Response to the National Institute of Clinical Excellence appraisal consultation document: Dronedarone for the treatment of Atrial Fibrillation

The Primay Care Cardiovascular Society, 16.1.2010

We agree that all relevant evidence has been taken into account for this technology appraisal. However we disagree with the clinical assessment and recommendation of the appraisal committee.

We agree that Dronedarone appears to be less effective than the comparator anti-arrhythmic drugs (AADs) Amiodarone, Sotalol and class Ic agents in the prevention of atrial fibrillation recurrence but offers distinct advantages over other AADs. Some of these advantages have not been observed so far in other anti-arrhythmics.

The primary driver for the reduction in the primary outcome of the ATHENA trial was hospital admission due to cardiovascular causes. This is an important clinical and economic outcome which has been used extensively and successfully in other areas of cardiovascular medicine but has only found its way into heart rhythm trials recently. Therefore no comparison is available in the mixed treatment analysis due to the lack of data for the older AADs. The only trial of other ADDs reporting hospital admissions as an outcome is CHF-AF. This trial used exclusively Amiodarone in the rhythm control arm and did not show any reduction in hospital admissions but does not fulfil the criteria for the mixed treatment comparison. Dronedarone on the other hand achieved an impressive 26% relative reduction in admissions due to cardiovascular causes which we feel needs to be taken into account. It was also reassuring to know that admissions for cardioversion was the reason in less than a quarter of admissions and that the result was replicated throughout the world in this global trial.

Dronedarone achieved a statistical significant reduction in cardiovascular deaths which was a pre-specified secondary outcome and a trend towards a reduction in all cause mortality which was not statistically significant. However the mixed treatment comparison of Dronedarone with Amiodarone and Sotalol showed a significant reduction of all cause mortality for Dronedarone. No comparable data was available for class Ic agents.
There was also a statistically significant reduction in strokes with Dronedarone but this was observed only in a post hoc analysis as was the significant reduction in all cause mortality of patients with a CHADS2 score of 4 or more. No statistically significant reduction of strokes was reported with any of the other AADs.

We feel that the lack of significant data on Amiodarone, Sotalol and class Ic agents disadvantages Dronedaone's appraisal by introducing uncertainty. If Dronedarone was the established medication it is hard to see how the comparator AADs would become first choice agents given the positive and significant results of Dronedarone.

In addition Dronedarone has demonstrated a favourable safety profile. Although it significantly prolongs QT interval only one episode of non-fatal torsades was found in over 6000 patients. Furthermore serious adverse events such as thyroid dysfunction, pulmonary fibrosis and neurological effects feared in Amiodarone were not significantly more common with Drondedarone than with placebo, the point estimate almost being identical with the line of unity. In the MTC both Amiodarone and Sotalol were associated with a higher incidence of serious adverse events although

with wide confidence intervals. The direct comparison of Dronedarone and Amiodarone in the DIONYSOS trial showed less discontinuation due to adverse effects (12.9% vs 17.6%), less thyroid dysfunction, fewer neurological effects, less increased QT interval, less significant bradycardia but a higher incidence of diarrhoea (9.2% vs 3.1%). The latter was the main cause for the increased adverse event rate in ATHENA compared with placebo (12.7% vs 8.1%) but the overall discontinuation rate was the same. The longest study period in a Dronedarone trial was 21 +/-5 months and concerns exist that this might not be long enough to be sure pulmonary toxicity does not occur but is unlikely.
Therefore it is important for this appraisal not to look only at the total number of adverse events but to take into account seriousness and duration as well.

Patient choice and selection has not been adequately considered in our view. Many patients are simply not willing to expose themselves to the risk of serious adverse events with Amiodarone, Sotalol and class Ic agents leaving their symptoms often poorly controlled.
Furthermore there are subgroups of patients in whom clinicians find it very difficult to chose an appropriate AAD. For example younger patients with structural heart disease who clinicians do not want to expose to long-term treatment with Amiodarone. Another example is older patients without structural heart disease in whom clinicians feel uncomfortable to use class Ic drugs for extended periods.
From experience many patients would chose a less effective drug with a good safety profile instead of a more efficacious drug associated with more serious adverse events.

We feel that patients should not be denied the choice of Dronedarone as a second line anti-arrhythmic drug for the treatment of non-permanent atrial fibrillation. We agree that Dronedarone should not be used as a rate controlling agent in the management of permanent atrial fibrillation.

As Drondearone is a new anti-arrhythmic agent it seems sensible that the initiation of this drug is restricted to heart rhythm specialists whilst clinicians become familiar with it and further data emerges.

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on behalf of the Primary Care Cardiovascular Society.