Comments on the ACD Received from the Public through the NICE Website

Name	
Role	NHS Professional
Other role	
Location	England
Conflict	no
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	We would support all concerns raised within the NICE appraisal. NHS Dorset has a higher prevalence of Atrial Fibrillation due to our older population (almost double national rate), but also a much higher proportion of patients already well controlled on warfarin (3 x higher than in the model). Warfarin is the most cost effective treatment in patients with atrial fibrillation with INR control within the recommended range. The manufacturer of dabigatran has assumed higher attendances for monitoring warfarin than is usual in clinical practice. Given current local costs of warfarin treatment, switching patients to dabigatran would cost an additional Â£7-14 milllion per year depending on dose of dabigatran. Time in therapeutic range should be considered in sensitivity analysis of clinical and cost effectiveness.
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	Time horizon should be included in further assessments of cost effectiveness. The time horizon influenced the ICER greatly with a 2-year time horizon resulting in ICERs of Â£75,891per QALY in people under 80yrs old and Â£23,403 per QALY in people over 80 old for the dabigatran sequential regimen vs warfarin Â No information is provided regarding dabigatran as a second line treatment in patients who are inadequately treated with warfarin. This is a potential treatment option that was not modelled in the manufacturer's submission but it should be considered in case it is a cost effective treatment in this specific patient group.
Section 4 (Consideration of the evidence)	We would support all of the concerns raised in the NICE appraisal. Safety - There is an increased risk of gastrointestinal bleed with dabigatran 150mg and there is no specific antidote in the event of haemorrhage or overdose. Â The RE-LY study was conducted over a 2 year period and further safety data over a longer time period should be requested. Patient Acceptability - Discontinuation rates in the RE-LY study were higher amongst patients treated with dabigatran than with warfarin. Â This is not clearly explained. Â Limitations to the quality of the research - Patients were treated in the RELY study who would not have been eligible for treatment in the UK, using the current NICE guidelines. This affects the generalisability of the RELY study to UK clinical practice.
Section 5 (Implementation)	Given current local costs of warfarin treatment, switching patients to dabigatran would cost an additional Â£7-14 milllion

	per year depending on dose of dabigatran.
Section 6 (Proposed recommendations for further research)	
Section 7 (Related NICE guidance)	
Section 8 (Proposed date of review of guidance)	
Date	9/8/2011 3:11:00 PM

Name	
Role	NHS Professional
Other role	
Location	England
Conflict	no
Notes	NA
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	We accept that NICE have undertaken an analysis based on what the manufacturer submitted. Our view is that NICE should ask BI to resubmit an analysis of clinical and cost effectiveness based on sub groups of the anticoagulated AF population split by time in therapeutic range. This data is available, and has been published (eg Wallentin et al, Lancet, 2010). It demonstrates the differential risk and benefit of dabigatran (compared to warfarin) by time in therapeutic range. Our interpretation of this evidence (though we note it was from a post hoc sub group analysis) is that in well controlled patients warfarin achieves better outcomes and is safer, in less well controlled patients dabigatran is superior. Cost effectiveness modelling should follow this. We therefore encourage NICE to ask the manufacturer to conduct analysis by TTR. As a minimum, TTR should be considered in sensitivity analysis of clinical and cost effectiveness. Â In the RE-LY study, mean TTR for warfarin in the UK was 72%. Â The RE-LY study did not demonstrate superiority of dabigatran over warfarin above a median TTR of 67%. In a well controlled population as in much of the UK, the results dont generalise well.
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	It is important that the variable costs of anticoagulation patient cost is modelled. There IS substantive variation in costs to commissioners. There is also significant difference between the price that commissioners might pay and actual provider costs. BI has assumed higher attendances for monitoring warfarin than is usual in clinical practice. They estimate 20 visits per year per patient for INR monitoring where clinical practice suggests that 5-8 visits is more realistic in established patients. Data from the NHS Reference cost database for anticoagulation does not match the data quoted in the ACD, by an order of magnitude. Both of the above points need to be incorporated into the economic analysis, preferably as a core component of the base case. we do not agree with the values of the utilities used. There are sufficient NICE Assessment reports on stroke and MI to enable us to validate the values used but NICE has

	not provided any detail. Â NICE should push BI to provide this info, especially given higher discontinuation rates with dabigatran etexilate 150 mg. we are surprised the costs of events has not been disclosed. Again we have comparative data from other NICE assessments.
Section 4 (Consideration of the evidence)	In the absence of evidence of rationale, we agree that dyspepsia should be modelled through the entire model, as a common adverse effect and given higher patient withdrawals for RE-LY with dabigatran, it seems plausible that patients would maintain the a/e and potentially reduce dose to 110mg BD thus reducing health benefit or that a patient would discontinue treatment and revert back to treatment with warfarin assuming no contraindication. 4.1.2 – we would ask for review of evidence to support the hypothesis that a stroke would be less severe after treatment with dabigatran than warfarin. Â At present we are uncertain of the evidence underpinning this assumption in the manufacturers model and it seems possible that there are a number of factors (e.g dose, drug interactions, co-morbidities) which may influence this assumption.
Section 5 (Implementation)	Our view is that by considering this indication in the way BI have submitted the data, NICE have reached a defensible conclusion ? in the whole cohort of patients with AF, using dabigatran over warfarin does not represent a rational (or affordable) use of NHS resources. We do think that NICE have not reached the right conclusion, however. We feel that dabigatran DOES have a place in the pathway of care. Our interpretation of the evidence available is that dabigatran is clinically significantly superior (and thus highly cost effective) in the cohort of patients whom despite efforts to attain good therapeutic control are unable to do so (measured by TTR less than 65%).
Section 6 (Proposed recommendations for further research)	obviously both the NICE CG on AF and commisisoning guidance is relevant here. Locally it would seem that disinvestment in anticoagulation services would be unlikely, therefore any direct costs for dabigatran would represent new investment. Â If significant number of patiuents are switched from warfarin to dabigatran it is likely to have an inflationary effect on the cost per patient as the clinics will have to cover the same fixed costs with less tariff income coming in. This should be factored into the impact model. There are significant numbers of patients with medium or high risk AF who are not receiveing anticoagulation currently. Our view is that Warfarin is and remains the drug of choice for this cohort. The evidence that dabigatran is superior to warfarin is not compelling – high NNT, not affordable, probably not cost effective. We would hope that NICE will reflect this in their eventual advice.
Section 7 (Related NICE guidance)	The composition of the Committee and experts seems rather GP light. This is important, both strategically and operationally given the emphasis on primary care led anticoagulation in AND in terms of GP taking on principal reposnsibility for commissioning.
Section 8 (Proposed date of review of guidance)	
Date	9/7/2011 5:12:00 PM

Name	
Role	NHS Professional
Other role	
Location	England
Conflict	no
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	Why would NICE need cost effectiveness data on the subgroup of people who are already well controlled on warfarin as warfarin is the most cost effective treatment. The focus should be on patients with poor INR control on warfarin.
Section 2 (The technology)	The marketing authorisation is not consistant with NICE CG36. The population used in the trial did not represent people at risk of AF in the UK. In practice there is a danger that patients will not be stepped down when they reach the age of 80, therefore risk of bleeding may be higher than that considered.
Section 3 (The manufacturer's submission)	Information on use of dabigatran as an option in patients who are not controlled with warfarin should be considered. 3.6 and 3.9 are not relevent to the licensed indication and TIAs in patients over 80 years old was not a primary outcome.
Section 4 (Consideration of the evidence)	I would disagree with the statement that patients in the trial were broadly representative of patients treated on the NHS in the UK. Saftey over a number of years should be a prime consideration (2 years is not enough). Any clinical commissioning group would be extemely unwise to adapt a black triangle drug with limited saftey data around a new service, and consequently decommission existing warfarin and INR monitoring clinics.
Section 5 (Implementation)	Any clinical commissioning group would be extemely unwise to adapt a black triangle drug with limited saftey data around a new service, and consequently decommission existing warfarin and INR monitoring clinics. I would advise that any such new drug for AF should be managed with caution and the primary drug/service should be the existing warfarin and monitoring clinics at least until long term safety data emerges. This is not simply a drug substitution for an existing drug but rather a service redesign - who would redesign a service around a new black triangle drug with limited safety data?.... There are other drugs also coming to the market for stroke prevention in AF (rivaroxiban and apixiban) - where will they fit in? Should data on these drugs also be considered?
Section 6 (Proposed recommendations for further research)	
Section 7 (Related NICE guidance)	
Section 8 (Proposed date of review of guidance)	
Date	9/7/2011 11:44:00 AM

Name	
Role	NHS Professional
Other role	
Location	England
Conflict	no
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	Warfarin should still be the first line treatment but Dabigatran will be a cost?effective option if it is going to prevent a stroke in a high risk patient (as defined by CHADS2)where there is an absolute contraindication to Warfarin or if they are currently on Warfarin treatment and their TTR is less than 65%.
Section 5 (Implementation)	
Section 6 (Proposed recommendations for further research)	
Section 7 (Related NICE guidance)	
Section 8 (Proposed date of review of guidance)	
Date	9/7/2011 9:08:00 AM

Name	
Role	NHS Professional
Other role	
Location	England
Conflict	no
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	It is important that variable costs of anticoagulation are modelled as we agree there is variation in commissioning costs. The manufacturer looks to have assumed higher attendances for monitoring warfarin than is usual. An estimate of 5-8 visits appears realistic in established patients. It is important to the NHS to understand the health outcomes of dabigatran versus warfarin and clarify if it is cost effective across the entire eligible patient population , in the analysis we want to understand whether warfarin dominates dabigatran and remains the most clinically and cost effective intervention for patients who are already well controlled with warfarin. Â A definition of well controlled INR on warfarin would be required (i.e. time in therapeutic range as X%) In the absence of evidence of rationale, dyspepsia should be continued through the entire model, as a common a/e and given higher patient withdrawals

	for RE-LY with dabigatran, it seems plausible patients would maintain the a/e and potentially reduce to 110mg BD thus reducing health benefit or that a patient would discontinue treatment and revert back to treatment with warfarin assuming no contraindication.
Section 2 (The technology)	No specific comment
Section 3 (The manufacturer's submission)	Dabigatran is expected to be prescribed in primary care and it essential that GP views are represented on this technology. Â The sequential model presented by the manufacturer is reflective of the license of the two doses of dabigatran etexilate however there are concerns in terms of the practical application of this model in clinical practice and the necessity to identify individuals 80 years+ for dose reduction. Should these individuals not be identified, this potentially exposes individuals to more harm in terms of bleeding risk, which negates overall perceived benefit of treatment. The treatment sequence at present does not permit patients to revert back to warfarin as a 2nd line agent, which seems to represent a likely scenario given the evidence from RE-LY indicated higher withdrawal rates for dabigatran compared to warfarin. Â We would ask that this sequence is included in analysis. We also ask subgroup analysis of patients currently well controlled on warfarin at present , as warfarin we believe may remain the most cost effective treatment for this group of patients. Â Would need to define good control e.g. time in therapeutic range (TTR)
Section 4 (Consideration of the evidence)	There are noted inconveniences with warfarin+monitoring, warfarin is a once daily therapy where, monitoring may provide support for concordance to treatment, one disadvantage of dabigatran is the necessity for twice daily dosing. Noted that the incidence of gastrointestinal bleeding was significantly higher for both doses of dabigatran dabigatran 150 mg BD was associated with a significantly higher incidence of major gastrointestinal bleeding and life threatening gastrointestinal bleeding. Â It is important to ensure that the health gain from lower incidence of stroke are balanced against the higher rate of GI bleeding with dabigatran. Locally disinvestment in anticoagulation services would be unlikely, therefore any direct costs for dabigatran represents new investment. Â There appears to be significant variation in the costs of anticoagulant monitoring, paid by commissioners. We ask for review of evidence that a stroke would be less severe after treatment with dabigatran than warfarin.At present, uncertain of the evidence of assumption in the manufacturers model and seems possible there are factors (e.g dose, drug interactions,co-morbidities) to influence this assumption
Section 5 (Implementation)	There are significant numbers of patients with medium or high risk AF who are not currently receiving anticoagulation. At present it appears that locally warfarin is and remains the gold standard treatment 1st choice and certainly is considered the agent which enables PCTs to ensure equitable affordable access and health gain for all eligible patients.
Section 6	

(Proposed recommendations for further research)	
Section 7 (Related NICE guidance)	
Section 8 (Proposed date of review of guidance)	
Date	9/6/2011 2:54:00 PM

Name	
Role	NHS Professional
Other role	
Location	England
Conflict	no
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	Agree
Section 2 (The technology)	There are also increasing concerns over safety, with increased risk of GI bleed. There is no antidote to treatment with dabigatran to reverse its action if needed - this needs to be noted I think. Also more patients in RELY taking Dabigatran discontinued compared to warfarin - is this because of poorer tolerability?
Section 3 (The manufacturer's submission)	Trial population - concerns about this - those excluded and agree with ERG concerns that the definition of AF not same as that in NICE guideline. Also disagree with warfarin monitoring costs - in practice INR is not done as frequently in the majority of llong term patients as assumed, so this could affect the cost effectiveness analysis. Also, no monitoring is given for Danigatran - on the contrary, with new drugs there is raised concerns and usually specialist initiation and possible folluw up (so more costly than GP appointments) and GP apointments may need to be more frequent with a newer therapy, particularly where tolerability issues have been identified in the trials. Given its cost, the most likely treatment pathway would be to use this second line after warfarin - but we have no information from the manufacturer of its place in therapy at this stage. Time in therapeutc range needs consideration.
Section 4 (Consideration of the evidence)	Agree Agree also about warfarin monitoring costs - we would still have to run this service e.g for all the patients on warfarin who cannot tolerate dabigatran, so there would be no cost savings in de-commissioning a service.
Section 5 (Implementation)	
Section 6 (Proposed recommendations for further research)	
Section 7 (Related NICE guidance)	
Section 8 (Proposed date of review	

of guidance)	
Date	9/6/2011 9:36:00 AM

Name	
Role	NHS Professional
Other role	
Location	England
Conflict	no
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	Warfarin is the most cost effective treatment in patients with atrial fibrillation with INR control within the recommended range. Â In this group, the ICER for dabigatran vs warfarin is Â£60,895 per QALY. Â The Committee has requested ?further comment and consideration' of cost effectiveness in this subgroup. Â The focus of further review should be on those patients with poor INR control where dabigatran might offer a cost effective treatment. The manufacturer of dabigatran has assumed higher attendances for monitoring warfarin than is usual in clinical practice. They estimate 20 visits per year per patient for INR monitoring where clinical practice suggests that 5-12 visits is more realistic. This makes warfarin appear more expensive and consequently makes dabigatran appear relatively cost effective Time in therapeutic range should be considered in sensitivity analysis of clinical and cost effectiveness. Â In the RE-LY study, mean TTR for warfarin in the UK was 72% . Â The RE-LY study did not demonstrate superiority of dabigatran over warfarin above a median TTR of 67%.
Section 2 (The technology)	The forthcoming review for National Screening Committee on screening for AF suggests: ?Among 12,000 UK patients with chronic AF only 57% of high-risk patients were receiving anticoagulant treatment, while 38% of low-risk patients were being prescribed anticoagulants
Section 3 (The manufacturer's submission)	Time horizon should be included in further assessments of cost effectiveness. The time horizon influenced the ICER greatly with a 2-year time horizon resulting in ICERs of Â£75,891per QALY in people under 80yrs old and Â£23,403 per QALY in people over 80 yrs old for the dabigatran sequential regimen vs warfarin Â No information is provided regarding dabigatran as a second line treatment in patients who are inadequately treated with warfarin. This is a potential treatment option that was not modelled in the manufacturer's submission but it should be considered in case it is a cost effective treatment in this specific patient group.
Section 4 (Consideration of the evidence)	Safety. Â There is an increased risk of gastrointestinal bleed with dabigatran 150mg and there is no specific antidote in the event of haemorrhage or overdose. Â The RE-LY study was conducted over a 2 year period and further safety data over a longer time period should be requested. Patient Acceptability: Discontinuation rates in the RE-LY study were higher amongst patients treated with dabigatran than with warfarin. Â This is not clearly explained. Â Warfarin, unlike dabigatran, is associated with a number of inconveniences such as food and drug interactions, regular monitoring and dose adjustments which

	can cause disruption and inconvenience. However a quantification of this impact was not presented in the ACD and factored into the cost effectiveness model. Proper quantification of this could affect the relative cost effectiveness of dabigatran compared to warfarin. There were limitations to the quality of the research: Patients were treated in the RELY study who would not have been eligible for treatment in the UK, using the current NICE guidelines. This affects the generalisability of the RELY study to UK clinical practice.
Section 5 (Implementation)	
Section 6 (Proposed recommendations for further research)	
Section 7 (Related NICE guidance)	
Section 8 (Proposed date of review of guidance)	
Date	9/5/2011 1:36:00 PM

Name	
Role	NHS Professional
Other role	
Location	England
Conflict	no
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	NHS Dudley supports the need for further data from the manufacturer. We support the indication not to support the use of dabigatran in all AF patients but would like to see more clarity over the use in patients intolerant to warfarin - including a definition of intolerance
Section 2 (The technology)	an alternative to warfarin is welcomed however the opportunity cost of investing in a new technology must be weighed against the high cost-effectiveness of warfarin.
Section 3 (The manufacturer's submission)	NHS Dudley has a number of concerns and questions: 1. Warfarin is still the most cost-effective treatment for AF for patients within the recommended INR range. It would be helpful for the manufacturer to focus on those patients where INR control is poor. 2. Warfarin monitoring costs submitted by manufacturer are much higher than those experienced locally. 3. Analysis of impact of TTR essential. Patients may wish to take dabigatran due to perceived ease of use when compared to warfarin however if outcomes are better with warfarin for well controlled patients then they should be aware of this! 4. Safety concerns - the high reporting of ADRs and tolerabilty with dabigatran are of concern. 5. Compliance issue - When patients are being monitored for INR non-compliance can be picked up but as there is no monitoring patients discontinuing dabigatran may adversely affect the impact of any budget that a commissioning organisation decides to invest in dabigatran
Section 4 (Consideration of the	

evidence)	
Section 5 (Implementation)	There is a considerable impact to the use of this drug both in budgetary and service terms. The managed introduction in order to target the drug at those patients most likely to benefit will be challenging not least because most patients intolerant to warfarin are not currently known by secondary care services but have been discharged back to primary care. Considerable resources will be required to identify suitable patients,ensure appropriate prescribing, education and clarity on the benefits of the drug especially in light of current media coverage.
Section 6 (Proposed recommendations for further research)	
Section 7 (Related NICE guidance)	
Section 8 (Proposed date of review of guidance)	
Date	9/2/2011 4:12:00 PM

Name	
Role	NHS Professional
Other role	GP
Location	England
Conflict	no
Notes	I am a rural general practitioner and many patients on warfarin are elderly, infirm, many having blood testing at the surgery or at home. Given their age and general medical complexity an oral non-monitored non-adjustable and non-interacting, efficacious, above those incorporated in most urban practices. I have had at least 1 death and many hospital admissions directly related to warfarin usage. i could see no general practitioners on your advisary body but trust PHCT members have been represented and costing include ruralety health care activity.
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	

Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Proposed recommendations for further research)	
Section 7 (Related NICE guidance)	
Section 8 (Proposed date of review of guidance)	
Date	9/2/2011 12:16:00 PM

Name	
Role	NHS Professional
Other role	
Location	England
Conflict	no
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	Agree with recommendation - no clear evidence that dabigatran will confer additional benefits over warfarin. Concerns re: long-term safety and risk of toxicity in older patients
Section 2 (The technology)	what is definition of severe renal impairment?
Section 3 (The manufacturer's submission)	Patients with good INR control with warfarin are unlikely to benefit from dabigatran. Â Would resources be better used to improve INR control in patients on warfarin especially if ttr is less than 60-65%
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Proposed recommendations for further research)	
Section 7 (Related NICE guidance)	
Section 8 (Proposed date of review of guidance)	
Date	9/1/2011 10:07:00 PM

Name	
Role	NHS Professional
Other role	
Location	England
Conflict	no
Notes	I am a Consultant in Public Health Medicine working on CVD prevention. Â I have been working with PCT commissioners on the provision of community based anticoagulation services and INR monitoring.
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	The cost-effectiveness analysis should take into account a more realistic assumption on the cost of anti-coagulation monitoring. Â I do not know on what basis the manufacturer estimates the cost of INR monitoring to be Â£414. Â Based on current prices a community based provider carrying out about 2000 tests per year will not cover costs at Â£240 per patient. So including a variable of Â£115.14 for a revised analysis is unrealistic.
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Proposed recommendations for further research)	
Section 7 (Related NICE guidance)	
Section 8 (Proposed date of review of guidance)	
Date	9/1/2011 10:55:00 AM

Name	
Role	NHS Professional
Other role	Pharmaceutical Adviser
Location	England
Conflict	no
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	The manufacturers estimate of the cost of warfarin monitoring is high. Â A HTA published in 2007 gave the costs as Â£69 a year and a Keele Medicines Management team estimated the costs to be around Â£200 a year
Section 4 (Consideration of the	No information is providing regarding dabigatran as a second line option for patients who frequently present with an INR

evidence)	outside of the therapeutic range. It is these patients for whom this drug may be a cost-effective option No specific antidote is a serious consideration to the use of this drug
Section 5 (Implementation)	
Section 6 (Proposed recommendations for further research)	
Section 7 (Related NICE guidance)	
Section 8 (Proposed date of review of guidance)	
Date	8/31/2011 1:46:00 PM

Name	
Role	Patient
Other role	
Location	England
Conflict	no
Notes	I am an example of an AF patient linked to tachy brady syndrome with multiple serious risk factors on long term triple therapy blood thinning (clopidogrel +aspirin + self injected low dose clexane)being clinically intolerant of warfarin, in my case because of embolism in big toe after 10 weeks on warfarin + aspirin resulting in hospitalisation on Flolan and then experiencing similar symptoms within 6 days of restarting warfarin. Cholesterol embolisation (purple toe) caused by warfarin can not be ruled out. Three consultants (cardiologist, vascular surgeon and haemotology) advise that this treatment should be replaced by a new anticoagulant alternative to warfarin + an antiplatelet as soon as this can be prescribed. Quite apart from the potential costs from potential stroke and bleeding, the headline drug cost to the NHS of my current treatment far exceeds the cost of dabigatran as the cost of the clexane alone is over Â£6.50 daily and it is far less effective.
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	The Committee, unlike NETAG or UKCPA or RPS in their very recent prescribing guidance, do not appear to have given sufficiently serious consideration to the most appropriate and effective provision for a minority of patients who are clinically unable to be prescribed warfarin. It is accepted that dabigatran is 35% more effective than warfarin in preventing strokes and systemic embolism from which it follows that dabigatran is even more effective than the current alternative treatments of aspirin, clopidogrel and aspirin or in my case clopidogrel, aspirin and daily self injected low dose clexane, the latter being required long term by three consultants (cardiologist, vascular surgeon and heamotology)because of the peculiar risks of my condition. I had the warfarin initially added to the aspirin after post operative DVTs. UKCPA, endorsed by RPS, state that aspirin, with or without clopidogrel, is not a suitable alternative to

	warfarin or NOACs in patients with AF.... as it offers far less protection against stroke. NETAG recommends the use of dabigatran for patients intolerant to warfarin. These patients have no choice and are to be denied Â effective licensed therapy.
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	The Committee appear to be willing to deny a great opportunity to provide effective treatment at last for those patients who can not be prescribed warfarin for clinical reasons. The cost to the NHS and patients and families and in some cases the wider economy from the now unnecessary additional strokes, embolisms and deaths in this category of patients will justifiably attract widespread clinical, moral and possibly even legal condemnation. The additional overall cost to the system of providing proper care for these patients is comparatively small compared to providing the new treatment for all patients most of whom have a reasonably effective alternative with the current therapy. Â I accept Â my case is unusual in that the cost to the NHS of my long term blood thinning triple therapy of clopidogrel, aspirin and low dose self injected clexane is nearly three times the projected cost of dabigatran, Â but there is something seriously wrong with the system if I am prevented from getting much more effective and safer therapy which would cost the NHS thousands of pounds less each year and for the long term.
Section 5 (Implementation)	
Section 6 (Proposed recommendations for further research)	
Section 7 (Related NICE guidance)	
Section 8 (Proposed date of review of guidance)	
Date	8/30/2011 9:53:00 PM

Name	
Role	NHS Professional
Other role	Pharmaceutical Advisor
Location	England
Conflict	no
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	I would concur with the Appraisal Committees recommendation of not to recommend the use of dabigatran in patients with AF. I am unconvinced of the cost-effectiveness of this treatment when its costs are more than three times the costs of warfarin + monitoring. It is important to remember that the RE-LY was a non-inferiority study and the results dmonstrate that dabigatran is non-inferior New guidance to physicans in Japan has raised concerns about the need to monitor renal function "Physicians

	in Japan are recommended to perform renal-function tests before and during treatment, with doses to be reduced or treatment stopped upon signs of renal impairment or bleeding' As a signigficant portion of the costs of warfarin involves monitoring, if we are simply to replace INR monitoring with U&E measurements, the cost-effectiveness of this treatment [dabigatran] seems even further reduced
Section 2 (The technology)	Although this novel technology has been promoted as being superior to warfarin, there is no evidence to suggest this is the case in the groups of patients who would typically require warfarin + monitoring. It would also seem the requirements to monitor for bleeding are implicit in treatment. Of some considerable importance is the fact that whilst warfarin bleeding can be reduced / stopped by Vit K administration, this approach will not work with dabigatran. This could have profound implications where there is signifiant bleeding.
Section 3 (The manufacturer's submission)	The use of anecdotal post - hoc sub group analysis is frought with potential dangers and may be likened to "data dredging". Any sub-group analysis needs to be pre-specified and justification for specifying such an analysis. I would agree with the Apraisal Committees change in the cost-effectiveness, the 110 mg BD is not associated with the same level of benefits.
Section 4 (Consideration of the evidence)	I believe that the Committee has summerised the evidence wery well and I would agree with the conslusions
Section 5 (Implementation)	The costs of implementaion for significant numbers of patients would eb considerable and place a considerably burden on local resources should the committee recommend use of dabigatran. Locally we could not afford to change significant numbers of patientv from warfarin to dabigatran and we would need to prioritise warfarin intolerant patients or those patients who were poorly controlled (INR) on warfarin. There are no new resources available to implement widespread use of dabigatran in significant numbers of patients at this time
Section 6 (Proposed recommendations for further research)	
Section 7 (Related NICE guidance)	I would recommend a review 2 years after guidance is finalised
Section 8 (Proposed date of review of guidance)	
Date	8/18/2011 10:43:00 AM

Dr Jane Adam
Chair
Appraisal Committee A
NICE

Dear Dr Adam

The consultation period for this TA was due to close today and I have tried to submit comments via the NICE website early this morning, but the facility to respond appears to have been removed already, so it appears that the consultation period has been closed slightly earlier than advertised.
I would like to make some observations that I hope will be of help to the ERG in their further consideration and finalising of this appraisal. I hope that these can be considered as they have been submitted within the advertised consultation period, despite the unorthodox route of submission.

1. I understand that the ERG "is minded not to recommend dabigatran...pending the receipt of further information" but this follows a lot of good evidence and statements that confirm increased efficacy and safety of dabigatran over warfarin in this setting; I hope that I have interpreted correctly that the main concern is over the model used to estimate cost-effectiveness and the uncertain cost-effectiveness of the recommended regimen in which the dose is reduced at age 80. Is it correct to assume that receipt of the requested further information could allow a more positive recommendation? Regrettably some people will not read past the first sentence of the summary, and I am concerned that progress with a potentially really useful treatment will be set back substantially by this negative wording.
2. The summary of clinical need is clear, but does not address the very real and quite large group of patients who have a strong and often seemingly irrational unwillingness to taking warfarin, based on hearsay or the experience of a single acquaintance or some other emotion that overrides any careful balance of risk and benefit in their case. Such people will usually refuse warfarin (to try to force it on them would create unreasonable anxiety and negative impact on their quality of life) and will be left at substantial risk of stroke, that could be reduced substantially by dabigatran. Not only do doctors have a duty of care to discuss all reasonable treatment options with these patients but also many such patients will arrive quite well informed, requesting prescription of their preferred drug for one of its licensed indications. This group of people is inevitably excluded from a randomised trial, so is not catered for in the cost-effectiveness models that the ERG has considered. Nevertheless it is clear from simple clinical reasoning that this is a group in which dabigatran is likely to be highly cost-effective, given that they are unwilling to take any other effective treatment to protect against stroke.
3. The evidence presented describes exactly what we expect from virtually any treatment, namely that the people who benefit most from the treatment are those at highest risk. In the case of dabigatran there are 2 main elements to this. Those unable to maintain stable warfarin control will be at increased risk of bleeding when the INR is too high and at increased risk of thromboembolism when it is too low. Dabigatran would be expected to protect against both these excess risks in this group. There is therefore a clear opportunity for NICE to make some useful positive recommendations (similar perhaps to those published by the North East Treatment Advisory Group in January:

http://www.netag.nhs.uk/files/recommendations/Decisionsummary.DabigatranAF-Jan2011.pdf), concerning which groups of patients will be most likely to benefit (cost-effectively) from dabigatran rather than warfarin, rather than outright rejection of dabigatran as an effective treatment. I think that there is a real danger that if this treatment is simply rejected in this way by NICE, its use will be haphazard, dictated by the willingness of some patients to shout loudly and demand the treatment that they want, by varying willingness of doctors to follow guidance without question or to use individual clinical reasoning and risk assessment in their choice of licensed treatment, and by other influences such as pharmacy advisers, whose primary focus may be budgetary or beaurocratic, rather than the best choice of treatment for an individual patient.

4. The other group of patients that, understandably, has not been considered in detail (by the RE-LY trial or by the consultation document) is those for whom a rhythm control strategy has been agreed and cardioversion is scheduled. The reality is that at present commencing warfarin prior to cardioversion and achieving effective anticoagulation can take an inordinate amount of time, depending largely on the willingness of patients and their GPs to focus intensively on achieving this. Depending to some extent on the local arrangements, scheduling cardioversion at the appropriate time is often difficult and may be quite costly/labour-intensive. As a result some patients have unacceptably long delays before their cardioversion, reducing the chance of successful treatment. There is clear potential benefit for dabigatran to provide uniform and timely access to cardioversion and to greatly simplify systems for scheduling cardioversion by providing consistent antithrombotic protection for 3-4 weeks before the procedure. The time and date of the procedure could be planned at the time of prescribing dabigatran, rather than entering a sometimes long period of INR monitoring and numerous interactions among patient, GP and hospital. The duration of and choice of drug for longer-term antithrombotic therapy would then need consideration in individual clinical circumstances.

I hope that these four points are of help and that they can be considered by the ERG as part of the consultation process. I look forward to seeing the final outcome of your deliberations. I am sure that this is only the start of discussions on this clinical topic, with other drugs such as rivaroxoban and apixaban also showing evidence of efficacy in this setting.

Consultant Cardiologist