, the functionality to vary subsequent risks was included and supported by evidence.	Thank you for your comment. We note the information provided. This has not been changed in the model as it is considered unlikely to impact conclusions. Numerically the total number of each event in year 1 occurring would necessarily remain the same (to retain consistency with the real-world data) and this would only impact how 31 day to 1 year events are distributed between people who had no event, MI or stroke 0 to 30 days. The number of people alive at the end of year 1, and so entering the Markov model, would remain the same. The change in distribution of events would mean the numbers entering different alive health states in the post-year one Markov model may change somewhat but as event rates are low not substantially. Differences between the models mean methods are not directly transferable and exploratory work showed this would make very little difference to the results and so this was not changed due to time constraints.
Bayer PLC	Economic analysis	091	037 - 042	The economic analysis report also recognises another limitation in that it was assumed that the rate of stroke or reinfarction	Thank you for your comment. We note the information provided. This has not been changed in the model as it is

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	report			beyond one year would be the same as that between 31 days and 1 year. This is indeed a limitation and in the model supporting TA335, the functionality to vary subsequent risks was included and supported by evidence.	considered unlikely to impact conclusions as these rates do not vary by DAPT option. Difference between the models mean methods are not directly transferable. For example, risks in TA335 were based on the data from an RCT for an overall ACS population whereas the committee wished to use UK real world data for separate ACS subtypes.
AstraZeneca	Evidence review A: antiplatelet therapy	092	044	Concern The Committee simultaneously presents contrasting statements regarding the relative efficacy of ticagrelor and prasugrel. Following its indirect treatment comparison of ticagrelor Vs clopidogrel and prasugrel Vs clopidogrel, on page 60 of the evidence review, the Committee states "*using the data for prasugrel and ticagrelor each compared to clopidogrel generated an odds ratio for ticagrelor versus prasugrel of 0.77 (0.61 to 0.97) which favours ticagrelor*". Further on, it states *"the direct evidence from ISAR-REACT 5 gave an odds ratio of 1.24 (0.90 to 1.70) which favours prasugrel"* and on page 92, the Committee concludes "*....that the strongest evidence about the relative treatment effects of prasugrel versus ticagrelor came from the ISAR-REACT 5 study that compared them head to head and reported 1 year outcomes*". AstraZeneca does not agree with the Committee's conclusion. The full weight of its recommendation favouring prasugrel appears to be dependent on the outcome of the ISAR-REACT 5 trial alone. The Committee has therefore disregarded a substantial body of evidence, including the Phase 3 data upon which the regulatory approvals of the two medicines were based. Whilst AstraZeneca clearly recognises the importance of the	Thank you for your comment. You are correct in stating that contrasting statements are presented in the discussion section of the Evidence Report, but this is done deliberately in order to demonstrate that some outcome measures did not unequivocally favour one treatment over another. It is incorrect to state that the recommendation favouring prasugrel is dependent on ISAR-REACT 5 alone. We believe that the discussion is balanced, acknowledges the discrepant data and tries to reconcile all of these. Your concerns: 1) The patient settings are indeed different, but this would also be the case if we relied on the large studies of prasugrel vs clopidogrel and ticagrelor vs clopidogrel. 2) Several different outcome measures were considered by the committee 3) There is inconsistency, as agreed above. However, even if we accept the hypothesis that the 2 drugs show equivalent efficacy, prasugrel would still be more cost-effective as intervention costs are much lower.

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				ISAR-REACT 5 study to the ACS field and the legitimate questions regarding the optimal ACS treatment strategy that it seeks to resolve, there does remain a number of limitations and concerns about its design that preclude its generalisability to UK clinical practice. These concerns are primarily the following: 1) The objective of ISAR-REACT 5 was to compare the efficacy and safety of two labelled treatment strategies in patients with ACS; this study is not a 'head-to-head' drug trial of ticagrelor Vs prasugrel in the same patient setting 2) The primary outcome of ISAR-REACT 5 is not at all consistent with the Phase 3 studies for ticagrelor and prasugrel Vs clopidogrel, PLATO and TRITON-TIMI 38 respectively 3) The primary outcome of ISAR-REACT 5 is not consistent with other indirect or direct treatment comparisons of ticagrelor Vs prasugrel; the vast majority of these studies demonstrate that ticagrelor and prasugrel are at least equivalent in terms of efficacy in PCI patients 4) Numerous editorials and review articles by experts in the field, expressly warn against over-interpretation of ISAR-REACT 5 data and its potential application to clinical practice today Evidence supporting these arguments is detailed below. <u>Supporting evidence for AstraZeneca's primary concerns</u> 1) ISAR-REACT 5 is a 'pragmatic' open-label randomised	4) In relation to your suggestion of over-interpretation, it is important to note that the results of ISAR-REACT 5 have been considered alongside the results of other studies and the recommendations of the committee are based on the data as a whole. The committee acknowledge the limitations of ISAR-REACT 5, but other studies included in the evidence review have their own methodological limitations. Since ISAR REACT 5 is the largest head to head comparison of ticagrelor and prasugrel, the committee deemed it important to include the data from this study, whilst taking into account the limitations of its design. The additional detailed points you make under "supporting evidence" are acknowledged, although the committee did not regard all of these as flaws. For example, they felt that the demographics of ACS patients in Germany and Italy, and also cardiology practice in both countries, are sufficiently similar to UK patients to allow application of the results of ISAR-REACT 5 to the UK. Careful consideration was given to the strengths and weaknesses of all the studies included in Evidence Review A. It is pertinent here to point out that when the committee first discussed the evidence early in the development process, before publication of ISAR-REACT 5, their preliminary conclusions were that prasugrel was as efficacious as ticagrelor and more cost-effective. The recommendation favouring prasugrel in people with STEMI is not wholly dependent on ISAR-REACT 5.

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				controlled trial designed to compare the efficacy of two different treatment strategies in patients with ACS intended for PCI involving dual antiplatelet therapy (Schüpke, 2019). The study was not designed to directly compare the efficacy and safety of ticagrelor and prasugrel in the same clinical treatment setting - had this indeed been the intent of the trial, then it is reasonable to assume that the investigators would have designed the study differently and standardised the patient population accordingly. The following related technical issues about the study design & execution have also been widely noted in the scientific literature: a. The study was open-label and conducted in a small number of centres located in only 2 countries (21 centres in Germany and 2 centres in Italy). b. Only 4,416 of the 8,434 patients screened for the study were eligible for inclusion; highlighting the limited eligibility of these study results to the general ACS population. c. Bias was introduced by the inclusion of patients who were medically managed (14.2% and 13.4%; ticagrelor and prasugrel, respectively) and those who were found not to have ACS (8.8% and 9.5%; ticagrelor and prasugrel, respectively); both these patient groups were subsequently excluded from the safety analysis. d. Study drug treatment rates at hospital discharge were 81.1% and 80.7% in the ticagrelor and	

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				prasugrel arms, respectively, meaning that 18.9% and 19.4% of patients, respectively, were not discharged on their assigned study drug. e. At 12 months, 15.2% and 12.5% of patients in the ticagrelor and prasugrel arms, respectively, had discontinued study drug. As discussed in more detail below, on-treatment analysis did not demonstrate a significant difference between ticagrelor and prasugrel treatment strategies. f. Of significant importance, a disproportionate number of patients were excluded from the safety analysis in this group (prasugrel: 11.6%; ticagrelor: 1.1%). g. Radial access accounts for 37.3% and 36.5% (ticagrelor and prasugrel arms, respectively) of access site in ISAR-REACT 5. This does not reflect contemporary clinical practice in the UK where radial access accounts for 87.2% of all PCIs. 2) The primary efficacy endpoint of the study, which considerably favoured prasugrel (HR, 1.36, [1.09-1.70], p=0.006), is not consistent with the pivotal Phase 3 trial evidence available for ticagrelor and prasugrel on which the regulatory approvals were based (Wallentin, 2009; Wiviott, 2007). The magnitude of treatment effect for the primary efficacy endpoint for prasugrel in ISAR-REACT 5 was considerably better than had been previously observed Vs clopidogrel in its pivotal Phase 3 trial, TRITON-TIMI 38	

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				(absolute rate in ISAR-REACT 5: 6.9% Vs TRITON-TIMI 38: 10.7%) and inconsistent with the prespecified hypothesis for ISAR-REACT 5 itself. In contrast, the efficacy of ticagrelor, in terms of absolute rate of all-cause mortality, MI, and stroke, was consistent with its Phase 3 trial PLATO (ISAR-REACT 5: 9.3% Vs PLATO: 10.2%) and the prespecified hypothesis for ISAR-REACT 5. Furthermore, the margin of benefit observed for prasugrel over ticagrelor (36% relative risk increase and 2.3% absolute risk increase for ticagrelor), is greater than was observed with either prasugrel or ticagrelor compared to clopidogrel in TRITON-TIM 38 and PLATO, respectively. 3) As correctly identified by the Committee, the totality of the Phase 3 evidence for ticagrelor and prasugrel (both compared with clopidogrel), suggests that ticagrelor is potentially more efficacious than prasugrel. Beyond this, there are a number of indirect treatment comparisons of ticagrelor and prasugrel, as well as direct head to head comparisons of the products in the real world setting in the published literature - all of these demonstrate equivalent efficacy between the two products (NICE Evidence Review for Antiplatelets, 2020). 4) There are numerous editorials and review articles in the literature that critique ISAR-REACT 5 and warn against over-interpreting the outcome of the trial and how it should be applied to clinical practice (Ostrowska, 2019; Kubica, 2019; Storey, 2019; Roe, 2019). As an example, in one of	

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				the more prominent editorials (Ostowska, 2019), it is stated "*given the significant limitations of the ISAR-REACT 5 study, the results obtained should be treated with extreme caution and cannot be considered sufficient to alter the current treatment strategy*". Beyond the major concerns highlighted above, AstraZeneca would also like to highlight some further technical issues that speak to the consistency of the data compared with the Phase 3 data for ticagrelor: <u>Additional Evidence</u> **On treatment analysis** On-treatment analysis of the primary endpoint in ISAR-REACT 5 demonstrated no significant differences between the study groups (ticagrelor oTT: 92 events, prasugrel oTT: 71 events; (HR, 1.34, [0.98–1.82]). To this end, as stated in the editorial authored by Kubica & Jaguszewski (2019), *"a primary endpoint at 1 year after randomization, occurred in 184 of 2012 patients (9.3%) in the ticagrelor group and in 137 of 2006 patients (6.9%) in the prasugrel group (HR, 1.36; 95% CI, 1.09 to 1.70; P = 0.006). Taking into account that the analysis of 4018 patients included 1262 (31.4%) who were supposed to be on study medication, whereas they were not treated according to the study protocol, the absolute difference in primary endpoint incidence of 47 events can hardly be considered relevant."*	

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				Ticagrelor treatment effects and adverse event profile are wholly inconsistent with all preceding data • The difference in the primary endpoint in ISAR-REACT 5 was driven by a significantly higher rate of MI with ticagrelor Vs prasugrel (4.8% Vs. 3.0%; HR, 1.63, [1.18-2.25]). There was no significant difference in CV death or all-cause death between ticagrelor and prasugrel (CV death event rate: 3.2% ticagrelor, 3.0% prasugrel; all-cause mortality: HR 1.23 [0.91–1.68]). • An unexpectedly high proportion of the MIs associated with ticagrelor were procedure related (Type 4a /4b, 39% compared to 22% in the prasugrel arm, Schüpke, 2019). The explanation for this is unclear and raises significant concerns. Furthermore, the data is inconsistent with clinical evidence from other contemporary trials (Mehta, 2019) which suggests a significantly lower risk of Type 4a/4b MI. In contrast, a clear discrepancy in the rates of MI for prasugrel was observed in ISAR-REACT 5 compared to TRITON-TIMI 38, where outcomes were significantly better in the former versus the latter (3.0% ISAR-REACT 5 Vs 7.3% TRITON-TIMI 38). • The pivotal Phase 3 trial PLATO demonstrated that ticagrelor significantly reduced all-cause mortality compared to clopidogrel (HR, 0.78, [0.69-0.89], p<0.001 (nominal)). These findings are consistent with those from the meta-analysis proposed by the Committee (scenario 1; OR, 0.77 [0.68 to 0.88]).	

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				Conversely, when results from the ISAR-REACT 5 study are included in scenario 2, the indirect comparison indicates that ticagrelor instead increased all-cause mortality vs. clopidogrel (OR, 1.24, [0.86-1.79]) which is clearly inconsistent with the findings of the PLATO trial. Recommendation AstraZeneca contends that the evidence supporting the Committee's position of prasugrel's superiority over ticagrelor in patients with STEMI or UA/NSTEMI intended for PCI is weak and inconsistent with all that precedes it. Rather, overwhelming burden of evidence suggests that the two products are equivalent on the composite of CV death, MI, or stroke, but that ticagrelor exhibits greater benefit in reducing the risk of CV mortality and all-cause mortality. **AstraZeneca requests the Committee to consider reflecting this evidence with recommendations for:** **A) ticagrelor in a parity position to prasugrel in STEMI-PCI patients** **B) ticagrelor as the preferred treatment option in UA/NSTEMI patients intended for PCI** References Kubica J & Jaguszewski M. *Cardiol J*. 2019;26:427-428 Mehta SR, Wood DA, M.D., Storey RF, Mehran R, Bainey KR, Nguyen H, et al. *N Engl J Med*. 2019. 381:1411-1421	

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				Motovska Z, Hlinomaz O, Miklik R, Hromadka M, Varvarovsky I, Dusek J, et al. *Circulation*. 2016. 22;134:1603-1612. Prasugrel Versus Ticagrelor in Patients With Acute Myocardial Infarction Treated With Primary Percutaneous Coronary Intervention: Multicenter Randomized PRAGUE-18 Study. NICE Evidence Review for Antiplatelets, 2020 Ostrowska M, Adamski P & Kubica J. *Folia Cardiologica*. 2019 14;5:488-492 Roe M & Bhatt D. Duke Clinical Research Institute. 2019. https://dcri.org/comparative-effectiveness-trials/ Schüpke S, Neumann FJ, Menichelli M, Mayer K, Bernlochner I, Wöhrle J, et al. *N Engl J Med*. 2019. 17;381:1524-1534 Storey RF & Sibbing D. Medscape – ESC 2019. 2019. https://www.medscape.com/viewarticle/917980 Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, et al. *N Engl J Med*. 2009. 10;361:1045-57 Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, et al. *N Engl J Med*. 2007. 15;357:2001-15	
ROVI Biotech	Evidence Review C	013	004	It is mentioned in this line that "*Other preparations of enoxaparin pre-filled syringes are also available: 20mg, 40mg, 50mg, 60mg, 80mg,* 4 *120mg and 150mg".* As far as we are aware of, there are not **50mg** pre-filled syringes of enoxaparin marketed in the UK	Thank you for your comment. This has been corrected.
ROVI Biotech	Evidence Review C	013	Table 4	The table mentions "Enoxaparin Becat 80mg/0.8ml solution for injection pre-filled syringes (ROVI Biotech Ltd)". Please note that "Enoxaparin BECAT" is no longer available in the UK market. ROVI Biotech changed the name of this product	Thank you for your comment. This unit cost table has been updated.

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				by the end of 2018 to AROVI. This name change was a request made by the MHRA. See further information here: https://www.medicines.org.uk/emc/search?q=AROVI - http://www.ggcprescribing.org.uk/blog/name-change-enoxaparin-becat-arovi-and-availabilit/	
ROVI Biotech	Evidence Review C	013	Table 4	The table indicates that the List Price of one (1) pre-filled syringe of ROVI Biotech's enoxaparin 80mg is £5.51. This information is incorrect as it is based in information from 2018. The current List Price for a box of 10 prefilled syringes of AROVI is £ 41.35. This means that the price of 1 pre-filled syringe is £ 4.135. This information can be officially checked in the DM+D browser: https://apps.nhsbsa.nhs.uk/DMDBrowser/DMDBrowser.do	Thank you for your comment. This unit cost table has been updated.
ROVI Biotech	Evidence Review C	013	Table 4	The table indicates that the List Price of one (1) pre-filled syringe of Techdown's INHIXA 80mg is £ 4.41 This information is incorrect as it is based in information from 2018. Please note that INHIXA changed its List Price effective October 2019 and the current price for a pack of 10 is £ 55.13, which means the cost of 1 pre-filled syringe is £ 5.513 These prices can be officially checked in the DM+D browser: https://apps.nhsbsa.nhs.uk/DMDBrowser/DMDBrowser.do	Thank you for your comment. This unit cost table has been updated.
ROVI Biotech	Evidence Review C	015	008	Taking into reference the comment above the prices mentioned in this line should be revisited.	Thank you for your comment. This has been updated.

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Bayer PLC	Evidence Review G	027	012	The incorrect cost is listed for 15mg rivaroxaban. The cost should state £1.80 per day and a cost per year of £657. Bayer request that this is changed for factual accuracy.	Thank you for your comment. This has been corrected.
Royal College of Nursing	General	General	General	Dear colleague, Many thanks for the opportunity to contribute to this guideline. We don't have any comments from the RCN on this occasion.	Thank you for confirming.
AstraZeneca	General	General	General	It appears that a cost-effectiveness threshold of £20,000 per QALY has been used to inform decision-making, rendering Ticagrelor + ASA not cost-effective for STEMI-PCI patients under Scenario 1 (probabilistic ICER £21,822). The cost-effectiveness threshold used for NICE clinical guidelines should mirror that used in NICE technology appraisals (TA), where a threshold of £20,000-£30,000 is used (NICE, 2013). Many TAs have recommended as a treatment option drugs with an ICER >£20,000 (NICE TAs: 354, 358, 388, 393), including the appraisal for ticagrelor for patients with a history of MI (TA420), where the most plausible ICER was deemed to lie in the range £20,636 to £24,711 (NICE TA 420). References National Institute for Health and Care Excellence. Guide to the methods of technology appraisal 2013. https://www.nice.org.uk/process/pmg9/chapter/foreword National Institute for Health and Care Excellence. Edoxaban for treating and for preventing deep vein thrombosis and pulmonary embolism, TA 354. https://www.nice.org.uk/guidance/ta354	Thank you for your comment. The NICE principles state: Interventions with an ICER of less than £20,000 per QALY gained are generally considered to be cost effective. Our methods manuals explain when it might be acceptable to recommend an intervention with a higher cost-effectiveness estimate. A different threshold is applied for interventions that meet the criteria to be assessed as a 'highly specialised technology'. Details of how recommendations are reached taking into account all factors are detailed in individual guideline or technology appraisal documentation. However, also note that following changes made in response to consultation comments the ICER you refer to is below £20,000 per QALY gained and so is not affected by this issue.

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				National Institute for Health and Care Excellence. Tolvaptan for treating autosomal dominant polycystic kidney disease, TA 358. https://www.nice.org.uk/guidance/ta358 National Institute for Health and Care Excellence. Sacubitril valsartan for treating symptomatic chronic heart failure with reduced ejection fraction, TA 388. https://www.nice.org.uk/guidance/ta388 National Institute for Health and Care Excellence. Alirocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia, TA393. https://www.nice.org.uk/guidance/ta393 National Institute for Health and Care Excellence. Ticagrelor for preventing atherothrombotic events after myocardial infarction, TA 420. https://www.nice.org.uk/guidance/ta420	
Joint response by the British Cardiovascular Society (BCS) and the British Cardiovascular Intervention Society (BCIS)	General	General	General	The BCS and BCIS notes that the intravenous antiplatelet drug, cangrelor, has not been considered in the recommendations. It may be a drug that is suited to bailout use, much as has been the case in the past for GPI.	Thanks for your comment. Cangrelor was not identified for inclusion in the guideline update when the scope was compiled and consulted on. It will be considered for inclusion when the guideline is next considered for review. This topic has been added to the NICE log of topics for future consideration.
Joint response by the British Cardiovascular Society (BCS) and the British Cardiovascular Intervention Society (BCIS)	General	General	General	Feedback from many colleagues commented on the cohesiveness of the guideline as a whole. Colleagues felt that it read as a series of individual statements, rather than as a cohesive document. This made some feel that the document was hard to read and absorb. Navigating around the document is not as easy as with comparable ESC guidelines. Surgical intervention is not considered. This may reflect the absence of a surgeon on the committee rather than the evidence base.	Thanks for your comment. When the guideline is published, it will be easier to navigate on the webpage and hyperlinks will be included to facilitate moving between different sections of the recommendations. Using the NICE Pathway should also help with navigating the guidance. Surgical management was not put forward for inclusion in the Scope, and therefore no surgeon was recruited to the committee. Recommendations included from existing

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					guidance (1.2.22 and 1.2.23) direct people to consider surgical revascularisation.
Joint response by the British Cardiovascular Society (BCS) and the British Cardiovascular Intervention Society (BCIS)	General	General	General	In relation to question 4 which NICE asks at the beginning of this document, "As part of the update to this guideline, we have removed recommendations regarding the use of glycoprotein inhibitors as part of the early management for people with unstable angina or NSTEMI. It was felt that they would be unlikely to be used in practice with the antiplatelet therapies that are now recommended (prasusgrel or ticagrelor) owing to the potential for increased bleeding. Do you agree with this approach?", the BCS agrees with this approach.	Thanks for your comment.
Royal College of Physicians	General	General	General	Further to the below the RCP would like to endorse the BCS and BCIS response.	Thanks for your comment.
Royal College of Nursing	General	General	General	Thank you for the opportunity to contribute to this. We do not have any comments on this occasion.	Thanks for your comment.
National Clinical Director for Heart Disease, NHS England & NHS Improvement	General	General	General	I am aware that this consultation has been sent to the British Cardiovascular Society who have submitted a detailed response. I would like to add my support to this response, which I believe is a measured and appropriate view.	Thanks for your comment
Sheffield Teaching Hospital NHS Foundation Trust	Guideline	General	General	The committee has not considered evidence on blood pressure management and how this impacts on the recommendations for ACE inhibitors/ARBs. This leads to inconsistency with the current ESC guidelines.	Thanks for your comment. The recommendations on ACEI/ARB's were not within the scope for the current update. Management of hypertension is covered in its own NICE guideline.
University Hospitals of Leicester NHS Trust	Guideline	General	General	There appears no mention of Cangrelor. As we see increasing numbers of Out of Hospital Cardiac Arrest (OHCA) it becomes increasingly difficult to ensure appropriate pre procedural anti-platelet therapy. This is specially so since there have been	Thanks for your comment. Cangrelor was not identified for inclusion in the guideline update when the scope was compiled and consulted on. It will be considered for inclusion when the guideline is next considered for review. This topic has been

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				concerns regarding use of naso-gastric tubes in the cath lab following cases of their misplacement. Cangrelor is an effective intra-venous P2Y12-receptor inhibitor, its efficacy being support by a number of large robust clinical trials (eg Pegasus) Furthermore this agent has been reviewed by NICE (Coronary revascularisation: Cangrelor Evidence summary [ESNM63] Published date: November 2015) and as summarised Summary *Cangrelor statistically significantly reduced the risk of periprocedural ischaemic events compared with clopidogrel in a large RCT of people receiving periprocedural aspirin who underwent percutaneous coronary intervention (PCI) for mixed indications without P2Y12 inhibitor pre-treatment, with a number needed to treat of 84 at 48 hours. However, it did not statistically significantly reduce mortality and clinical benefits were described by the European Medicines Agency as modest. Bleeding and dyspnoea events were more frequent in the cangrelor group (numbers needed to harm of 26 and 142 at 48 hours for mild bleeding and dyspnoea respectively). There are no published studies comparing cangrelor with other oral antiplatelet agents for people undergoing PCI. In the pivotal study, the treatment pathway differed from usual UK practice regarding choice of oral antiplatelet drug and this limits the applicability of the evidence to UK practice where prasugrel and ticagrelor have superseded clopidogrel as the standard of care for people with unstable angina, non-ST-segment-elevation myocardial infarction and myocardial infarction with ST-segment-elevation. Cangrelor, co-administered with aspirin, is therefore a second-line treatment option for use in people with coronary artery disease undergoing PCI for whom oral therapy*	added to the NICE log of topics for future consideration.

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				with P2Y12 inhibitors is not feasible or desirable. *Cangrelor was considered appropriate for a NICE technology appraisal but NICE is unable to make a recommendation about the use in the NHS of cangrelor for the licensed indication because no evidence submission was received from the manufacturer of the technology.* *Regulatory status: Cangrelor received a European marketing authorisation in March 2015 and was launched in the UK in July 2015.* That said when there is no alternative as the patient is intubated because of OHCA I would strongly recommend that NICE take a position on Cangrelor and indeed recommend its use in those patients unable to receive oral pre- STEMI/ MSTEMI dual anti-platelet therapy	
Boston Scientific	Guideline	General	General	BSC have reviewed the guidance and welcome the 2020 amendments. We have limited additional commentary but would like to highlight the following publication to reinforce the guidance in point 1.1.19 and the endorsement of DES. 1. Varenne O, Cook S, Sideris G, Kedev S, Cuisset T, Carrié D, Hovasse T, Garot P, El Mahmoud R, Spaulding C, Helft G. Drug-eluting stents in elderly patients with coronary artery disease (SENIOR): a randomised single-blind trial. The Lancet. 2018 Jan 6;391(10115):41-50.	Thanks for your comment.
Bayer PLC	Guideline	General	General	Bayer is concerned that whilst there is cross-reference to TA335 (on pages 8 and 14), it is not fully incorporated. We would like to make four key points supporting the greater prominence given to patients who may be suitable for rivaroxaban. **1. Rivaroxaban in combination with aspirin alone**	Thank you for your comment. We acknowledge that our scope suggested that TA335 would be incorporated in this guideline but NICE have changed their procedures since the scoping phase and now cross-refer to TAs at appropriate points within their guidelines rather than incorporating them. Please see the section 'Referring to technology appraisals in

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				TA335 recommends (point 1.1) that: *rivaroxaban is recommended as an option within its marketing authorisation, in combination with aspirin plus clopidogrel* ***or aspirin alone****, for preventing atherothrombotic events in people who have had an acute coronary syndrome with elevated cardiac biomarkers.* Whilst the economic analysis report states that: *The analysis did not include* ***aspirin alone*** *as this comparison was not included in the review protocol for this question in the guideline update (see Evidence report A for review protocol) because use of DAPT is well established in ACS,* Bayer do not consider that these patients should be omitted from the guideline. The option to use rivaroxaban with aspirin alone is an important option: • For patients intolerant of P2Y12 • For patients unresponsive to clopidogrel but intolerant of ticagrelor • For patients who have failed on P2Y12 e.g. stent thrombosis • That facilitates extended therapy for those at high ischaemic risk moving from acute to chronic as per the COMPASS regime (Eikelboom *et al*. N Engl J Med 2017;377:1319-1330). This separate indication was recommended as a treatment option by NICE TA607 in October 2019. **2. Outcomes with rivaroxaban 'compared' with ticagrelor/ prasugrel**	recommendations' in 'Developing NICE guidelines: the manual' for further details of the current process: https://www.nice.org.uk/process/pmg20/chapter/linking-to-other-guidance#related-nice-technology-appraisal-guidance Two cross references to TA335 have been added to the guideline. Technology appraisals will also be included in the Pathway. The committee were aware of trial data re administering rivaroxaban with ticagrelor or prasugrel, but the scope did not include provision to change or amend TA335 and this, as you know, refers only to use with aspirin +/- clopidogrel.

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				Whilst not within the licensed indication, the combination of rivaroxaban with ticagrelor and prasugrel was tested in the GEMINI ACS 1 trial (Ohman *et al*.- Lancet 2017; 389: 1799-1808). The rivaroxaban 2.5mg b.d. dose in combination with dual antiplatelet therapy was also tested in the PIONEER AF PCI trial (Gibson *et al.* N Engl J Med 2016; 375: 2423-2434). All these trials despite different designs, patient populations and combinations provide a consistent positive profile for the use of this regime in ACS. When considering the antiplatelet trials for prasugrel (TRITON Wiviott *et al*. N Engl J Med 2007; 357:2001-2015) or ticagrelor (PLATO Wallentin *et al*. N Engl J Med 2009; 361:1045-1057) as well as the rivaroxaban ATLAS ACS 2 TIMI 51 trial (Mega *et al*.- N Engl J Med 2012; 366:9-19), all 3 trials had broadly similar but different patient populations and definitions. As such, comparison of the trial outcomes would suffer from limitations. However, the outcomes for these 3 trials were similar in terms of prevention of MACE events, stent thrombosis and major bleeding vs aspirin and clopidogrel. The rivaroxaban licensed population did deliver a significant relative risk reduction for cardiovascular death of 45% (p-Value <0.001) and all-cause mortality of 42% (p-Value <0.001). This is around double the relative risk reductions seen in the TRITON & PLATO trials. **3. Thrombus properties** Anticoagulants are an important component of therapy for ACS in the acute setting. However, excess thrombin generation has been found to persist in stable patients for at least 6–12 months beyond the acute presentation of ACS, providing a rationale for	

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				long-term oral anticoagulant therapy for the prevention of recurrent events. The use of anticoagulant therapy in combination with antiplatelet therapy targets complementary mechanisms associated with thrombus formation in patients with ACS. Rivaroxaban is a highly selective direct factor Xa inhibitor with oral bioavailability. Inhibition of Factor Xa interrupts the intrinsic and extrinsic pathway of the blood coagulation cascade, inhibiting both thrombin formation and development of thrombi. The dual pathway treatment strategy, which recognises the importance of thrombin generation following ACS events and the role that rivaroxaban can play in this, on top of dual antiplatelet therapy offers a treatment paradigm to prevent further atherothrombotic events and provides significant mortality benefit. Importantly, rivaroxaban is the only oral anticoagulant licensed for prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers. Similarly, rivaroxaban is the only anticoagulant indicated for the prevention of atherothrombotic events in adult patients with coronary artery disease (CAD) or symptomatic peripheral artery disease (PAD) at high risk of ischaemic events. There is some evidence that fibrin rich clots which are resistant to endogenous lysis independently predict adverse outcome in ACS patients. In patients with certain comorbidities, e.g. Diabetes mellitus (DM), Chronic kidney disease (CKD), and PAD, all high-risk conditions for cardiac ischaemia, studies have shown associations with adverse fibrin rich clot characteristics	

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				(Fibrin clot properties independently predict adverse clinical outcome following acute coronary syndrome: a PLATO substudy (Sumaya et al. European Heart Journal 2018) (Viswanathan et al; Thromb Res 2014; doi: 10.1016/j.thromres.2014.01.033. [Epub ahead of print]). Rivaroxaban 2.5mg b.d. dose in combination with ASA (in the CAD vs ACS population i.e. COMPASS vs ATLAS) has demonstrated additional MACE risk reductions in these patient groups CKD, PAD & DM. These high risk groups were identified as having the greatest net benefit in the COMPASS study: Rivaroxaban Plus Aspirin Versus Aspirin in Relation to Vascular Risk in the COMPASS Trial (Annand et al. Journal of the American College of Cardiology 2019; Vol 73, No 25; 3272-3280). **4. Role of rivaroxaban in ACS** In the UK, use of rivaroxaban in ACS is limited but it is an important option for clinicians. In addition to the co-morbidities listed above which have demonstrated altered fibrin content and structure which predict poorer clinical outcomes with DAPT, below are listed some additional specific areas where clinicians have expressed a preference or consideration to use rivaroxaban in ACS. **DAPT Failure:** • For those patients who have a second MI whilst on DAPT; patients who receive recommended dual antiplatelet therapies still have a 10% residual risk of	

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				experiencing a major CV event during the 12–15 months after ACS has occurred (Yusuf et al. 2001; Wiviott et al. 2007; Wallentin et al. 2009). • Stent thrombosis whilst on DAPT (approximately 2-4% of patients in the TRITON & PLATO trials suffered stent thrombosis whilst on DAPT- stent thrombosis rates with rivaroxaban in the licensed population were less than 1%) **Medically managed patients**: • Patients with multivessel diffuse disease with no clear stenting option • Those with planned cardiac or other procedures (the quick "off" time for a DOAC was deemed to aid in managing bleeding risk during planned procedures). • Late presentation MI (long standing clot would be assumed to have a higher fibrin content and may benefit from a dual pathway approach) **Hypercoagulatory state:** In these cases, there are observable or predictable increases in baseline thrombin levels and so patients may benefit from a dual pathway approach. • High thrombus burden • Complex vasculature i.e.unruptured, unstented friable plaques at a higher risk of triggering the coagulation cascade **Lower Pressure/Lower Flow:** These are scenarios where the physics of fluid dynamics may predict a higher fibrin component in arterial clots: • Coronary artery ectasia	

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				• Significant distal disease • Stent malapposition • Stents across aneuryitic vessels that leave "quiet" pockets between the stent and lumen wall • poor left ventricular function	
Bayer PLC	Guideline	General	General	The guideline makes several references to secondary prevention and longer-term (beyond 12 months) use of antiplatelets. Since the initiation of the guideline update, rivaroxaban has been appraised by NICE for preventing atherothrombotic events in people with coronary or peripheral artery disease (TA607). Appropriate places to cross-reference to TA607 in the guideline are suggested as set out below: - Page 10 (risk assessment) – ideally the physician would also assess longer-term risk given there is now evidence for the benefit of dual therapy beyond 12 months whereas prior there was only evidence for the benefit of SAPT - Page 18 (line 23) – there is reference to the use of aspirin in patients with MI over 12 months prior. This would also be a suitable place to cross-reference to TA607 - Page 20 (line 18) – this section considers the need for continuing therapy beyond 12 months and would be a suitable place to cross reference to TA607	Thanks for your comment. We have now included a cross reference to TA607.
AstraZeneca	Guideline	General	General	SUMMARY AstraZeneca would like to thank NICE for its continued commitment to advancing clinical care for patients with ACS. AstraZeneca also remains fully committed to advancing care for patients across the spectrum of coronary artery disease, as demonstrated by our continued efforts in developing medicines to treat this debilitating and often fatal disease. With this shared	Thank-you for your comments. Please see responses to comment ID7 above, and the committee's consideration of the available data (including the studies you quote, PLATO, TRITON-TIMI, and ISAR-REACT 5) in Evidence Report A of the Guideline update. To summarise the latter, the committee discussed the concerns you express regarding the impact of prasugrel's labelling

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				ambition and commitment in mind, AstraZeneca welcomes the opportunity to respond to the draft 2020 Guideline proposed by the NICE Committee. In the light of the COVID-19 pandemic, in which patients with underlying cardiovascular disease are at a higher risk of COVID-19-related mortality than the general population, and those with ACS may be further compromised as they delay going to hospital in a timely manner to avoid COVID-19 infection, it is of paramount importance that the NICE Committee prioritises 'simplicity' of care for healthcare professionals and patients in the new guideline above all else. Any potential for complexity or delay to dual antiplatelet treatment should be eliminated at all costs, ensuring patients receive rapid, effective care in order to deliver the best clinical outcomes. **AstraZeneca supports the majority of the Committee's recommendations in the draft guideline, particularly with respect to the management of patients with STEMI and UA/NSTEMI not intended for PCI. However, we have identified two predominant areas of concern in the proposed guideline with respect to the treatment of patients intended for PCI:** 1. **the recommendation that prasugrel is to be offered as the ONLY antiplatelet treatment for STEMI-PCI patients, and** 2. **the recommendation for PARITY positioning of both ticagrelor and prasugrel in UA/NSTEMI-PCI patients.**	restrictions which limit its use to those undergoing PCI and took them into account in the recommendations covering people with NSTEMI, and people with ACS managed medically, which do not recommend prasugrel as the drug of choice. However, for the majority of people with STEMI, who will proceed quickly to cardiac catheterisation, the committee agreed that it is perfectly feasible to use prasugrel within its licensing restrictions. They noted that prasugrel is currently used in a minority of cases in the UK and that audit data shows no evidence of worse outcomes. Other patient-specific labelling restrictions for prasugrel (such as those on age and prior stroke) will have to be taken into account on an individual basis, but the same applies to ticagrelor albeit with a different list of contraindications and cautions.

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				AstraZeneca's concerns regarding the above are founded on A) the lack of compelling evidence supporting prasugrel as the treatment of choice for PCI patients, the ISAR-REACT 5 study alone cannot be used to make this recommendation B) labelling restrictions with prasugrel that will complicate treatment pathways, hinder implementation across the country and increase risk to patient safety, and C) the overall negative impact of these recommendations on the speed, quality and continuity of care for ACS patients, of particular relevance at a time of national crisis. To provide context, 'ticagrelor' is a reversible P2Y12 inhibitor used, in combination with low dose aspirin, as a standard of care therapy to reduce the risk of recurrent atherothrombotic events in patients with ACS. The evidence underpinning ticagrelor's product licence is extensive and comprises the randomised, double-blind controlled pivotal Phase 3 trials PLATO (Wallentin, 2009) and PEGASUS (Bonaca, 2015), which involved over 39,000 patients. Ticagrelor's indication in the EU enables treatment of patients with STEMI and UA/NSTEMI, regardless of their intended management strategy (invasive or medical management). Of note, the use of ticagrelor in both settings is reflected prominently in the Class I recommendations in the latest ESC (Valgimigli, 2017) and ACC/AHA (Levine, 2016) clinical guidelines. In the pivotal PLATO trial, ticagrelor reduced both CV mortality (HR, 0.79, [0.69-0.91], p=0.001) and all-cause mortality (HR, 0.78, [0.69-0.89], p<0.001 (nominal)) compared to clopidogrel in	

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				patients with ACS (Wallentin, 2009). The superiority of ticagrelor over clopidogrel has been further reported in a substantial body of real-world evidence. Specifically, the SWEDEHEART PRACTICAL study, which included more than 45,000 patients in the real-world setting, reported a reduction in the composite of death, MI, and stroke, and all-cause mortality with ticagrelor Vs clopidogrel (HR, 0.85, [0.78-0.93], HR, 0.83, [0.75-0.92], respectively), (Sahlén, 2016). In contrast, the EU licence for prasugrel, an irreversible P2Y12 inhibitor, is restricted to ACS patients undergoing PCI only. In prasugrel's pivotal Phase 3 trial, TRITON-TIMI 38 (n=13,608), prasugrel was superior to clopidogrel in reducing a composite of CV death, MI, or stroke (HR, 0.81 [0.73-0.90], p<0.001) but did not demonstrate a significant reduction in CV or all-cause mortality (HR, 0.89, [0.70-1.12], p=0.31; HR, 0.95, [0.78-1.16], p=0.64, respectively) in the trial, unlike ticagrelor in PLATO. Beyond this tangible difference in the level of robustness of the clinical evidence supporting the use of ticagrelor over prasugrel, there are also labelling restrictions for prasugrel that have the potential to negatively impact the widespread implementation of the Committee's recommendation to use prasugrel in ACS patients intended for PCI. Such restrictions include, but are not limited to, 1) dose adjustments based on weight and age due to bleeding risk, 2) contraindication for prior stroke, 3) limited flexibility on means of administration in the emergency setting, 4) known coronary anatomy prior to loading, and 5) insufficient evidence to support unilateral switch from a pre-loaded P2Y12	

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				inhibitor to prasugrel. All of these labelling issues have the potential to reduce quality of care and impact patient safety. Finally, with regard to the use of these products in clinical practice in the UK today, evidence suggests that 47.5% of STEMI-PCI patients and 40.2% of UA/NSTEMI-PCI patients are treated with ticagrelor versus only 7.2% of STEMI-PCI and 1.0% of UA/NSTEMI-PCI patients treated with prasugrel (BCIS 2017-2018 Audit Report). This evidence alone reflects the broad consensus of the UK Cardiology community on the respective clinical importance of these two antiplatelet medicines, which clearly favours ticagrelor. A recommendation to fundamentally change the use of these products in a particular ACS patient population (for example in STEMI-PCI) nationally, in light of the labelling restrictions for prasugrel detailed above, can only add complexity for healthcare professionals at a time when simplicity should be the priority. In summary, there is extensive evidence and rationale to support a prominent role for ticagrelor in all ACS patients in the UK moving forward, regardless of intended management strategy (PCI/no PCI, CABG). AstraZeneca respectfully requests the Committee to consider two important amendments to the guideline for ACS patients intended for PCI: 1. **For STEMI patients intended for primary PCI, ticagrelor is recommended in a parity position to prasugrel**. This recommendation is based on robust clinical evidence, clear demonstration of cost	

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				effectiveness (see comments 3 to 6), and evidence of ticagrelor's extensive use in UK clinical practice in this setting (see comments 2 and 7). 2. **For UA/NSTEMI patients intended for PCI, ticagrelor is recommended as the preferred option.** This recommendation is based on extensive clinical evidence and cost effectiveness analyses. It is supported by ticagrelor's broad label for all patients with ACS regardless of treatment strategy (no licence or guideline imposed restrictions), as well as a number of important practical considerations that make it a mainstay of clinical care today, such as ability to be loaded at first medical contact, potential to administer via multiple dosing routes, and clinical data that supports loading in patients pre-loaded with clopidogrel (see comments 2 and 7). References BCIS 2017-2018 Audit Report. http://www.bcis.org.uk/wp-content/uploads/2019/02/BCIS-Audit-2017-18-data-for-web-ALL-excl-TAVI-as-27-02-2019.pdf Bonaca MP, Bhatt DL, Cohen M, Steg PG, Storey RF, Jensen EC, et al. *N Engl J Med*. 2015. 7;372:1791-800 Levine GN, Bates ER, Bittl JA, Brindis RG, Fihn SD, Fleisher LA, et al. *Circulation*. 2016. 6;134:e123-55 Sahlén A, Varenhorst C, Lagerqvist B, Renlund H, Omerovic E, Erlinge D, et al. *Eur Heart J*. 2016. 21;37:3335-3342 Valgimigli M, Bueno H, Byrne RA, Collet JP, Costa F, Jeppsson A, et al. *Eur Heart J*. 2018. 14;39:213-260 Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, et al. *N Engl J Med*. 2009. 10;361:1045-57	

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Beat SCAD	Guideline	General	General	Beat SCAD supports people who have experienced Spontaneous Coronary Artery Dissection (SCAD). SCAD is a non-atherosclerotic cause of ACS and, based on research findings to date, requires different considerations for its management compared with atherosclerotic ACS. These considerations include caution regarding the administration of thrombolytic therapy and performing percutaneous coronary intervention (PCI) as both strategies have been documented with poorer outcomes in the setting of SCAD. As the current guidelines focus on atherosclerotic ACS, we believe this can impede the considerations required for SCAD. Although the guidelines and specifically the Chest pain algorithm indicate that symptoms of ACS should not be assessed differently in men and women or among different ethnic groups, and that central chest pain may not be the main symptom, some SCAD patients are being filtered out of the algorithm because ACS is not being suspected in this patient population. This is almost entirely seen in women and usually because they have no conventional cardiovascular risk factors and no prior history of chest pain (or other, such as back, jaw and/or arm pain or discomfort). If an ECG is done, it is often normal. Some SCAD patients are being told they are "too young" to be having a heart attack. However, SCAD has been documented across a wide age range (18-84 years), with a mean age of between 44-53 years. The algorithm requires specific mention of non-atherosclerotic causes of ACS including SCAD to ensure a 'red flag' is raised before ruling out ACS in a person who appears to be low risk for cardiovascular events.	Thanks for your comment. Thanks for your comment. The guideline is based on management of atherosclerotic coronary artery disease, the commonest cause of ACS in men and women. It is not possible to add content about SCAD into the ACS guideline because SCAD was not in the scope, and the developer and committee have not searched for and reviewed the relevant literature.. The guideline has been amended to clarify that it does not include management of SCAD (Page 1). NICE has no plans to develop a guideline in this area at this time.

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				We believe the guidelines should be amended as follows: • Clarify throughout that the advice and data in the guidelines are for atherosclerotic ACS and management of non-atherosclerotic conditions such as SCAD may be different. • Clarify where management of non-atherosclerotic conditions differs from the current guidance. • Include a separate section to include issues pertinent to non-atherosclerotic ACS, such as SCAD. References: Adlam D, Alfonso F, Maas A, Vrints C; Writing Committee. European Society of Cardiology, acute cardiovascular care association, SCAD study group: a position paper on spontaneous coronary artery dissection. Eur Heart J. 2018 Feb 22. doi: 10.1093/eurheartj/ehy080. Hayes SN, Kim ESH, Saw J, Adlam D, Arslanian-Engoren C, Economy KE, Ganesh SK, Gulati R, Lindsay ME, Mieres JH, Naderi S, Shah S, Thaler DE, Tweet MS, Wood MJ; American Heart Association Council on Peripheral Vascular Disease; Council on Clinical Cardiology; Council on Cardiovascular and Stroke Nursing; Council on Genomic and Precision Medicine; and Stroke Council. Spontaneous Coronary Artery Dissection: Current State of the Science: A Scientific Statement From the American Heart Association. Circulation. 2018 May 8;137(19):e523-e557. doi: 10.1161/CIR.0000000000000564. Epub 2018 Feb 22. Review.	
St. Georges University	Guideline	General	General	A 12 month check-up point is imperative in order to review the ACS medications that would have been started from a	Thanks for your comment. The scope for the current guideline update did not include a review of duration of anti-platelet and

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Hospitals NHS Foundation Trust				secondary and tertiary standpoint. Whilst beta-blockers are one medication that can be reviewed, it would be a good point to review any antiplatelet therapy and gastro-protection prescribed at this point from a poly-pharmacy perspective.	gastro-protection therapies. However, a link to the NICE medicines adherence guideline is given, and this makes your point regarding regular review.
St. Georges University Hospitals NHS Foundation Trust	Guideline	General	General	Patients who are started on an anticoagulant + antiplatelet should be initiated on gastro-protection for the duration of therapy to reduce the risk of GI bleed.	Thanks for your comment. This is common practice but we have not reviewed any relevant evidence for this update.
Action on Smoking and Health (ASH)	Guideline	General	General	**ASH welcomes the inclusion of smoking cessation in the draft guidelines. Smoking cessation is effective and cost-effective for secondary prevention following diagnosis of acute coronary syndromes. More broadly, ensuring smoking cessation is embedded across treatment pathways contributes to healthy and resilient populations, the need for which COVID-19 has made clear, and meets objectives set out in the NHS Long Term Plan.** In particular, ASH welcomes reference to the need for users of the guidance to offer both referral to a smoking cessation service and, where someone is not able or is unwilling to accept this referral, to offer pharmacotherapy. Interventions should follow the evidence base for Very Brief Advice, as set out in NICE guidance NG92 to which this draft guidance refers,[1] and patients	Thanks for your comments with which the guideline committee agree.

[1] NICE. [NG92] Stop smoking interventions and services. March 2018.

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				should be asked about their smoking status at all follow-up appointments. Smoking cessation services[2] and pharmacotherapy[3] for smoking cessation are proven to improve a person's likelihood of successfully quitting and it is important they are widely offered by health professionals given around half of all quit attempts made in England are done so unaided.[4] Support for smoking cessation is still poorly implemented in much of primary[5] and secondary care.[6] Smoking cessation should be regarded as a key component of disease management and recovery for people diagnosed with acute coronary syndromes who smoke. A 2000 meta-analysis found that smoking cessation results in a 50% reduction in mortality after myocardial infarction.[7] Similarly, a 2011 cohort study showed comparable reductions in mortality risk for patients who quit within 3 months of acute myocardial infarction, acute coronary syndrome or coronary artery intervention.[8] More recently and with respect to acute coronary syndrome more	

[2] Stead LF, Koilpillai P, Fanshawe TR, Lancaster T. Combined pharmacotherapy and behavioural interventions for smoking cessation. Cochrane Database of Systematic Reviews 2016, Issue 3. Art. No.: CD008286. DOI: 10.1002/14651858.CD008286.pub3.
[3] Cahill K, Stevens S, Perera R, Lancaster T. Pharmacological interventions for smoking cessation: an overview and network meta-analysis. Cochrane Database of Systematic Reviews 2013, Issue 5. Art. No.: CD009329. DOI: 10.1002/14651858.CD009329.pub2.
[4] Public Health Matters: Stop smoking – what works? (2018) [accessed June 2020]
[5] Rosenberg G, Crawford C, Bullock S, Petty R, Vohra J. Smoking Cessation in Primary Care: A cross-sectional survey of primary care health practitioners in the UK and the use of Very Brief Advice. 2019.
[6] British Thoracic Society. National smoking cessation audit 2019. June 2020.
[7] Wilson K, Gibson N, Willan A, Cook D. Effect of smoking cessation on mortality after myocardial infarction: meta-analysis of cohort studies. *Arch Intern Med* 2000;160:939–44.
[8] Breitling LP, Rothenbacher D, Vossen CY *et al*. Validated smoking cessation and prognosis in patients with stable coronary heart disease. *J Am Coll Cardiol* 2011;58:196-7

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				broadly, a 2017 study found that among a contemporary cohort of acute coronary syndrome patients, those who continued to smoke had an 80% risk of lower survival than those who had quit, who in-turn had comparable survival to lifelong non-smokers.[9] One long-term study following a cohort of acute coronary syndrome patients in Greece over 10 years found that active smoking following acute coronary syndrome remained a substantial clinical threat, increasing mortality by 57.8% and increasing the risk of a subsequent acute coronary syndrome event by 24.6%.[10] There is, therefore, a clear and important role for smoking cessation in secondary prevention following acute coronary syndrome. In addition to its clinical efficacy for secondary prevention of acute coronary syndrome, smoking cessation is highly cost-effective. The 2018 Royal College of Physicians report *Hiding in Plain Sight: Treating tobacco dependency in the NHS*[11] includes a comparison of cost-utility analyses for smoking cessation interventions and for a range of routine standard practice or other widely used therapies and interventions identified in searches of NICE guidelines including acute coronary syndrome, heart failure, myocardial infarction, stroke and stable angina. The median incremental cost-effectiveness ratios (ICERs) of	

[9] Yudi MB, Farouque O, Andrianopoulos N on behalf of the Melbourne Interventional Group, *et al* The prognostic significance of smoking cessation after acute coronary syndromes: an observational, multicentre study from the Melbourne interventional group registry *BMJ Open* 2017;**7:**e016874. doi: 10.1136/bmjopen-2017-016874

[10] Notara V, Panagiotakos D B, Kouroupi S, et al. Smoking determines the 10-year (2004–2014) prognosis in patients with Acute Coronary Syndrome: the GREECS observational study. Tobacco Induced Diseases. 2015;13(November):38. doi:10.1186/s12971-015-0063-6.

[11] Royal College of Physicians. Hiding in plain sight: treating tobacco dependency in the NHS. London: RCP, 2018.

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				smoking cessation interventions was £634 compared to £7,556 for cardiovascular disease (inclusive of acute coronary syndrome etc as described above), thereby demonstrating that "smoking cessation interventions are not only cost-effective in their own right, but especially so in relation to routine therapies for diseases caused or exacerbated by smoking that clinicians prioritise over smoking cessation."[11] The NHS Long Term Plan[12] sets the objective that "By 2023/24, all people admitted to hospital who smoke will be offered NHS-funded tobacco treatment services."[12] For this objective to be met, smoking cessation needs to be systematically embedded across all treatment pathways. The inclusion of smoking cessation in the draft guidelines is welcome in supporting the ambition of the Long Term Plan, but must be delivered on consistently if patients are to be able to access support to quit.	
Resuscitation Council UK	Guideline	General	General	The document is very extensive and in Feb 2020 would have been extremely well received, and in general is superbly evidence based. There is, however, no mention within the ACS or any guidance on the treatment of out of hospital cardiac arrest (OHCA in the setting of ACS) or other causes. Should OHCA have its own section within ACS (around 60% of OHCA have ACS as an underlying cause). We would welcome an OHCA sub-heading to delineate specific evidence-based treatments that OHCA should be able to expect to standardise	Thanks for your comment. OHCA was not included in the scope for this update, and so the developer team and guideline committee did not search for and review the relevant evidence. Therefore, we are unable to include any recommendations about OHCA in this current ACS guideline. This topic can be considered for inclusion when the guidance is next reviewed and has been added to the NICE log of topics for future consideration.

[12] NHS England. The NHS Long Term Plan. January 2019.

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				the treatment of this vulnerable group of patients. A CAC might have specific treatment features (24-hour access to cath lab, interventional cardiologists, ECHO, ICU, Temperature management, neuro prognostication, EP cardiologists) to be defined by NICE (rather like the Resuscitation to Recovery document) We know that only around 50% of OHCA are offered cardiac rehab and wonder if this could be developed if OHCA had its own guidance. A minimal NICE Cardiac arrest recovery programme could be considered. Pre-discharge neuro-cognitive screening should/could be considered an important part of this. Other areas that could be considered are access to survivor and family of councillor, cardiac rehab, Clinical psychologist, community neuro rehab RC(UK) would consider involvement in any OHCA guidance. These are a forgotten patient group who experience huge neuro-cognitive and psychological challenges for both survivor and family.	
Resuscitation Council UK	Guideline	General	General	**COVID-19 related issues which may wish to be considered in a future version** March 2020 and the COVID pandemic unfortunately brings to light challenges in delivery of ACS treatment which may be considered. a) Timing and choice of reperfusion therapy. If two STEMI patients present at the same time (out of hours with only one cath lab and team on call) and there is a suspicion of COVID-19	Thanks for your comment and for responding with respect to particular issues posed by Covid-19. The developer team and NICE considered that it is not appropriate to address these particular points in the updated Acute coronary syndromes guideline. The points that you have highlighted have been passed on to a dedicated Covid-19 surveillance team within NICE for further consideration.

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				could lead to cath lab being compromised by infection control and cleaning prior to treating the next patient. b) The use of Defibrillator pads for all STEMI undergoing PPCI could be encouraged so that in the event of cardiac arrest (VF/VT) DCC can be delivered rapidly and potentially without CPR if the team are not adequately prepared with necessary PPE. (Most PPCI centres are still using full PPE for all STEMI cases). c) COVID-19 swab testing of NSTEMI prior to cath lab / invasive approach	
Bayer PLC	Guideline	001	General	The box on page 1 of the guideline refers to those technology appraisals that are incorporated yet it does not mention incorporating TA335 Rivaroxaban for preventing adverse outcomes after acute management of acute coronary syndrome. As this TA is cross referenced in the guideline, Bayer consider this should be noted on the first page of the guideline.	Thank you for your comment. NICE has changed its procedure for referring to technology appraisals within a guideline since the scope for the Acute coronary syndromes guideline update was produced. The box on page 1 will no longer be included. Please see the section 'Referring to technology appraisals in recommendations' in 'Developing NICE guidelines: the manual' for further details of the current process: https://www.nice.org.uk/process/pmg20/chapter/linking-to-other-guidance#related-nice-technology-appraisal-guidance Cross reference to TA335 is now included at 2 appropriate places within the guideline. Technology appraisals will also be included in the Pathway.
AstraZeneca	Guideline	005	0`24	Concern **There are a number of challenges that AstraZeneca would like to highlight that would preclude widespread implementation of the Committee's recommendation for the use of prasugrel in STEMI and UA/NSTEMI patients intended for PCI across all centres in the UK. These challenges are**	Thanks for your comments. The guideline committee do not believe that the Covid-19 pandemic impacts on the choice between ticagrelor and prasugrel. Regarding your other points: • Dose adjustment is required for prasugrel, but this is

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				predominantly driven by limitations in the product label for prasugrel, which if disregarded, could prevent a significant proportion of patients from receiving the appropriate therapy, but could also compromise patient safety. These considerations have the potential to add significant complexity for healthcare professionals treating ACS patients and therefore are even more critical in light of the current COVID-19 pandemic. There are a number of 'practical' as well as patient safety considerations that need to be assessed by the Committee to ensure patients receive rapid and sustained access to novel antiplatelet therapy. Such considerations include the requirement for dose adjustments based on weight, age and bleeding risk, contraindications, options for administration, evidence to support antiplatelet therapy switching and long-term treatment. A recommendation to utilise one single product in all STEMI-PCI patients, such as prasugrel, which is in many ways less practical to use and is limited to a smaller proportion of patients than ticagrelor, risks delaying care in the emergency setting and could compromise the ACS community's ability to deliver outstanding clinical outcomes for patients. It should be noted that these practical considerations have the potential to impact all patients with ACS, not just those with STEMI intended for PCI. Per its product label, prasugrel can only be administered orally (without crushing or breaking the tablet), requires dose adjustment and is contraindicated in patients that have had a prior stroke. In contrast, ticagrelor is licenced for all ACS patients, regardless of whether patients are invasively or	not the case for the initial dose so there is no need to measure weight in the emergency setting. • The committee agrees that the contraindications of the two drugs are different • The committee agrees that PLATO showed that switching to ticagrelor in patients pre-treated with clopidogrel was safe, whereas similar data for switching to prasugrel from clopidogrel are not available. However, in line with European Society of Cardiology Guidelines, the Committee did not feel that this was likely to be a major safety issue and do not believe that patients pre-loaded with clopidogrel, could not go onto be treated with prasugrel after PCI • In UA/NSTEMI patients in whom it is possible to perform angiography quickly, prasugrel could be given. We agree that if there is any delay it would be easier to use ticagrelor. This is covered in the discussion section of the evidence review, and is part of the reason for offering ticagrelor and prasugrel as options in UA/NSTEMI • NICE TA420 states that ticagrelor is an option for preventative treatment in those at high risk of future cardiovascular events, but does not state that it is the only option • We agree that ticagrelor is easier to administer in certain circumstances, but do not believe that this outweighs prasugrel's superior clinical and cost-effectiveness

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				medically managed, can be administered orally, via nasogastric tube or orodispersible formulation, and no dose adjustment is required. Careful consideration should be given to the labelling restrictions of prasugrel as a matter of patient safety, especially given the nature of antiplatelet therapy in the emergency setting. These considerations, which strongly support the use of ticagrelor over prasugrel, are reflected in current national and international guidelines, including ESC 2017 DAPT (Valgimigli, 2017). Details of the labelling advantages and disadvantages of the respective products are provided below. <u>Supporting evidence</u> • **Prasugrel requires dose adjustment in patients ≥75 years old and <60 kg.** These populations are at an increased risk of bleeding with prasugrel, as demonstrated in post-hoc sub-analysis of TRITON-TIMI 38 (19.6% of TRITON-TIMI 3 population, Wilcox, 2014). Measuring weight and adjusting dose in the emergent setting can be challenging. This is particularly concerning when robust efficacy data for 5 mg prasugrel is lacking and >30% of UK PCI patients are ≥75 years old (BCIS 2017-2018 Audit Report). *No dose adjustment is necessary for ticagrelor.* • **Prasugrel is contraindicated in patients who have a history of stroke.** Identification of these patients is challenging, particularly in the primary-PCI setting. Evidence suggests that up to 1 in 10 ACS patients	Longer term treatment with DAPT was not part of the scope for this guideline update and the recommendation you request cannot be added

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				requiring antiplatelet therapy may have had a prior stroke (Abtahian, 2011). *Ticagrelor 90 mg can be used in patients who have a history of stroke.* • **Limited evidence of switching from a pre-loaded P2Y12 inhibitor to prasugrel.** Patients in TRITON-TIMI 38 were P2Y12 inhibitor naïve; no randomised controlled trial data exists that provides evidence for the safety of loading prasugrel in patients previously treated or loaded with another P2Y12 inhibitor such as ticagrelor or clopidogrel. On the contrary, in the ACCOAST study in NSTEMI patients, prasugrel loading dose 4 hours prior to coronary angiography increased the risk of major and minor peri-procedure bleeding compared to prasugrel loading dose at the time of PCI (Montalescot, 2014). *In contrast, 46% of patients in the ticagrelor arm of PLATO had been pre-loaded with clopidogrel providing safety data on switching from clopidogrel to ticagrelor, if required.* • **Patients must be treated with antiplatelet therapy prior to angiography.** In UA/NSTEMI patients, where coronary angiography is performed >48 hours after admission, the loading dose should only be given at the time of PCI. This is further supported by ESC guidelines which do not recommend loading of prasugrel in UA/NSTEMI in whom coronary anatomy is not known (class III, level B, Valgimilgi, 2017). *This represents the majority of UA/NSTEMI-PCI patients in*	

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				the UK (BCIS 2017-2018 Audit Report). It is not reasonable to assume that, given the high-risk of recurrent events, elective-PCI patients remain DAPT naïve during the 2.3 - 3.3 days (average time to angiography for UA/NSTEMI patients in the UK) prior to angiography. *Ticagrelor with aspirin is widely prescribed in these patients currently as it is licenced for use in both invasively and medically managed patients*. • **Exclusive positioning of prasugrel in STEMI-PCI leads to uncertainty in the long-term management of high-risk patients.** The draft recommendation for preferential positioning of prasugrel in STEMI-PCI patients introduces considerable complexity into the therapeutic algorithm and significantly impacts the probability of PCI patients transitioning to long-term DAPT therapy with 60 mg ticagrelor and aspirin. NICE's HTA for ticagrelor 60 mg (NICE TA 420) supports the argument that ticagrelor 60 mg plays an important role in the long-term management of patients at high risk of recurrent CV events. • **Alternative ways to administer ticagrelor in the emergency setting provide significant benefit to patients and HCPs:** – Ticagrelor licence allows crushing for nasogastric tube administration	

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				– Ticagrelor is also presented as an orodispersible formulation (90 mg) that rapidly disperses in the mouth with or without the need for water; offers convenient administration to patients and clinicians via nasogastric tube in the event of an emergency or in people with difficulty or inability to swallow tablets in the emergency setting Clinical implications Ticagrelor is the antiplatelet therapy of choice in the UK, based on the BCIS 2017-2018 Audit Report. This is a result of ticagrelor's broad indication, its compelling efficacy (especially mortality data), its ability to be loaded at first medical contact via alternative dosing routes, and clinical data supporting loading in patients pre-loaded with clopidogrel. In contrast, prasugrel is not accepted as an appropriate option for all PCI patients in the UK. This is due to licencing limitations, dose adjustment requirements, contraindications and limited administration potential. There is a significant proportion of PCI patients who are not eligible for prasugrel and indeed, in whom, as a matter of patient safety, prasugrel should not be a treatment option even considered. The lack of supporting data for loading of prasugrel in patients pre-loaded with a P2Y12 inhibitor, provides no solution for DAPT therapy during the critical period between admission and PCI. Advice on these critical considerations regarding the prasugrel label is absent in the draft guideline. The exclusive offering of prasugrel in STEMI-PCI patients provides no alternative option for patients for whom prasugrel is unsuitable. This omission may become a matter of	

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				patient safety and therefore AstraZeneca respectfully requests the guideline Committee to review this matter further. **<u>Recommendation</u>** **Given the unsuitability of prasugrel for a significant proportion of patients intended for PCI, an alternative antiplatelet therapy such as ticagrelor must be recommended by the Committee in this setting. As stated previously, AstraZeneca would like to request the following amendments to the guideline:** **A) Recommend ticagrelor in a parity position to prasugrel in STEMI-PCI patients** **B) Present ticagrelor as the preferred treatment option in UA/NSTEMI patients intended for PCI** **AstraZeneca requests that, in all circumstances, the Committee consider adding clear guidance on the labelling requirements/restrictions of prasugrel, in order to ensure that patient safety is not compromised.** **AstraZeneca would also be grateful if the Committee would consider adding a further recommendation regarding long-term DAPT in MI patients at high risk of subsequent CV events, with the potential to include ticagrelor 60 mg (in combination with aspirin) for the treatment of post-MI patients following completion of 12 months of DAPT therapy based on the randomised double-blind pivotal Phase 3 trial PEGASUS (Bonaca, 2015). In the current climate of the COVID-19 pandemic, ensuring continuity of care and prevention of subsequent ACS events now becomes a**	

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				critical requirement for the NHS. References Abtahian F, Olenchock B, Ou FS, Kontos MC, Saucedo JF, Scirica BM et al. *Am J Cardiol.* 2011. 15;107:1441–1446. BCIS 2017-2018 Audit Report. http://www.bcis.org.uk/wp-content/uploads/2019/02/BCIS-Audit-2017-18-data-for-web-ALL-excl-TAVI-as-27-02-2019.pdf Bonaca MP, Bhatt DL, Cohen M, Steg PG, Storey RF, Jensen EC, et al. *N Engl J Med*. 2015. 7;372:1791-800 National Institute for Health and Care Excellence. Ticagrelor for preventing atherothrombotic events after myocardial infarction, TA 420. https://www.nice.org.uk/guidance/ta420 Valgimigli M, Bueno H, Byrne RA, Collet JP, Costa F, Jeppsson A, et al. *Eur Heart J*. 2018. 14;39:213-260 Wilcox R, Iqbal K, Costigan T, Lopez-Sendon J, Ramos Y, Widimsky P. *Curr Med Res Opin*. 2014. 30:2193-205	
Sheffield Teaching Hospital NHS Foundation Trust	Guideline	005	024 - 027	This recommendation does not acknowledge the UK label for prasugrel, which contraindicates use in patients with prior stroke or TIA and generally recommends against use in patients aged 75 years or greater. The committee has not considered all of the limitations of the ISAR REACT 5 study – (1) this was an open-label strategy trial with ticagrelor given before angiography and prasugrel given after angiography only in patients proceeding to PCI, combined with 62% use of femoral artery access versus less than 15% in most UK centre now, inevitably increasing the bleeding risk with ticagrelor; (2) rates of stent thrombosis were much higher than seen in contemporary UK practice (observational UK data supporting this have not been assessed); (3) discontinuation rates were very high, which markedly limits the quality of the evidence and translatability to UK practice.	Thanks for your comment. Prasugrel and ticagrelor have different licensing restrictions. Prasugrel's includes contraindication in prior stroke or TIA, and stipulates a dose reduction in those over 75. Ticagrelor is contraindicated in those with prior cerebral bleeding and that there are various cautions which do not apply to prasugrel including common diseases like asthma and COPD. We agree that the recommendation for prasugrel should point out the particular cautions regarding use in those aged 75 and over and have amended the wording. The committee consider that the relative increased risk of bleeding with femoral access would affect ticagrelor and prasugrel equally, rather than specifically biasing against

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				Whilst these limitations do not change the fact that prasugrel is substantially cheaper than ticagrelor now, it does question whether NICE should encourage clinicians to use prasugrel outside its label.	ticagrelor. All RCTs come with limitations and the committee acknowledge the limitations of ISAR REACT 5 that have been highlighted in the Consultation process. However, its strengths must also be acknowledged. It was a randomised trial (albeit open label) performed by an experienced clinical trial group that recruited a large number of all-comer ACS patients in European Healthcare systems with likely similar demographics and cardiology practice to the UK. It specifically addresses one of the key questions of our review by comparing prasugrel and ticagrelor head-to-head, and the Committee felt that its results could therefore not be ignored. It should also be noted that the recommendations favouring prasugrel were based on a wide-ranging evidence review which included pairwise meta-analysis of 28 studies of anti-platelet drugs in ACS, a novel network meta-analysis of outcomes at 30 days (which did not include any ISAR-REACT 5 data), and a novel Health Economics model. The recommendations were informed by the results of ISAR REACT 5, but by no means solely based on it
South London primary and secondary care cardiovascular pharmacist's group	Guideline	005	025	The proposed changes that may impact secondary and primary care are: 1) **Prasugrel with aspirin for acute STEMI and primary PCI.** Currently prasugrel is prescribed less than ticagrelor or clopidogrel in ACS- please ensure that contra-indications (CVA/TIA) and dose reduction requirements (age>75 and weight <60kg) are made clear in the guidance and that it is ONLY to be	Thanks for your comment. NICE guidance assume that prescribers take note of contra-indications of all medicines mentioned and it is not usual practice to include these in a guideline.

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				administered post PCI. We will have to monitor bleeding rates with this change as there have been concerns previously with prasugrel. This recommendation is in line with ESC guidance from 2017.	
Joint response by the British Cardiovascular Society (BCS) and the British Cardiovascular Intervention Society (BCIS)	Guideline	005	025	1.1.12 Prasugrel is recommended over Ticagrelor for STEMI - The BCS and BCIS have concerns that there may be insufficiently robust evidence to justify this recommendation. The preference for prasugrel over ticagrelor in STEMI is currently a minority view amongst most UK cardiac centres. To persuade centres that currently use ticagrelor to change to prasugrel in this setting would require a convincing evidence base for superiority. BCS and BCIS members who contributed to this consultation response were predominantly in favour of retaining ticagrelor *as an option* for use in acute MI, with a minority supporting the use of prasugrel over ticagrelor. We feel the following meta-analyses and studies give a mixed picture in ACS patients who are managed invasively, particularly for STEMI: • A head to head meta-analysis (BMC Pharmacol Toxicol 2017: 18: 80) of four studies including 563 patients. This was underpowered, with a trend toward increased mortality with Ticagrelor, but a trend toward reduced MI, MACE, stroke and stent thrombosis. • A network metanalysis looking at trials between 2005 and 2012 (J Thromb Thrombolysis 2013;36:223) found no differences except a possible superiority of Prasugrel in terms of stent thrombosis. • Network meta-analysis (Cardiovasc Revasc Med 2017:18:79) found no differences in patients undergoing PCI.	Thanks for your comments. We recognise that ticagrelor has been preferred to prasugrel by most cardiology centres in the UK, and the recommendation in favour of prasugrel in STEMI patients was not made without careful consideration. The results of the meta-analyses and studies which you cite do not clearly favour one agent over the other, although it should be noted that if the 2 are equivalent then prasugrel would be the more cost-effective as it is lower cost. The publication of ISAR-REACT 5 pushes the clinical effectiveness verdict towards a position more favourable to prasugrel. The weaknesses of this study were recognised by the Guideline Committee and were taken into account, but were not thought to be sufficient to preclude using its results. ISAR-REACT 5 has been scrutinised in minute detail because of its surprising result, but other large studies of either ticagrelor or prasugrel are also imperfect when examined closely. We also acknowledge that switching to prasugrel adds practical complications related to its licence for use only once coronary anatomy has been defined. This is discussed in the evidence review. The committee felt that this was less of an issue in STEMI where best practice is to take the patient promptly to the catheter lab. .

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				• RENAMI registry - https://www.ncbi.nlm.nih.gov/pubmed/31030413 - which showed benefit of prasugrel over ticagrelor in ACS, more so with NSTEMI than with STEMI. • Prasugrel, but not ticagrelor, was found to be superior to clopidogrel in a separate metanalysis https://www.internationaljournalofcardiology.com/article/S0167-5273(15)01108-0/abstract • A possible mechanism for prasugrel being more effective was suggested in a small study which showed better platelet inhibition, improvement in FMD and endothelial dysfunction. https://academic.oup.com/eurheartj/advance-article-abstract/doi/10.1093/eurheartj/ehz917/5695774?redirectedFrom=fulltext • There was a strong association shown with reduced mortality and prasugrel use (relative to ticagrelor) in a large UK registry https://heart.bmj.com/content/104/20/1683.full.. Similar findings were reported in a smaller UK registry https://openheart.bmj.com/content/6/1/e000951. These were not randomised data, so they were not included in the NICE evidence review, but may support its preference for prasugrel use over ticagrelor. The BCS and BCIS note the key relevance of the ISAR REACT 5 trial in NICE's recommendation. This is appropriate as it is the largest randomised controlled trial comparing the two treatments in ACS. However, we feel that the trial has some weaknesses that need to be considered before depending on it as the main reason for recommending prasugrel over ticagrelor in patients	

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				with STEMI. From a methodological perspective, the initial hypothesis of the ISAR REACT 5 trial was that ticagrelor would be superior to prasugrel, rather than the converse. Prior to this trial there was no compelling evidence to suppose superiority (or inferiority) of prasugrel, to ticagrelor. Whilst observational data must trump theory, Doll & Hill require that statistical observations from a single study are insufficient to conclude 'cause and effect'. On this basis, an unexpected finding (the opposite of what was anticipated) is hypothesis generating and should (in principle, at least) be confirmed in a subsequent study. The design of the ISAR REACT 5 trial was pragmatic, with an open label (rather than double blinded) design. The power calculations for the trial used an 80% power. This is not unheard of, but most large trials in this area have a higher power to detect differences of 90%. We also have some concerns about the interpretation of the results of ISAR REACT 5. The ISAR REACT 5 trial was not primarily a STEMI trial, so the data extracted represent only a minority of patients in the trial. The main trial which did look specifically at the two drugs in STEMI patients, the PRAGUE 18 trial, was abandoned due to futility when it was unable to show any meaningful difference between the two agents. We feel that the results of the STEMI population of the ISAR REACT 5 trial are hypothesis generating rather than definitive evidence for a difference that was not found in the trial dedicated to this specific question, PRAGUE 18.	

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				Whilst the primary endpoint of the trial was in favour of prasugrel, the difference was largely driven by endpoints which were not cardiovascular. In particular, the non-cardiovascular death rate was double that of the prasugrel group in patients who were allocated to ticagrelor, (1.4% v 0.7%). Importantly, cardiovascular death was not significantly lower in this trial with prasugrel than ticagrelor (3.2% v 3.0%). Since the main objective with the use of either of these antiplatelet agents is to reduce deaths due to heart attacks, we are concerned that making a clear recommendation to use prasugrel rather than ticagrelor when it has not shown such a benefit may be unjustified. Similarly, there were difficult to explain differences in heart attack rates following the initial event. The main difference in events was due to lower rates of type 4 (procedure-related) myocardial infarctions rather than due to a reduction in conventional, spontaneous (type 1) MIs. It is difficult to explain this mechanistically so we are concerned that this may be an anomalous result rather than a signal of a more efficacious antiplatelet effect in STEMI patients. Potential contributing factors to the results of the trial include the lower than expected event rate in the prasugrel population (nearly half what would be predicted from previous data) and the early discontinuation of ticagrelor without adequate systems in place to ensure transition to an alternate agent (nearly 70% received some other agent, but the shorter duration of platelet inhibition and earlier discontinuation may have been relevant). We acknowledge that it is highly unlikely that a large comparative trial between prasugrel and ticagrelor will be repeated. We also acknowledge that ISAR REACT 5, unlike	

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				most other large antiplatelet studies, was an academic- rather than industry-driven study, from a recognised group of investigators. Its results are important and need to be considered carefully, but not uncritically. There are some important practical implications in requiring a change to prasugrel over ticagrelor. For example, the contraindications to prasugrel use include previous stroke or transient ischaemic attack. Since these too are often due to atherosclerotic disease they are not uncommon events in patients presenting with an acute MI. NICE has not indicated what clinicians should offer to patients in whom prasugrel is contraindicated. Prasugrel dose adjustment is needed based on weight, which is not always known in the very acute setting of an acute STEMI. Respondents were also concerned about the specific evidence for the lower dose of prasugrel which would be prescribed in a not insignificant number of patients (age> 75 years, weight < 60 Kg). Some cardiologists expressed a concern that using a range of antiplatelet medications and doses for similar conditions may cause confusion or even errors. Ticagrelor has the advantage that it is approved for use in all ACS settings, including STEMI. This facilitates simple, network-wide, treatment algorithms. However, the BCS and BCIS acknowledge that some centres have used prasugrel in STEMI patients for many years In conclusion, both BCS and BCIS have insufficient confidence in the evidence base to justify the proposed recommendation by NICE to prefer prasugrel over ticagrelor in STEMI. We feel that either ticagrelor or prasugrel are reasonable choices in STEMI. It is possible that the cost effectiveness analysis favours prasugrel,	

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				but the change to practice for many centres in the UK is a significant disadvantage.	
Sheffield Teaching Hospital NHS Foundation Trust	Guideline	006	001 - 004	The committee has not considered the evidence that morphine delays the absorption of prasugrel, ticagrelor and clopidogrel and therefore the guidance is not based on contemporary evidence. Routine use of a 6-hour infusion of tirofiban has been associated with a reduction in acute stent thrombosis (Zwart B et al. Platelets 2020; 31(2):174-178). Consequently the recommendation is of limited use.	Thanks for your comment. The question addressed in this update of the guideline was to determine the best agent to combine with aspirin as DAPT, comparing prasugrel, ticagrelor and clopidogrel. The role of additional glycoprotein IIb/IIIa inhibitors was not part of the scope and the observational paper cited was therefore not considered.
Joint response by the British Cardiovascular Society (BCS) and the British Cardiovascular Intervention Society (BCIS)	Guideline	006	005	1.1.14 - Use of bivalirudin in the UK is very infrequent. BCIS data for 2017-18 showed that it was used in 0.1% of PCI cases for NSTEMI/UA and 0.7% of cases for STEMI, so it has become largely irrelevant in UK practice. Most catheter laboraties do not stock it. Femoral cases comprise a decreasing minority of PCI cases in the UK. This applies equally to STEMI cases as for non-emergent cases. Use of an unfamiliar agent in a small minority of cases may lead to errors in drug preparation, especially in the pressurised situation of a primary PCI. Nor do we feel that there is robust evidence to support the use of bivalirudin over unfractionated heparin in the subgroup of patients undergoing primary PCI via the femoral route.	Thanks for your comment. The committee agree that bivalirudin is rarely used in the UK, but it is still available. As detailed in the relevant evidence review, when all data is taken into account heparin is not unequivocally more cost-effective than bivalirudin and although our recommendations clearly favour heparin the committee felt that allowing bivalirudin as an option in certain circumstances was the most appropriate evidence-based conclusion.
Sheffield Teaching Hospital NHS Foundation Trust	Guideline	006	005 - 007	Bivalirudin is associated with increased risk of acute stent thrombosis in primary PCI patients, particularly if not used with glycoprotein IIb/IIIa inhibitor, and is markedly more expensive than unfractionated heparin so this recommendation is outdated.	Thanks for your comment. The evidence on acute stent thrombosis is considered and taken into account. Please see the evidence review in the full guideline for further detail.
Joint response by the British Cardiovascular Society (BCS) and the British	Guideline	007	003	1.1.17 Complete v culprit revascularisation - The BCS and BCIS agree that there is evidence to support complete revascularisation. The best timing for this, however, remains controversial. The largest trial in this setting, COMPLETE, supports both in-hospital non-culprit revascularisation and its	Thanks for your comment. We agree that individual considerations will affect the timing of complete revascularisation in each case, and that the evidence on optimal timing is not straightforward. The recommendation deliberately distinguishes between offering complete

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Cardiovascular Intervention Society (BCIS)				deferral for up to 45 days. We feel that the proposed guidance does not adequately support the option of deferred revascularisation within that time frame. We acknowledge that non-clinical factors such as cost effectiveness or patient preference may support full revascularisation during the index admission, but we would welcome a recommendation that allows for the procedure to be performed shortly after the index admission to account for individual circumstances and clinical factors such as kidney disease which may warrant deferred non-culprit revascularisation.	revascularisation and the weaker advice to consider this during the index admission, which clearly recognises the need to defer the procedure in some cases.
Joint response by the British Cardiovascular Society (BCS) and the British Cardiovascular Intervention Society (BCIS)	Guideline	007	006	1.1.18 Culprit only for cardiogenic shock during MI - The BCS and BCIS agree that, in shock patients, there is not evidence to support complete (non-culprit) revascularisation at presentation and that culprit-only PCI should generally be performed. However, we feel that the recommendation should make it clear that it relates solely to performing culprit-only revascularisation *at the index procedure*. It is not clear whether or not complete revascularisation should be undertaken at a later date in patients who have recovered from shock and this should be clear from the recommendation.	Thanks for your comment. We agree and have amended the recommendation.
South London primary and secondary care cardiovascular pharmacist's group	Guideline	010	001	2) Please add **more definition to the terms**: advancing age, known bleeding complications, renal impairment and low body weight, when deciding on antithrombotic therapies.	Thanks for your comment. We understand why you request this, but there is not enough evidence to define any particular age, body weight etc. The recommendation is simply designed to prompt prescribers to recognise the particular risks of these medicines and to use clinical judgement before starting treatment
South London primary and secondary care	Guideline	010	008	3) For unstable angina and NSTEMI: recommends single loading dose of aspirin and then fondaparinux (UFH if high bleeding risk/Cr >265)- recommending **NOT to offer DAPT to patients presenting with CP** before a	Thanks for your comment. DAPT should only be given as set out in the updated recommendations once a diagnosis of ACS has been made.

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cardiovascular pharmacist's group				diagnosis is made. This differs from current practice in most units of administering DAPT loading on admission and the length of time between admission and angio/PCI in some centres will have to be considered.	The Committee were concerned of a risk of harm to patients with undifferentiated chest pain receiving DAPT
Joint response by the British Cardiovascular Society (BCS) and the British Cardiovascular Intervention Society (BCIS)	Guideline	010	008	1.2.6 Do not offer dual antiplatelet therapy to people with chest pain before a diagnosis of unstable angina or NSTEMI is made- The BCS and BCIS support this recommendation; patients without an ACS diagnosis should not be given DAPT.	Thanks for your comment.
St. Georges University Hospitals NHS Foundation Trust	Guideline	010	008	We are concerned that this recommendation may imply that patients who are a strong candidate for unstable angina or NSTEMI may not receive antiplatelet therapy in a timely manner. The phrasing of the sentence could perhaps be better phrased so this does not occur.	Thanks for your comment. The recommendation states DAPT should be given as soon as an ACS is diagnosed. If someone is a strong candidate for this diagnosis there should be little delay, but the recommendation will stop DAPT being given to patients with chest pain of different aetiology.
South London primary and secondary care cardiovascular pharmacist's group	Guideline	011 016 024	001 001 005	4) Please add a requirement for a **lipid profile and liver function tests (LFTs)** (on admission bloods or or in primary care at 3 months post event)- for statin therapy and antiplatelets (CI in moderate to severe liver failure).	Thanks for your comment. NICE guidance assume that prescribers take note of contra-indications of all medicines mentioned and it is not usual practice to include these in a guideline.
Joint response by the British Cardiovascular Society (BCS) and the British Cardiovascular Intervention	Guideline	011	012	1.2.12 Immediate intervention if unstable ACS - Wefeel that the term, "unstable ACS" needs to be defined more clearly and supported by appropriate evidence.	The committee considered that most cardiologists would know that clinical instability encompasses a range of clinical indicators including (but not limited to): ongoing symptoms, ongoing ECG evidence of ischaemia, hypotension, or ventricular arrhythmias, and that this did not need to be specifically set out, thus allowing clinicians freedom to use their clinical judgement.

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Society (BCIS)					
Joint response by the British Cardiovascular Society (BCS) and the British Cardiovascular Intervention Society (BCIS)	Guideline	011	014	1.2.13 Early invasive Consider catheter < 72 Hr if ACS & 6 mo risk > 3%; low bleeding risk - The BCS and BCIS note that the evidence regarding risk scoring has not been reviewed in this latest NICE guidance, although the use of mortality scores remains part of the updated recommendations such as this one. We accept that objective risk assessments may be of some value in determining appropriate treatments, but we have major misgivings about the application of GRACE scoring in clinical practice.. The draft guidelines make recommendations on treatment according toexact risk score cut-off points for six-month mortality which t may not be justified. We feel that this lack of confidence in the robustness of risk scoring systems should be reflected in the updated recommendations. The guidance refers to patients with low bleeding risk but does not provide guidance on how bleeding risk should be quantified. What bleeding risk score is recommended? This also applies to recommendations 1.1.26, 1.2.19, 1,2,20, 1.4.18	Thanks for your comment. The previous guideline committee undertook a detailed analysis of risk assessment and its application, and we do not believe that there is new data which would invalidate this. We acknowledge that objective scoring systems can be less reliable in people whose data is distant from the mean, for example unusually young people with ACS, and have added a recommendation to acknowledge this. We did not compare different bleeding risk scores. These differed between studies and the committee felt that it was reasonable to use any validated score.
Joint response by the British Cardiovascular Society (BCS) and the British Cardiovascular Intervention Society (BCIS)	Guideline	011	019	1.2.14 Consider catheter for ACS if 6mo risk < 3% and evidence of ischaemia - An early invasive approach involving direct angiography rather than non-invasive testing has been shown to reduce rates of death and myocardial infarction in patients presenting with NSTEMI. The absolute benefit is likely to be greater in those most at risk. However, the predicted risk of mortality at 6 months using the GRACE risk score is strongly influenced by age and does not closely correlate with the risk of myocardial infarction. The BCS and BCIS have concerns that younger patients with ECG changes and/or raised cardiac biomarkers may have low GRACE risk of *mortality (<3% at 6*	Thanks for your comment. The previous guideline committee undertook a detailed analysis of risk assessment and its application, and we do not believe that there is new data which would invalidate this. We acknowledge that objective scoring systems can be less reliable in people whose data is distant from the mean, for example unusually young people with ACS, and have added a recommendation to acknowledge this.

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				months), but substantial risk of myocardial infarction (up to 20% at 6 months: GRACE calculator https://heart.bmj.com/content/heartjnl/96/22/1859.3.full.pdf) and would therefore benefit from an early invasive approach to prevent non-fatal myocardial infarction. Facilities to provide an early invasive approach are well developed in the UK; a strategy involving a significant shift to prior non-invasive testing followed by angiography in those found to have ischaemia, would result in significantly prolonged hospital stays in those patients. In addition, "evidence of ischemia" is not well described and the evidence relating to detection of ischemia on non-invasive tests has not been reviewed in order to support this recommendation. .	
Leeds Teaching Hospitals NHS Trust	Guideline	012	008	The recommendation here is unhelpful for clinicians managing patients with acute coronary syndrome, as no recommendation is made on which initial anti-platelet therapy should be considered in patients admitted with acute coronary syndrome who will later be selected for prasugrel therapy. The panel should be aware that in UK practice, dual antiplatelet therapy is almost universally prescribed as soon as the diagnosis of acute coronary syndrome is reached - before proceeding to the cardiac catheter laboratory. The recommendation here seems to imply that it is reasonable for patients with acute coronary syndrome to be managed with aspirin monotherapy prior to coronary angiography and then commence prasugrel once the coronary anatomy is known. Notwithstanding the gaps in the evidence base in this setting, this represents a major change in UK practice which is likely to create uncertainty and lack of consistency in practice.	Thank you for your comment There is undoubtedly a gap in the evidence here. It is standard practice to preload ticagrelor and clopidogrel at the time of diagnosis before angiography, but not prasugrel. At the time of drafting recommendations, there were no data to show that a delay of up to 72-96 hours without a 2nd anti-platelet drug is actually harmful, whereas there is evidence to show that PCI patients have long-term benefit from being treated with prasugrel, but are harmed if they are preloaded before PCI in NSTEMI/UA. In people with STEMI the delay in proceeding to the catheter lab is usually such that there would be little delay in receiving prasugrel. In the UK the time before catheterisation is typically longer for those with NSTEMI and we therefore include the option of using either ticagrelor or prasugrel. Ongoing UK and international trials of immediate versus delayed angiography in NSTEMI/UA, may provide insights into the optimal timing not only of angiography but

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					also, by association, initiation of dual anti-platelet therapy.
South London primary and secondary care cardiovascular pharmacist's group	Guideline	012	008	**5) Prasugrel or ticagrelor for UA or NSTEMI**- the complication with prasugrel is that this cannot be given until coronary artery (CA) anatomy is known and if PCI is intended- this is a UK license restriction. There are concerns that patients could be without dual antiplatelet therapy (DAPT) for several days if angiography is delayed. **Would ticagrelor/clopidogrel be more appropriate first line options in UA/NSTEMI?**	Thanks for your comment. The clinical and cost-effectiveness data do not allow a clear preference for prasugrel or ticagrelor in UA/NSTEMI. Both are given as options, and a delay in angiography is a scenario where clinicians may prefer ticagrelor.
Joint response by the British Cardiovascular Society (BCS) and the British Cardiovascular Intervention Society (BCIS)	Guideline	012	008	1.2.16 Prasugrel or ticagrelor in NSTEMI - This recommendation is derived from trials that had very short delays to coronary angiography. In such a scenario it may well be reasonable to defer giving the second antiplatelet agent until the coronary anatomy is known in order to have the option to use prasugrel (as opposed to ticagrelor). However, in healthcare systems where there may be delays to angiography (the recommendation here is for <72 hours), this guideline creates a scenario which we feel is undesirable. It is unclear whether or not NICE is recommending that a second antiplatelet agent should not be given during the in-hospital period prior to angiography when this may be a number of days. We would have some concerns that this lack of antiplatelet treatment may increase the risk of further ischemic events while awaiting angiography. Given that there is no evidence regarding the safety or otherwise of a deferred prasugrel strategy where delays are long, we feel the recommendation should support the use of ticagrelor, used from the point of diagnosis, in preference to prasugrel that does not have evidence in this setting. Ticagrelor also has the advantage that it can be given to all	Thank you for your comment There is undoubtedly a gap in the evidence here. It is standard practice to preload ticagrelor and clopidogrel at the time of diagnosis before angiography, but not prasugrel. At the time of drafting recommendations, there were no data to show that a delay of up to 72-96 hours without a 2nd anti-platelet drug is actually harmful, whereas there is evidence to show that PCI patients have long-term benefit from being treated with prasugrel, but are harmed if they are preloaded before PCI in NSTEMI/UA. In people with STEMI the delay in proceeding to the catheter lab is usually such that there would be little delay in receiving prasugrel. In the UK the time before catheterisation is typically longer for those with NSTEMI and we therefore include the option of using either ticagrelor or prasugrel. In NSTEMI cases where it is possible to proceed quickly to angiography prasugrel is a viable option, accepting that the typical time to catheterisation would favour use of ticagrelor.

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				NSTEMI patients – those having angiography and those managed medically, those having stents and those going on to have surgery (shorter half-life than prasugrel an advantage here too) and those with previous stroke/TIA. This makes error and confusion less likely than a system where some patients receive one drug while others get another. In practice there are some concerns that giving prasugrel to patients immediately after angiography and before the follow on PCI (ie 'on the table") may be inpractical and less effective. Some of these patients will have had sedation and will be draped and lying flat, making administration of the antiplatelet difficult.	
Joint response by the British Cardiovascular Society (BCS) and the British Cardiovascular Intervention Society (BCIS)	Guideline	013	002	1.2.17 DES v BMS - The BCS and BCIS are happy in general with this recommendation. The use of DES compared with drug coated balloons could be highlighted as an area where further research is warranted.	Thank you for your comment. We did not look for evidence comparing DES to drug coated balloons and NICE research recommendations are limited to topics which have been reviewed but produced no, or inconclusive, data. This point will be passed on the NICE's Surveillance team for consideration in future updates.
Sheffield Teaching Hospital NHS Foundation Trust	Guideline	013	005 - 009	The largest contribution to risk is age and revascularisation has been shown to be beneficial in MI patients (i.e. those with elevated troponin). Does the committee not consider a 3% 6-month mortality risk in a 35-year-old NSTEMI patient to be important and associated with a significant loss of QALYs? Have younger patients been consulted on this for their perspective? The recommendation to consider conservative management in	Thanks for your comment. The previous guideline committee undertook a detailed analysis of risk assessment and its application, and we do not believe that there is new data which would invalidate this. We acknowledge that objective scoring systems can be less reliable in people whose data is distant from the mean, for

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				inevitably-younger MI patients is discriminatory and unacceptable.	example unusually young people with ACS, and have added a recommendation to acknowledge this.
AstraZeneca	Guideline	013	011	AstraZeneca supports the recommendation to offer ticagrelor, as part of dual antiplatelet therapy including aspirin, to STEMI and UA/NSTEMI patients when PCI is not indicated (unless they have a high bleeding risk). As highlighted above, the evidence underpinning the broad indication for ticagrelor across all ACS patients including PCI, CABG and medically managed, is founded upon strong clinical data from the randomised, double-blind controlled Phase 3 trial, PLATO (Wallentin, 2009). A pre-specified analysis in a sub-group of patients planned for non-invasive management in PLATO (5,216 of the 18,624 patients), demonstrated the strong and consistent benefits of ticagrelor on CV death, MI, or stroke, and indeed all-cause mortality, compared with clopidogrel and when compared to the main trial population (James, 2011). As observed in studies such as PLATO, patients who were medically managed typically have a higher long-term risk of cardiovascular events and mortality compared to those intended for invasive management. Such findings have also been observed in real world data and in post-hoc analyses from other clinical trials, showing ~2-fold higher rate of mortality compared with patients who have revascularisation (1 year mortality: 2.3% for non-invasive and 5.6% for invasive management strategy, Ottervanger, 2004). The high risk of ischaemia in medically managed patients is acknowledged in international guidelines. Similarly, the clinical benefit of ticagrelor in these high-risk	Thank you for your comment

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				patients is also recognised, with class 1A recommendations in ESC (Valgimigli, 2017) and ACC/AHA (Levine, 2016) clinical guidelines. AstraZeneca therefore welcomes the Committee's acknowledgement of the high level of risk in medically managed patients, and the recommendation to treat these patients with ticagrelor (unless they have a high bleeding risk). <u>Supporting evidence</u> • In the PLATO trial, ticagrelor significantly reduced the primary end point of CV death, MI, or stroke (HR, 0.84, [0.77-0.92], p<0.001) in an all-ACS population regardless of treatment strategy (Wallentin, 2009). • Ticagrelor also reduced both CV mortality (HR, 0.79, [0.69-0.91], p=0.001) and all-cause mortality (HR, 0.78, [0.69-0.89], p<0.001 (nominal)) compared to clopidogrel in patients with ACS regardless of invasive or non-invasive treatment strategy (Wallentin, 2009). • Specifically, in PLATO patients not intended for invasive management, ticagrelor reduced the primary endpoint of CV death, MI, or stroke (HR, 0.85, [0.73-1.00], p=0.04), CV mortality (HR, 0.79, [0.61-0.96], p=0.019), and all-cause mortality (HR, 0.75, [0.61-0.93], p=0.01) compared to clopidogrel (James, 2011). <u>Recommendation</u> AstraZeneca support the recommendation to treat STEMI, UA/NSTEMI patients not intended for PCI with ticagrelor (unless they have a high bleeding risk).	

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				References James SK, Roe MT, Cannon CP, Cornel JH, Horrow J, Husted S, et al. *BMJ*. 2011. 17;342:d3527 Levine GN, Bates ER, Bittl JA, Brindis RG, Fihn SD, Fleisher LA, et al. *Circulation*. 2016. 6;134:e123-55 Ottervanger JP, Armstrong P, Barnathan ES, Boersma E, Cooper JS, Ohman EM, et al. *Eur Heart J*. 2004. 25:1494-501. Valgimigli M, Bueno H, Byrne RA, Collet JP, Costa F, Jeppsson A, et al. *Eur Heart J*. 2018. 14;39:213-260 Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, et al. *N Engl J Med*. 2009. 10;361:1045-57	
Leeds Teaching Hospitals NHS Trust	Guideline	016	008	The recommendations in this section miss one important opportunity to intervene. Patient identified in the pre-diabetes range (HbA1c 42-47mmol.mol) should be considered for referral to the National Diabetes Prevention Programme.	Thanks for your comment. Management of hyperglycaemia was not one of the sections updated in this revision of the guideline.
Leeds Teaching Hospitals NHS Trust	Guideline	017	004	The recommendations in this section miss one important aspect of secondary prevention and risk modification – the opportunity to recommend review of therapy in people with type 2 diabetes mellitus and identify patients with atherosclerotic cardiovascular disease who would benefit from sodium glucose co-transporter 2 inhibitor therapy or glucagon-like peptide receptor agonist therapy. It is acknowledged that initiation of these agents may not be appropriate in the acute setting, however a recommendation can be made to identify people who may benefit once their condition has stabilised.	Thanks for your comment. Management of hyperglycaemia and/or diabetes was not one of the topics updated in this revision of the guideline
Royal College of General Practitioners	Guideline	017 024	011 001	Communication to the GP (1.7) and the Management plan to the GP (1.4.2) should both concur and include every aspect of ongoing care required in primary care. This will aid communication, encourage seamless patient treatment and	Thanks for your comment. These topics were not revised in this update of the guideline.

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				reduce re-referrals or requirements for consultant advice months post discharge. The draft document is currently confusing as it contains different advice in the two sections. Discharge letters are increasingly processed by pharmacists or non-clinical personnel who will then transfer the data onto the patient record. The following list is drawn from the whole document and would be usefully summarised within the document tin one place to enable discharge summaries to accurately reflect ongoing care needs • Confirmation of diagnosis • Results of investigations • Annual HBa1c measurement where appropriate • The duration of the dual platelet therapy recommended (standard 12 months) • The need to up titrate the Ace inhibitor and B blocker (if required) over 4-6 weeks • Repeat blood tests recommended • The need to continue aspirin, ACE, and statin indefinitely • Recommendation on use of B blockers • Recommendation for ongoing anticoagulation after 12 months	

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South London primary and secondary care cardiovascular pharmacist's group	Guideline	017	014 015	6) For the **management plan post MI and sent to GP**, please include heart rate (HR) monitoring with BP recommendation and electrolytes with renal function monitoring.	Thanks for your comment. This section of the guideline was not part of the current update
South London primary and secondary care cardiovascular pharmacist's group	Guideline	017	016	7) Please add **dosing guidance for antiplatelets and course length plan** both acutely, at discharge and at 1 year, especially for ticagrelor.	Thanks for your comment. This section of the guideline was not part of the current update.
South London primary and secondary care cardiovascular pharmacist's group	Guideline	018	001	8) There is mention of **ACEI and ARB combination** 1.4.6 under ACEI, please refer to MHRA guidance that this combination should not be co-prescribed.	Thanks for your comment. The MHRA guidance states that there are occasional circumstances when dual prescription may be considered. The current recommendation is compatible with this advice.
Royal College of General Practitioners	Guideline	018	020	Can the committee clarify whether aspirin should be used with patients on anticoagulation for other reasons (DOAC or warfarin) and if so, for how long?	Thanks for your comment. The committee only considered the use of antiplatelet agents with a DOAC in patients with ACS and a co-existing condition for which an anticoagulant (warfarin or a DOAC) would usually be prescribed. Rec 1.4.20 states that in some such patients aspirin plus a DOAC can be given. The intended duration of aspirin treatment in these patients is no different from those who do not need a DOAC. Other reasons for giving aspirin would be outside our scope.
Sheffield Teaching	Guideline	018	025 - 028	The evidence supporting a role for ticagrelor monotherapy versus DAPT with aspirin + ticagrelor from 3 months post-ACS	Thanks for your comment. This topic was not in our scope.

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Hospital NHS Foundation Trust				has not been considered here.	
Leeds Teaching Hospitals NHS Trust	Guideline	019	001	I am concerned that this recommendation may imply that clopidogrel monotherapy is acceptable as sole anti-platelet therapy for a patient with aspirin hypersensitivity and acute coronary syndrome who has undergone PCI. Due to the individual variation in response to clopidogrel, this recommendation incurs an unacceptable risk of stent thrombosis and recurrent atherothrombosis. It is acknowledged that there is an absence of evidence to guide management in this setting. However, recommending clopidogrel monotherapy is a misguided and risk-prone strategy. It would be more appropriate to accept the absence of data but to recommend monotherapy with a more a more potent P2Y12 receptor inhibitor – e.g. ticagrelor or prasugrel. There is accumulating evidence outside of the context of aspirin hypersensitivity that ticagrelor monotherapy is safe and effective follwoign a period of dual anti-platelet therapy. In the absence of higher quality data, it is reasonable to extrapolate these observations to the setting of aspirin hypersensitivity.	Thanks for your comment. This recommendation was not reviewed as part of the current update. We acknowledge that there is some evidence relating to monotherapy with P2Y12 inhibitors other than clopidogrel, but at present they are only licensed for use with aspirin
Bayer PLC	Guideline	019	019 - 025	Section 1.4.18 of the guideline lists those factors which should be taken into account for people who have had an acute coronary syndrome and who have a separate indication for anticoagulation. There are differences in the licensed indications of the direct oral anticoagulants, so Bayer consider that a bullet point should be added to the list: 'licensed indications'.	Thanks for your comment. NICE guidance assumes that clinicians will be familiar with the licensed indications and contra-indications of medicines they prescribe and does not usually add this to recommendations.
South London	Guideline	019	022	9) In **AC and AP section 1.4.18** please	We understand why you request this, but there is not enough

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primary and secondary care cardiovascular pharmacist's group				define/quantify/add tools for bleeding risk, thromboembolic risk, cardiovascular risk, person's wishes (ie after explaining risk: benefit of treatment).	evidence to provide definitions. The recommendation is simply designed to prompt prescribers to recognise the particular risks of these medicines and to use clinical judgement before starting treatment.
Sheffield Teaching Hospital NHS Foundation Trust	Guideline	019	022 - 025	Has does 'thromboembolic risk' different from 'cardiovascular risk'? This is not stated and is unclear.	Both these terms are commonly used in NHS England documents and the committee believes them to be widely understood. Cardiovascular risk relates to risk of circulatory diseases chiefly, but not exclusively, associated with atherosclerosis. Thromboembolic risk relates to disorders in which blood clots migrate through the circulation.
Joint response by the British Cardiovascular Society (BCS) and the British Cardiovascular Intervention Society (BCIS)	Guideline	019	026	Evidence review G. 1.4.19-22 DAPT and anticoagulation - Multiple BCS and BCIS respondents felt that this recommendation is unclear. Most of the trials in this area included a period of time on DAPT and oral anticoagulant before Aspirin was stopped, such that the PCI was performed while on DAPT, but this is not mentioned in the guidance. BCIS feel that the recommendation about dual therapy needs to be clear that this is evidence for what to do after PCI. The BCS is also anxious about the lack of use of Aspirin in ACS settings even when an anticoagulant is also used. Both BCS and BCIS feel that the issue of Aspirin in this area needs to be discussed more fully. A pragmatic list of options for combination therapy would be preferable, including guidance on duration of triple therapy and when to use reduced doses of NOAC. A clear explanation on the use of short term triple therapy would be welcome clarification of this area.	Thank you for your comment. Unfortunately the evidence on this topic is not consistent (please see evidence review G for fuller discussion). We agree that most of the trials randomised subjects after acute treatment of their ACS and that triple therapy with DAPT and an anticoagulant was used initially. We have therefore amended the recommendations in the acute section to include people who have a separate indication for anticoagulation (recommendations 1.1.11 and 1.2.17)) and have altered the recommendations you mention in section in 1.4 to try to make this clearer. However, there is no clear evidence on the optimal duration of triple therapy, although the Committee noted that in the Dabigatran, rivaroxaban and edoxaban studies aspirin was not continued once a DOAC was started

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Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
Leeds Teaching Hospitals NHS Trust	Guideline	019	026	I am concerned that this recommendation makes no comment about concurrent aspirin therapy. It is possible that patients may be prescribed clopidogrel (for up to 12 months) and an oral anticoagulant in addition to aspirin – exposing them to a high risk of bleeding. It is acknowledged that the evidence on aspirin therapy in addition to P2Y12 inhibitor and anti-coagulant therapy continues to accrue, however the available evidence currently is sufficient to recommend that if aspirin is employed, it should be continued for the shortest time possible taking into account atherothrombotic and bleeding risk, to minimise the risk of serious bleeding.	Thank you for your comment. Unfortunately the evidence on this topic is not consistent (please see evidence review G for fuller discussion). Most of the trials on anticoagulation plus antiplatelet therapy after an ACS randomised subjects after acute treatment of their ACS. Triple therapy with DAPT and an anticoagulant was used initially but there is no clear evidence on the optimal duration of triple therapy. A cautionary note has been added to Recommendation 1.4.18 to make explicit the risk of bleeding with triple therapy.
Sheffield Teaching Hospital NHS Foundation Trust	Guideline	019 - 020	General	What does 'adjust and monitor dose' mean? ESC CCS 2019 guidelines now recommend using NOAC at licensed dose for AF thromboprophylaxis as a default strategy. This should be '*consider* adjusting and monitoring dose'.	Thank you for your comment. We have changed the wording of this recommendation.
St. Georges University Hospitals NHS Foundation Trust	Guideline	019	General	Current practice in our Trust revolves around giving triple therapy (aspirin + clopidogrel + DOAC) in patients who have undergone stenting and require anticoagulation. This is currently in line with the European Cardiology Society Guidelines, whereby a maximum duration of 6 months triple therapy can be used. In reality the vast majority of patients will receive 1-3 months of triple therapy depending on the number and the location of the stents (this would be a consultant led decision). During this period, patients do not routinely receive a lower dose of DOAC unless there is an overt risk of bleeding. With the proposed change to "double therapy" with an anticoagulant + antiplatelet, is there an increased likelihood of post-stent thrombosis?	Thank you for your comment. Unfortunately the evidence on this topic is not consistent (please see evidence review G for fuller discussion). Most of the trials on anticoagulation plus antiplatelet therapy after an ACS randomised subjects after acute treatment of their ACS. Triple therapy with DAPT and an anticoagulant was used initially. However, there is no clear evidence on the optimal duration of triple therapy, but the Committee noted that in the Dabigatran, rivaroxaban and edoxaban studies aspirin was not continued once a DOAC was started.
St. Georges University	Guideline	020	008	Is it worth putting in any guidance regarding unlicensed use of DOACs/warfarin in conjunction with antiplatelets? In rare	Thanks for your comment. The evidence in this area is not strong enough for us to make any specific recommendations

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Hospitals NHS Foundation Trust				circumstances, patients are started on DOACs or warfarin for LV thrombus post MI	about unlicensed use of these agents.
Sheffield Teaching Hospital NHS Foundation Trust	Guideline	020	015 - 017	ESC guidelines recommend against the use of prasugrel or ticagrelor in a triple therapy combination but the CCS 2019 guidelines state that they may be considered in dual therapy combination with OAC as an alternative to using triple therapy with OAC, aspirin and clopidogrel which makes pharmacological sense.	Thanks for your comment. This is not the committee's interpretation of the ESC guidance which states that there is limited evidence for use of prasugrel or ticagrelor with OAC's.
Joint response by the British Cardiovascular Society (BCS) and the British Cardiovascular Intervention Society (BCIS)	Guideline	021	006	Beta blocker use 1.4.26 Evidence Review H - The BCS and BCIS feels that this statement is of limited value in clinical practice. It is not known whether or not to continue beta-blockers in this context. Patients 12 months out from their index event will generally have been discharged from hospital care. It is not desirable or practical to offer routine review in hospital at 12 months where a discussion about continued beta blocker use can be held. Primary care physicians may not feel confident to address this issue. There is therefore a risk that either the discussion will not happen at all, or that there will be a large number of queries from primary care to hospital teams relating to this issue, with no clear guidance as to what individual patients should do. In the absence of any strong evidence either way, we suggest that no recommendation should be made at all on this issue.	Thanks for your comment. There is no firm evidence, as stated in the review, but currently many people are continued on beta-blockers because stopping is not discussed. The committee believe that primary care physicians are well able to manage this discussion.
Sheffield Teaching Hospital NHS Foundation Trust	Guideline	021	006 - 013	There is no evidence to support the use of beta-blocker in NSTE ACS patients who don't have reduced LV ejection fraction so these recommendations cannot be supported and beta blockers can either be avoided or stopped earlier in patients who are successfully revascularised and have preserved LV ejection fraction, consistent with ESC 2015 NSTE ACS guidelines.	Thanks for your comment. Much of the data on the benefits of beta-blockers is relatively old and difficult to interpret in the light of current management of ACS. The current committee was asked to review data on when to stop beta-blockers and did not find any evidence which allowed recommendation of a clear stop date.

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South London primary and secondary care cardiovascular pharmacist's group	Guideline	021	008	10) **Beta-blockers-** states to continue for 12 months post MI then stop unless reduced LVEF- **no mention of how to review this/stop safely** (?gradual step down in dose, heart rate (HR) monitoring etc)- please could this be added to the guidance?	Thanks for your comment. The guidance only says to discuss stopping. The BNF advocates a gradual step down.
South London primary and secondary care cardiovascular pharmacist's group	Guideline	023 017	011 010	11) Please add "**high intensity statins**" as is the evidence-base post ACS.	Thanks for your comment. The section on statins was not part of this guideline update.
South London primary and secondary care cardiovascular pharmacist's group	Guideline	023	027	12) Section **1.6.2 people with hypertension**, please refer to latest 2019 NICE guideline on hypertension (HT) in adults.	Thanks for your comment. We have amended the hyperlink. The date label is the date the recommendation was produced, not the date of the guideline to which it refers.
South London primary and secondary care cardiovascular pharmacist's group	Guideline	024	009	13) Under **cardiac rehab** should we be including referral to community pharmacists or GP practice-based pharmacists for new medicines service (NMS) and discharge medicines services?	Thanks for your comment. The cardiac rehabilitation guidance was not part of this Guideline update.
Royal College of General	Guideline	025	026	Consider adding "writing to the GP" if the measures included in section 1.8.14 fail to encourage a patient to join cardiac	Thanks for your comment. This section was not part of the current Guideline update

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Practitioners				rehabilitation to enable ongoing encouragement when seen for follow up in the community	
Action on Smoking and Health (ASH)	Guideline	030	001 - 008	The guidelines should also include reference to smokeless tobacco (SLT) products and to NICE guidance PH39 'Smokeless tobacco: South Asian communities.'[13] Parallel with and in addition to monitoring and treatment of smoking, patients should be asked if they use SLT products, advised to quit and referred to available support. SLT products are estimated to have accounted for 204,309 deaths from ischaemic heart disease globally in 2010 alone[14] and are linked to an increased risk of myocardial infarction and stroke.[15] SLT products are predominantly used in the UK by South Asian communities who experience disproportionately high rates of coronary disease[16] and are therefore more likely to present in the population of patients affected by this guidance. The available national data, shows that in 2004 self-reported SLT use among Indian and Pakistani men (4% and 2%, respectively) and women (approximately 1%) remained comparable to 1999 estimates.[17] A significant decline was observed in Bangladeshi	Thanks for your comment. This section was not part of the current Guideline update and changes are outside the remit of the Guideline committee.

[13] NICE. [PH39] Smokeless tobacco: South Asian communities. September 2012
[14] Siddiqi, K., Shah, S., Abbas, S.M. et al. Global burden of disease due to smokeless tobacco consumption in adults: analysis of data from 113 countries. BMC Med 13, 194 (2015). https://doi.org/10.1186/s12916-015-0424-2
[15] Boffetta Paolo, Straif Kurt. Use of smokeless tobacco and risk of myocardial infarction and stroke: systematic review with meta-analysis BMJ 2009; 339 :b3060
[16] Zaman MJS, Philipson P, Chen R, et al. South Asians and coronary disease: is there discordance between effects on incidence and prognosis? Heart 2013;99:729-736
[17] NHS Digital. Health Survey for England – 2004, Health of Ethnic Minorities. 2006.

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				men and women from 19% and 26%, respectively, in 1999 to 9% and 19% in 2004.[17] On the contrary, cotinine adjusted prevalence estimates of any tobacco use were higher than self-reported estimates, especially among Bangladeshi men (60% adjusted vs 44% self-reported), Bangladeshi women (35% adjusted vs 17% self-reported) and Pakistani women (14% adjusted vs 7% self- reported). The adjusted estimates, especially in women which were twice as high as self-reported estimates, point towards the possibility of higher SLT use than that observed through self-report. The association between SLT use and coronary disease and that both are independently more prevalent among South Asian communities provides clear rationale for SLT use to be addressed in guidance relating to acute coronary syndromes. Failing to include reference to SLT use in this guidance would be a missed opportunity and would risk not adequately addressing the range of behavioural factors relevant to the management and treatment of acute coronary syndromes.	
St. Georges University Hospitals NHS Foundation Trust	Questions	001		Which areas will have the biggest impact on practice and be challenging to implement? Please say for whom and why. Acute medicine, A&E and cardiology areas will have the biggest change in practice. A&E may be harder to implement prescribing changes in, but with the roll-out of electronic prescribing this should hopefully help prevent any errors.	Thanks for your comment.
St. Georges University Hospitals NHS Foundation	Questions	002		Would implementation of any of the draft recommendations have significant cost implications? None at present.	Thanks for your comment.

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Trust					
St. Georges University Hospitals NHS Foundation Trust	Questions	003		What would help users overcome any challenges? (For example, existing practical resources or national initiatives, or examples of good practice.) Local guidelines will have to be amended in order to reflect any changes from NICE. In addition electronic prescribing plans for ACS would have to be amended to reflect the switch to prasugrel as first line for STEMI/NSTEMI patients undergoing PCI. This will hopefully prevent errors in prescribing and dosage selection for the prasugrel (where dose is reduced to 5mg OD if <60kg or >75 years of age).	Thanks for your comment.
St. Georges University Hospitals NHS Foundation Trust	Questions	004		As part of the update to this guideline, we have removed recommendations regarding the use of glycoprotein inhibitors as part of the early management for people with unstable angina or NSTEMI. It was felt that they would be unlikely to be used in practice with the antiplatelet therapies that are now recommended (parusgrel or ticagrelor) owing to the potential for increased bleeding. Do you agree with this approach? Abciximab has not been ordered into our Trust since 2017, so unlikely to make much impact to our current practice.	Thanks for your comment.

Document processed	Organisation name – Stakeholder or respondent	Disclosure on tobacco funding / links	Number of comments extracted	Comments
Consultation Comments	Bayer PLC	Yes	7	Bayer does not have direct or indirect links with, or funding from, manufacturers, distributors or sellers of smoking products but Bayer provides pesticides for crops, which would therefore include tobacco crops.

				Bayer is a member of the Cooperation Centre for Scientific Research Relative to Tobacco (CORESTA) (http://www.coresta.org/) within the scope of recommendations of pesticides used for protection of tobacco plants. It is also a member of country and EU business federations such as the Confederation of British Industry (CBI) and 'Business Europe', which include tobacco companies. In 2006, Bayer and its subsidiary Icon Genetics piloted a new process for producing biotech drugs in tobacco plants. Icon Genetics was acquired by Nomad Bioscience GmbH from Bayer in 2012.