Amiodarone for the Atrial Fibrillation: A Dead Man Walking?

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Originally developed as an anti-angina drug because of its vasodilatory properties, amiodarone is now rarely (if ever) used for its original indication due to its potential for serious side effects. As a serendipitous discovery in the late 60s, its anti-arrhythmic properties and the dearth of anti-arrhythmic alternatives allowed amiodarone to avoid discontinuation. Usage of amiodarone as an anti-arrhythmic agent increased over the next decades [1] but subsequently, and with the advent of catheter ablation, the use of this drug has curtailed somewhat [2].

As lipophilic structures, amiodarone and its metabolites accumulate in tissues at high concentrations (e.g. adipose tissue, liver, lung, skin, thyroid, eyes and nervous system), interacting with metabolism and eventually causing toxicity. Even though the lungs account for less than 5% of all amiodarone-related complications, pulmonary involvement has the most clinically significant impact, and can contribute to patient mortality [3]. Pneumonitis, a dose-dependent adverse event, can occur in 0.1 to 1.6% of patients on a 200mg daily dose, usually after 18 to 24 months of treatment. Importantly, amiodarone withdrawal may not be sufficient for reversal of lung damage and pulmonary fibrosis may develop, with mortality ranging from 10 to 33%, depending on disease progression at the time of diagnosis [4].

In the early 2000s, while discussions were being held about the survival benefit of antiarrhythmic agents in AF patients, a secondary analysis of the AFFIRM trial suggested that, despite not leading to a cardiovascular mortality benefit, amiodarone could significantly increase the hazard of non-cardiovascular death when compared with rate control agents [5]. Concerns raised by these alarming findings were later quelled with a systematic review and meta-analyses of trials investigating the use of anti-arrhythmic drugs for the treatment of persistent AF patients [6]. Results were, however, disappointing with a lack of survival benefit or reduction of hospitalizations in amiodarone-treated patients.

A meta-analysis of randomized controlled trials looking at prophylactic amiodarone for the prevention of arrhythmic death in high-risk patients with recent myocardial infarction or congestive heart failure, revealed high incidence of *"lung infiltrates"* (3.1%, 4.8% and 6.3%) in three trials, even with a short mean follow-up duration ranging from 1.62 to 2.15 years [7]. Adding 10 more trials, most with even shorter follow-up duration, the pooled results still showed a higher rate of lung infiltrates in the amiodarone treated group: 1.6% vs. 0.5% (OR=3.1, 95%CI 2.65-3.55, P=0.0003, Number Needed To Harm - NNTH=90.9 patients). A subsequent systematic review of four trials (two post-myocardial infarction and two on congestive heart failure patients) on the adverse effects of lower-dose amiodarone showed a similar trend for increased risk of pulmonary side effects in amiodarone treated patients: 1.9% vs. 0.7% (OR=2.22, 95%CI 0.93-5.23, P=0.073, NNTH=83.3 patients), with low heterogeneity observed across trials [8]. Mean follow-up duration was 12 months for two of the trials, and for the remaining this was 20 and 45 months.

The study by *Tsaban* and colleagues published in this Issue of the *European Heart Journal* tried to clarify the association of low-dose amiodarone therapy with the occurrence of interstitial lung disease (ILD), lung cancer and all-cause mortality in a Nationwide Israeli cohort study, comparing 6,039 amiodarone-exposed (200mg daily dose) patients with new-onset AF vs. matched unexposed-controls [9]. The primary analysis of the study comprised patients exposed to consistent amiodarone therapy and controls never exposed to amiodarone, which

was achieved using inverse probability treatment weighting (IPTW) methodology. The authors need to be congratulated for the elegant study design, and for skilfully dealing with the encountered violation of the proportional hazards model assumptions (the functions were not proportional over time). To deal with the latter, multiple sensitivity analyses, including a target trial emulation sensitivity analysis (with intention-to-treat (ITT) and as-treated analyses), analysis of the pre-Covid 19 era, the entire cohort analysis, and risk differences and risk ratios per follow-up year were suitably presented.

Lung Toxicity

After a mean follow-up of 4.2 years, ILD was observed in 2.0% (n=242) patients. The hazard ratio after IPTW analysis suggested a trend for ILD in the amiodarone-exposed group (HR=1.45, 95%CI 0.97-2.44, P=0.09). Two sensitivity analyses (including the whole cohort and the as-treated analysis of the target trial emulation) showed a significant association of amiodarone treatment with increased risk of ILD (Figure). Furthermore, the provided risk ratios per year during the 10-year follow-up showed a significantly increased risk for ILD between the 2nd and the 8th year. Numbers of participants at risk steeply drop after year 8 and the crossing of curves suggest that the proportional hazards assumption no longer applies after that period. It is possible, an additional sensitivity analysis starting after the initial year of amiodarone exposure (when the complications usually start developing) and whilst the proportional hazard assumptions are respected, would have been of interest. Furthermore, whenever a relatively rare complication is assessed, the spectre of low statistical power looms over the results, and we are left wondering if increasing the sample by only 10% would provide more support to the narrative on amiodarone-associated ILD risk (yielding similar results to the whole cohort analysis).

Lung Cancer Risk

At a median follow-up of 4.1 years, primary lung cancer (PLC) occurred in 97 patients (0.8%). On the main analysis, amiodarone exposure was not related to increased risk of PLC (HR=1.17, 95% CI 0.76-2.08, P=0.53). Interestingly, sensitivity analyses yielded diverging results: a trend for increased risk of primary lung cancer in the entire population sub-analysis (HR =1.28, 95%CI 0.96-1.70, P=0.088), no association in the ITT target trial emulation sensitivity analyses (HR 0.96, 95%CI 0.84-1.11), and lower risk of lung cancer on the as-treated analysis (HR=0.84, 95%CI 0.82-0.86).

Despite the conflicting findings within this Israeli nationwide study, fears of a potential association of amiodarone with all-cause cancer had been raised by the results of a previous Taiwan National Health Insurance Research database analysis. The study suggested a dose-dependent risk of incident cancer, especially in male patients [10]. Reassuringly, these results, were, not confirmed by a subsequent Danish nationwide cohort analysis [11].

All-Cause Mortality

All-cause death occurred in 2,185 patients (18.1%) at a median follow-up of 4.9 years. On the main analysis amiodarone exposure was related to a lower risk of all cause-death (HR=0.65, 95%CI 0.60-0.72, P<0.001). This reduction was consistent across all sensitivity analyses, except

for the ITT target trial emulation sensitivity analysis, where the magnitude of the association was much lower (HR = 0.95, 95%CI 0.93-0.97). Interestingly, this finding is contrary to recent and contemporary observations in UK and Danish nationwide studies, which showed no mortality benefit for amiodarone in this setting [2, 12]. On the other hand, both studies reported a mortality reduction in patients treated with flecainide, propafenone and sotalol [2, 12].

Catheter ablation, the main option for non-pharmacological rhythm control in the AF population, is also associated with feared complications such as atrio-esophageal fistula and procedure related mortality. The 90-day mortality rate directly due to AF ablation procedural complications has been recently estimated as 0.06% (NNTH= 1666.7 patients) [13]. This retrospective analysis of data from the Mayo clinic (2013 to 2021) reported only 4 peri-procedural deaths out of 6723 patients during the study period. Two were due to atrio-esophageal fistula (n=2) and the remainder cause by stroke within the first month. No cases of procedural mortality related to cardiac tamponade were reported in this series. A large multinational registry of AF ablation (the POTTER-AF study) reported atrio-esophageal fistula in 0.025% of procedures (138 out of 553,729 procedures; median time for diagnosis 21 days, range: 2-63 days), which corresponds to a NNTH of 4000 patients [14]. Compared with severe pulmonary toxicity in patients treated with amiodarone (NNTH 80 to 90 patients), these values seem to be on a completely different scale (severe side effects are 20 to 40 times more likely in the amiodarone-treated group). In other words, the risk of severe and potentially fatal side effects from chronic amiodarone treatment outweighs the risk of severe complications from AF ablation, although the former is diluted over time while the latter occurs on a specific time period during and in the weeks after ablation. Furthermore, when deciding on the best rhythm control strategy, besides looking at potential complications, the efficacy at preventing AF relapse, reducing AF burden and improving quality of life should also be considered. In this regard, catheter ablation is vastly superior to any antiarrhythmic drug [15], with the added benefit of substantially reducing mortality in patients with heart failure.

In sum, the *Tsaban* and colleagues' findings should be taken with a sign of caution. As the authors rightfully say, their findings will need validation by other studies. At this moment, it is premature to recommend amiodarone ≤200mg daily in AF patients even when catheter ablation is not being contemplated. When rhythm control using a pharmacological approach is being attempted, the guidelines still recommend that owing to amiodarone's extra-cardiac toxicity, *"other antiarrhythmic drugs should be considered first whenever possible"* [15].

Figure – Overview of evidence on amiodarone vs. rate control medical therapy and impact on interstitial lung disease, lung cancer and all-cause mortality

Legend: * all-cancer diagnosis; ILD – interstitial lung disease; Effect sizes: dark blue triangles – odds ratio; brown circle – hazard ratio; dark green square – relative risk; orange square – standardized incidence ratio.

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