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Age-specific associations of invasive treatment with long-term mortality of patients with acute myocardial infarction: Results of a real-world cohort analysis

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ABSTRACT

Background: To investigate the age-specific association between invasive treatment, that is percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) at acute myocardial infarction (AMI) and all-cause long-term mortality.

Methods: The analysis was based on 4964 hospitalized AMI patients (age 25–84 years) registered by the population-based Augsburg Myocardial Infarction Registry between 2010 and 2017. The median follow-up time was 4.7 years (IQR: 2.7; 6.8). All-cause mortality was obtained by regularly checking the vital status of all registered AMI patients in cooperation with the regional population registries. In multivariable adjusted Cox regression analyses the age-specific associations between invasive therapy (PCI or CABG versus no invasive therapy) and all-cause mortality were investigated.

Results: During follow-up 1224 patients (805 men and 419 women) died. In patients younger than 55 years 7.6 %, in the age group 55–64 years 7.1 %, in the age group 65–74 years 12.2 %, and in the age group 75–84 years 21.6 % did not undergo invasive therapy (PCI or CABG) during hospital stay. Invasive therapy using PCI or CABG significantly reduced mortality risk in all age-groups in comparison to AMI patients without invasive treatment. Even 75–84 years old benefited very impressively from invasive therapy regarding long-term all-cause mortality (PCI: HR 0.55; 95 % CI 0.44–0.70; CABG: HR 0.43; 95 % CI 0.30–0.62).

Conclusions: Invasive or surgical therapy procedures in the treatment of AMI patients are effective in all age groups. Therefore, also old AMI patients should receive guideline-compliant therapy to achieve a better outcome.

1. Introduction

In 2022, 6.1 % of the German population was over 80 years old corresponding to around 5.1 million people. By 2050, the proportion is expected to rise to 14.5 %, or 10 million people, with an estimated population decline to just 69 million inhabitants [1]. Due to this development, an increasing proportion of older patients with heart attacks is to be expected in the future [2]. Although the international guidelines for the treatment of AMI do not differentiate according to the age of the patient, invasive procedures are used less frequently in older AMI patients and they are therefore often undertreated [3]. This is because this patient population is often underrepresented in studies and there is a lack of clinical data for decision-making [4,5]. However, there is increasing evidence that percutaneous coronary intervention (PCI) and/or coronary artery bypass graft (CABG) can reduce short-term [6] and long-term mortality even in older AMI patients [7–9]. Population-representative studies are needed to help clarify the extent to which ambiguities and uncertainties about the effectiveness of invasive or surgical therapeutic procedures in the treatment of older AMI patients are justified and whether guideline-compliant invasive therapy in older AMI patients leads to an equally good outcome in terms of long-term mortality as in younger patients.

Therefore, this study aimed to examine whether and to what extent AMI patients, in particular elderly patients, benefit from PCI or CABG compared to no invasive therapy in terms of long-term survival. The Augsburg Myocardial Infarction Registry is a long-term register

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representative of the general population, thereby collecting real world data and enabling generalizable patient-specific research into the therapy and outcomes of hospitalized AMI patients.

2. Methods

The data for this study came from the Augsburg Myocardial Infarction Registry. The registry was established in 1984 as part of the MONICA project (Monitoring Trends and Determinants in Cardiovascular Disease); From 1996 to 2020 it was continued as the KORA Myocardial Infarction Registry, and since 2021 the project is fully based at the Augsburg University Hospital. The study area comprises the city of Augsburg and two neighboring districts comprising a total population of around 680,000 people. All cases of hospitalized AMI were recorded if the patients survived longer than 24 h after admission, were between 25 and 84 years old (since the year 2009) and had their main residence in the study area. All AMI cases from the study area that were treated with an incident infarction in one of the participating hospitals in the study region and registered by the registry between 2010 and 2017 were included in the analysis. Of a total of 6325 patients, 188 were excluded due to missing information on relevant covariables, leaving 6137 patients. Furthermore, patients who died within the first 28 days after the event (n = 1173) were also excluded, resulting in 4964 patients with a hospitalized AMI aged 25–84 years for analysis.

The study was approved by the Ethics Committee of the Bavarian Medical Association and complies with the requirements of the "Declaration of Helsinki" [10]. A signed declaration of informed consent was obtained from all subjects. The study was registered at the German Register of Clinical Studies (DRKS, project number DRKS00029042).

2.1. Data collection

Trained study nurses conducted personal interviews with the patients during their hospital stay using a standardized questionnaire. Additional data was obtained from the patients' medical records. This allowed comprehensive information to be collected for each AMI case, including socio-demographic characteristics, risk factors, comorbidities, diagnostic procedures, and invasive and non-invasive treatment. Detailed information of patient recruitment and data acquisition can be found in previous publications [11].

Pre-existing comorbidities and risk factors such as diabetes, hyperlipidemia and hypertension as well as smoking status and typical chest pain symptoms at the time of the event were determined during the interview and validated by reviewing the medical records where possible. The admission ECG was analyzed by a physician and each case was assigned to one of the following three groups: ST-elevation myocardial infarction (STEMI), non-ST-elevation myocardial infarction (NSTEMI), bundle branch block ECG. Estimated glomerular filtration rate (eGFR) was calculated based on creatinine levels at admission using the CKD-EPI formula [12]. The following categories were defined: "normal renal function" (eGFR $\geq$ 60 mL/min/1.73 m^2), "mildly impaired renal function" (eGFR between 30 and 59 mL/min/1.73 m^2), "severely impaired renal function" (eGFR < 30 mL/min/1.73 m^2). Two categories were built for left ventricular ejection fraction (EF): "severely impaired left ventricular EF" ($\leq$30 %) and "not severely impaired EF" (>30 %). Finally, the prescription of important medications at hospital discharge was documented (yes/no).

2.2. Exposure

With regard to acute treatment, it was recorded whether invasive procedures were performed in direct relation to the AMI event (within the hospital stay). One categorical variable for the invasive treatment was created including three levels: PCI, CABG, no invasive therapy. If a patient underwent both PCI and CABG, he/she was included in the CABG group, as this represented the definitive treatment.

2.3. Outcome

The primary outcome of this study was all-cause long-term mortality. Mortality was ascertained by regularly checking the vital status of all registered AMI patients in cooperation with the regional population registries. Death certificates were obtained from local health departments and the major cause of death was coded according to ICD-10. The last major update of the vital status was performed in 2019.

2.4. Statistical analysis

Age was divided into the groups "<55 years old", "55–64 years old", "65–74 years old", and "75–84 years old". BMI was categorized into the groups "<18 kg/m^2 low", "18–24 kg/m^2 normal", "25–29 kg/m^2 high" and "$\geq$30 kg/m^2 obese". Categorical variables are represented by totals and percentages and the chi-square test was used to identify significant differences. Continuous variables are represented by median and IQR and the Shapiro-Wilk test was used to test for normal distribution. The assumption of normal distribution was also visually verified using histograms and Q-Q plots.

Cox regression models were calculated to analyze the association between therapy (PCI, CABG versus no therapy) and survival. This analysis considered long-term mortality including only those patients who had survived more than 28 days after the acute event. Potential risk factors and comorbidities identified in previous studies, as well as variables hypothesized to influence mortality, were considered as confounders. We used a directed acyclic graph (DAG) and the disjunctive cause criterion to determine confounding variables. The final model was adjusted for sex (categorical), age (continuous), chest pain status (categorical), admission ECG pattern (categorical), diabetes (categorical), smoking status (categorical), eGFR (continuous), therapy with antiplatelet (categorical), ACE inhibitor or angiotensin receptor blocker (categorical), betablocker (categorical), and statin (categorical) at discharge. The continuous variables age and eGFR were tested for linearity in the Cox regression by including a squared term.

The graphical representation of the survival time was visualized using Kaplan-Meier survival curves. These were also used to visually check for a possible violation of the proportional hazards assumption. In addition, a log-rank test was used to analyze whether the treatment differed in terms of survival time within the age cohorts. Cox regressions with time-dependent covariables were additionally used to test the proportional hazards assumption for each individual variable (categorical and continuous).

Additionally, we performed the same analysis stratified for sex. Moreover, we calculated the Cox regression models without cases with no invasive therapy in order to compare the long-term mortality risk between the PCI group (reference) and the CABG group.

Finally, we analyzed the association between invasive therapy and cause-specific mortality (CVD-mortality and non-CVD-mortality) for the different age-groups. In the CVD mortality group, all deaths with a major cause of death coded as I00-I99 according to ICD-10 were combined. The non-CVD mortality group accounted for all other major causes of death.

Statistical power was calculated using the open source software PS (Power and Sample Size Calculations, Version 3.0). The analyses were conducted using IBM SPSS (version 29.0).

3. Results

A total of 4964 incident AMI cases (3534 men, 1430 women) were included in the analysis. Of those, 1224 patients (805 men and 419 women) died during a median follow-up period of 4.7 years (IQR 2.7; 6.8).

The characteristics of the AMI patients by long-term mortality are listed in Table 1. Overall, the patient population was predominantly male (71.2% male vs. 28.8% female, $p < 0.001$). In comparison to the

Table 1
Characteristics of the study sample by survival status. Categorical variables are given as total numbers and %, continuous variables as median and IQR. N corresponds to the number of patients included.

Variables	All-cause mortality		p-value	N
	Survivors 3740 (75.3)	Deceased 1224 (24.7)		
Gender			<0.001	4964
Men	2729 (73.0)	805 (65.8)		
Women	1011 (27.0)	419 (34.2)		
Age			<0.001	4964
<55 years old	960 (25.7)	64 (5.2)		
55–64 years old	947 (25.3)	148 (12.1)		
65–74 years old	1109 (29.7)	361 (29.5)		
75–84 years old	724 (19.4)	651 (53.2)		
BMI			<0.001	4837
<18 kg/m^2	19 (0.5)	18 (1.6)		
18–24.9 kg/m^2	1011 (27.3)	403 (35.4)		
25–29.9 kg/m^2	1640 (44.3)	426 (37.4)		
≥30 kg/m^2	1029 (27.8)	291 (25.6)		
Therapy			<0.001	4958
PCI	2978 (79.7)	705 (57.6)		
CABG	482 (12.9)	161 (13.2)		
No invasive therapy	276 (7.4)	356 (29.1)		
Typical chest pain			<0.001	4937
Yes	3200 (85.8)	832 (68.9)		
No	529 (14.2)	376 (31.1)		
ECG			<0.001	4786
STEMI	1493 (41.3)	351 (29.9)		
NSTEMI	1935 (53.6)	694 (59.1)		
Bundle branch block	183 (5.1)	130 (11.1)		
Hypertension			<0.001	4964
Yes	2804 (75.0)	1029 (84.1)		
No	936 (25.0)	195 (15.9)		
Diabetes			<0.001	4964
Yes	1007 (26.9)	535 (43.7)		
No	2733 (73.1)	689 (56.3)		
Smoking status			<0.001	4767
Current smoker	1288 (34.9)	254 (23.5)		
Ex-smoker	1122 (30.4)	421 (39.0)		
Never smoker	1277 (34.6)	405 (37.5)		
Hyperlipidemia			<0.001	4964
Yes	2127 (56.9)	607 (49.6)		
No	1613 (43.1)	617 (50.4)		
LVEF			<0.001	4563
≤30 %	158 (4.5)	130 (12.6)		
>30 %	3372 (95.5)	903 (87.4)		
eGFR			<0.001	4872
≥60 ml/min/1.73 m^2	2874 (78.3)	513 (42.6)		
30–59 ml/min/1.73 m^2	722 (19.7)	522 (43.4)		
<30 ml/min/1.73 m^2	73 (2.0)	168 (14.0)		
Platelets at discharge			<0.001	4777
Yes	3604 (98.9)	1054 (93.1)		
No	41 (1.1)	37 (3.3)		
Died before discharge	0 (0)	41 (3.6)		

Table 1 (*continued*)

Variables	All-cause mortality		p-value	N
	Survivors 3740 (75.3)	Deceased 1224 (24.7)		
ACE inhibitor*/angiotensin receptor blocker *at discharge			<0.001	4775
Yes	3222 (88.4)	889 (78.6)		
No	422 (11.6)	201 (17.8)		
Died before discharge	0 (0.0)	41 (3.6)		
Betablocker at discharge			<0.001	4777
Yes	3438 (94.3)	1002 (88.5)		
No	207 (5.7)	89 (7.9)		
Died before discharge	0 (0)	41 (3.6)		
Statin at discharge			<0.001	4777
Yes	3447 (94.6)	942 (83.2)		
No	198 (5.4)	149 (13.2)		
Died before discharge	0 (0)	41 (3.6)		

surviving patients, deceased patients during follow-up were significantly older and had a lower BMI. Furthermore, AMI patients who died during follow-up were more often suffering from hypertension, diabetes, impaired ventricular ejection fraction, impaired kidney function, they more frequently were ex-smokers, and less often presented with a STEMI infarction in comparison to survivors. Long-term survivors had more often received platelet inhibitors, beta-blockers, statins and ACE-inhibitors/AT-1 antagonists than patients who died during follow-up.

In patients younger than 55 years 7.6 %, in the age group 55–64 years 7.1 %, in the age group 65–74 years 12.2 %, and in the age group 75–84 years 21.6 % did not undergo invasive therapy (PCI or CABG) during hospital stay. A steady decline in PCI was observed across all age categories, with 85.2 % in patients below 55 years, 80.4 % in the age group 55–64 years, 71 % in patients aged 65–74 years, and 64.8 % in patients aged 75–84 years. The opposite was largely true for CABG (7.1 % in AMI cases below 55 years, 12.4 % in the age group 55–64 years, 16.8 % in the group 65–74 years, and 13.6 % in the age group 75–84 years).

3.1. Kaplan-Meier survival analyses

In the whole study sample as well as in all age-groups the median survival time after invasive therapy was higher than without invasive therapy. The greatest differences were observed in the age-group 75–84 years (see Figs. 1 and 2).

3.2. Results of the Cox regression analyses

In AMI patients aged 25–54 years, invasive treatment was not independently associated with lower long-term mortality risk compared to patients, who received no invasive therapy (Table 2). In the age-group 55–64 years, invasive treatment was inversely associated with long-term mortality in comparison to patients with no invasive therapy (PCI: HR 0.43 [0.25–0.75]; CABG: HR 0.50 [0.26–0.93]). In the age-group 65–74 years, there was also a significant advantage of both invasive therapies compared to no invasive treatment. Furthermore, patients aged 75–84 years had a significant advantage when treated with PCI (HR 0.55 [0.44–0.70]) or an even more pronounced advantage, when receiving CABG (HR 0.43 [0.30–0.62]) compared to no invasive therapy.

3.3. Power calculation

Based on 3683 PCI-patients as well as 643 CABG-patients that were compared to 632 controls without an invasive therapy, the calculated statistical power for all odds ratios given in Table 2 was approximately

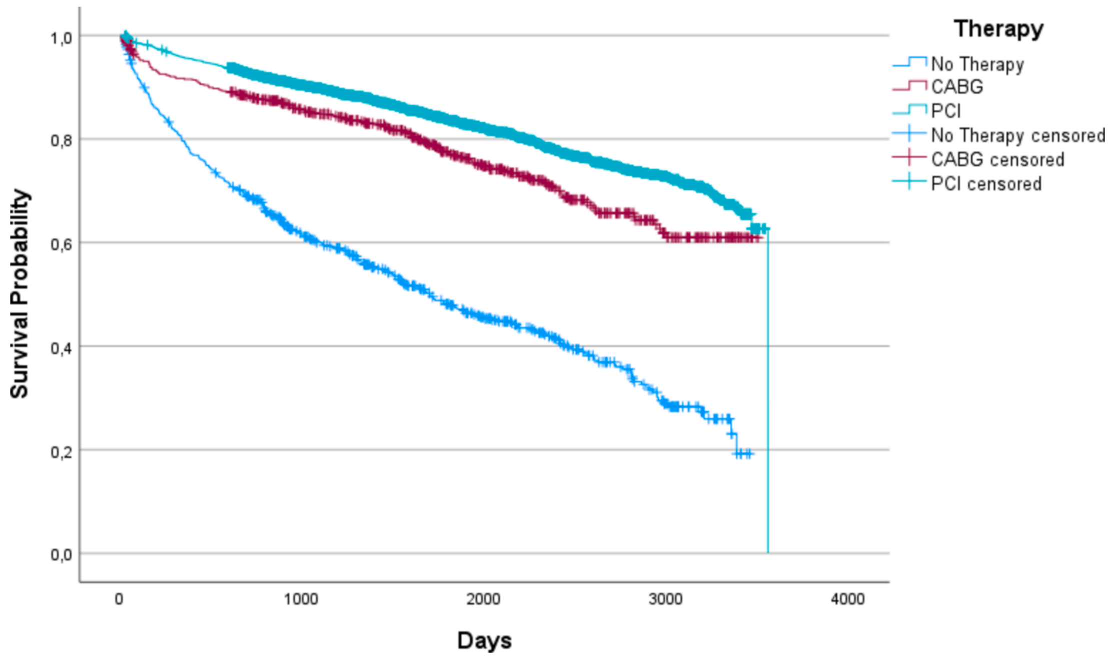

Fig. 1. Kaplan-Meier survival curves by therapy, whole study sample including all patients aged 25–84 years. Log-rank test: $p < 0.001$.

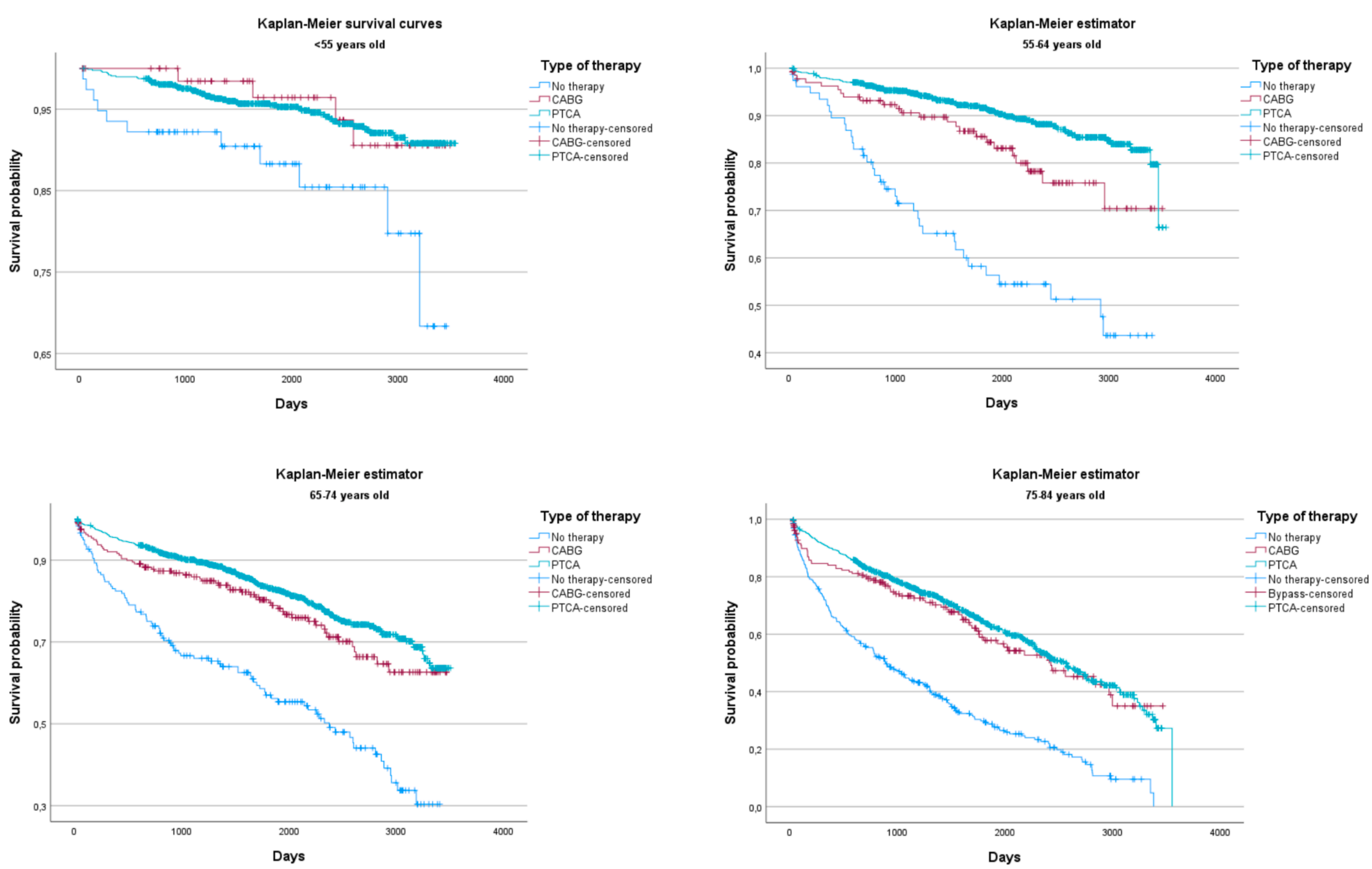

Fig. 2. Kaplan-Meier survival curves by therapy for the different age groups. Log-rank test for the age group <55 years old: $p = 0.004$. Log-rank test for the remaining age groups: $p < 0.001$.

1. A Type I error of 0.05 and a median survival time of 1700 days for patients without invasive therapy were used for the calculations.

3.4. Results of additional analyzes

In the supplementary material the results of the Cox proportional hazards models stratified for sex are presented (see table S1). The

Table 2
Results from the Cox-proportional regression analyses by age-groups.

	Age			
	<55 years	55–64 years	65–74 years	75–84 years
Long-term mortality	64 of 1024	148 of 1095	361 of 1470	651 of 1375
	HR (95 % CI)	HR (95 % CI)	HR (95 % CI)	HR (95 % CI)
No invasive therapy	1.00	1.00	1.00	1.00
PCI	0.56 [0.21–1.53]; $p = 0.259$	0.43 [0.25–0.75]; $p = 0.003$	0.48 [0.35–0.67]; $p < 0.001$	0.55 [0.44–0.70]; $p < 0.001$
CABG	0.39 [0.10–1.47]; $p = 0.163$	0.50 [0.26–0.93]; $p = 0.029$	0.48 [0.32–0.73]; $p < 0.001$	0.43 [0.30–0.62]; $p < 0.001$

All Cox models were adjusted for sex (categorical), age (continuous), chest pain status (categorical), admission ECG pattern (categorical), diabetes (categorical), smoking status (categorical), eGFR (continuous), therapy with antiplatelet (categorical), ACE inhibitor or angiotensin receptor blocker (categorical), betablocker (categorical), and statin (categorical) at discharge.

inverse associations between invasive treatment and all-cause mortality could be confirmed in males and females in all age-groups. While the associations were significant for men except in the lowest age group, there were no significant results for women, probably due to the low number of cases.

When comparing CABG versus PCI regarding long-term all-cause mortality for the total sample, there was no significant difference between these two invasive therapies in any of the four age groups (see table S2).

Finally, the Cox regression models for cause-specific long-term mortality showed inverse associations between invasive therapy (PCI or CABG) and CVD mortality as well as non-CVD mortality in all age groups (see Table S3), yet not all results did reach statistical significance.

4. Discussion

The present study investigated the age-specific long-term mortality in AMI patients with special focus on the impact of invasive treatment using real-world data from a population-based myocardial infarction registry. It could be shown that invasive therapy using PCI or CABG significantly reduced mortality risk in all age-groups, except for the youngest group (with few fatal cases) in comparison to AMI patients without invasive treatment. Even 75–84-years old benefited very impressively from invasive therapy regarding long-term all-cause mortality. The inverse associations between invasive treatment and all-cause mortality could be confirmed in males and females in all age-groups with significant results among men but not women. Regarding cause-specific long-term mortality inverse associations between invasive therapy (PCI or CABG) and CVD as well as non-CVD mortality in all age groups were found.

Consistent with other studies, all-cause long-term mortality was lowest among younger AMI patients and increased strongly with age [13–16]. With increasing age, the risk of frailty, multimorbidity and the burden of atherosclerotic changes increases. Younger individuals are usually more physically active than the elderly and thus have better constitutional fitness leading to a better regenerative capacity of the heart and consequently better survival after AMI [17]. Prior studies reported that frail patients with NSTEMI are less likely to be treated with medication and receive less invasive diagnostics. They show more complex coronary artery diseases, have a longer hospital stay [18], and *per se* a higher mortality risk, more heart attacks, strokes, unplanned revascularizations, and more critical bleedings [19]. Multimorbidity is also associated with a worse prognosis in elderly acute coronary syndrome patients, especially in association with anemia, thrombocytopenia, renal insufficiency, diabetes, and cancer [20–24]. In NSTEMI patients, multimorbidity is associated with an increased risk of long-term adverse cardiovascular events, especially increased all-cause mortality [25]. Undiagnosed cognitive impairment is also common in NSTEMI patients and associated with an increased risk of cardiovascular events after one year [26].

4.1. PCI and CABG

The present study found that the decrease of the median survival time with increasing age was greater in the CABG group than in the PCI group. This is partly in line with existing data that have compared both procedures for interventions on the left main coronary artery [27]. In patients above 75 years of age, a survival advantage of PCI over CABG was demonstrated [27]. In contrast, patients younger than 75 years treated with CABG showed an advantage in overall survival compared to the PCI cohort [27].

Although the survival curves indicated certain differences between the therapies, the multivariable Cox models showed a significant advantage for both interventional procedures (versus no interventional procedures) in the present study. However, when comparing CABG versus PCI, there was no significant difference between these two invasive therapies in any of the four age groups regarding long-term all-cause mortality.

4.2. Gender-specific analyses

We observed inverse associations between invasive treatment and all-cause mortality in both males and females in all age-groups, yet due to a lower number of cases, the results did not reach statistical significance in women. A study including 833 STEMI-patients (25.2 % women) found a similar incidence of major adverse cardiac events after a median follow-up of 60 months in men and women undergoing PCI with coronary stenting [28]. Other studies also showed that there were no differences in long-term mortality risk between females and males after PCI [29,30]. However, comparisons between the studies are difficult due to different study settings, inclusion of patients, different years of selection and follow-up length.

4.3. Possible factors contributing to the decision for or against a specific invasive treatment

Explanations for a higher proportion of CABG surgery in older compared to younger patients could include the following. Acquired limitations of coronary artery anatomy and access routes via the radial or femoral arteries may necessitate primary CABG [31]. Furthermore, elderly patients frequently suffer from left main disease or multi-vessel disease leading to poor outcome [32]. These limitations are more likely to be found in older patients due to chronic degenerative processes and higher morbidity [33].

In acute cases, a change in procedure to CABG rarely takes place after the failure of PCI, as the prognosis no longer improves significantly due to the time delay associated with the switch [34–36]. Nevertheless, the guideline continues to recommend the primary use of PCI, as the benefit of the intervention is usually higher than the risk of discontinuation of therapy [31].

4.4. Less invasive therapies in old age

This study showed that invasive therapies decreased with increasing age. However, looking at the results regarding the median survival time, 75–84-year-olds seem to benefit particularly from invasive therapy. In no other age group, the difference in survival time between invasive and no invasive therapy was as clear as in this age group. However, there may be a bias here: it is possible that the patients who died prematurely without invasive therapy were already too morbid for surgery, while conversely, the patients who received such therapy may still have had sufficient health reserves for an intervention or surgery.

Patients older than 75 years are still often excluded or underrepresented in studies, even though age is a large independent predictor of worse outcome [4,5]. In STEMI patients, PCI has been shown to improve outcomes at all ages [37]. Even in a smaller RCT, it was shown that in NSTEMI patients over 80 years of age invasive measures were associated with a better outcome compared to conservative therapy, even though the benefit has decreased with age [38].

The therapy decision remains a challenge for very old AMI patients. In the absence of clear study data, a holistic approach is recommended to individualize invasive and pharmacological treatment after careful consideration of risks and benefits. The following factors must be taken into account in the process of decision making: risk of ischemia and bleeding, comorbidities and life expectancy, quality of life, the need for non-cardiac surgery, frailty, cognition and functional impairments, and for sure the patient's will [31]. Quality of life is of particular importance here, as it depends largely on the social environment after PCI, so socially isolated, elderly patients have a significantly higher mortality rate [39]. Survey instruments, such as questionnaires, can be a valuable clinical aid in decision-making. For example, the assessment of frailty (e.g. Frailty Index; [40,41]) and comorbidity (e.g., Charlson Index; [42]) is recommended for elderly patients [31]. Despite the diverse and quite complex influencing factors in decision-making, the ESC guideline "Guidelines for the Management of Acute Coronary Syndromes" conclusively sticks to a simple principle: in acute cases, PCI should also be performed in older patients [31].

5. Strengths and limitations

One of the strengths of this population-based study with complete enrollment is the large number of included cases of hospitalized AMI, which minimized the risk of selection bias. Data were assessed in a standardized manner by trained and certified study nurses. Furthermore, contrary to other studies, the present study included AMI patients up to 84 years. However, the exclusion of patients over 84 years limits its applicability to the growing demographic of very elderly individuals. In regard of demographic trends, patient collectives over the age of 84 should also be included in future studies, as otherwise an increasing part of the population will not be taken into account and therefore no reliable conclusions can be given about the treatment of very old patients with heart attacks. Furthermore, no information on angiographic parameters (which and how many vessels were affected) was available. Also, no data on the number of stents (drug-eluting or bare metal) or grafts (arterial or venous) was obtained. The absence of that data reduces the ability to pinpoint which specific interventions were most beneficial. Furthermore, the lack of data on quality of life outcomes omits a key factor in treatment decision-making, especially for older patients. Although the analyses were adjusted for a high number of relevant variables including kidney function and comorbidities, unmeasured confounding cannot be excluded. Moreover, the study sample included AMI patients predominantly of German nationality, consequently the present results may not be transferable to other ethnicities.

6. Conclusion

In conclusion, the results of this study could be a further building block for reducing ambiguities and uncertainties about the effectiveness of invasive or surgical therapy procedures in the treatment of older AMI patients and enabling these people, as well as younger AMI patients, to receive a therapy that is in line with the guidelines across the board and thus to achieve a better outcome.

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CRediT authorship contribution statement

Michael Kraus: Writing – original draft, Visualization, Formal analysis, Data curation. **Timo Schmitz:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Conceptualization. **Dennis Freuer:** Writing – review & editing, Supervision, Methodology. **Philip Raake:** Writing – review & editing, Resources, Investigation. **Jakob Linseisen:** Writing – review & editing, Resources, Investigation. **Christa Meisinger:** Writing – review & editing, Supervision, Resources, Project administration, Investigation, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2024.101524.

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