Age-Dependent Effect of Beta Blockers in Preventing Vasovagal Syncope

Running title: Sheldon et al.; Beta blockers, age, and syncope

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Abstract:

Background - Beta-blockers have little effectiveness in preventing vasovagal syncope in unselected populations, but they might be effective in older patients. We determined whether beta-blockers prevent vasovagal syncope in an age-related fashion.

Methods and Results - Two populations were studied. A proportional hazards analysis was performed on an observational cohort study of 153 patients with vasovagal syncope, 52 of whom received beta-blockers. A multivariable proportional hazards model stratified by center was performed on 208 participants in the randomized Prevention of Syncope Trial (POST), examining the interaction between age group and treatment with metoprolol. Age–specific hazard ratios were estimated for both studies, and combined using the inverse variance meta-analytic method. In the cohort study the hazard ratio for syncope if treated with beta-blockers was 1.54 (95% CI 0.78 to 3.05) for patients <42 years, and 0.48 (95% CI 0.12 to 1.92) for patients ≥42 years. In POST the proportional hazards model showed interactions between age and treatment effect (p = 0.026). The hazard ratio for patients ≥42 years who received metoprolol was 0.53 (95% CI 0.25 to 1.10); in patients <42 years, the hazard ratio was 1.62 (95% CI 0.85 to 3.10). A pooled analysis of both studies yielded an estimate of the hazard ratio for patients <42 years of 1.58 (CI 1.00–2.31) and the hazard ratio for patients ≥42 years was 0.52 (CI 0.27–1.01). The two age groups differed significantly in response to beta-blockers (p = 0.007).

Conclusions - Beta-blocker treatment may suppress vasovagal syncope in middle-aged patients aged ≥42 years.

Key words: aging; beta-blockers; clinical trials; syncope
Introduction

Vasovagal syncope is a common clinical problem that frequently proves difficult to treat. One of the earliest treatments to be attempted was beta receptor blockade 1. After initial enthusiasm 2-4 this treatment was questioned 5, 6, and subjected to at least 5 randomized clinical trials with syncope as the primary outcome 4, 7-10. They culminated in little evidence for the effectiveness of beta-blockers in preventing vasovagal syncope in the general population. These results were surprising, given the ability of isoproterenol to induce syncope on tilt table tests 2, 11, and the large volume of evidence that beta-blockers prevent positive responses to tilt table testing 12.

One explanation might be an age-dependent effect of beta-blockers in preventing the vasovagal reflex. Natale et al reported an observational study of 112 patients who were treated with metoprolol 13. Patients appearing to respond to metoprolol were older (55±12 years vs 42±15 years), and age >42 years was associated with a lower likelihood of syncope on metoprolol. Similarly in a small study of 32 subjects, Leor et al 14 reported that patients appearing to respond to metoprolol were older (28±14 vs. 22±3 years).

To test the hypothesis that beta-blockers prevent syncope recurrences in older patients we performed analyses on two separate populations and then pooled the results using a meta-analytic method using variance weighted least squares. The first study was an observational cohort 6, 15, 16 and the second was a randomized controlled trial, the Prevention of Syncope Trial (POST) 9, 17, in which patients were randomized to receive metoprolol or placebo. In a prespecified and stratified analysis there was a trend towards benefit in older subjects in POST. Here we assess whether there was an age-dependent effect in the observational cohort, then use a meta analysis to provide a point estimate and confidence intervals of the effect for the total population of the cohort and randomized studies.
Methods

Observational Cohort Study

The observational cohort\textsuperscript{6,15,16} from southern Alberta was enrolled and followed between January 1989 and December 2002. The global population consisted of 227 sequentially consenting patients referred for the assessment of syncope who underwent tilt table testing if they had had: 1) two or more syncopal spells; or 2) one syncopal episode and four or more presyncopal episodes; or 3) a single episode of syncope causing serious injury. 153 patients had positive tilt table tests and 74 had negative tests. Only the 153 patients with a positive tilt test were included in this analysis, to align them with the POST population, all of whom had positive tilt tests. Following passive head-up tilt testing with or without subsequent isoproterenol infusion if the first stage was negative, 52 patients were subsequently treated at physician discretion using the limited contemporary understanding of patient and treatment selection with beta-blockers and 101 remained drug-free. The mean daily doses of the drugs used were: atenolol 47.5 mg (n = 30), metoprolol 105 mg (n = 10), propranolol 71.4 mg (n = 7), nadolol 93.3 mg (n = 3), timolol 20 mg (n = 1), and pindolol 20 mg (n = 1). There were no evidence-based guidelines at the time. All patients were asked to notify the syncope clinic of their first occurrence of syncope and all patients were also contacted every six months. They were followed up to 47 months. Syncope was defined for the patients as a complete loss of consciousness resembling the syncope that led to their assessment.

POST Randomized Controlled Trial.

The multi-center Prevention of Syncope Trial (POST) was a randomized, placebo-controlled, double blind, trial designed to assess the effects of metoprolol in vasovagal syncope\textsuperscript{9}. The population was enrolled and followed for up to one year between October 1998 to April 2004,
and was described in detail elsewhere\(^9\). The POST subjects were from 5 countries: Canada (151), Germany (26), Columbia (15), United States (14), and Australia (2). The study was approved by the University of Calgary Conjoint Health Research Ethics Board, and by the institutional review boards of all participating institutions. The University of Calgary Syncope Clinic coordinated the trial and managed data storage and analysis. Patients were eligible for randomization in POST if they had a positive response to passive head-up tilt with or without subsequent isoproterenol infusion if the first stage was negative, and one or both of \(\geq 3\) lifetime syncopal spells preceding the tilt test \((n = 206)\), or \(\geq 1\) syncope recurrence within 6 months of a positive tilt test \((n = 2)\). An earlier unpublished analysis of the cohort study with all 227 patients from the syncope clinic showed evidence of a significant interaction between \((\log)\) age and beta-blocker use \((p = 0.016)\). The hazard ratio for treatment with beta-blockers depended on the age of the patient. Younger patients were more likely to faint when treated with beta-blockers whereas older patients were less likely to faint. The instantaneous risk was equal to 1 when age is approximately equal to 42, and therefore randomization in POST was stratified according to ages \(<42\) and \(\geq 42\) years. Patients were excluded if they had other causes of syncope, could not give informed consent, had important non-cardiovascular or cardiovascular diseases or a permanent pacemaker, had a pressing need for or contraindication to beta blockers, or had used beta blockers at a dose greater than the equivalent of metoprolol 25 mg bid for the purpose of suppressing the symptoms of vasovagal presyncope or syncope. Syncope was documented in a case report form and adjudicated by an outcomes adjudication committee.

**Statistical Analysis:**

For this analysis the cohort was limited to patients with a positive tilt table test \((n = 153)\). The characteristics of patients in the cohort who were treated using beta blockers versus those not
treated by beta blockers were described using the median (interquartile range) for continuous variables and percentages for categorical variables and compared using t-tests for normally distributed variables (after applying a logarithmic transformation where necessary) and Fisher’s Exact tests for categorical variables. Characteristics of the POST population were described similarly but differences between the arms were not tested since this was a randomized clinical trial. Differences in treatment effect for both studies were illustrated using Kaplan-Meier syncope-free survival curves.

Proportional hazards analysis was used to analyze outcomes. The proportional hazards model is a regression model for survival data. The hazard rate is a function of follow-up time and is the number of events observed (here first syncope) per unit time divided by the number at risk. In proportional hazards regression the natural logarithm of the hazard function at any time is modeled as the (log) baseline hazard multiplied by a linear function of the predictor variables (similar to that in linear regression). The effect of a variable on outcome is then assessed by the statistical significance of its coefficient. The exponential of the coefficient is termed the hazard ratio and can be interpreted similarly to the odds ratio as a comparison of risk between 2 groups.

As explained in the CONSORT statement, the strongest analyses of a difference in treatment effect in complementary subgroups should be based on a test of interaction, not on the examination of p-values of the treatment effect in subgroups. Thus in both the analysis of the cohort study and in POST, the primary analysis of interest is the test of significance of the interaction term between beta-blocker use and age group, using a proportional hazards model predicting time to first syncope. Patients who did not faint within the respective follow-up periods were censored. During model building in the cohort study, due to the lack of power with a small sample size, a p-value of 0.10 for the interaction was considered preliminary evidence of
a significant age-dependent effect of treatment with beta-blockers. For the POST study a more stringent p value of 0.05 was considered significant. For the POST analysis, the proportional hazards model was stratified by centre. Schoenfeld residuals were used to examine the assumption of proportional hazards. There was no evidence against the assumption of proportional hazards for any of the variables in the model (p > 0.05). For both studies, age was stratified at 42, to align with the randomization for POST. Age-specific (≤ 42 years and > 42 years) hazard ratios (with 95% confidence intervals) were estimated from the proportional hazards analysis for each study and after assessing the within age group heterogeneity, were combined using inverse variance analytic method and differences in the summary hazard ratios between the two age groups were tested using variance weighted least squares.

Results

Observational Cohort

In the cohort population there were 153 patients, 52 of whom were treated with beta-blockers (Table 1). Patients treated with beta blockers were older than those not treated with beta blockers (p = 0.028), and had a higher frequency of syncopal spells (p = 0.018). Kaplan-Meier curves showing the difference in syncope free survival for the two age-groups are presented in Figure 1. When examined in this group of 153 patients with positive tilt tests, the interaction between (log) age and beta-blocker use approached significance (p = 0.053). When the binary variable for age was used (<42 years and ≥42 years) in the interaction, the p value was larger (p = 0.140), with wide confidence intervals for the hazard ratio estimates. From this proportional hazards model, the estimated hazard ratio for patients <42 years is 1.54 (CI 0.78 – 3.05), and for patients ≥ 42 years is 0.48 (95% CI 0.12 – 1.92).

Randomized trial population (Table 2): In the POST population there were 208 patients,
of whom 108 received beta-blockers and 100 did not. The mean age was 42±18 years and 134 were female (64%). During a median follow-up duration of 143 days, 39 patients (36%) treated with beta-blockers had at least one syncopal spell, and 36 patients (36%) not treated with beta-blockers had a syncopal spell. The Kaplan-Meier estimates of syncope free survival for POST are presented in Figure 2. In the proportional hazards model predicting syncope recurrence, stratified by center, the interaction between age group and beta-blocker use was significant (p = 0.026). The hazard ratio for patients ≥42 years who received metoprolol was 0.53 (95% CI 0.25 to 1.10), whereas in patients <42 years, the hazard ratio was 1.62 (95% CI 0.85- 3.10).

**Combined populations**

Using variance-weighted least-squares regression, there was a significant difference in response to beta blockers between age groups in the combined hazard ratios (test for interaction p = 0.007). The estimated treatment hazard ratio in the younger group was 3.03 times that in the older group (95% CI 1.36, 6.67). Figure 3 shows combined point estimate for hazard ratios for treatment with beta-blockers for patients <42 years and patients ≥42 years. There was little heterogeneity between studies within age groups (I² = 0.0%, Q (1 df) = 0.01, p = 0.914 for age < 42 and I² = 0.0%, Q(1 df) = 0.02, p = 0.901 for age ≥ 42). Figure 3 shows combined point estimate for hazard ratios for treatment with beta-blockers for patients <42 years and patients ≥ 42 years. There was little heterogeneity between studies within age groups (Q (1 df) = 0.01, p = 0.914 for age <42 and Q(1 df) = 0.02, p = 0.901 for age ≥42). The estimate of the pooled hazard ratios for patients <42 years was 1.58 (CI 1.00 to 2.51) and the pooled hazard ratio for patients ≥42 years was 0.52 (CI 0.27 to 1.01).

**Discussion**

This analysis of two distinct study populations revealed a markedly age-dependent effect of beta
Beta blockers and vasovagal syncope

After early promise of effectiveness, beta-blockers were not found to have therapeutic benefit in 5 randomized clinical trials with syncope as the primary outcome. The beta-blockers in the studies include atenolol, metoprolol, propranolol, and nadolol. The study populations included patients with a wide range of ages, and none of the studies reported an age-dependent effect. (We attempted a patient-specific meta-analysis of extant databases but were unable to merge the databases.) The mean ages in the studies ranged from 32 to 44 years. However both Natale et al and Leor et al reported in small, non-randomized studies that patients who appeared to respond to beta blockers were older than those who did not respond. The general lack of effective medical treatment for vasovagal syncope, coupled with the observations of Natale et al and Leor et al, prompted us to stratify patients before randomization in the POST study according to ages <42 and ≥42 years. As hypothesized, there was a significant age-dependent effect.

A similar effect was noted in the observational cohort study. This is reassuring for several reasons. The population was from a different era, having been enrolled 10 years prior to the randomized study. The patients were enrolled based on clinical judgment, in the context of
contemporary general medical sense. Finally, it represents a “real life” patient population, without the well-known limitations of the setting of a formal randomized controlled trial.

**Clinical implications**

Taken together, the studies are internally consistent and suggest that beta-blockers may be effective in older patients, but should not be generally used in younger patients. If so, they will prove to be a useful addition to medical treatment. Only midodrine has reasonable evidence of effectiveness\textsuperscript{20-22}, and it cannot be used in patients with hypertension. It is the subject of the Prevention of Syncope Trial 4, a randomized placebo-controlled study of midodrine in moderately severe vasovagal syncope\textsuperscript{23}. Fludrocortisone was recently assessed in the Prevention of Syncope Trial 2, a randomized placebo-controlled study of fludrocortisone in moderately severe vasovagal syncope\textsuperscript{24}, and also should not be used in patients with hypertension. Permanent pacing is effective in highly selected patients with documented asystole during clinical syncope\textsuperscript{25}. The formal demonstration of the effectiveness of beta blockers will require a randomized clinical trial in patients $\geq 40$ years old.

**Physiologic insights**

The source of this age-dependent effect is uncertain. There are no age-dependent effects on trough blood pressure or trough heart rate at the time of presyncope and syncope during passive and nitroglycerin tilt tests\textsuperscript{26, 27}, suggesting that the age-dependent effect lies upstream. The beta$_1$- and beta$_2$-adrenoceptors both diminish with age, with a commensurate loss in responsiveness to catecholamines\textsuperscript{28, 29}. Notably, older patients are also less likely to have a positive isoproterenol-tilt table test, have a slower progression of symptoms during the test, and are more likely to develop presyncope than syncope\textsuperscript{30-32}. This alone does not explain the clinically observed effect.
It may be that a proportion of the older patients have age-related orthostatic intolerance, and that this is more easily prevented than is vasovagal syncope of younger patients. There is still some debate as to whether these are separate disorders, or simply age-related manifestations of the same disorder. However both older and younger patients have the same age of onset of syncope, arguing for a single disorder 33.

This unusual effect may arise due to the complex interaction of the adrenergic receptor systems with the venous system. Shigemi et al 34 reported that beta-receptor activation had no direct effect on unstressed venous volume, but it dilated hepatic outflow resistance during hypotensive stress. This was opposed by alpha-adrenergic mediated constriction. Beta blockade caused a large increase in venous volume, presumably by uncovering alpha adrenergic-mediated hepatic venous outflow resistance. Given that venous capacitance declines with age 35, it may be that beta blockade worsens syncope by causing an increase in the venous volume that precedes syncope 36. Older patients would be spared this deleterious effect, and have a beneficial response, possibly due to blockade of the beta-adrenergic effect on central cardiopulmonary baroreceptors. Finally there may be an age-independent effect at another site that does not diminish with age 37.

**Analytic method**

RCTs are the gold standard for estimating treatment effect, but since the randomized sample is almost never a random sample of the population of interest, results may lack generalizability. Observational studies, on the other hand, can suffer from bias because of non-random assignment but are in general more representative of the target population. Thus consideration of RCTs alone may be appropriate when assessing the efficacy of the treatment, but assessment of the effectiveness within a more general target population can be improved by considering the evidence from observational studies. The concept of complex synthesis (i.e. combining results...
across different study types) but has received much attention recently in the development of statistical methodology. Applications of this methodology have been published for cardiovascular events, and complex synthesis is recommended for the assessment of adverse events.

The analysis presented here is a simple example of a meta-analysis across different study types, but with only one study within each study type. We initially considered using a random effects model, whose assumptions include random effects within multiple studies of the same study type. However this would not be appropriate because here there is only one study within each study type. Therefore the random effects model was replaced by a fixed effects model and the combined treatment effect was estimated using variance weighted least squares.

Two findings attest to the robustness of this approach. Not only was there no evidence of heterogeneity between the two studies, but the same results were obtained from a randomised population selected using strict inclusion and exclusion criteria and from a less exclusive, broadly-based clinic population.

Tests of statistical significance

The CONSORT statement provides for analyses such as these by explicitly stating that the strongest analysis of a difference in treatment effect (here, beta blockers) is with a test of interaction. With this it is appropriate to use a single p-value from the interaction term in the proportional hazards regression model, and not the examination of the separate statistical significances of the treatment effect in subgroups. The measurement of treatment effect here is the hazard ratio and therefore the difference in treatment effects between the two groups is a comparison of the hazard ratios in the younger group and the older group, which is provided by the coefficient for the interaction term (between treatment and age group) in the model. We
provided the p-value for the interaction term in each analysis (cohort, POST, combined) but did not present the CI since the interpretation of the single interaction coefficient is not meaningful. Instead we used the estimated regression coefficients to estimate the hazard ratio in each group involved and the 95% confidence intervals for each hazard ratio.

**Limitations**

The upper limits of the confidence intervals of the pooled effect estimates hovered at 1.0, and this dampens the strength of our conclusions. The observational cohort study was not randomized, and there was no formalized treatment routine. This did introduce at least one confounding influence, as patients who had a positive tilt test, a higher peak heart rate, or a lower trough blood pressure were more likely to receive beta-blockers. Patients in the observational studies were not treated with maximum doses of beta-blockers, although the doses were similar to those used in other studies. In POST we used only metoprolol, which is hydrophilic and $\beta_1$-selective, while the observational study used 6 beta blockers. However, 40/52 patients used metoprolol or atenolol, both hydrophilic and beta-1 selective. There is some evidence that hydrophobic or non-selective beta-blockers are more effective in preventing syncope during tilt testing $^{12}$. Only passive- and isoproterenol-tilt tests were used in POST, and this might have inserted a selection bias. Indeed, Delepine et al $^{30}$ reported only partial agreement in tilt test outcomes when comparing isoproterenol versus nitroglycerin in the same patient. However almost all patients who had a positive test without provocative medication also fainted after nitroglycerin provocation, and POST 1 included patients with positive responses to either passive tilt or isoproterenol tilt testing. POST 1 also reported similar outcomes in patients with either passive or isoproterenol tilt tests. However nitroglycerin tilt tests were not used in POST 1, and therefore whether older patients with positive nitroglycerin tilt tests respond to beta blockers.
Complicating all of this is the recommendations of guidelines to use the history to establish the diagnosis, and only use tilts where reasonable doubt persists."43

The cohort population was selected based on best clinical judgment from 1989-1992, without formal diagnostic criteria. However patients with positive and negative tilt tests were very similar in baseline clinical and demographic characteristics and clinical outcome. Furthermore a multivariable regression model using the baseline characteristics predicted outcomes equally well in the populations with positive and negative tilt tests. These findings suggested that the two populations were very similar, and the only detectable difference between the two was tilt test outcome. A secondary analysis in the Syncope Symptom Study supported this conclusion."44 Therefore the observational cohort included a large majority of patients with vasovagal syncope.

**Conclusion**

Beta-blockers may be effective in preventing syncope in older patients (≥42 years) and should not be used in younger patients.

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**Conflict of Interest Disclosures:** None.

**References:**


Table 1: Baseline characteristics of the 153 participants in the observational cohort study according to whether they were treated with beta-blockers or not. The results are presented as medians with interquartile ranges (IQR) for continuous variables and n (%) for categorical variables. P-values are for the t test for continuous variables (*logarithm transformed variable) and Fisher exact tests for categorical variables.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Beta-blockers</th>
<th>No Beta-blockers</th>
<th>p</th>
</tr>
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<tbody>
<tr>
<td>N</td>
<td>52</td>
<td>101</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>38 (26 – 58)</td>
<td>33 (20 – 50)</td>
<td>0.028</td>
</tr>
<tr>
<td>Females</td>
<td>22 (42)</td>
<td>43 (43)</td>
<td>1.00</td>
</tr>
<tr>
<td>Tilt test outcome: Syncope</td>
<td>32 (62)</td>
<td>49 (49)</td>
<td>0.171</td>
</tr>
<tr>
<td>Lifetime syncopal episodes</td>
<td>5 (2 – 25)</td>
<td>4 (2-17)</td>
<td>0.744*</td>
</tr>
<tr>
<td>Duration of symptoms (months)</td>
<td>24 (6 – 75)</td>
<td>32 (6 – 84)</td>
<td>0.626*</td>
</tr>
<tr>
<td>Frequency of spells (spells/month)</td>
<td>0.50 (0.16 – 1.15)</td>
<td>0.25 (0.10 – 1)</td>
<td>0.018*</td>
</tr>
<tr>
<td>Tilt test peak heart rate, bpm</td>
<td>140 (119 – 147)</td>
<td>130 (115 – 150)</td>
<td>0.142</td>
</tr>
<tr>
<td>Tilt test peak systolic blood pressure</td>
<td>127 (107 – 143)</td>
<td>123 (108 – 137)</td>
<td>0.708</td>
</tr>
<tr>
<td>Tilt test trough heart rate, bpm</td>
<td>70 (60 – 88)</td>
<td>70 (61 – 80)</td>
<td>0.474</td>
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<tr>
<td>Tilt test trough systolic blood pressure</td>
<td>62 (51 – 74)</td>
<td>61 (52 – 76)</td>
<td>0.813</td>
</tr>
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</table>

Table 2: Baseline characteristics of the 208 participants in the POST randomized clinical trial according to whether they were treated with beta-blockers or not. The results are presented as medians with interquartile ranges (IQR) for continuous variables and n (%) for categorical variables. Baseline differences were not reported in accordance with the CONSORT guidelines \(^\text{18}\), although no significant differences were found on post hoc analysis.

<table>
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<th>Characteristic</th>
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<th>Placebo</th>
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<tr>
<td>N</td>
<td>108</td>
<td>100</td>
</tr>
<tr>
<td>Age (years)</td>
<td>40 (27 – 58)</td>
<td>36 (25 – 53)</td>
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<tr>
<td>Females</td>
<td>66 (61)</td>
<td>68 (68)</td>
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<tr>
<td>Positive Drug Free test</td>
<td>46 (43)</td>
<td>45 (45)</td>
</tr>
<tr>
<td>Lifetime syncopal episodes</td>
<td>8 (4 – 20)</td>
<td>9 (5 -20)</td>
</tr>
<tr>
<td>Duration of symptoms (years)</td>
<td>12.5 (3.3 – 30.1)</td>
<td>10.1 (3.2 – 20.3)</td>
</tr>
<tr>
<td>Frequency of spells (spells/year)</td>
<td>1.2 (0.3 – 3.9)</td>
<td>1.2 (0.6 – 4.4)</td>
</tr>
<tr>
<td>Supine heart rate, bpm</td>
<td>70 (61 – 76)</td>
<td>72 (65 – 79)</td>
</tr>
<tr>
<td>Supine blood pressure</td>
<td>125 (116 – 138)</td>
<td>120 (110 – 132)</td>
</tr>
</tbody>
</table>
Figure Legends:

**Figure 1.** Kaplan-Meier curves showing the difference in syncope-free survival for the two age-groups for the cohort study. The left panel shows that younger patients appear to do worse if treated with beta blockers, while the right panel shows that older patients appear to do better if treated with beta blockers.

**Figure 2:** Kaplan-Meier curves showing the difference in syncope free survival for the two age-groups for the POST randomized clinical trial. The left panel shows that younger patients appear to do worse if treated with beta blockers, while the right panel shows that older patients appear to do better if treated with beta blockers.

**Figure 3:** Hazard ratios for a patient having a recurrence of syncope in both studies, for patients $<42$ years and $\geq 42$ years. The randomized study hazard ratio is calculated after stratification based on randomization centre. The pooled estimates of hazard ratios were calculated using the inverse variance meta-analytic method. The combined point estimate for hazard ratios for treatment with beta-blockers for patients $<42$ years was 1.58 (CI 1.00 to 2.51), and for patients $\geq 42$ years it was 0.52 (CI 0.27 to 1.01).
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