

# Atenolol - Revisited

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## Introduction

$\beta$ -blockers are useful in managing angina and reducing mortality after myocardial infarction and in heart failure. In younger patients  $\beta$ -blockers should remain first time antihypertensives, together with diuretics, calcium channel blockers, and angiotensin converting enzyme inhibitors and adrenergic receptors blockers, the choice is individualized. Mostly all  $\beta$ -blockers are equivalent in cardiovascular protective effects and it seems inferior to other antihypertensive drugs in reducing stroke and total mortality. We reevaluate the real world consequences of recent clinical trial findings of common Beta-blockers including atenolol.

### 1. Myocardial Infarction and Atenolol

Long term treatment with oral  $\beta$ -blockers reduces mortality after acute myocardial infarction (AMI).<sup>1</sup> Pharmacologic properties like cardio selectivity and intrinsic sympathomimetic activity (ISA), may influence the efficacy of various  $\beta$ -blockers after AMI.<sup>2</sup> There is wide variation in the type of  $\beta$ -blockers prescribed after AMI. This variation might partly result from physicians assuming that all exert the same effect.<sup>3,4</sup> Yet given the differences in the pharmacologic properties among,  $\beta$ -blockers, as well as the absence of head to head comparison, the assumption of such a class effect is questionable. In a recent population-based analysis of class effect of  $\beta$ -blockers after myocardial infarction, metoprolol was found to be less effective in reducing mortality when compared with another cardio-selective agent atenolol in the post -AMI setting.<sup>5</sup> In retrospective cohort study by Redelmeier et al, there was reduced effectiveness of metoprolol compared with atenolol for the prevention of perioperative adverse events after non-cardiac surgery.<sup>6</sup>

Although there are abundant data from clinical trials to support the metoprolol's post - AMI long term efficacy, the two small placebo to controlled trial atenolol failed to suggest improved survival with this agent.<sup>7,8</sup> Furthermore, a recent meta analysis of all atenolol versus placebo trials reported no significant reduction in mortality in hypertensive patients and a significantly higher risk of death with atenolol treatment compared with other antihypertensive agents, which questioned the efficacy of this drug as first time therapy in hypertension.<sup>9</sup> In contrast, a recent study by Rinfret et al comparing different  $\beta$ -blockers in AMI settings<sup>5</sup> suggests long term effectiveness with atenolol. In the above study 31,567 patients who were 65 years or older discharged from hospital with a diagnosis of AMI were compared for metoprolol, acebutolol or atenolol within 90 days after discharge. Clinical characteristics and proportion of days covered with  $\beta$ -blockers prescription were similar across groups. Although controlling for time dependent covariates representing current use and dosage, as well as for age, sex, congestive heart failure and several other comorbidities, patient who filled a prescription for acebutolol (hazard ratio 0.71, 95%, CI 0.62-0.81) or atenolol (hazard ratio 0.79, 95%, CI 0.73-0.83) had significantly lower

mortality in comparison with metoprolol. This study is one of the few head to head comparison of the three  $\beta$ -blockers most commonly prescribed after AMI. Although most  $\beta$ -blockers have demonstrated efficacy in terms of reducing mortality post AMI, this study found a lower effectiveness of metoprolol for this indication. There was improved survival with atenolol and acebutolol, agents for which there is insufficient evidence on post AMI survival from long term randomized clinical trials.

The observed differences might be explained at least in part by different patterns of drug use. It is well recognized that drug adherence is better with once— a day dosing as compared with twice -a-day dosing drugs. Although adherence, measured as the number of days covered with the  $\beta$ -blockers, was similar across the 3 study agents, the twice daily dosing of metoprolol might have favoured recurrent acute  $\beta$ -blockers withdrawal in patients who forget to take one of the 2 doses during the same day, lowering its effectiveness. Although this can happen with the 2 other agents, their longer half- life might mitigate against this effect. However, the fact that drug dosage was below target for all 3 agents, although highlighting the opportunity to improve post. AMI care, cannot account for the reduced benefit observed with use of metoprolol. Moreover, accounting for drug dosage when comparing the 3 agents, and there were no interactions between dosage and different  $\beta$ -blockers, indicating that the impact of dose was similar across the 3 drugs.

The plasma concentration time profiles of the 3 agents are also unlikely to explain the findings. Although uneven profiles have been documented when comparing short versus long-acting forms of metoprolol<sup>11,13</sup> the same has also been documented for atenolol over a 24 hour dose interval.<sup>14,15</sup> Yet, it remains possible that the twice daily dosing of metoprolol partly explains the lower effectiveness of metoprolol in the elderly population. In other words, the increased effectiveness observed for atenolol might be attributable to longer duration of action rather than to specific pharmacologic properties. Nevertheless, it is important to stress that this study did not demonstrate the absence of a benefit with metoprolol, but rather a smaller benefit as compared with the other 2 drugs.

In conclusion, these findings suggest that  $\beta$ -blockers do not exert a class effect only after AMI. The reasons why patients who fill prescriptions for metoprolol do not benefit to the same extent as patients who filled prescriptions of acebutolol or atenolol remain uncertain, and are unlikely to be related to dosage or indication. Although refill compliance and persistence were overall similar for all 3 agents, we believe that the twice – daily dosing of metoprolol in most patients, with possible acute withdrawal resulting from missed doses, might at least partly explain our findings. Although still hypothetical, missed doses, might at least partly explain our findings. Although still hypothetical, missed doses of a longer-acting agent may be less deleterious. These hypotheses – generating findings provide unique information as to the long – term effectiveness of these medications on mortality.

## Hypertension and Atenolol

Atenolol has traditionally been considered an appropriate choice for the initial management of patients with uncomplicated hypertension.<sup>17,18</sup> The effectiveness of atenolol in this role has, however, recently been questioned.<sup>19,20</sup> Three recent analysis suggest it does not confer the same cardio and /or stroke protection properties of other first line agents when used as initial therapy.<sup>21,23</sup> The possible explanations for this reduced cardiovascular protection include inferior control of central blood pressure or an effect on pulse pressure.<sup>25</sup> On the basis of this information, atenolol was recently removed from National Institute of Health and Clinical Excellence guidelines and it has been suggested that other jurisdictions should followed suit.<sup>20</sup> It is plausible that the small differences in effectiveness in clinical trials<sup>22,23</sup> may be magnified (or diminished) in real life time settings in which blood pressure mediations may not be titrated as aggressively as algorithm driven protocols in clinical trials.<sup>26</sup>

A retrospective cohort study by Blackburn et al<sup>26</sup> that subjects started on their first ever antihypertensive medication to evaluate whether atenolol was associated with a significant excess of cardiovascular morbidity/mortality compared with other first-line agents. At baseline, the vast majority of subjects were similarly free from major co-morbidities, as indicated by the lack of previous hospitalizations and concurrent drug use. These subjects were typical of uncomplicated hypertensive patients in whom atenolol has been recommended as initial therapy. Compared with subjects initiated on ACEI, hydrochlorothiazide, or calcium antagonists, atenolol treated patients exhibited a very similar rate of clinical outcomes (i.e myocardial infarction, unstable angina, stroke or death), even after adjustment for a number of potential co-morbidities and confounding factors.

In contrast to previous studies,<sup>27,28</sup> above study did not observe increased morbidity / mortality in the subgroup of patients 60 years and older. Null finding, in this subgroup has several potential explanations. First, clinical trials commonly enroll patients with existing hypertension, whereas this analysis was restricted to first time antihypertensive users only. It may be that in this low-risk, uncomplicated group beta-blockers provide similar cardioprotection compared with other agents.

In the younger subgroup of patients, for whom beta-blockers have been traditionally considered equally effective to other first-line agents, there is no indication that atenolol was associated with greater morbidity / mortality than other agents. Event rates for all cohorts were extremely low and all-cause mortality was essentially equal. Similar observations were reported in the metaanalysis by Khan and Mc Alister.<sup>28</sup> This study observed a higher rate of PTCA procedures and nitrate use in the atenolol cohort, compared with the other groups. PTCA procedures occurring within 6 months of starting antihypertensive therapy are probably a result of a higher baseline frequency of angina rather than a complication of choosing atenolol. However, these patients are included in the overall analysis to ensure that eligible events in the atenolol group were not missed. Considering null findings, this strategy was a much more conservative approach to evaluate the safety of atenolol.

In a further attempt to identify safety concerns with atenolol, all-cause mortality rates were recorded using an 'intention to treat' type of approach. The extended follow up of all eligible patients past the date of the last prescription dispensation to study exit (coverage termination or the end of the study period). This extended follow-up period added approximately 2 years to the mean followup time of each cohort. Consistent with

the primary analysis, all-cause mortality rates were lower or essentially equal with atenolol compared with all other cohorts, suggesting that the long term consequences of choosing atenolol as initial therapy were minimal.

In summary we cannot eliminate the possibility that atenolol has resulted in excessive morbidity/ mortality in its current role as a first line agent for patients with uncomplicated hypertension. Considering the low event rates and similar results for all cohorts examined, however, we feel it unlikely that atenolol is a major threat to the health of low-risk, hypertensive patients. Although further study is required, it appears that atenolol is being, appropriately used in patients with uncomplicated hypertension.

## Congestive Heart Failure and Atenolol

Congestive heart failure (CHF) Randomized trails have demonstrated the favourable effect of selected  $\beta$ -adrenergic receptor blockers in Heart Failure (HF) with reduced left ventricular systolic function (e.g extended release metoprolol succinate<sup>29</sup> bisoprolol<sup>30</sup> carvedilol<sup>31,32</sup> and nebulolol.<sup>33</sup> Despite generally positive findings for selected  $\beta$ -blockers, arguments against general class effect come from negative trials of other  $\beta$ -blockers (bucindilol<sup>34</sup> and Xamoterol.<sup>35</sup> Few head to head randomized comparisons of outcomes exist among available  $\beta$ -blockers and have primarily involved carvedilol and shorter acting metoprolol tartarate.<sup>36</sup> According to published literature there are few/no published large scale evaluations of clinical outcomes comparing  $\beta$ -blockers including the widely used atenolol. In one study by GO AS et al<sup>37</sup> the adjusted rates of rehospitalization for HF did not vary significantly with atenolol, metoprolol tartarate, or carvedilol use, although information on mortality was unavailable. In a recent study by CO AS et al<sup>38</sup> a large cohort of adults hospitalized for HF, were compared for affectiveness of different  $\beta$ -blockers on the subsequent risk at death. In above study a substantial proportion of patients received a  $\beta$ -blockers at discharge and/or during follow up, with atenolol, shorter -acting metoprolol tartarate and carvedilol being the most frequently used. Among nearly 8000 high risk patients with HF receiving  $\beta$ -blockers, there were also notable differences in patient characteristics by type of  $\beta$ -blockers, with carvedilol-treated patients being significantly younger and having a low comorbidity burden but also receiving more HF related therapies than those receiving atenolol or metoprolol tartarate.

Few large studies exist outside of randomized trial settings that have examined whether outcomes vary by the type of  $\beta$ -blockers in HF. Fonarow and colleagues<sup>40</sup> studied 2373 patients hospitalized for new onset or worsening HF and reduced systolic function in the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with heart Failure (OPTIMIZE HF) registry received carvedilol. Compared with not receiving,  $\beta$ -blockers at discharge, the adjusted risk of death during the 60 to 90 days after discharge was significantly lower of carvedilol (HR, 0.46, 95%, CL, 0.30-0.73) and for metoprolol succinate or bisoprolol (HR 0.49; 95%, CI, 0.28-0.86), but not for the combined group of any other  $\beta$ -blockers like atenolol (HR, 0.66; 95% CI, 0.37, - 1.17)

As of today the additional evidence is needed to clarify whether clinical effectiveness or  $\beta$ -blockers for HF in clinical practice extends beyond the currently approved  $\beta$ -blockers options of carvedilol, metoprolol succinate, and bisoprolol, especially for patients who are receiving a different  $\beta$ -blocker like atenolol.

## Conclusion

The different pharmacologic properties of atenolol and non-atenolol  $\beta$ -blockers may account for their different cardiovascular protective effects in different patients. Good data now show that atenolol is inferior, but the data are not conclusive enough to require using a substitute in all patients.

Before starting or continuing with atenolol, though a cautious clinician would ask whether another  $\beta$ -blockers could be used. Atenolol is hydrophilic, has minimal hepatic metabolism and is excreted in the urine, its long half life allows once daily dosage. It is inexpensive and has little interaction with drugs that are metabolized in the liver, these features account for its popularity. However, its pharmacokinetic profile can be disadvantageous elder patients with renal impairment, which slows clearance of atenolol.

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