Impact of resting heart rate on mortality, disability and cognitive decline in patients after ischaemic stroke

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Aims
Recurrent stroke is a frequent and disabling event. A high heart rate is associated with cardiovascular outcomes. We investigated the effects of the resting heart rate on cardiovascular and neurological outcomes after recurrent stroke in the high-risk population of the PRoFESS study.

Methods and results
A total of 20,165 patients after ischaemic stroke (mean age 66.1, SD 8.6 years) assigned to the treatment arms of the PRoFESS trial were pooled divided by quintiles of the baseline heart rate and analysed according to cardiovascular and functional outcomes after stroke: recurrent stroke and major cardiovascular outcomes such as stroke, myocardial infarction, and worsening or new-onset heart failure as well as death from cardiovascular and non-cardiovascular causes. Pre-defined endpoints were disability after a recurrent stroke, assessed with the modified Rankin scale (mRS) and the Barthel index at 3 months, and cognitive function, assessed with the Mini-Mental State Examination (MMSE) score at 4 weeks after randomization and at the penultimate visit. Patients in the two highest quintiles of heart rate (77–82 and >82 b.p.m.) were at a higher risk for total death [hazard ratio (HR) 1.42, 95% CI 1.19–1.69 and HR 1.74, 95% CI 1.48–2.06, P = 0.0001] compared with the lowest quintile. Similar results were observed for vascular death [71–≤76 b.p.m., HR 1.39 (1.11–1.74), P = 0.0001] and non-vascular death [from >82 b.p.m., HR 1.66 (1.29–2.13), P = 0.0016]. Myocardial infarction (P = 0.7084) and recurrent stroke (P = 0.1379) were not significantly associated with the baseline heart rate. Hazard ratios were adjusted to multiple confounders including the baseline blood pressure. In the group of patients with a recurrent stroke, an association of a lower heart rate to better outcomes was measured with the Barthel index across all heart rate groups. In addition, there was a significant association of the baseline heart rate to the occurrence of significant cognitive decline according to an MMSE score ≤24 points at 1 month and at the penultimate visit or a decline of ≥2 points between these two time periods. Better independence score at a low heart rate were observed.

Conclusion
The heart rate is a risk indicator for mortality in patients with stroke and, importantly, a low heart rate is associated with a better functional outcome and less cognitive decline after an ischaemic stroke.

Trial registration: ClinicalTrials.gov, number NCT00153062.

Keywords
Heart rate • Stroke • Cardiovascular outcomes • Cognitive decline • Dementia

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Introduction

Several epidemiological and clinical studies indicate that the intrinsic heart rate at rest predicts cardiovascular death in the general population, and in patients with hypertension, coronary artery disease, high-cardiovascular risk, and heart failure. Experimental studies have shown that heart rate reduction with the If-channel inhibitor, ivabradine, slows atherosclerosis and reduces the stroke size. Although the effects of blood pressure on vascular outcomes, mortality, and functional outcomes after stroke are well characterized, no such information is available for the heart rate.

The Prevention Regimen for Effectively Avoiding Second Stroke trial (PRoFESS) compared the effectiveness of prophylactic treatment with aspirin and extended release dipyridamole vs. treatment with clopidogrel as well as treatment with telmisartan or placebo in a two by two factorial design in patients who have had an ischemic stroke. There was no evidence that telmisartan was superior to placebo or that the combination of aspirin and extended release dipyridamole was superior to clopidogrel in the prevention of recurrent stroke or with regard to neurological outcomes. This post hoc analysis of PRoFESS aimed at evaluating associations of the resting heart rate at baseline with cardiovascular outcomes and neurological outcomes among patients who recently experienced an ischemic stroke or suffered a recurrent stroke. Data of patients from the treatment arms, which did not show different outcomes, were pooled for this analysis.

Methods

In brief, from September 2003 to July 2006, 20,332 patients from 695 centres in 35 countries were assigned to the different treatment arms after they had had a non-cardioembolic ischemic stroke. Patients who experienced an ischemic stroke within 120 days prior to randomization were aged 55 years or older or patients aged 50–54 years had to have two additional cardiovascular risk factors. The trial had a two by two factorial design to compare for treatment regimens containing extended release dipyridamole plus aspirin compared with clopidogrel or telmisartan, compared with placebo. All patients were on optimum medical treatment at the discretion of the investigators including drugs for controlling blood pressure. Ischemic stroke qualified for inclusion, if there was a focal neurological deficit of cardiovascular origin >24 h. In patients whose symptoms persisted <24 h, they had to have evidence of a current ischemic stroke on computed tomography or magnetic resonance imaging. Primary hemorrhagic stroke, severe disability after the qualifying stroke, or contraindications to one of the drug treatments or other factors, as summarized in the design paper, were reasons for the exclusion of the patients. After qualifying, stroke patients could be randomized, being still in the hospital, up to the follow-up of 120 days after stroke. The following evaluations were done at 1 week, and at 1, 3, and 6 months as well as every 6 months thereafter. Patients who were unable to come to the hospital were contacted by telephone. The heart rate was taken at entry in a sitting position together with blood pressure. Blood pressure was measured by using a standard and validated Omron sphygmomanometer (Omron Health Care Inc.) with an appropriately sized cuff. Baseline data were to be collected the same day as randomization. The median time from the index stroke to the baseline heart rate assessment was 15 days, 7 and 39 days being the 25th and 75th percentiles.
Table 1  Baseline characteristics of study participants by quintiles of the resting heart rate

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Q1 (≤64) (n = 4835)</th>
<th>Q2 (65 to ≤70) (n = 3772)</th>
<th>Q3 (71–≤76) (n = 4236)</th>
<th>Q4 (77–≤82) (n = 3509)</th>
<th>Q5 (&gt;82) (n = 3813)</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Summary statistic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Age in years</td>
<td>67.36 (8.50)</td>
<td>66.19 (8.48)</td>
<td>65.90 (8.55)</td>
<td>65.46 (8.52)</td>
<td>65.46 (8.63)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Female sex (%)</td>
<td>30.82</td>
<td>34.62</td>
<td>38.05</td>
<td>37.25</td>
<td>40.05</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>BMI at baseline</td>
<td>26.86 (4.81)</td>
<td>26.9 (4.90)</td>
<td>26.79 (4.87)</td>
<td>26.71 (5.14)</td>
<td>26.8 (5.32)</td>
<td>0.0463</td>
</tr>
<tr>
<td>Tobacco use (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>37.39</td>
<td>41.49</td>
<td>44.36</td>
<td>45.34</td>
<td>46.05</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Currently</td>
<td>21.86</td>
<td>21.47</td>
<td>20.21</td>
<td>21.00</td>
<td>21.58</td>
<td></td>
</tr>
<tr>
<td>Previously</td>
<td>40.72</td>
<td>36.98</td>
<td>35.39</td>
<td>33.63</td>
<td>32.36</td>
<td></td>
</tr>
<tr>
<td>Alcohol use (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 drinks/week</td>
<td>59.23</td>
<td>61.64</td>
<td>66.17</td>
<td>68.20</td>
<td>69.74</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>1–14 drinks/week</td>
<td>34.15</td>
<td>31.55</td>
<td>28.64</td>
<td>26.19</td>
<td>24.97</td>
<td></td>
</tr>
<tr>
<td>15+ drinks/week</td>
<td>5.98</td>
<td>6.31</td>
<td>4.67</td>
<td>4.76</td>
<td>4.56</td>
<td></td>
</tr>
<tr>
<td>TOAST classification of qualifying stroke (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Large-artery atherosclerosis</td>
<td>27.36</td>
<td>28.69</td>
<td>26.65</td>
<td>29.67</td>
<td>31.31</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cardioembolism</td>
<td>1.92</td>
<td>1.38</td>
<td>1.37</td>
<td>1.77</td>
<td>2.68</td>
<td></td>
</tr>
<tr>
<td>Small-artery occlusion (lacune)</td>
<td>49.87</td>
<td>52.76</td>
<td>54.32</td>
<td>53.66</td>
<td>50.04</td>
<td></td>
</tr>
<tr>
<td>Acute stroke of other determined cause</td>
<td>2.28</td>
<td>1.72</td>
<td>1.96</td>
<td>2.31</td>
<td>1.94</td>
<td></td>
</tr>
<tr>
<td>Stroke of undetermined cause</td>
<td>18.53</td>
<td>15.32</td>
<td>15.65</td>
<td>12.54</td>
<td>14.00</td>
<td></td>
</tr>
<tr>
<td>Modified Rankin scale score (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–2</td>
<td>81.43</td>
<td>77.55</td>
<td>77.86</td>
<td>73.55</td>
<td>69.24</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>3–4</td>
<td>18.57</td>
<td>22.45</td>
<td>22.14</td>
<td>26.45</td>
<td>30.74</td>
<td></td>
</tr>
<tr>
<td>5–6</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>Baseline NIHSS score (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–1</td>
<td>45.60</td>
<td>40.27</td>
<td>40.08</td>
<td>35.77</td>
<td>35.04</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>2–3</td>
<td>28.89</td>
<td>30.38</td>
<td>28.78</td>
<td>30.44</td>
<td>29.19</td>
<td></td>
</tr>
<tr>
<td>4+</td>
<td>25.46</td>
<td>29.35</td>
<td>31.14</td>
<td>33.80</td>
<td>35.77</td>
<td></td>
</tr>
<tr>
<td>Previous stroke or TIA (%)</td>
<td>24.80</td>
<td>24.42</td>
<td>23.96</td>
<td>24.08</td>
<td>25.65</td>
<td>0.4233</td>
</tr>
<tr>
<td>CHF (%)</td>
<td>2.67</td>
<td>2.68</td>
<td>2.53</td>
<td>2.42</td>
<td>2.88</td>
<td>0.7749</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>75.68</td>
<td>72.53</td>
<td>73.87</td>
<td>73.07</td>
<td>74.48</td>
<td>0.0095</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>21.80</td>
<td>25.85</td>
<td>29.04</td>
<td>30.92</td>
<td>35.43</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hyperlipidaemia (%)</td>
<td>50.49</td>
<td>45.86</td>
<td>46.08</td>
<td>44.40</td>
<td>45.21</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Atrial fibrillation (%)</td>
<td>2.87</td>
<td>2.17</td>
<td>2.03</td>
<td>2.34</td>
<td>3.93</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Use of medications at baseline (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium-channel blocker</td>
<td>24.38</td>
<td>22.77</td>
<td>24.06</td>
<td>24.54</td>
<td>26.49</td>
<td>0.0054</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>38.47</td>
<td>37.41</td>
<td>36.57</td>
<td>35.54</td>
<td>36.22</td>
<td>0.0054</td>
</tr>
<tr>
<td>Statin</td>
<td>51.23</td>
<td>46.37</td>
<td>45.14</td>
<td>44.74</td>
<td>47.76</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diuretic</td>
<td>23.10</td>
<td>20.97</td>
<td>20.35</td>
<td>18.50</td>
<td>20.85</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>35.76</td>
<td>21.45</td>
<td>17.19</td>
<td>14.79</td>
<td>10.81</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>MMSE score at 1 month</td>
<td>27.16 (3.77)</td>
<td>27.14 (3.86)</td>
<td>27.05 (3.98)</td>
<td>26.86 (4.35)</td>
<td>26.54 (4.61)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Baseline diastolic blood pressure</td>
<td>82.17 (10.478)</td>
<td>82.76 (10.44)</td>
<td>83.79 (10.12)</td>
<td>84.54 (10.01)</td>
<td>86.30 (10.60)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Baseline systolic blood pressure</td>
<td>145.42 (17.15)</td>
<td>143.45 (16.40)</td>
<td>143.73 (16.25)</td>
<td>143.64 (15.95)</td>
<td>143.93 (16.70)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*χ² test used for categorical variables; the Kruskal–Wallis test used for continuous variables.
were performed using the SAS statistical software version 9.2 (SAS Institute Inc.).

### Table 2  Hazard ratios of a primary outcome stroke and the secondary outcomes of myocardial infarction, new-onset or worsening of heart failure as well as death, cardiovascular death, and non-cardiovascular death

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Q1 (≤64) Adjusted</th>
<th>Q2 (65 to ≤70) Adjusted</th>
<th>Q3 (71 to ≤76) Adjusted</th>
<th>Q4 (77 to ≤82) Adjusted</th>
<th>Q5 (≥82) Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Reference</td>
<td>0.98 (0.84–1.14)</td>
<td>1.05 (0.91–1.22)</td>
<td>0.96 (0.82–1.12)</td>
<td>1.11 (0.96–1.29)</td>
</tr>
<tr>
<td>Myocardial infarction&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Reference</td>
<td>1.05 (0.76–1.45)</td>
<td>1.18 (0.86–1.60)</td>
<td>1.05 (0.74–1.49)</td>
<td>1.30 (0.93–1.81)</td>
</tr>
<tr>
<td>CHF&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Reference</td>
<td>0.75 (0.52–1.09)</td>
<td>1.07 (0.77–1.49)</td>
<td>0.94 (0.65–1.37)</td>
<td>1.05 (0.74–1.49)</td>
</tr>
<tr>
<td>Death&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Reference</td>
<td>1.11 (0.93–1.33)</td>
<td>1.32 (1.11–1.56)</td>
<td>1.42 (1.19–1.69)</td>
<td>1.74 (1.48–2.06)</td>
</tr>
<tr>
<td>Vascular death&lt;sup&gt;e&lt;/sup&gt;</td>
<td>Reference</td>
<td>1.20 (0.95–1.52)</td>
<td>1.39 (1.11–1.74)</td>
<td>1.51 (1.20–1.90)</td>
<td>1.78 (1.44–2.22)</td>
</tr>
<tr>
<td>Non-vascular death&lt;sup&gt;f&lt;/sup&gt;</td>
<td>Reference</td>
<td>0.99 (0.75–1.30)</td>
<td>1.19 (0.92–1.53)</td>
<td>1.25 (0.95–1.64)</td>
<td>1.66 (1.29–2.13)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Adjusted hazard ratio adjusted for the following baseline characteristics: age (years), sex, tobacco use (never/currently/previous), exercise category (sedentary/some activity/intense activity), small-artery occlusion (lacune) TOAST classification of qualifying stroke, modified Rankin scale score (0–2/3–5), NIHSS score (0–1/2–3/4+), medical conditions (hypertension, diabetes mellitus, atrial fibrillation), use of medications (beta-blocker), and systolic blood pressure.

<sup>b</sup>Adjusted hazard ratio adjusted for the following baseline characteristics: age (year), sex, race (Asian), tobacco use (never/currently/previous), alcohol use (0/1–14/15+ per week), exercise category (sedentary/some activity/intense activity), medical conditions (atherosclerotic disease, diabetes mellitus), use of medications (beta-blocker), diastolic blood pressure, and systolic blood pressure.

<sup>c</sup>Adjusted hazard ratio adjusted for the following baseline characteristics: age (year), waist circumference (cm), exercise category (sedentary/some activity/intense activity), small-artery occlusion (lacune) TOAST classification of qualifying stroke, medical conditions (atherosclerotic disease, diabetes mellitus, atrial fibrillation, valvular disease), use of medications (beta-blocker, diuretic), diastolic blood pressure, and systolic blood pressure.

<sup>d</sup>Adjusted hazard ratio adjusted for the following baseline characteristics: age (year), sex, race (Asian, black, white), tobacco use (never/currently/previous), alcohol use (0/1–14/15+ per week), obesity, exercise category (sedentary/some activity/intense activity), small-artery occlusion (lacune) TOAST classification of qualifying stroke, modified Rankin scale score (0–2/3–5), NIHSS score (0–1/2–3/4+), medical conditions (atherosclerotic disease, hypertension, diabetes mellitus, hyperlipidaemia, atrial fibrillation, valvular disease), use of medications (ACE inhibitor, beta-blocker, statin, calcium-channel blocker), and diastolic blood pressure.

<sup>e</sup>Adjusted hazard ratio adjusted for the following baseline characteristics: age (year), sex, race (white), alcohol use (0/1–14/15+ per week), exercise category (sedentary/some activity/intense activity), small-artery occlusion (lacune) TOAST classification of qualifying stroke, modified Rankin scale score (0–2/3–5), NIHSS score (0–1/2–3/4+), medical conditions (atherosclerotic disease, hypertension, diabetes mellitus, hyperlipidaemia, atrial fibrillation, valvular disease), use of medications (ACE inhibitor, beta-blocker).

<sup>f</sup>Adjusted hazard ratio adjusted for the following baseline characteristics: age (year), race (Asian, Black, White), tobacco use (never/currently/previous), obesity, exercise category (sedentary/some activity/intense activity), modified Rankin scale score (0–2/3–5), medical conditions (atherosclerotic disease, diabetes mellitus), use of medications (statin, calcium-channel blocker), and diastolic blood pressure.

Role of funding

The sponsor was involved in the study design, collection, and interpretation of the data. The sponsor was not involved in the decision to submit the paper for publication. All authors had full access to the data and analyses and vouch for the currency and completeness of the data reported. All authors were involved in the final decision to submit the manuscript.

Results

All PRoFESS patients with the baseline heart rate collected (20 165 out of the 20 332 patients randomized) entered the analysis. The mean age was 66 (SD 8.6) years and 36% of the population were women. The baseline characteristics including ethnic groups and pre-existing diseases according to quintiles of the heart rate at baseline were summarized in Table 1. Several of these baseline parameters were similar. However, patients with a high heart rate were younger and more likely women and less likely to drink alcohol or to smoke. Beta-blocker treatment was more prevalent in low than in high heart rate groups. Interestingly, patients with a higher heart rate have a higher TOAST classification indicative of large artery atherosclerosis as well as the difference according to the mRS score at baseline and the NIHSS score (Table 1).

When the total population was divided by heart rate quintiles at baseline, the primary endpoint of recurrent stroke was not significantly different between all heart rate groups (log rank $P = 0.1379$). This holds true for the unadjusted data as well as for data adjusted for age, sex, tobacco use, exercise, small artery occlusion, TOAST classification, mRS, NIHSS and previous medical conditions, use of medications, and blood pressure (Table 2, Figure 1A). There was also no significant association with stroke, myocardial infarction or new onset or worsening of heart failure (Table 2A). Total death was associated with the resting heart rate (Figure 2A). The threshold of an increased risk for adjusted and unadjusted death occurred at a heart rate of 71 – 76 b.p.m. with an adjusted HR of 1.32 (95% CI 1.11–1.56). At a heart rate >82 b.p.m., the risk of death increased to an HR of 1.74 (95% CI 1.48–2.06) after the adjustment for covariates. Similar data were obtained for cardiovascular death (Figure 2B, Table 2). The HR was 1.39 (1.11–1.74) at a resting heart rate of >82 b.p.m. by log (time) was a concern ($P = 0.02$). So, a Kolmogorov-type supremum test was performed for each of the covariates and that yielded $P = 0.06$ for the baseline heart rate >82 b.p.m. covariate. In addition, an inspection of the log[−log[S(t)]] plot vs. log(time) was performed and the conclusion was that the assumption of proportional hazards was met.

All endpoints reported were pre-specified in a publication statistical analysis plan that was written after study results were reported, except the statistical test for the 3-month post-stroke mRS, which was requested after initial results were reviewed. The overall significance level for the study was 0.05 using the two-sided test. All analyses were performed using the SAS statistical software version 9.2 (SAS Institute Inc.).
71–≤76 b.p.m., and amounted to 1.78 (1.44–2.22) at a heart rate >82 b.p.m. (Table 2). A similar but a weaker association was observed for non-cardiovascular death with a significant HR of 1.66 (1.29–2.13) at a heart rate >82 b.p.m. (Figure 2C, Table 2).

To study the interaction of systolic or diastolic blood pressure with the heart rate, the interaction of blood pressure with the heart rate was examined. Since the correlation was low, blood pressure was included in the covariates for selection into the adjusted model. Adding systolic or diastolic blood pressure, there was no change of risk, indicating that the effects of the heart rate on risk are independent of the blood pressure (not shown).

To determine whether the baseline heart rate has an impact on the patients’ global disability scale according to the mRS, individuals with a recurrent stroke (n = 1627) were scaled into seven categories. There was a better functional outcome 3 months after the recurrent stroke with a lower heart rate (P = 0.0191, Table 3, Figure 3). Furthermore, quintiles of the heart rate were associated with disability according to the mRS at baseline (P < 0.001) and 3 months after the recurrent stroke (P = 0.0002, Figure 3). To measure an index of daily life activities and independence, the Barthel index was evaluated 3 months after the first stroke. We could show that after the index stroke in 1529 patients, the Barthel index was higher in patients in the first lower quintiles of the heart rate (P = 0.0002, Table 3).

Cognitive function was evaluated with an MMSE at 1 month and after the penultimate visit. It is shown that heart rate quintiles were related to impaired cognitive function (MMSE ≤24) at 1 month and during the follow-up until the penultimate visit (P = 0.0001). Furthermore, at a heart rate >82 b.p.m. more patients had a decrease of two points in the MMSE between 1 month and the penultimate visit (Table 3). The judged cut-off value is ~70 b.p.m. for cognitive decline according to the MMSE.

Discussion
Our results show that in patients after a first stroke, a higher heart rate at baseline is associated with an increased risk of total death, vascular death, and non-vascular death starting at a rather low heart rate threshold of 76 b.p.m., while there was no significant association with recurrent stroke, myocardial infarction, and new-onset or worsening congestive heart failure. Interestingly, poor functional independence in patients with a recurrent stroke according to the Barthel index score and cognitive decline associated with a cut-off of the MMSE ≤24 were significantly associated with an increasing resting heart rate and a trend towards poorer functional outcome of patients after the first stroke according to the mRS.

Stroke is a disabling condition regarded as the second most frequent cause of death leading to disability, cognitive impairment,
Impact of resting heart rate on mortality

and a huge economic burden on health care systems. Hypertension is regarded as one leading risk factor for stroke and reducing blood pressure has been shown to reduce morbidity and mortality due to stroke in large hypertension trials. Recent studies have associated increases in blood pressure but also resting heart rate changes thereof at the follow-up in response to stress as risk indicators for cardiovascular outcomes. The heart rate is regarded as a risk indicator in hypertension and cardiovascular disease and as a modifiable risk factor in heart failure as heart rate lowering with an If-channel inhibitor reduces events. In an

Figure 2 Kaplan–Meier curves for the cumulative probability of death (A), cardiovascular death (B), and non-cardiovascular death (C). Q1–5 denote the quintiles of the baseline heart rate. Hazard ratios were calculated with the use of the Cox model, which was adjusted to baseline characteristics.

Table 3 Neurological outcomes by baseline heart rate quintiles

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Q1 (≤64) Summary statistic</th>
<th>Q2 (65–≤70) Summary statistic</th>
<th>Q3 (71–≤76) Summary statistic</th>
<th>Q4 (77–≤82) Summary statistic</th>
<th>Q5 (&gt;82) Summary statistic</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modified Rankin scale score (at 3 months after a recurrent stroke) (n = 1633)</td>
<td>58.66 (47.10)</td>
<td>50.59 (49.03)</td>
<td>45.37 (45.37)</td>
<td>0.0191</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–2</td>
<td>58.66 (47.10)</td>
<td>50.59 (49.03)</td>
<td>45.37 (45.37)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3–4</td>
<td>26.24 (33.45)</td>
<td>29.88 (29.18)</td>
<td>31.34 (31.34)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5–6</td>
<td>15.10 (19.45)</td>
<td>19.53 (21.79)</td>
<td>23.28 (23.28)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Barthel index scorea (at 3 months after the first stroke) (n = 1412)</td>
<td>83.54 (26.92)</td>
<td>78.36 (28.42)</td>
<td>77.93 (30.42)</td>
<td>75.50 (31.44)</td>
<td>75.18 (31.25)</td>
<td>0.0002</td>
</tr>
<tr>
<td>MMSE ≤24 (at month 1) (n = 18 879)</td>
<td>16.12 (16.00)</td>
<td>17.59 (17.88)</td>
<td>21.08 (21.08)</td>
<td>&lt;.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMSE ≤24 (at the penultimate visit) (n = 15 465)</td>
<td>13.96 (13.80)</td>
<td>14.04 (15.43)</td>
<td>19.07 (19.07)</td>
<td>&lt;.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥2 patients decrease in MMSE, from month 1 to the penultimate visit (n = 15 049)</td>
<td>18.41 (17.91)</td>
<td>18.38 (17.53)</td>
<td>20.66 (20.66)</td>
<td>0.0319</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

MMSE, mini-mental state examination.
aContinuous variables with summary statistic mean (SD) and Kruskal–Wallis P-value. All other endpoints are categorical with summary statistic per cent of quintile and χ² P-value.
Experimental model subjected to mental stress, there was an impairment of endothelial function with an increase in the experimental stroke size but, in turn, a reduction in the stroke size after heart rate lowering. The high-risk cardiovascular population of the PRoFESS trial appeared appropriate to investigate the effect of heart rate as a predictor of cardiovascular outcomes and also on functional neurological outcomes after an ischaemic recurrent stroke.

Herein, we report that vascular death and also non-vascular death adjusted to multiple confounders including blood pressure are associated with the resting heart rate. These data show that in elderly patients after stroke, the heart rate is a general predictor of mortality, beyond specific effects in well-characterized pathologies in vascular disease. No significant effects could be found for recurrent stroke and myocardial infarction. One study showed that the baseline heart rate \( >70 \text{ b.p.m.} \) was associated with plaque rupture in coronary arteries. Furthermore, the BEAUTIFUL study has shown an association of a heart rate \( >70 \text{ b.p.m.} \) to non-fatal myocardial infarction in a population after a first myocardial infarction with impaired left ventricular function. This population might have been more sensitive to a second myocardial infarction and the heart rate in the overall population of PRoFESS might have been too low to show associations with myocardial infarction. This might explain why this analysis does not show heart rate associations with myocardial infarction. However, cardiovascular death and total death might be carried by multiple micro- and macro-vascular pathophysiological. The heart rate is also a marker of early ageing and death in many animal species and potentially representing a marker of general ageing, potentially modifiable by pharmacological heart rate reduction.

In mice, a fixed occlusion of the cerebral arteries is a model for the stroke size, in which different stress models were leading to increases in stroke sizes, which could be reduced by heart rate lowering associated with an improvement of endothelial function. Therefore, not only plaque rupture, but also the general vascular endothelium might be important. Interestingly, collateral growth after hindlimb occlusion was enhanced by a lowering heart rate due to a reduced expression of anti-angiogenetic cytokines and pro-inflammatory cytokines. Therefore, vascular compensatory mechanisms might be induced at a lower heart rate. Therefore, we set out to investigate functional neurological outcomes after stroke, which could be the clinical consequence of stroke size reduction as shown in experimental studies. Indeed, the present analysis showed that there was a significant association with functional independence determined by the Barthel index score according to quintiles of the heart rate. Furthermore, there was a significant association between the heart rate and the modified Rankin scores 3 months after the recurrent stroke. Fewer patients with severe cognitive decline (\( >2 \) points decline in the MMSE) at 1 month between the index stroke and at the end of the study visit in the lower heart rate quintile were identified. Consistently, less number of patients declined to an MMSE \( \leq 24 \) points indicative of dementia. These results show an improvement of functional consequences after stroke or lower stroke sizes despite the lack of prevention of recurrent stroke by a low heart rate. An increased heart rate in a model with intermittent stress developed intracerebral oxidative stress indicated by an

![Figure 3](image_url) Comparison of modified Rankin scale scores at baseline and at 3 months after the recurrent stroke according to the baseline heart rate and quintiles (Q1–5); P-values were calculated from a one-way ANOVA test.
up-regulation of brain lipid hydroperoxides, superoxide produc-
tion, and increase in the angiotensin II-type AT1 receptors.7,29
Heart rate lowering improved brain capillary density as judged by
CD31-expressing cells in the brain of stressed mice.7 Although
these mechanisms cannot be directly shown in patients, these
studies might provide the mechanistic explanation for the func-
tional improvement of neurological outcomes after stroke according to
the heart rate.

Our analysis from the PROFESS trial has limitations. Caution is
advised, because this analysis is a retrospective post hoc analysis of a
randomized trial with a neutral outcome and patients were not
assigned in a randomized fashion to different groups of heart
rate. However, differences in baseline values are small and we
appropriately took care of this by adjustment methods. Furthermore,
the size of the trial allowed adequate power compared with previ-
ous analyses to detect the association of the heart rate to out-
comes. The association with outcomes after stroke were
observed in heart rates <60 to >83 b.p.m., which are quite low
and have to be regarded as being in the normal range. This analysis
provides the first evidence that different physiological heart rates are
risk indicators for cognitive decline and a general mortality
marker in patients after an ischaemic stroke independent from
the blood pressure. One might suggest that in the trial heart
rate and changes of the heart rate at the follow-up vs. the heart
rate at baseline might be more closely related to outcomes.
However, the heart rate at follow-up visits was taken in a less
standardized fashion. Therefore, we cannot provide reliable informa-
tion of heart rate changes. Furthermore, heart rate changes
might be dependent on developing comorbidities during this long-
term follow-up. Therefore, we took the conservative approach to
explore the resting heart rate close to the index stroke as a risk
predictor for long-term outcomes.

It is concluded that a baseline heart rate >76 b.p.m. is associated
with mortality in the population of patients after the ischaemic
stroke. Myocardial infarction and recurrent stroke are not asso-
ciated with these heart rate levels, but functional neurological out-
comes after the recurrent stroke are better at a low heart rate and
could be an indicator of smaller stroke sizes as suggested by experi-
mental studies. This analysis is hypothesis generating and sets the
stage for the evaluation of potential pharmacological interventions
to reduce the heart rate in patients after an ischaemic stroke.

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