Long-term clinical outcome of elderly patients with acute coronary syndrome treated with early percutaneous coronary intervention

Nammas, Wail

2017-01


http://hdl.handle.net/10138/233949
https://doi.org/10.1016/j.ejim.2016.07.027

Downloaded from Helda, University of Helsinki institutional repository.

This is an electronic reprint of the original article.

This reprint may differ from the original in pagination and typographic detail.

Please cite the original version.
Long-term clinical outcome of elderly patients with acute coronary syndrome treated with early percutaneous coronary intervention: Insights from the BASE ACS randomized controlled trial

Bioactive versus everolimus-eluting stents in elderly patients

Wail Nammas a, Adam de Belderb, Matti Niemelä c, Jussi Sia d, Hannu Romppanen c,e, Mika Laine f, Pasi P. Karjalainen a,⁎

a Heart Center, Satakunta Central Hospital, Pori, Finland
b Department of Cardiology, Brighton and Sussex University Hospital NHS Trust, Brighton, UK
c Department of Internal Medicine, Division of Cardiology, University of Oulu, Oulu, Finland
d Department of Cardiology, Kokkola Central Hospital, Kokkola, Finland
e Heart Centre, Kuopio University Hospital, Kuopio, Finland
f Helsinki University Hospital, Helsinki, Finland

Abstract

Background: The BASE ACS trial demonstrated an outcome of titanium–nitride–oxide-coated bioactive stents (BAS) that was non-inferior to everolimus-eluting stents (EES) in patients presenting with acute coronary syndrome (ACS). We performed a post hoc analysis of elderly versus non-elderly patients from the BASE ACS trial.

Methods: We randomized 827 patients (1:1) presenting with ACS to receive either BAS or EES. The primary end-point was major adverse cardiac events (MACE): a composite of cardiac death, non-fatal myocardial infarction (MI), or ischemia-driven target lesion revascularization (TLR). Follow-up was planned at 12 months and yearly thereafter for up to 7 years. Elderly age was defined as ≥65 years.

Results: Of the 827 patients enrolled in the BASE ACS trial, 360 (43.5%) were elderly. Mean follow-up duration was 4.2 ± 1.9 years. MACE was more frequent in elderly versus younger patients (19.7% versus 12.0%, respectively, p = 0.002), probably driven by more frequent cardiac death and non-fatal MI events (5.3% versus 1.5%, and 9.7% versus 4.5%, p = 0.002 and p = 0.003, respectively). The rates of ischemia-driven TLR were comparable (p > 0.05). In propensity score-matched analysis (215 pairs), only cardiac death was more frequent in elderly patients (6% versus 1.4%, respectively, p = 0.01). Diabetes independently predicted both MACE and cardiac death in elderly patients.

Conclusions: Elderly patients treated with stent implantation for ACS had worse long-term clinical outcome, compared with younger ones, mainly due to a higher death rate.

© 2016 European Federation of Internal Medicine. Published by Elsevier B.V. All rights reserved.

Keywords:
Elderly
Acute coronary syndrome
Titanium–nitride–oxide-coated stents
Everolimus-eluting stents

1. Introduction

With improved survival of the general population, more elderly patients are referred for percutaneous coronary intervention (PCI) with stent implantation [1]. Elderly patients have higher-risk clinical and lesion characteristics and suffer more often short- and long-term adverse outcome following PCI [2,3]. First-generation drug-eluting stents (DES) improved the long-term efficacy – and to a lesser extent the safety – outcome of PCI, compared with bare-metal stents, in unselected elderly patients, and in elderly patients undergoing primary PCI for acute ST-segment elevation myocardial infarction (MI) [3–5]. Implantation of the second-generation everolimus-eluting stents (EES) in elderly patients was associated with a better mid-term angiographic and long-term clinical outcome compared with paclitaxel-eluting stents, mainly driven by a lower incidence of repeat revascularization [6,7].

The safety of titanium–nitride–oxide-coated bioactive stents (BAS) was demonstrated in real-world unselected cohorts [8,9], and in randomized controlled trials of patients presenting with acute coronary syndrome (ACS) [10,11]. The adequately powered BASE ACS trial showed non-inferiority of BAS versus EES, for the primary endpoint of major adverse cardiac events (MACE) in patients with ACS, at 12-month, 2-year, and 4-year follow-up [11–13]. Yet, the comparative outcome of BAS versus EES in elderly patients presenting with ACS is
still unknown. In a post hoc analysis, we explored the long-term clinical outcome of the BASE ACS trial in elderly patients (65 years or more), with stent-based analysis of the outcome in the elderly and younger subgroups.

2. Material and methods

2.1. Patient selection and study design

The trial design was previously described elsewhere [11]. In brief, the BASE ACS trial was a prospective single-blinded multicentre randomized controlled trial conducted in 14 centers. From January 2009 to September 2010, we randomized 827 patients (1:1) presenting with ACS who underwent early PCI to receive either Titan-2® BAS (Hexacath, Paris, France) or Xience V® EES (Abbott Vascular, Santa Clara, California, USA). Follow-up was planned at 12 months, and yearly thereafter for up to 7 years.

2.2. Ethical issues

The trial was initiated by the investigators and conducted according to the ethical guidelines of the 1964 Declaration of Helsinki, as revised in 2013. Informed written consent was obtained from every patient after explanation of the trial protocol; the protocol was approved by the ethics committees of the coordinating center (Satakunta Central Hospital) and the other participating centers. The trial is registered with ClinicalTrials.gov, number NCT00819923.

2.3. Pharmacological interventions

Patients not previously maintained on aspirin were pretreated with aspirin at a loading dose of 250 mg orally or 250–500 mg intravenously and continued at a dose of 75–150 mg daily indefinitely. Oral clopidogrel was initiated at a loading dose of 300–600 mg before or immediately after the procedure and continued at a dose of 75 mg daily. Patients in either group were prescribed oral clopidogrel for a minimum of 6 months, and thereafter, for extended periods (maximum 12 months) at the operator’s discretion. During the procedure, low-molecular-weight or unfractionated heparin was administered intravenously in the standard dosage. Use of glycoprotein IIb/IIIa inhibitors or bivalirudin was left to operator’s discretion.

2.4. Definitions and study endpoints

Elderly patients were defined as those having age of 65 years or more. The diagnostic criteria for non-ST-segment elevation ACS and ST-segment elevation MI were previously described [11]. The primary endpoint was the first occurrence of MACE: a composite of cardiac death, non-fatal MI, or ischemia-driven target lesion revascularization (TLR). Secondary endpoints included non-cardiac death and death, non-fatal MI, or ischemia-driven target lesion revascularization.

2.5. Statistical analysis

Continuous variables were presented as mean ± standard deviation, whereas categorical variables were described with absolute and relative (percentage) frequencies. Comparisons between the two subgroups (elderly versus younger) were performed using the unpaired t-test for continuous variables, and the Pearson chi-square test or Fisher’s exact test for categorical variables, as appropriate. Data analysis was based on the intention-to-treat principle. We observed significant differences between the two subgroups in several baseline characteristics. Therefore, we performed a propensity score-matched analysis of the two subgroups. Propensity score was calculated using a logistic regression model in which we included clinical and procedural variables with a difference between the two subgroups as indicated by a p < 0.1 in univariate analysis. The stent types were included in the logistic regression model as a dichotomous covariate in order to account for any possible stent-related differences in outcome. Hosmer-Lemeshow test was used to assess the fit of the logistic regression model (chi-square: 7.37, p = 0.497). Propensity score was employed for propensity score-matched analysis to estimate the impact of age ≥ 65 years on the clinical outcome. Matching was performed based on an estimated caliper width of 0.2, the standard deviation of the propensity score logit. Comparisons of clinical outcome were also performed based on the stent group allocation within either subgroup individually (elderly and younger). Time-to-event curves were constructed with the use of Kaplan-Meier estimates, based on all the available follow-up data for MACE, and were compared with the log-rank test. In order to identify the independent predictors of outcome (MACE and cardiac death) within the elderly subgroup, univariate analysis was initially performed for each of the baseline clinical, angiographic, and procedural variables. Then, the variables significantly associated (2-sided p < 0.1) with the dependent variable in univariate analysis were included as covariates in a multivariable Cox regression hazard model in which the dependent variable is the outcome variable (MACE or cardiac death). The results of multivariable regression were presented as hazard ratio (HR) with 95% confidence interval (CI). All tests were two-sided and statistical significance was set at 5%. Data were analyzed with SPSS version 16.

Table 1

<table>
<thead>
<tr>
<th>Variable</th>
<th>Elderly patients N = 360</th>
<th>Non-elderly patients N = 467</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>73.9 ± 6.2</td>
<td>54.6 ± 7.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female gender</td>
<td>122 (33.9)</td>
<td>76 (16.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Current smoking</td>
<td>45 (12.5)</td>
<td>233 (49.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>191 (53.1)</td>
<td>197 (42.2)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Hypertension</td>
<td>228 (63.3)</td>
<td>185 (39.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Family history of IHD</td>
<td>138 (38.3)</td>
<td>293 (51.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Presentation by STEMI</td>
<td>121 (33.6)</td>
<td>200 (42.8)</td>
<td>0.007</td>
</tr>
<tr>
<td>Prior MI</td>
<td>58 (16.1)</td>
<td>38 (8.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prior PCI</td>
<td>43 (11.9)</td>
<td>40 (8.6)</td>
<td>0.19</td>
</tr>
<tr>
<td>Prior CABG</td>
<td>25 (6.9)</td>
<td>12 (2.6)</td>
<td>0.003</td>
</tr>
<tr>
<td>ACC/AHA lesion type B/C</td>
<td>321 (89.2)</td>
<td>410 (87.8)</td>
<td>0.54</td>
</tr>
<tr>
<td>Thrombus</td>
<td>135 (37.5)</td>
<td>229 (49.9)</td>
<td>0.001</td>
</tr>
<tr>
<td>Calcified lesions</td>
<td>195 (54.2)</td>
<td>157 (33.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>bifurcation lesions</td>
<td>80 (22.2)</td>
<td>97 (20.8)</td>
<td>0.61</td>
</tr>
<tr>
<td>Reference vessel diameter (mm)</td>
<td>3.12 ± 0.43</td>
<td>3.15 ± 0.43</td>
<td>0.25</td>
</tr>
<tr>
<td>Lesion length (mm)</td>
<td>13.8 ± 6.4</td>
<td>14.8 ± 5.6</td>
<td>0.02</td>
</tr>
<tr>
<td>Stent diameter (mm)</td>
<td>3.12 ± 0.44</td>
<td>3.17 ± 0.44</td>
<td>0.16</td>
</tr>
<tr>
<td>Stent length (mm)</td>
<td>17.8 ± 5.4</td>
<td>18.6 ± 5.4</td>
<td>0.03</td>
</tr>
<tr>
<td>Total stent length per lesion (mm)</td>
<td>19.9 ± 8.8</td>
<td>21.2 ± 8.9</td>
<td>0.04</td>
</tr>
<tr>
<td>Number of vessels treated per patient</td>
<td>1.16 ± 0.43</td>
<td>1.13 ± 0.36</td>
<td>0.17</td>
</tr>
<tr>
<td>Number of lesions treated per patient</td>
<td>1.22 ± 0.53</td>
<td>1.17 ± 0.48</td>
<td>0.20</td>
</tr>
<tr>
<td>Direct stenting</td>
<td>90 (25)</td>
<td>170 (36.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Thrombus aspiration</td>
<td>45 (12.5)</td>
<td>109 (23.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Post-dilatation</td>
<td>155 (43.1)</td>
<td>202 (43.3)</td>
<td>0.95</td>
</tr>
<tr>
<td>Stent failure</td>
<td>2 (0.6)</td>
<td>3 (0.6)</td>
<td>1.00</td>
</tr>
<tr>
<td>Procedural success</td>
<td>360 (100)</td>
<td>465 (99.6)</td>
<td>0.50</td>
</tr>
<tr>
<td>Unfractionated heparin</td>
<td>72 (20)</td>
<td>143 (30.6)</td>
<td>0.001</td>
</tr>
<tr>
<td>Low-molecular-weight heparin</td>
<td>225 (62.5)</td>
<td>258 (55.2)</td>
<td>0.036</td>
</tr>
<tr>
<td>GP IIb/IIIa inhibitor</td>
<td>74 (20.6)</td>
<td>168 (36.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Bivalirudin</td>
<td>61 (16.9)</td>
<td>60 (12.8)</td>
<td>0.098</td>
</tr>
</tbody>
</table>

Continuous variables are presented as mean ± SD, whereas categorical variables are presented as frequency (percentage). BAS indicates bioactive stent; CABG, coronary artery bypass grafting; EES, everolimus-eluting stent; GP, glycoprotein; MI, myocardial infarction; PCI, percutaneous coronary revascularization.
3. Results

3.1. Baseline clinical, angiographic, and procedural data

Of the 827 patients enrolled in the BASE ACS trial, 360 (43.5%) were elderly (≥ 65 years). Median follow-up duration was 5.0 years; mean (SD) 4.2 (1.9) years. Compared with younger patients, elderly ones had a higher prevalence of female gender, were more likely to be hypertensive and dyslipidemic, more likely to have prior coronary events, and presented less often with ST-segment elevation MI (p = 0.05 for all). They had more often calcified but less often thrombotic coronary lesions and had shorter lesion length (p < 0.05 for all). They underwent more often predilation, but less often thrombus aspiration, received shorter stents, and received less often glycoprotein IIb IIIa inhibitors during the procedure (p < 0.05 for all). The baseline clinical, angiographic, and procedural data are summarized in Table 1.

3.2. Long-term clinical outcome in crude population

The cumulative incidence of MACE at long-term follow-up was more frequent in elderly versus younger patients (19.7% versus 12.0%, respectively, p = 0.002) (Table 2 and Fig. 1). This was driven by more frequent cardiac death and non-fatal MI events (5.3% versus 1.5%, and 9.7% versus 4.5%, p = 0.002 and p = 0.003, respectively). The rates of ischemia-driven TLR and definite ST were comparable between the two subgroups (p > 0.05 both) (Table 2).

3.3. Long-term clinical outcome in matched subgroups

Propensity score matching yielded 430 patients (215 pairs) with balanced baseline characteristics (Table 3). In the propensity score-matched pairs, the incidence of cardiac death was higher in elderly versus younger patients (6% versus 1.4%, respectively, p = 0.01). Non-cardiac death was also more frequent in the elderly (7.9% versus 2.3%, respectively, p = 0.009). MACE and the other individual endpoints were comparable between the two matched subgroups (p > 0.05 for all) (Table 4).

3.4. Stent-based analysis of the two subgroups

In elderly patients, MACE was comparable between the two stent arms (16.1% versus 23.3%, for BAS versus EES, respectively, p = 0.08). Definite ST occurred less frequently with BAS versus EES (0.6% versus 5.6%, respectively, p = 0.006). The other individual endpoints were comparable (p > 0.5 for all) (Fig. 2A). Comparably, in younger patients, MACE and all the individual endpoints were comparable between the two stent arms (p > 0.5 for all) (Fig. 2B).

3.5. Analysis of adverse outcome in the elderly subgroup

In univariate analyses, the predictors of MACE in the elderly subgroup were diabetes (p = 0.03), hypertension (p = 0.09), stent type (p = 0.08), and lesion calcification (p = 0.08). In multivariable analysis, the only independent predictor of MACE was diabetes (HR 1.67, 95% CI 0.99–2.80, p = 0.051). Similarly, in univariate analyses, the predictors of cardiac death in the elderly subgroup were diabetes (p = 0.01), hypertension (p = 0.05), and use of glycoprotein IIb IIIa inhibitor (p = 0.09). In multivariable analysis, the only independent predictor of cardiac death was diabetes (HR 3.17, 95% CI 1.27–7.88, p = 0.013).

---

Table 2
Clinical outcome in the 2 study groups at long-term follow-up.

<table>
<thead>
<tr>
<th></th>
<th>Elderly patients</th>
<th>Non-elderly patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 360</td>
<td>N = 467</td>
</tr>
<tr>
<td>MACE (%)</td>
<td>71 (19.7)</td>
<td>56 (12.0)</td>
</tr>
<tr>
<td>Cardiac death (%)</td>
<td>19 (5.3)</td>
<td>7 (1.5)</td>
</tr>
<tr>
<td>Non-fatal MI (%)</td>
<td>35 (9.7)</td>
<td>21 (4.5)</td>
</tr>
<tr>
<td>Ischemia-driven TLR</td>
<td>30 (8.3)</td>
<td>29 (8.1)</td>
</tr>
<tr>
<td>Non-cardiac death (%)</td>
<td>45 (12.5)</td>
<td>38 (8.1)</td>
</tr>
<tr>
<td>Definite ST (%)</td>
<td>11 (3.1)</td>
<td>7 (1.5)</td>
</tr>
</tbody>
</table>

Variables are presented as frequency (percentage). BAS indicates bioactive stent; EES, everolimus-eluting stent; MACE, major adverse cardiac events; MI, myocardial infarction; TLR, target lesion revascularization; ST, stent thrombosis; HR, hazard ratio; CI, confidence interval.

3.6. Kaplan–Meier estimates of the primary endpoint (a composite of cardiac death, non-fatal myocardial infarction, or ischemia-driven target lesion revascularization) in the two subgroups at long-term follow-up. MACE indicates major adverse cardiac events.
elderly patients with ACS. The current report over, the long-term clinical outcome of BAS was comparable to that of predicted both MACE and cardiac death in such patient subgroup. More-

4. Discussion

4.1. Main findings

The current post hoc analysis of the BASE ACS trial demonstrated that elderly patients presenting with ACS who were treated with early PCI had worse long-term clinical outcome, compared with younger ones, mainly due to a higher death rate. Diabetes independently pre-
dicted both MACE and cardiac death in such patient subgroup. Moreover, the long-term clinical outcome of BAS was comparable to that of EES in the elderly, as well as in the younger subgroup. The current report is the first to address the comparative outcome of BAS versus EES in elderly patients with ACS.

4.2. Outcome of percutaneous coronary intervention in elderly patients

PCI is particularly challenging in elderly patients. In the current report (43.5% elderly), the incidence of MACE was higher in elderly patients in the crude subgroup comparison. This is probably due to worse baseline clinical and angiographic characteristics in the elderly, versus younger, subgroup (Table 1); MACE rates were comparable in the propensity-score-matched subgroups. Interestingly, both cardiac and non-cardiac death rates were remarkably higher in the elderly subgroup, even after propensity-score-matched analysis. Aligned with this finding, prior studies consistently reported worse long-term mortality rates in unselected elderly patients undergoing PCI, versus younger ones, using various age cutoff points. In 2 separate studies from the bare-metal stents era, patients above 75 years had higher death rates at 6-month and 3-year follow-up, compared with younger ones; the difference was insigni-
cant in the 6-month report due to the small sample size; interestingly, repeat revascularization was similar in the 6-month report, and lower in the elderly in the 3-year report [15,16]. In another study, patients above 75 years had 91% survival at 12 months (no comparison group) [17]. Similarly, patients above 70 years had lower event-free survival at 2-year follow-up, compared with younger ones [18]. In another report of bare-metal stents, age independently predicted late mortality; the 1-year death rate increased step-wise with advancing age (3 age subgroups with cutoff at 70 and 80 years) [19]. Likewise, in a large registry from the DES era (patients received
either first-generation DES or bare-metal stents), the all-cause death was higher in the oldest 2 quintiles, compared with the younger ones, at 3-year follow-up [3]. Finally, death rates were higher in patients above 70 years, versus younger ones, from pooled data of 5 prospective trials of paclitaxel-eluting stents through 5 years of follow-up, as well as in 2 post-market registries of the same stent through 2 years: interestingly, the rates of MI, ST, and TLR were comparable between the 2 age groups in the trial data, and lower in elderly patients in the registry data [20]. In the original report of the BASE ACS trial, age independently predicted MACE at 12-month follow-up [11].

The mechanisms underlying increased cardiac mortality in the elderly patients with ACS undergoing PCI are still unclear. In an early pooled analysis of the PAMI trials (bare-metal stents), patients above 75 years had higher cardiac and non-cardiac in-hospital mortality; age ≥ 75 years was an independent predictor of in-hospital mortality, along with lower left ventricular ejection fraction, lower final TIMI flow, higher Killip class, need for an intra-aortic balloon counterpulsation, and post-MI stroke/transient ischemic attack, or significant arrhythmia, [21]. In post hoc analysis of the CADILLAC trial in patients with acute MI undergoing primary PCI, 1-year mortality increased exponentially after the age of 65 years, independent of the reperfusion modality or the use of abciximab; both age and absent ST-segment resolution were independent predictors of 30-day MACE [22,23]. Yet, in patients with ST-segment elevation MI treated by primary PCI, increasing age was associated with poor myocardial perfusion (as reflected by myocardial blush grade 0–1 and ST-segment resolution <50%); both age and poor myocardial perfusion were independent predictors of 1-year mortality [24]. Comparably, in the current report, diabetes independently predicted both MACE and cardiac death in elderly patients at long-term follow-up. Surrogates of myocardial perfusion were not investigated in the current trial. Nevertheless, in a small study of patients undergoing primary PCI for ST-segment elevation MI, diabetes was associated with surrogates of poor myocardial perfusion in multivariable analysis [25]. Finally, elderly patients have a higher risk of non-cardiac mortality, for instance, due to more deaths from cancer and lung diseases. Investigation of these factors was out of scope of the current study.

In the current study, ischemia-driven TLR was comparable between elderly and younger patients in the crude subgroup analysis and remained so in the propensity-score-matched analysis (Tables 2 and 4); this is consistent with data from the prior reports [15–17,19,20]. In the elderly subgroup, TLR rates were comparable between the 2 stent arms (Fig. 2A). Comparably, EES implantation in the elderly was associated with lower rates of ischemia-driven TLR and MACE, compared with paclitaxel-eluting stents, in pooled data from the SPIRIT III and SPIRIT IV trials [6,7]. In turn, paclitaxel-eluting stent implantation in the elderly was associated with lower rates of ischemic target vessel revascularization, compared with bare-metal stents [5]. Similarly, in the current report, definite ST was comparable between elderly and younger patients both in the crude and propensity-score-matched analyses (Tables 2 and 4). This is consistent with pooled data from prior trials through 5 years [20]. In the elderly subgroup, however, patients treated with BAS, versus EES, had a significantly lower rate of definite ST at long-term follow-up (Fig. 2A). This finding is consistent with the previous reports of the BASE ACS trial [11–13]. Nevertheless, these findings should be taken with caution, since both the trial population and the elderly subgroup were underpowered to detect a difference in a rare event such as definite ST, and therefore, this finding might be due to type I error. It is noteworthy that stent type was not a predictor of MACE or cardiac death in the elderly subgroup.

4.3. Limitations of the study

The BASE ACS trial was not designed a priori to explore specific differences in outcome based on age. Due to the retrospective nature of this post hoc analysis, some data relevant to the outcome might have been missed. In addition, the trial may be underpowered for specific subgroup analysis; therefore, we cannot rule out a type II error as the cause for failure to demonstrate significant difference between the subgroups, or between the study stents in either subgroup. Moreover, analysis of patient data in one subgroup with different stent designs should also be interpreted with caution. Finally, the current post hoc analysis was a non-randomized subgroup analysis; this might limit the conclusiveness of the results.

5. Conclusion

Elderly patients presenting with ACS who were treated with early PCI had worse long-term clinical outcome, compared with younger ones, mainly due to a higher death rate. The long-term outcome of BAS was comparable to that of EES in the elderly, as well as in the younger subgroup.

Funding

The current post hoc analysis did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interests

The authors declare that there is no conflict of interest.

Acknowledgment

The authors thank Tuija Vasankari, Eija Niemelä, and Minna Ampio, for their support in the conduct of this study.

References


