Exclusion of Elderly People from Randomized Clinical Trials of Drugs for Ischemic Heart Disease

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Exclusion of elderly persons in randomized clinical trials of drugs for ischemic heart disease

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1 **ABSTRACT**

2 **Background/Objectives.** Evidence-based and patient-centered care of elderly adults

3 with ischemic heart disease requires clinical trials that study the patient population seen

4 by clinicians in practice. We aimed to measure the exclusion of elderly persons from

5 randomized trials studying drug interventions for ischemic heart disease and describe

6 the characteristics of these trials.

7 **Design and setting.** Interventional clinical trials studying a drug intervention for

8 ischemic heart disease and started 2006 and after were identified in ClinicalTrials.gov.

9 Data were extracted on study features, including age-based inclusion criteria. Data on

10 participants and their age distribution were collected from trial publications, investigator

11 inquiry, and result data in ClinicalTrials.gov.

12 **Measurements.** Proportion of trials excluding patients based on age, mean age of trial

13 participants, and proportion of enrolled participants who were ≥65 years and ≥75 years.

14 **Results.** Of 839 identified trials, 446 (53%) explicitly excluded elderly persons. The

15 most frequent upper age limits were 80 (n=164) and 75 (n=114) with a median upper

16 age limit of 80 (IQR 75, 80). Trials with upper age limit exclusions tended to be smaller

17 (median number of participants 100 vs 201, p<0.001) and were more likely to be funded

18 primarily by non-industry sources (78.3% vs 70.0%, p=0.006). The overall mean age of

19 trial participants was 62.7 years with a mean maximum age of 74 years. The estimated

20 proportion of participants that was ≥65 years was 42.5% and the estimated proportion

21 that was ≥75 years was 12.3%.

1   **Conclusion.** Despite the high burden of ischemic heart disease among elderly patients,

2   the majority of drug trials do not enroll participants reflective of age-related prevalence

3   of the disease.

4   **Key Words:** ischemic heart disease, evidence-based medicine, research methodology

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INTRODUCTION

Patients 65 years of age and older comprise only 14% of the US population, but bear a large and disproportionate amount of the healthcare burden.[1,2] Greater than 60% of patients with cancer, for example, and nearly 65% of patients hospitalized with heart disease are older than 65 years.[3,4] Overall, this age group consumes greater than a third of total U.S. personal health care expenses every year as well as 30% of all prescription drug costs.[2] However, there is strong evidence that elderly patients are persistently excluded or underrepresented in clinical trials across a spectrum of conditions including osteoarthritis, diabetes, and various cancer types.[5-7] As many as half of all clinical trials have explicit upper age limitations while others limit the participation of older patients based on indirect exclusion criteria such as the presence of comorbid conditions, cognitive impairment, or polypharmacy.[5,8-10]

Ischemic heart disease represents a leading and increasing healthcare burden among elderly patients worldwide, resulting in greater than 900,000 deaths annually in the U.S. alone.[11,12] Many more adults live with chronic symptoms and disability related to angina pectoris, nonfatal myocardial infarction, and ischemic heart failure.[11] Age-specific pathophysiological processes and unique features of disease management in the elderly require treatment decisions that are carefully tailored to this population.[13,14] A number of trials examining cardiovascular disease over the past decade have specifically focused on the study of elderly persons, but many trials—including those influencing current treatment guidelines—study primarily younger patients.[13,15,16] Quantifying this gap and identifying the types of trials most likely to exclude elderly

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1 patients may inform policies addressing research needs. Our aim was to measure the

2 extent to which elderly persons are excluded from randomized trials studying drug

3 interventions for ischemic heart disease and describe the characteristics of these trials.

4

5 **METHODS**

6 **Search strategy and inclusion criteria**

7 Clinical trials were selected from ClincialTrials.gov, a publicly accessible, web-based

8 registry administered by the National Institutes of Health. As a result of federal

9 legislations and journal editor policies mandating trial registration prior to patient

10 enrollment, prospective trial registration has become standard practice.[17,18]

11 ClinicalTrials.gov represents the most comprehensive trial registry and currently holds

12 data on approximately 218,000 trials, making it a powerful tool for the examination of

13 research activity and practices.

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15 We searched ClinicalTrials.gov on a single day (January 15th, 2016) for interventional

16 trials addressing ischemic heart disease using the term "ischemic heart disease" in the

17 condition field of the registry's advanced search form. Studies were considered eligible

18 if they were randomized controlled trials assessing drugs with a start date on or after

19 January 1st, 2006. Trials that were terminated or withdrawn were excluded, as were

20 trials specific to pediatric and adolescent populations, pregnancy and reproduction, or

21 sexually transmitted diseases.[19] All trials were manually reviewed to ensure that they

22 studied the treatment or prevention of ischemic heart disease and that they met all

23 inclusion criteria.

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Collection of participant age data

3 Publications describing trial results were sought for each of the trials in the study cohort.

4 We first searched the "publication" section of ClinicalTrials.gov and, if a publication was

5 not identified in the trial entry, Medline was searched via PubMed without language

6 restrictions using a systematic protocol.[20,21] We considered a trial published if we

7 identified a peer-reviewed publication reporting on trial results. If multiple publications

8 were identified for a single trial, we reviewed each one to identify relevant participant

9 age data.

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11 If a publication was not identified, or if it did not contain all the required data for our

12 analysis, we sought to contact the investigators. Email addresses for investigators were

13 identified in ClinicalTrials.gov, in prior publications, and via online searches. A standard

14 email was sent to investigators with one reminder sent two weeks later if no response

15 was received. For industry sponsored trials, if no investigator email address was

16 available or if no response was received after the total of four weeks, we attempted to

17 contact the pharmaceutical company via a company email address or online form on the

18 company website. Finally, if we were unable to identify a publication or to obtain all

19 relevant data for a trial, we searched for results within the ClinicalTrials.gov database.

20

Data extraction for trial characteristics

22 Data on trial characteristics were extracted from ClinicalTrials.gov, including year of

23 registration, study start and completion dates, primary funding source, trial phase,

1   primary outcome, sample size, participant age eligibility criteria, and characteristics of

2   the study design (e.g. comparator type, number of centers; Supplementary File S1). The

3   sample size listed in the registry entry initially represents the anticipated enrollment

4   number and can be updated by investigators to reflect the actual enrollment figure at the

5   end of the study. Since this field is not consistently updated and we examined studies

6   in various stages of conduct, we use sample size to refer to anticipated or actual

7   enrollment.

8

9   For each publication matched to a trial, we recorded the total number of participants

10   enrolled and extracted data on the age distribution of participants, including minimum

11   and maximum ages, mean (with standard deviations [SD]) or median ages (with

12   interquartile ranges [IQR]), and number of participants above specific age thresholds.

13   Data was collected for the entire study population as well as for each of the study arms,

14   whenever available.

15

16   **Statistical Analysis**

17   Descriptive statistics were used to present the proportion of trials excluding elderly

18   persons, the distribution of upper age limits, and the characteristics of the trials with and

19   without upper age limits. The maximum ages of patients actually enrolled were

20   estimated, whenever this information was not available, as the mean age + 2 standard

21   deviations (SD, Supplementary File S2)[5]. Univariate analysis with χ^2 tests and the 2-

22   sided t tests or Mann-Whitney tests were used for categorical and continuous variables,

23   respectively, to examine the association of trial characteristics with the explicit exclusion

1   of elderly persons. We performed a logistic regression to test for trends over time in the

2   prevalence of elderly exclusion, with upper age limit as the dependent variable and year

3   of study registration as the independent variable. We also performed a multivariate

4   logistic regression with all variables found to be significant in the univariate tests to

5   further examine factors predicting exclusion of elderly persons. Both forward and

6   backward stepwise procedures were used, and the Hosmer-Lemeshow goodness of fit

7   test was considered. Two-sided P values of <0.05 were considered statistically

8   significant.

9

10   The mean age for the entire enrolled trial population was calculated as a weighted

11   mean based on the sample size of each trial, and a combined SD was calculated based

12   on the mean age of the entire cohort and the sample size, standard deviation and mean

13   age of each trial.[22] Different formulas were used for these calculations according to the

14   sample sizes (Supplementary File S2).[22,23]

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16   The proportions of participants above specific age thresholds enrolled in the trials were

17   calculated using age distribution information and the cumulative distribution function

18   (Supplementary File S2). For these calculations we assumed that the mean age and SD

19   were derived from a truncated normal distribution, as each trial has either a lower age

20   limit for the enrolled population (whenever not mentioned, a lower age limit of 18 was

21   assumed) or lower and upper age limits.[24-26] All statistical analyses were conducted in

22   IBM SPSS Statistics version 23.0.

23

RESULTS

Characteristics of trials and exclusion of elderly persons

We identified 3777 registered interventional trials studying ischemic heart disease, of which 839 met our inclusion criteria and represented randomized controlled trials of drug interventions (Figure 1). The majority of these trials was funded primarily by non-industry sponsors (74%) and conducted at single centers (60%) (Table 1). Over two-thirds (68%) were phase 3 or 4 trials and 55% included a safety outcome. Only 23% had sample sizes of 500 or more subjects, with a median of 120 subjects per trial. The most common specific drug classes studied were anti-thrombotic agents (N=355 trials), lipid-modifying agents (N=132 trials), and antihypertensive medications (N=67 trials).

A total of 446 trials (53%) explicitly excluded elderly persons. The most frequent upper age limits were 80 (n=164) and 75 (n=114) with a median upper age limit of 80 (IQR 75, 80) (Supplementary Figure S1). Overall, 43% (n=361) of trials had an upper age limit of 80 or even lower. Among trials that did not have such an upper age limit, and for which we could identify or impute the maximum age of participants (n=200), 17% (n=34) had enrolled no patients who were over 80 years old. Logistic regression found a small but significant increase in the proportion of trials that excluded elderly persons over the study period (odds ratio 1.06 per year, 95% confidence interval [CI] 1.01 to 1.12; P=0.016) (Figure 2). When we limited the analysis to 2008 through 2015 (in order to address potential biases in early adoption of ClicialTrials.gov), there continued to be a significant trend (odds ratio 1.07 per year, 95%CI 1.003 to 1.15; P=0.04)

1   Several trial characteristics were associated with trials that excluded elderly persons

2   (Table 1). Trials with upper age limit exclusions were more likely to be funded primarily

3   by non-industry sources, tended to be smaller, did not employ a multicenter design, and

4   were shorter in duration. An additional analysis was performed focusing on trials that

5   enrolled only patients less than 80 years of age (Supplementary Table S1). Study

6   phase, sample size, and study duration were associated with this age restriction.

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8   In multivariate analysis, study phase, sample, size, multicenter status, and study

9   duration remained significantly associated with the use of any upper age limits (Table

10   2).

11

12   **Age of trial participants**

13   Publications describing trial results were identified for 308 (37%) of the trials. Based on

14   participant age data in these publications and using additional age information obtained

15   from investigators and from the results posted in ClinicalTrials.gov, we identified

16   participant age data for a total of 340 trials, representing 327,672 participants. For 334

17   of these trials, we identified data on the mean age and standard deviation (or median

18   and interquartile range) of participants. For 46 of the trials we identified information on

19   proportion of patients aged 65 or older available (either through a publication, a

20   ClinicalTrials.gov entry, or provided by the investigator), and we imputed this

21   information for the remainder, as described above. There were similar numbers of trials

22   with and without upper age eligibility criteria that had participant age data available (161

23   and 179 trials, respectively).

The overall mean age of participants in the trials was 62.7 years with a mean maximum

age of 74 years. The estimated proportion of participants that was 65 years and older

was 42.5% and the estimated proportion that was 75 years and older was 12.3%.

Figure 3 demonstrates the distribution of estimated proportion of patients who were 65

years or 75 years and older for each of the trials.

DISCUSSION

Our results suggest that clinical drug trials across the spectrum of ischemic heart

disease are not adequately enrolling elderly patients, with greater than half the trials

explicitly excluding patients based on upper age limits. Overall, there has been a slight

increase in such exclusions over the past 10 years, in part due to changes in certain

trial characteristics. Upper age limits were most frequently set at 75 and 80 years of

age, resulting in a pronounced drop in the enrollment of participants 75 years of age

and older.

The mean age of participants across trials for ischemic heart disease was 62.7 years,

which is lower than the mean age reported for patients seeking medical care for

ischemic heart disease. In a population-based surveillance study conducted in Olmsted

County, Minnesota between 2005 and 2010, the mean age of 1244 patients hospitalized

with acute coronary syndrome was 67.7 years.[27] Another large community-based study

in the U. S. reported a mean age of 69 years among 46,086 patients hospitalized with

myocardial infarction between 1999 and 2008.[28] In Sweden, in a national registry

1   comprised of almost 200,000 patients admitted to coronary care units for symptoms

2   suggestive of acute coronary syndromes between 1996 and 2008, the mean patient age

3   was 71 years.[29] The mean age in population studies is even about a decade higher for

4   patients with heart failure, a common complication of coronary artery disease.[30-32]

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6   The proportion of participants enrolled in clinical trials that were 65 years and older and

7   75 years and older was 42.5% and 12.3%, respectively.   When compared to the age

8   distribution of patients with ischemic heart disease, these rates appear low, particularly

9   for those 75 years of age and older, and less so for those 65 years or older. For

10   instance, based on the U.S. National Health Interview Survey conducted in 2012, 55.7%

11   of patients with coronary heart disease were 65 years and older.[33] Another study based

12   on a national sample of greater than 260,000 patients undergoing percutaneous

13   coronary intervention for acute myocardial infarction in the U.S. from 2001 through

14   2009, found that 45.9% of patients were 65 years of age and older.[34] These rates are

15   not much higher than the rate we estimated for the trial participants. Conversely, the

16   divergence from population data becomes much more prominent at the 75 year

17   threshold. For example, in a community study in Olmsted County, among 2816 patients

18   hospitalized for myocardial infarction between 1987 and 2006, 39% were 75 years of

19   age or older.[35] Similarly, an analysis of 1.3 million hospitalizations for acute coronary

20   syndrome in Canada between 1994 and 2006 revealed that 40% of patients were older

21   than 75 years.[36]

22

1   Our results are consistent with prior studies assessing the representation of elderly in

2   clinical trials related to ischemic heart disease. One study of 194 randomized controlled

3   trials cited in American Heart Association guidelines for acute coronary syndromes

4   found that the mean age of participants was 61 years, with 18% of trials attaining a

5   mean participant age of 65 years or older and none with mean ages of 75 years or

6   older.[16] Another study examining 11 phase III clinical trials of patients with non-ST-

7   segment-elevation acute coronary syndrome between 1994 and 2010, revealed that

8   53% of participants were 65 years or older and only 20% were 75 years or older.[15] Our

9   study adds to these findings by examining a large cohort of 839 randomized controlled

10   trials conducted over the past 10 years and addressing the wide spectrum of ischemic

11   heart disease. We provide new data indicating that the elderly continue to be excluded

12   from the most rigorous clinical studies—randomized controlled trials—and that this

13   practice has the greatest impact on the clinical evidence available to guide care for

14   patients 75 years of age and older.

15

16   Our study also demonstrates a registry-based approach for the ongoing assessment

17   and monitoring of elderly patients across a large number of trials. Mandatory

18   registration of interventional trials has led to an almost comprehensive dataset of clinical

19   trials in ClinicalTrials.gov, which can be used to examine participant enrollment

20   practices, including age-based exclusion. Ongoing monitoring would help inform

21   guidance and requirements for the enrolment and study of elderly patients.

22

Results derived from trials on younger patients cannot necessarily be extrapolated to

the elderly because of age-related differences in pathophysiology and unique

considerations in defining patient-centric therapeutic targets. [3,37] In addition, the

pharmacologic characteristics and toxicity of certain medications are age-specific, with

the tolerability and effectiveness reduced among older patients.[13,38,39] On the other

hand, claimed age differences in treatment effectiveness and/or harms may represent

spurious findings of subgroup differences that are prone to false-positive results.[40] In the

absence of sufficient evidence on elderly participants one runs the risk of missing

important age-treatment interactions as well as of falsely claiming such interactions.

Recommendations have been issued by regulatory agencies to encourage the study of

pharmaceuticals in elderly persons.[41,42] A guideline developed by the FDA in 1989,

states that "there is no good basis for the exclusion of patients on the basis of age

alone, or because of the presence of any concomitant illness or medication, unless

there is reason to believe that the concomitant illness or medication will endanger the

patient or lead to confusion in interpreting the results of the study".[41] The International

Conference of Harmonization also published a guideline in 1993 recommending the

inclusion of elderly patients in clinical drugs trials that are likely to be relevant in this

population.[42] By contrast, the U.S. Congress in the National Institutes of Health (NIH)

Revitalization Act of 1993 included provisions for the inclusion of women and minorities

in clinical trials, but unfortunately did not include requirements for older patients.[43] The

NIH should consider requiring that investigators outline plans to recruit elderly patients

1 and provide targets for the proportions to be recruited in certain age groups, in line with

2 disease distribution in the general population.[44]

3

4 One of the limitations of this study is that we examined the exclusion of elderly patients

5 only due to explicit age criteria and many more elderly patients may be excluded due to

6 indirect exclusions such as the presence of co-morbid conditions or functional

7 impairments.[9,45] We could indirectly document the additional impact of such exclusions,

8 because we found that many trials did not have any participants over 80 years old, even

9 though they did not include an upper age eligibility criterion. Our results may therefore

10 underestimate the overall exclusion of elderly patients. In addition, because data in

11 ClinicalTrials.gov are provided by investigators, the information cannot be verified and

12 include occasional incomplete data elements. However, data entered in the registry

13 undergo quality assurance measures by ClinicalTrials.gov prior to public posting and we

14 were able to obtain additional data as needed through direct contact with investigators.

15 Nonetheless, we were not able to obtain all participant age information from the registry

16 or publications, and certain imputations were required. We performed several quality

17 control checks to examine the procedures and these indicated that the methods and

18 results were highly reliable (see Supplementary File 2).

19

20 In conclusion, despite the high burden of ischemic heart disease among elderly

21 patients, the majority of drug trials for this condition continues to exclude elderly

22 patients, with patients 75 years of age and older particularly underrepresented. Current

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1 trial practices and policies around the inclusion of elderly patients should be reexamined

2 in order to ensure the applicability of trial findings to this growing population.

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19 **SUPPLEMENTARY INFORMATION**
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21 **Supplementary File S1.** Coding and Definitions of Trial Characteristics
22 **Supplementary File S2.** Statistical Analysis
23 **Supplementary Figure S1.** Distribution of Upper Age Limits
24 **Supplementary Table S1.** Characteristics of randomized controlled trials studying drug
25 interventions for ischemic heart disease by presence of an upper age limit lower than 80 years
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Table 1. Characteristics of randomized controlled trials studying drug interventions for ischemic heart disease by presence of an upper age limit

Variable		Upper Age Limit		Total (N=839)	P-Value
		Yes (N=446)	No (N=393)		
Primary industry funding, N (%)	No	349 (78.3)	275 (70.0)	624 (74.4)	0.006
	Yes	97 (21.7)	118 (30.0)	215 (25.6)	
Study phase, N (%)	Phase 1	27 (6.1)	6 (1.5)	33 (3.9)	< 0.001
	Phase 2	84 (18.8)	73 (18.6)	157 (18.7)	
	Phase 3	77 (17.3)	123 (31.3)	200 (23.8)	
	Phase 4	211 (47.3)	159 (40.5)	370 (44.1)	
	Unknown	47 (10.5)	32 (8.1)	79 (9.4)	
Sample size, Median (IQR)[1]		100.0 (55.75-222.75)	200.5 (82.0-910.0)	120.0 (60.0-431.75)	< 0.001
Active comparator, N (%)	No active comparator	322 (72.2)	273 (69.5)	595 (70.9)	0.385
	Active comparator	124 (27.8)	120 (30.5)	244 (29.1)	
Blinding, N (%)	Double Blinding	222 (49.8)	201 (51.1)	423 (50.4)	0.069
	Single Blinding	74 (16.6)	44 (11.2)	118 (14.1)	
	No Blinding	150 (33.6)	148 (37.7)	298 (35.5)	
Multicenter design[2], N (%)	No	306 (69.1)	194 (49.9)	500 (60.1)	< 0.001
	Yes	137 (30.9)	195 (50.1)	332 (39.9)	
Registration year [3], N (%)	2006	27 (6.1)	28 (7.2)	55 (6.6)	0.015
	2007	32 (7.2)	37 (9.5)	69 (8.3)	
	2008	45 (10.1)	41 (10.5)	86 (10.3)	
	2009	32 (7.2)	39 (10.0)	71 (8.5)	
	2010	46 (10.3)	42 (10.7)	88 (10.5)	
	2011	49 (11.0)	54 (13.8)	103 (12.3)	
	2012	60 (13.5)	44 (11.3)	104 (12.4)	
	2013	56 (12.6)	32 (8.2)	88 (10.5)	
	2014	45 (10.1)	42 (10.7)	87 (10.4)	
	2015	53 (11.9)	32 (8.2)	85 (10.2)	
Trial includes any safety outcome, N (%)	No	205 (46.0)	173 (44.0)	378 (45.1)	0. 572
	Yes	241 (54.0)	220 (56.0)	461 (54.9)	
Study duration (Years)[4], Median (IQR)		1.6 (1.0-2.4)	2.2 (1.3-3.1)	1.8 (1.0-2.8)	< 0.001

Anti-thrombotic agents, N (%)	No	257	(57.6)	227	(57.8)	484	(57.7)	0.968
	Yes	189	(42.4)	166	(42.2)	355	(42.3)	
Lipid modifying agents, N (%)	No	372	(83.4)	335	(85.2)	707	(84.3)	0.467
	Yes	74	(16.6)	58	(14.8)	132	(15.7)	
Antihypertensive drugs, N (%)	No	413	(92.6)	359	(91.3)	772	(92.0)	0.504
	Yes	33	(7.4)	34	(8.7)	67	(8.0)	

[1] One trial with missing data on sample size
[2] Seven trials with missing data on multicenter design status
[3] Three trials registered during 2004-2005 exclude
[4] For 9 trials we were unable to calculate study duration, due to missing completion dates.

Table 2. Trial characteristics associated with the exclusion of elderly persons in multivariate analysis

Variable		OR	95% CI	P-Value
Study phase	Phase 1	-	-	0.023
	Phase 2	0.38	(0.14, 0.98)	
	Phase 3	0.25	(0.10, 0.66)	
	Phase 4	0.40	(0.16, 1.01)	
	Unknown	0.43	(0.16, 1.18)	
Sample size		0.9998	(0.9997, 1.0000)	0.006
Multicenter design	No	-	-	0.001
	Yes	0.59	(0.43, 0.82)	
Study duration (Years)		0.86	(0.77, 0.97)	0.010

LEGENDS

Figure 1. Flow chart for trial inclusion. Age data was collected on the mean age and standard deviation (or median and interquartile range) for the study population or for each treatment arm and on the number of participants above specific age thresholds.

Figure 2. Explicit exclusion of elderly persons according to study registration year. Percent of trials with an upper age limit was calculated from the 836 trials with registration date between 2006 and 2015 (3 trials registered during 2004-2005 were excluded). The proportion of trials with an upper age limit increased over time (odds ratio 1.06 per year, 95% confidence interval 1.01 to 1.12; P=0.016).

Figure 3. Distribution of proportion of patients who are 65 years and older and 75 years and older for each trial. There were 340 trials with data on proportion of patients 65 years and older and 334 trials with data for patients 75 years and older (6 trials gave proportion for age 65 years and older, but did not give proportion for age 75 and older or mean age and SD that could be used to calculate this proportion). The median proportion of patients 65 years and older was 38% (IQR 26%-48%, range 0%-100%) and the median proportion of patients 75 years and older was 9% (IQR 2%- 14%, range 0%-47%).