Outcomes in elderly patients with acute coronary syndromes randomized to enoxaparin vs. unfractionated heparin: results from the SYNERGY trial

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Aims
Elderly patients are at high risk from non-ST-segment elevation acute coronary syndromes (NSTE ACS) as well as from treatment-related complications. Age-associated changes in physiology may alter the risk and benefit expected from therapy. The SYNERGY database was used to study the influence of age on treatment outcomes with enoxaparin vs. unfractionated heparin (UFH) in patients with high-risk NSTE ACS.

Methods and results
Age was analysed as a continuous and categorical variable (<65, 65–74, and ≥75 years, and <75 and ≥75 years) for descriptive purposes. Logistic regression was used to adjust the outcomes of 30-day death, death or myocardial infarction (MI), and major bleeding for baseline characteristics. Odds ratios compared outcomes by age and by treatment within age groups. Model interaction terms were used to test for statistically different outcomes by treatment and age. Overall, 9977 randomized patients had age information, of whom 25.5% (2540) were ≥75 years of age. Elderly patients (≥75 years) had more cardiovascular risk factors, prior cardiac disease, and higher acuity at presentation. After adjustment, advanced age (per 10 years) was associated with 30-day death, death or myocardial infarction (MI), and major bleeding for baseline characteristics. Odds ratios compared outcomes by age and by treatment within age groups. Model interaction terms were used to test for statistically different outcomes by treatment and age. Overall, 9977 randomized patients had age information, of whom 25.5% (2540) were ≥75 years of age. Elderly patients (≥75 years) had more cardiovascular risk factors, prior cardiac disease, and higher acuity at presentation. After adjustment, advanced age (per 10 years) was associated with 30-day death or MI [risk odds ratios (ROR): 1.14, P = 0.002], 30-day death (ROR: 1.54, P < 0.0001), and 1-year death (ROR: 1.47, P < 0.0001), as well with TIMI major bleeding (ROR: 1.21, P = 0.001), GUSTO severe bleeding (ROR: 1.20, P = 0.047), and transfusion (ROR: 1.04, P = 0.324). Although there was a higher rate of GUSTO severe bleeding noted with enoxaparin in elderly patients, the overall relationships between treatment (UFH or enoxaparin) and outcomes did not vary significantly as a function of the patient’s age.

Conclusion
Although higher rates of adverse events are seen in the oldest subgroup (age ≥75 years) treated with enoxaparin, statistical comparisons confirm similar efficacy and safety of enoxaparin and UFH across age subgroups as was demonstrated overall in SYNERGY.

Keywords
Non-ST-segment elevation acute coronary syndromes • Age • Enoxaparin • Unfractionated heparin • Outcomes

Introduction
Antithrombotic therapy plays an important role in the pathophysiology and treatment of non-ST-segment elevation acute coronary syndromes (NSTE ACS).⁵ This is particularly true for elderly patients (≥75 years of age), who are at higher risk from recurrent thrombotic events and death, and for whom aggressive treatment may yield the greatest benefits.⁶–⁸ Elderly patients are also at

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higher risk from bleeding as a complication of antithrombotic therapy.1

Clinical guidelines differ on whether low-molecular-weight heparin (LMWH, i.e. enoxaparin) or unfractionated heparin (UFH) is the preferable antithrombotic therapy for patients with NSTE ACS.1,6 Owing to the inherent differences between these heparins, the decision focuses on the balance between antithrombotic and bleeding effects.7 Furthermore, because of the differences in drug metabolism and effect in the elderly, such comparisons are particularly relevant in this subgroup.8 Therefore, using data from the Superior Yield of the New Strategy of Enoxaparin, Revascularization, and Glycoprotein IIb/IIIa inhibitors (SYNERGY) trial, we investigated outcomes in high-risk NSTE ACS patients according to age subgroups (<65, 65–74, and >75 years) assigned to either LMWH or UFH.

Methods

SYNERGY population

The rationale, design, and primary results of SYNERGY have been previously reported.9 SYNERGY patients had NSTE ACS with high risk for adverse clinical outcomes at 30 days. In brief, patients presenting with ischaemic symptoms of at least 10 min duration within the previous 24 h to any of 467 participating sites in 12 countries were eligible for enrolment if they met two of three inclusion criteria: age ≥60 years, troponin or creatinine kinase-MB elevation above the upper limit of normal for the local laboratory, or definitive ST-segment changes on 12-lead electrocardiogram (ECG). Patients were excluded if they had contraindications to UFH or LMWH, elevated international normalized ratio >1.5, past or present bleeding disorder, or creatinine clearance (CrCl) less than 30 mL/min. Patients were randomized to receive either UFH or enoxaparin in an unblinded fashion. Use of other American College of Cardiology (ACC)/American Heart Association (AHA) guidelines-recommended therapies and procedures, including aspirin, glycoprotein (GP) IIb/IIIa inhibitors, and early cardiac catheterization, was encouraged. Most patients were treated with an early invasive strategy (coronary angiography within 48 h of hospital presentation) according to the ACC/AHA guidelines recommendations. Patients were contacted at 30 days, six months, and 1 year to determine interval cardiac events and vital status. Enrolling centres obtained institutional review board or ethics committee approval for patient enrolment, and all patients provided written informed consent for participation. The primary end point for efficacy was death or MI during the first 30 days after randomization and for safety was in-hospital bleeding.

Study design

This is a pre-specified age-subgroup analysis of the SYNERGY trial. All SYNERGY patients (n = 10,027) except those with no recorded age (n = 50) were included in the final analysis population (n = 9977).

Antithrombin treatment

UFH was given intravenously by weight-adjusted nomogram for initial bolus (60 U/kg, maximum of 5000 U) and infusion (12 U/kg per hour, maximum of 1000 U/h). Subsequent adjustments in UFH were to a goal-activated, partial thromboplastin time of 1.5–2.0 times the institutional upper limit of normal (i.e. 50–70 s). Enoxaparin was given subcutaneously at a dose of 1 mg/kg every 12 h. Treatment continued until antithrombin therapy was no longer required or until angiography or revascularization was performed.

Statistical analysis

Counts and percentages for various demographic characteristics, medical history, procedures, and concomitant medications are shown by age group (<65, 65–74, and >75 years). The mean, median, and standard deviation are provided for continuous variables. Categorical baseline characteristics were compared with age using the non-parametric Kruskal–Wallis test, and Spearman’s rank correlation was used for continuous variables. The association between age and each of the outcomes was evaluated using restricted cubic spline transformations. A model including age as a linear factor was compared with one with the age transformed. Comparison of the model likelihood ratio χ² tested the need for non-linear terms. If this test was statistically significant, then appropriate transformations were derived by evaluating the shape of the plots of the predicted values from the models which included spline transformations.

The continuous relationship between age and outcomes was adjusted using previously developed multivariable logistic regression models in the SYNERGY trial.10–12 The following pre-randomization predictors were included in the models: age, sex, weight, smoking history, race, geographic region of randomization, baseline CrCl, baseline heart rate, baseline rales, baseline atrial fibrillation, ST-depression on baseline ECG, history of hypertension, baseline systolic and diastolic blood pressure, history of diabetes, angina, congestive heart failure (CHF), coronary artery bypass graft (CABG), myoccardial infarction (MI), family history of coronary artery disease, medication use (statins, β-blockers, GP IIb/IIIa inhibitors), haemoglobin, haematocrit, baseline platelet values, and Killip class at presentation. Each model also included the interaction of age as a continuous measure with treatment to evaluate whether the treatment effect on the outcome varied with increasing age. Each model was performed controlling for antithrombotic pre-treatment prior to randomization (enoxaparin or UFH).

SAS® statistical software was used for all analyses. P-value of 0.05 was used for the critical value to declare statistical significance, bearing in mind the exploratory nature of these analyses.

Results

Baseline characteristics

The baseline characteristics by age group are shown in Table 1. Of the 9977 SYNERGY patients with age information, 7437 (74.5%) were <75 years of age and 2540 (24.5%) were ≥75 years of age. Older patients were more often female, had higher systolic blood pressure, previous MI, stroke or transient-ischaemic attack, CHF, higher rates of Killip class III and IV, prior history of hypertension, angina, percutaneous coronary intervention (PCI), and CABG, and more normal baseline ECG. Older patients also had lower weight, lower diastolic blood pressure, less ST-segment elevation, and less incidence of current smoking. They had lower values for CrCl, haemoglobin, and platelet levels at baseline as well. There were no significant differences in heart rate across age groups.

In-hospital treatment

The use of in-hospital procedures by age is shown in Table 2. There were no statistically significant differences in the rates of and time to CABG. However, increased age was associated with more days
of hospitalization, lower left ventricular ejection fraction, more rates of 3-vessel disease, less in-hospital coronary angiogram, lower rates of PCI, and more time to catheterization and PCI. Concomitant medications during baseline hospitalization are also shown in Table 2. There was no difference in the use of aspirin across age groups. However, elderly patients were more often given warfarin, angiotensin receptor blockers or angiotensin-converting enzyme (ACE) inhibitors, diuretics, calcium channel

<table>
<thead>
<tr>
<th>Table 1 Baseline characteristics and medical history by age categorya</th>
<th>Age &lt;65 (n = 3836)</th>
<th>Age 65–74 (n = 3601)</th>
<th>Age ≥75 (n = 2540)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)b</td>
<td>84.9 (74.0, 97.0)</td>
<td>80.0 (70.0, 90.0)</td>
<td>74.0 (65.0, 83.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female sex</td>
<td>25.5</td>
<td>35.7</td>
<td>43.9</td>
<td>&lt;0.001</td>
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<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>White</td>
<td>81.2</td>
<td>87.2</td>
<td>90.2</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>8.0</td>
<td>5.5</td>
<td>5.1</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>6.6</td>
<td>4.5</td>
<td>2.7</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>4.0</td>
<td>2.7</td>
<td>2.1</td>
<td></td>
</tr>
<tr>
<td>Killip class</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>I</td>
<td>91.5</td>
<td>87.2</td>
<td>81.8</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>6.7</td>
<td>10.2</td>
<td>14.7</td>
<td></td>
</tr>
<tr>
<td>III–IV</td>
<td>1.7</td>
<td>2.5</td>
<td>3.6</td>
<td></td>
</tr>
<tr>
<td>Rales</td>
<td>6.7</td>
<td>11.1</td>
<td>16.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)b</td>
<td>128.0 (114.0, 144.0)</td>
<td>132.0 (119.0, 148.0)</td>
<td>134.0 (119.0, 150.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)b</td>
<td>74.0 (64.0, 83.0)</td>
<td>71.0 (63.0, 80.0)</td>
<td>70.0 (60.0, 80.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heart rate (b.p.m.)b</td>
<td>72.0 (63.0, 81.0)</td>
<td>70.0 (62.0, 80.0)</td>
<td>72.0 (62.0, 82.0)</td>
<td>0.582</td>
</tr>
<tr>
<td>ECG changes</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ST-elevation</td>
<td>17.9</td>
<td>9.7</td>
<td>9.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ST-depression</td>
<td>59.3</td>
<td>50.5</td>
<td>54.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>T-wave inversion</td>
<td>24.1</td>
<td>24.6</td>
<td>21.8</td>
<td>&lt;0.032</td>
</tr>
<tr>
<td>No changes</td>
<td>14.7</td>
<td>26.0</td>
<td>24.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Creatinine clearanceb</td>
<td>98.0 (80.1, 119.6)</td>
<td>71.3 (58.3, 86.4)</td>
<td>52.8 (41.6, 65.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Creatinine clearance ≤60</td>
<td>6.7</td>
<td>27.6</td>
<td>65.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Positive biomarker prior to enrolment</td>
<td>86.9</td>
<td>78.9</td>
<td>78.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HGB baseline (g/dL)b,d</td>
<td>14.4 (13.4, 15.3)</td>
<td>13.8 (12.7, 14.8)</td>
<td>13.3 (12.2, 14.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HCT baseline (%)b,d</td>
<td>42.3 (39.2, 45.0)</td>
<td>40.8 (37.9, 43.9)</td>
<td>39.3 (36.0, 42.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Baseline platelet count after conversionb</td>
<td>239 (202, 284)</td>
<td>229 (188, 273.5)</td>
<td>223 (185, 269)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>59.7</td>
<td>71.9</td>
<td>75.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypercholesterolaemia</td>
<td>59.2</td>
<td>61.7</td>
<td>54.3</td>
<td>&lt;0.022</td>
</tr>
<tr>
<td>Family history of CAD</td>
<td>53.2</td>
<td>43.8</td>
<td>37.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CABG</td>
<td>12.6</td>
<td>18.7</td>
<td>19.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PCI</td>
<td>17.8</td>
<td>22.4</td>
<td>20.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Angina</td>
<td>40.1</td>
<td>48.4</td>
<td>50.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MI</td>
<td>24.0</td>
<td>30.7</td>
<td>30.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CHF</td>
<td>6.1</td>
<td>9.5</td>
<td>13.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TIA or stroke</td>
<td>4.5</td>
<td>8.7</td>
<td>13.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PVD</td>
<td>6.0</td>
<td>11.5</td>
<td>13.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Current smoker</td>
<td>41.8</td>
<td>17.2</td>
<td>7.2</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>


aAll data are percentages, and tests are Kruskal–Wallis, unless otherwise indicated.
bMedian (25th, 75th percentiles).
cTest of Spearman correlation.
dConverted to standard.
blocks, and nitrates and less often given statins, thienopyridine, or β-blockers.

**Association between age and outcomes**

The association between age (as a continuous variable) and clinical outcomes is shown in Figure 1. The adjusted risk odds ratios (ROR) and 95% confidence interval (CI) of 30-day mortality for each 10-year increase in age are 1.54 and 1.29–1.84 (P = 0.0001). The adjusted ROR for 10 years increase of age for death to 1 year in 30-day survivors, death from zero days to 1 year, and death or MI to 30 days were 1.26 (95% CI: 1.08–1.48, P = 0.0037), 1.47 (95% CI: 1.32–1.64, P < 0.0001), and 1.14 (95% CI: 1.05–1.24, P = 0.0016), respectively. Older age was also associated with more bleeding outcomes. There was a statistically significant association between age and GUSTO severe bleeding (ROR = 1.20; 95% CI: 1.03–1.43, P = 0.0047), but not between age and transfusion (adjusted ROR = 1.04; 95% CI: 0.96–1.11, P = 0.324). The association between age and TIMI bleeding was different for those aged <75 years vs. those aged ≥75 years. For age <75, increasing age was associated with an increased risk of TIMI bleeding (adjusted ROR = 1.21; 95% CI: 1.08–1.37, P = 0.001). However, in the age group ≥75 years, increasing age was associated with a decrease in TIMI bleeding (adjusted ROR = 0.80; 95% CI: 0.61–1.05, P = 0.085) (Figure 1). These results were similar when the pre-treatment (enoxaparin or UFH) was included in the model.

**Association between antithrombin treatment, age, and outcomes**

The rates of 30-day death or MI, 30-day death, and 1-year death were higher in older age groups, but there was no difference in the effectiveness of treatment with UFH or enoxaparin in either younger or older patients. However, the rates of TIMI major bleeding, GUSTO severe bleeding, and transfusion all appear to be higher in older age groups treated with enoxaparin (Figure 1). Despite a borderline interaction between age and treatment with enoxaparin for GUSTO severe bleeding (P = 0.085), none of the interactions between age and treatment reached statistical significance (Figure 1). This finding implies that the association between age and outcomes is similar in patients randomized to
Discussion

This age-subgroup analysis from SYNERGY finds similar comparative efficacy and safety in the oldest patient subgroup (age \( \geq 75 \) years) as was demonstrated in the overall trial population. Importantly, this analysis finds no significant age-by-treatment interaction in safety or efficacy outcomes with enoxaparin or UFH. However, the higher bleeding and transfusion rates in older patients treated with enoxaparin raises a note of caution. Although not statistically significant, these results may be clinically significant as they illustrate a consistent trend in the association between enoxaparin and adverse outcomes in older patients. Despite this cautionary note, these data do not change the existing knowledge regarding the selection of antithrombin therapy based on patient factors, supporting the use of either agent in patients at high risk from NSTE ACS.

Despite a large number of studies comparing the efficacy and safety of LMWH and UFH\(^{13-19}\) in NSTE ACS, there are no other age-subgroup analyses that compare the safety and efficacy of heparins in older adults.\(^8\) The SYNERGY population is uniquely suited for such an age-subgroup comparison of enoxaparin and UFH in the contemporary era. It includes the largest older adult population of any randomized clinical trial comparing these forms of heparin.\(^{20}\) This is because age \( \geq 60 \) years was one of the three high-risk inclusion criteria for SYNERGY. As a result, 62.8% of the enrolled patients were \( \geq 65 \) years of age and 25.5% were \( \geq 75 \) years of age (median age of 68 years). This trial therefore affords the best opportunity to extend the knowledge of antithrombotic treatment in the elderly subgroup.

In 2004, a systematic overview of six NSTE ACS randomized clinical trials, including SYNERGY, analysed outcomes in patients treated with either enoxaparin or UFH.\(^{20}\) This overview found a reduction in the combined end point of death or MI at 30 days with enoxaparin compared with UFH without a higher rate of

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**Figure 1** Relationship between age and death or MI (A), TIMI bleeding (B), GUSTO bleeding (C), and transfusion (D). The dashed line represents the probability of the outcome according to the age of the patient based on an unadjusted model. The dotted line represents the expected event rate for the patients treated with enoxaparin, and the solid line represents those treated with unfractionated heparin. The treatment differences across age were not statistically significantly different for any of the four outcomes. GUSTO, Global Use of Strategies to Open Occluded Coronary Arteries; MI, myocardial infarction; TIMI, thrombolysis in myocardial infarction. 

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enoxaparin or UFH. These findings also did not change after including pre-treatment (enoxaparin or UFH) in the model.
major bleeding, but did not report the use in the oldest subgroups. Two contemporary registry analyses also demonstrated comparable efficacy between patients treated with either enoxaparin or UFH, without differences in observed bleeding rates.\textsuperscript{21,22} Comparisons of therapies differ between clinical trials and real-world populations, but these findings are supportive of the current analysis.

Differences in baseline characteristics and concomitant medications between trials and registries may be accentuated in the oldest subgroups. The strategy of management (conservative vs. invasive) may also alter the safety and efficacy balance between these two types of heparins. Specifically, the rates of in-hospital percutaneous intervention and CABG in older patients in SYNERGY were much higher than in similarly aged cohorts from registries.\textsuperscript{2,23} The times to catheterization, PCI, and CABG are also shorter, and the use of aspirin, thienopyridine, β-blockers, and statin is higher in elderly patients in SYNERGY than in registries. For high-risk patients undergoing early percutaneous coronary intervention, the use of enoxaparin is associated with higher rates of bleeding and similar efficacy when compared with UFH.\textsuperscript{24} For those patients with ACS where a conservative approach is planned, enoxaparin with aspirin and GP IIb/IIIa inhibitor is associated with higher efficacy and similar rates of bleeding when compared with UFH.\textsuperscript{25} Thus, the invasive management strategy in older SYNERGY patients should be considered when interpreting these findings.

In addition, dosing may also alter the safety and efficacy balance between these two types of heparins. Concerns about bleeding with antithrombotic therapy are particularly relevant to community practice, where patients with severe kidney disease (CrCl < 30 mL/min) are commonly treated. In community NSTE ACS populations, standard dosing algorithms for antithrombotic therapy are exceeded approximately 20% of the time, which increases the risk of bleeding.\textsuperscript{26,27} Therefore, the clinical use of antithrombotic therapy should adhere to existing dosing recommendations. Moreover, a recent trial in patients with ST-segment elevation MI devised a reduced-dosing algorithm for enoxaparin with fibrinolytic therapy specifically for the elderly and for those with renal insufficiency.\textsuperscript{28} In that trial, modified-dose enoxaparin further reduced the risk of major bleeding without compromising efficacy of fibrinolytic therapy in patients ≥75 years of age. Therefore, the evaluation of enoxaparin dosing and safety across management strategies in the elderly NSTE ACS population may also be warranted.

Study limitations

This study has some limitations. First, age ≥60 years was one of the high-risk features used for study inclusion. Therefore, because two risk factors were required for entry, younger (<60 years) patients had to have two other risk factors to be enrolled, whereas older patients may have had only one. This may have improved the risk profiles of older patients when compared with younger ones. In addition, patients with a creatinine clearance less than 30 mL/min were excluded. The increased bleeding in the oldest subgroup may have been due to age and/or some level of renal impairment of this group. Yet our findings certainly have relevance to real-world populations, where the average creatinine clearance is lower\textsuperscript{8} and LMWH is often the preferred antithrombotic agent.\textsuperscript{23} This limitation is most relevant for LMWH, which should be dose-reduced at this level of renal function. Finally, while we did a sensitivity analysis in patients who did not receive any antithrombotic therapy prior to randomization, we did not account for cross-over between the two types of heparins after randomization. The effect that this may have on our analysis is unknown, as our understanding of this phenomenon continues to evolve.

Conclusion

In NSTE ACS, increased age was associated with worse outcomes of death and MI, as well as with a higher risk of treatment-related bleeding. These outcomes were similar in those patients aged less than 75 years randomized to either enoxaparin or UFH. However, older adult patients (age ≥75 years) had trends towards higher treatment-related bleeding and death or MI when treated with enoxaparin. Therefore, while statistical comparisons across age subgroups between these forms of heparin are reassuring, a clinical note of caution with enoxaparin in the oldest old remains.

Conflict of interest: R.D.L., K.P.A. and G.M. had no conflict to declare. H.D.W., J.C., P.E.A., R.M.C., and K.W.M. were supported by research grants from sanofi-aventis. S.S. received honoraria from sanofi-aventis.

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References

Outcomes in elderly patients with acute coronary syndromes


The above article uses a new reference style being piloted by the EHJ that shall soon be used for all articles.