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The Durban World Congress Ethics Round Table II: Withholding or withdrawing of treatment in elderly patients admitted to the Intensive Care Unit

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Abstract:

Introduction: Life sustaining treatment (LST) limitation for elderly patients is highly controversial. In that context, it is useful to evaluate the attitudes to LST in the elderly among experienced ICU physicians with different backgrounds and cultures.

Methods: A panel of 22 international ICU physicians from 13 countries responded to a questionnaire related to withholding (WH) and withdrawing (WD) LST in elderly patients, using a semi-Likert scale.

Results: Most experts disagree or strongly disagree (77%) that age should be used as the sole criterion for WH or WD LST and almost all disagree (91%) that there should be a specific age for such decision making. However, the vast majority (91%) acknowledge that age should be an important consideration in conjunction with other factors. Disagreement for consideration of prioritizing the young over the old in normal ICU operations was reported in 68% while in an emergency triage situation disagreement dropped to 18%.

Conclusions: There is a consensus among ICU physicians that age cannot be the sole criterion on which healthcare decisions should be made. In that perspective, it is important to provide data showing that outcome differences between elderly and non-elderly patients are partly related to decisions to forgo LSTs.

Key words: elderly, intensive care, ethics, life sustaining treatment

In the constitution of many countries, it is clearly stated that discrimination is prohibited and that no choice should be based on age alone. Similarly, when a panel of international experts in intensive care medicine issued a list of criteria that could assist the decision making processes regarding admission or refusal of admission of patients to ICU there was a strong consensus that age should not be considered as a sole decision making criterion [1]. Nevertheless, economic pressures, the need for rationing of ICU beds [2] and changing demographics -in particular the aging of most populations - might jeopardize this idealized view of ICU access and treatment for elderly patients [3]. While clearly there is a need to favor access to costly and scarce ICU care to patients that would most benefit from such treatments, it is also the individual responsibility of intensivists to consider the rights of the individual patient presenting for admission to the ICU. However, in the larger context of health care resource allocation the ethical principle of social (or distributive) justice should also be considered in decision-making. Unrestricted access to ICU treatment could lead to restrictions in other health services (such as preventive medicine), as well as other social priorities such as education, housing and the environment. Thus it is imperative that appropriate allocation of ICU therapy (such as cardio-pulmonary resuscitation, mechanical ventilation, renal replacement therapy, vasoactive drugs, and extra corporeal membrane oxygenation) should be considered in all cases. Trade-offs between different criteria and ethical principles will be unavoidable and the principles of autonomy and distributive justice need to be balanced against each other.

The decision to limit ICU therapy in an individual patient, already receiving intensive therapy, depends on several factors, including predicted mortality as estimated by primary physicians and the ICU team; but also the burden of treatment, quality of Life (QOL) and expected functional status after ICU discharge [1]. Expected short- and long-term prognoses are central to the decision to continue, withhold or withdraw treatment. While there is a continuum of care from the time of ICU admission to discharge, this paper focuses on goals of care, as assessed by decisions to forgo life sustaining treatment (LST) of patients in the ICU. It does not consider admission and readmission policies. We acknowledge that this approach is somewhat conceptual/theoretical since admission policy is substantially linked to LST policy. On the one hand, a very liberal admission policy that could be characterized as an “ICU trial”, is usually associated with a reassessment of the patient’s condition after a few days in order to decide whether continued maximal treatment should still apply or the patient should be discharged from the ICU. Whereas on the other hand, a very restrictive admission policy will select out candidates for ICU treatment who are much less likely to fail a “trial of ICU” so that discussions regarding withholding/withdrawal of therapy are likely to be far less common. In the latter situation, ICU survival might be better but this relates to many potentially salvageable patients (especially the elderly) being denied ICU admission.

This paper addresses issues related to withholding (WH) and withdrawing (WD) life-sustaining treatments (LST) in elderly patients.

Methods

A group of invited speakers to the 11th congress of the World Federation of Societies of Intensive and Critical Care Medicine (WFSICCM) with special interest on ethics elaborated and answered a survey dealing with end-of-life decision.

Prior to the meeting, an iterative process was performed by email in order to choose the most pertinent questions relating to these items for further work and discussion at the Congress. Initially 70 questions related to withholding and withdrawal of LSTs were sent to participants. Five topics were chosen with one topic dedicated to elderly.

During the meeting, the different questions were discussed and adapted in order to avoid bias related to misunderstanding and to language. It was decided that each question has to be answered using a Likert scale (strongly agree, agree, neutral, disagree and strongly disagree).

Following the meeting, specific questions pertaining to elderly patients [4] were finalized and distributed to the same participants. The response rate was 100%.

Results

We obtain response from 22 participants coming from 13 different countries. There was an over representation of South African and US participants. In order to adjust for this imbalance, we performed several additional analyses testing agreement between raters with slight kappa test. All analyses were made using the R software (v 2.12.0; http://cran.r-project.org).

The global multi-reader kappa was fair 0.22 considering all experts. It was very similar among US experts: 0.20, among south African experts: 0.20 and the rest of the world 0.19. This indicates that individual response is not influenced by countries. When substituting mean of response for each country in order to have a single response per country (only 13 responses instead of 22), the reported percentage for each response are very similar.

The responses of the panel of experts to questions focusing on the elderly are shown in Table 1. Most experts disagree or strongly disagree (77%) that age should be used as the sole criterion for WH or WD LST and almost all disagree (91%) that there should be a specific age for such decision making. However, the vast majority acknowledge that sometimes age should be an additional important consideration in conjunction with other factors (91%). Disagreement for considering prioritizing the young over the old in normal ICU operations was reported in 68% while in an emergency triage situation disagreement dropped to 18%. For these two questions, 16 experts changed their votes and 15 out of 16 were in favor of more LST limitation in case of bed shortage ($p < 0.001$; Mc Nemar test).

Several responder comments highlights the issue: “Age cannot be looked at in isolation” and “the decision to WH or WD should be based on an individualized assessment which takes into account co-morbidities as well as age”, “The actual age should not on its own confer an initial advantage”.

Discussion

1. Methodology and limitations of the study

The questionnaire was not formally validated; however, it was intended to be used only once and by specialist of the domain. Moreover, the respondents were the ones who designed the survey thus preventing bias related to lack of understanding. Language is usually a major issue in questionnaire methodology, however, responders were international speakers able to understand properly the questions.

Given the low number of respondents and their specific characteristics, some bias in the distribution of the response cannot be excluded. Nevertheless, in most surveys the proportion of respondents is lower than 30% while for our survey it was 100%.

The strength of the study is that the panel was made of 22 internationally recognized ICU physicians originating from 13 different countries Interestingly enough, it seems that individual response is not influenced by country. Although it is difficult to generalize the findings, our results suggest some consensus regarding EOL decision worldwide.

The main findings of the study were that most participants agree that age alone should not be, and is not, a sole criterion in decisions regarding WH or WD LST in ICU patients, but that in certain circumstances, age, together with a number of other factors, may be a consideration in such decision making. Furthermore, most experts agree that in the case of normal ICU operations, without limitation of resources, the “life cycle principle” should not be a consideration, but that in the emergency triage situation, particularly when there are limitations of resources, it may be a consideration.

In the following discussion we will present published data and thoughts in order to highlight the discrepancies between some answers and the expected outcome of elderly patients admitted in ICU.

In the field of ethic, we face always the same difficulty according to cultural and religious background of respondents. For some ICU physicians, even if the odd of survival is very low, it not acceptable to limit the treatment while for others, the threshold is much higher. In any case, the financial and demographic constraints will challenge our decisions.

2. ICU organization to cope with the demand.

Using current admission policies for ICUs in the developed world, intensive care resources must either be expanded rapidly or will become quickly overwhelmed. Bagshaw et al. predicted that by 2015, the rate of ICU admission for patients older than 80 years will increase by 72%, representing roughly 1 in 4 admissions to the ICU [5]. Although there is variation in the current supply of critical care services across developed countries, these changes are likely to be seen worldwide [6-7)]. Given constrained healthcare financing and uncertainty regarding the benefits of critical care in some instances, simply increasing the quantity of critical care services will most likely not occur. Instead, a more practical approach would be to define the most accurate criteria for identification of those likely to benefit from ICU therapy regardless of age [8].

A study analyzing change in end-of-life care for medical insurance beneficiaries has documented an increase in ICU use in the last 30 days of life, with more patients receiving mechanical ventilation [9]. The use of ICU during terminal hospitalizations in England and the US has been shown to decrease with age. Of note, the percentage of ICU use during terminal hospitalization is much higher in the US

than in England and is greater for surgical patients than for medical patients [10]. Intensive care was used for 32% of medical deaths and 61% of surgical deaths in the United States versus 1.9 and 8.5% of deaths in England.

Cook et al. noted that “rationing implies that, because of cost constraints, not everyone will get every service they need, want or even deserve” [11]. At the ICU level, expensive resources in short supply are preferentially provided to individuals who have a longer life expectancy. Therefore elderly patients are particularly at risk of being denied admission to the ICU. Denying ICU admission based solely on age is highly controversial [12]. However, age-based rationing is reported for transient ischemic attack and minor stroke in patients over 80 years, with less investigation and thus less treatment [13]. The principle of allocating scarce health care resources to those “who benefit the most” is known as the distributive justice principle. Nevertheless, it is extremely difficult to make individual choices on this basis and ICU physicians are not inclined to follow this principle [14]. During an influenza pandemic situation, allocation decisions are based primarily on patients' chances of survival to hospital discharge. This approach allows selecting patients according to functional impairment and certain chronic conditions rather than simply age [15]. In the review by Sinuff et al., factors associated with both ICU bed refusal and increased mortality rate were increased age, severity of illness, and medical diagnosis [16].

3. Impact of age on decisions

Age is often cited as a reason for withholding LST. In the SUPPORT study, 85% of patients expressed specific wishes regarding do-not-resuscitate (DNR) orders; only 23% had discussed those wishes with their physician, and in half these cases, the patient did not want to be resuscitated [17]. Fifty-eight percent did not want to discuss those wishes with their physician and among these patients 25% did not want to be resuscitated [17]. In 50% of cases, DNR orders were written by the physicians or requested by the families without the patients’ consent. In a prospective study involving more than 100 ICUs and 7000 patients, the patient’s willingness to limit his or her own care was known in only 8% of the cases and only 0·5% of the patients were involved in decisions [18]. Similar results were reported in the Ethicus study including 17 European countries with information known in only 20% and patient involvement in 3% [19]. In one study, physicians underestimated the desire of older patients to receive resuscitation, even after a multivariate analyses adjusting for patient preferences and prognosis [20]. Moreover, the opinions of relatives or friends may not always reflect the patient’s wishes [21].

In a recent study, 100 elderly patients (mean age 85 years) were asked about their desire to receive specific treatment if admitted to an ICU [22]. Among them 27% refused non-invasive mechanical ventilation, 43% invasive mechanical ventilation and 63% renal replacement therapy (RRT) for patients already receiving invasive mechanical ventilation [22]. The expected quality of life was a major contributor to the patients’ choice. A panel of 4 intensivists was asked the same questions for the different case-scenarios. The results highlighted a great heterogeneity among the physicians and much more aggressive treatments suggested than what patients’ wished [23]. However, after receiving information about the patient’s choices, physicians’ decision to administer ICU treatment decreased

dramatically [23]. This emphasizes the need to communicate with the patient and his/her family whenever possible. In the ICE-CUB1 study with inclusion of 2646 patients older than 80 and visiting ED for a potential ICU admission [24], the family was present in 41 % of the cases but their opinion about ICU admission was asked in only 10% of the cases. Involvement of the patient and/or family in the decision-making process had a profound impact on ICU admission rate (BG - personal data). The patient's relatives in most countries have no legal right to be involved in decision making to limit LST. However, they should be contacted to determine the patient's wishes [25]. In Israel, the Dying Patient Law does give family members some rights for these decisions [26]. In the USA, the American College of Critical Care Medicine recommends that a family meeting should take place within 72 hours of a patient being admitted to the ICU [27]

4 Advance directives

Advance directives include living wills and durable powers of attorney. Living wills are written by competent persons providing requests for specific medical treatments to be given or not in the event that these individuals no longer have decision making capacity. They should take precedence over any other non-medical opinion expressed. However, even after change of legislation in Germany, advance directive with living and therapeutic wills were available in less than 10% of the cases [28]. In the Ethicus study, performed in 17 European countries, the primary reason given by physicians for end of life decisions was the living will in only 1% of cases [19]. A recent review on the subject stressed "that the success of advance care planning should not be defined on the basis of completed paper work alone" [29], emphasizing importance of communication and building trust over time [30]. In a prospective study involving patients aged 80 or more, it was shown that advance care planning was able to improve end of life care, patient and family satisfaction while reducing stress, anxiety and depression among surviving relatives [31].

5. Intensity of treatment

Several studies have documented a higher rate of treatment limitations in aged patients compared to younger patients. In a study including 9000 ICU patients in the US, LST limitation occurred in 2% of patients younger than 50 years and 25% in patients older than 80 years [32]. In the study by Hakim et al. [33], the rate of DNR orders increased with age (21% <54 years; 27% 55-65 years; 33% 65 -74 years ; 42% 75-84 years and 55% for patients > 84 years). DNR orders were also written earlier in elderly than in younger patients. In the SUPPORT study, the rate of decisions to withdraw treatment increased for every increase in patient's age of 10 years: 15% for mechanical ventilation, 19% for surgery and 12% for RRT [32]. In a study from Australia and New Zealand, the length of stay (LOS) of elderly non-survivors was shorter than survivors suggesting that end of life (EOL) decisions were made sooner in patients older than 80 years [5]. In a matched-cohort study, 2299 patients over 80 years were matched (severity, organ failure, type of ICU stay, gender, Charlson comorbidity index) to 2299 patients aged from 65 to 79 years [34]. The oldest patients had a lower LOS, lower workload, were less often mechanically ventilated, and had less renal support and tracheostomy than matched "young old patients" [34].

6. Prognosis of elderly patients

Table 2 reports the short-term prognosis of elderly patients [5,35-42]. To date, there has been no randomized, controlled study and available data comes from observational studies with their inherent limitations (retrospective collection of data and the lack of a control group). An ongoing cluster stratified randomized controlled trial (ICE-CUB2), funded by the French ministry of health (Clinical trials : NCT01508819) aims to determine whether a strategy consisting of recommending ICU admission to all patients over 75 years visiting the emergency department (ED) with a life threatening condition, but without cancer, and good functional and nutritional status, will decrease the 6 month mortality of these patients. More than 2200 patients have already been included. In a multicenter, observational study (including a majority of medical admissions), Boumendil et al. demonstrated that admission to ICU vs. a regular ward did not improve long term survival of patients older than 80 [47]. Martínez-Sellés et al. reported that the outcome of patients > 90 years admitted with acute myocardial infarction was not influenced by admission to a coronary care unit [48]. Recent data suggest that a greater age and a high level of severity of illness are predictive of poor outcomes. Sligl et al. reported in a multicenter British cohort study that among critically ill adult patients with pneumonia, age ≥ 80 years was an independent risk factor for death at 30 days as well at 1 year [41]. In the Eldicus study, the multivariate analysis showed that age accounted for increased mortality, controlling for underlying or acute disease, confirming previous studies showing age and not just underlying or acute diseases was associated with higher mortality [37].

Farfel et al., in a single center Brazilian cohort study of elderly patients admitted in the ICU, found that an age of ≥ 75 years was an independent risk factor for death but only for patients requiring invasive mechanical ventilation [49]. A further analysis of large cohort studies is presented in Table 3. It indicates that post-ICU mortality is much higher among patients older than 80 years of age, as compared to younger patients, raising the concern about either the appropriateness of ICU admission, or admission discharge timing and location.

The long- term outcome is particularly poor for elderly patients admitted in ICU for medical reasons or for unscheduled surgery. In a large multicenter cohort study of 120,123 admissions across 57 ICUs from Australia and New Zealand, Bagshaw et al. found that the main reason for ICU admission of elderly patients 80 years or older was planned surgery [5]. For this subgroup of patients, ICU and hospital mortality were 12 and 25%, respectively. Among survivors, 72% were discharged to home. In a Dutch single center cohort study, De Rooij found that 57% of patients who had planned surgery survived at one year, and 75% of patients living at home before ICU admission were still living at home [50]. In a small cohort, 1 year mortality was 80% in the sub-group of medical patients and 67% in the sub-group of unscheduled surgery and 25% in the group of scheduled surgery [34]. These results are in agreement with the results of De Rooij et al. reporting a 1 year mortality rate of 89% for medical and unplanned surgical admissions [50].The Danish National patient registry identified 47,596 patients [45]. Among patients older than 80, the 30-day mortality was 43.7% in medical, 39.6% in acute surgical and 11.6% in elective surgical patients. The “31-365year” mortality was 25.4% in medical,

26.9% in acute surgical and 11.9% in elective surgical patients. At 2 years after hospital discharge, Roch et al. estimated that the standardized mortality ratio was 2.56 [2.08-3.12] in comparison to the age and gender-adjusted mortality of general population [51]
In the ICE-CUB1 study with inclusion of 2646 patients older than 80 years and presenting to the ED with a condition that potentially required ICU admission, only 12% were finally admitted to the ICU. Their 6-month mortality rate was 51% and 63% for a composite score of mortality and decline of functional status [24]. The adjusted hazard ratio (HR) was 1.20 (95%CI : 1.01-1.43)[47]. Wunsch et al. showed that Medicare beneficiaries who survived intensive care (mean age 78±7 years) had higher 3 year mortality than hospital controls HR: 1.07 (95%CI : 1.04-1.10) and the general population HR: 2.39 (95%CI : 2.31-2.48) [52]. However, in the Eldicus study, the elderly seem to benefit from ICU admission with higher mortality in the non-admitted patients in particular for patients aged more than 85. The long-term outcome of elderly patients with circulatory failure is very poor with a mortality rate of 92% at 6 months and 97% at 12 months [53]. Iwashyna et al demonstrated that severe sepsis in older adults is associated with cognitive impairment and functional disability [54].

Conclusion

We do not intend to write recommendations or guidelines regarding EOL decision in elderly patients admitted in ICU but rather to highlight the diversity/homogeneity of responses and the discrepancy between responses and published data. A panel of 22 internationally recognized ICU physicians working in 13 different countries is worth considering because it provides valuable information about decision-making process for EOL decision for elderly worldwide.
Ageism can be deemed a form of discrimination, which thus should not be accepted as a valid criterion for medical decision making. The issue of treatment in ICU for elderly patients is highly controversial. The panel has reached a consensus regarding LST for these patients. The responses are decidedly “politically correct” and do not suggest that elderly patients should receive less treatment than the younger patients. The main message is that age cannot be the ONLY criteria on which healthcare decisions can be made. But nonetheless, the authors are committed to remind readers of the prognostic value that age actually carries for high intensity critical care. In this perspective, it is important to provide data showing there are outcome differences between elderly and non-elderly patients that are at least partly related to decisions to forgo LSTs.
However, decisions regarding WH or WD LSTS are not “stable” since according to “pressure”, the decision might change. This indicates that beside objective criterion, several other factors are considered by ICU physicians when deciding to limit LST for elderly: availability of beds, culture, law, patients/relatives wishes, and several others.

We need to improve the whole process of intensive therapy for elderly patients. Advance directives are currently of little help but may be very effective if advance care planning is discussed with elderly patients prior to the onset of critical illness. An active communication strategy during the ICU stay brings quicker and more frequent EOL decisions [55]. Intensivists need to identify the patients that could benefit most from ICU therapy. Several factors should be considered besides the mere

chronological age including: underlying disease, cognitive impairment, baseline functional status and quality of life. The best criteria (current gold standard?) that should be used to judge the appropriateness of the decisions to limit LST in elderly patients include hospital mortality and post discharge functional capacity and mortality. Quality of life and functional status are important considerations. Implementation of a liberal ICU admission policy in order to avoid discrimination against elderly patients (ageism) may result in an unsustainable demand for ICU therapy with limited returns in terms of non-dependent survival. Given the expense and scarcity of ICU resources, an active policy for WH and WD of LST should be advocated for patients' not responding to therapy or not willing to continue ICU treatment, with consideration of age as a prognostic factor rather than a sole criterion.

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Table 1: Ethics Round Table Answers (n=22)

	Strongly agree	Agree	Neutral	Disagree	Strongly disagree
Should the age of the patient ever make a difference in decisions regarding withholding (WH) or withdrawing (WD) life-sustaining treatments (LST) ?					
Age alone **should** be used as the sole criterion for WH or WD LST.	0	4	1	6	11
There **should** be a specific age for WH or WD LST.	0	0	1	4	17
Sometimes age **should** be an additional important consideration in conjunction with other factors when deciding on WH or WD LST.	6	14	1	0	1
The "life cycle principle" (prioritizing the young over the old since the old have already had the chance to live through life's stages) should be a consideration in WH or WD LST therapy					
in "normal ICU operations" when there is no limitation of resources ?	14	4	3	1	0
i**n an emergency triage situation** when there are limitations of resources?	11	9	2	0	0

Table 2 : Studies reporting short-term prognosis of elderly patients

1st author year	age Categories	Inclusion Criteria	N	Main results
Kass 1992 [36]	≥ 85y	All ICU patients	105	Mortality for old patients 29.5% vs. 9% for patients younger than 85 Multivariate analysis, no impact of age on mortality.
Somme 2003 [37]	≥ 75y	All ICU patients	410	No mortality difference in the different age categories : 75-79 ; 80-85 ; > 85y.
Bagshaw 2009 [5]	65-80 ≥ 80y	All ICU patients	15 640	In-ICU mortality : 9.8% In-ICU mortality : 12%
Sprung 2012 [38]	75-84 ≥85y	All ICU patients	1068 188	D28 mortality : 35.5% D28 mortality : 41.5%
Ihra 2012 [39]	≥ 80y ≥ 70y	All ICU patients	17126 21 354	In-ICU mortality 20.2% vs 11.4% for patients younger than 80 Mortality: 45% if age < 60y ; 60% if age ≥ 80y.
Ely 2002 [40]	≥ 70y	Mechanical ventilation	173	Patients older than 70 have an X2increase risk of mortality after adjustment on severity and comorbidities.
Martin 2006 [41]	≥ 65y	Septicemia	> 1 000 000	Patients older than 70 have an X2.3 increase risk of mortality after adjustment on severity and comorbidities.
Sligl 2010 [42]	≥ 80y	Pneumonia	54	Patients older than 70 have an X2.5 increase risk of mortality as compared to patients younger than 60y.

Brandberg 2013 [43]	65-79	All ICU patients	386	In Hospital mortality : 22.8%
	>80y		219	In Hospital mortality : 33.7%
Reinikainen 2007 [44]	70-74	All ICU patients	10,788	In Hospital mortality : 20.3%
	75-79		9022	In Hospital mortality : 24.1%
	≥80y		7025	In Hospital mortality : 28.4%
Nielsson 2014 [45]	65-79	Medical ICU patients	5523	D30 mortality : 27.7%
	≥80y		2332	D30 mortality : 43.7%
	65-79	Elective surgery	6690	D30 mortality : 4.6%
	≥80y		1353	D30 mortality : 11.6%
Andersen 2012 [46]	70-74	All ICU patients	3972	In Hospital mortality : 23.1%
	75-79		4360	In Hospital mortality : 28.6%
	80-84		3909	In Hospital mortality : 30.8%
	85-89		2288	In Hospital mortality : 34.4%
	>90		738	In Hospital mortality : 35.1%

Table 3: Mortality in ICU, hospital and in hospital after ICU discharge (CUB-Rea and Euricus 1 and 2 : personal data)

	Countries	n ICUs	< 80y	> 80y	p
In ICU mortality (%)					
Euricus I (1994-1996)	12 European countries	89	11	20	< 0.001
Euricus II (1997-1999)	9 European countries	39	13	20	< 0.001
Bashaw (2000-2005) * versus (65 to 80y)	Australia and New Zealand	57	9.8*	12	< 0.001
Ihra (1998-2008)	Austria	41	11.4	20.2	< 0.001
CUB-REA (2011)	Ile-de-France	32	17.5	30.7	< 0.001
Reinikainen (1998-2004)	Finland	26	8.1	12.5	< 0.001
In hospital mortality (%)					
Euricus I (1994-1996)	12 European countries	89	16	31	< 0.001
Euricus II (1997-1999)	9 European countries	39	18,9	32	< 0.001
Bashaw (2000-2005) * versus (65 to 80y)	Australia and New Zealand	57	16.6*	24	< 0.001
Ihra (1998-2008)	Austria	41	15.9	31	< 0.001
CUB-REA (2011)	Ile-de-France	32	21.8	39	< 0.001
Reinikainen (1998-2004)	Finland	26	15	28.4	< 0.001
Delta between in-hospital and in-ICU mortality (%)					
Euricus I (1994-1996)	12 European countries	89	5	11	< 0.001
Euricus II (1997-1999)	9 European countries	39	5.9	12	< 0.001
Bashaw (2000-2005) * versus (65 to 80y)	Australia and New Zealand	57	6.8*	12	< 0.001
Ihra (1998-2008)	Austria	41	4.5	10.8	< 0.001
CUB-REA (2011)	Ile-de-France	32	4.3	8.3	< 0.001
Reinikainen (1998-2004)	Finland	26	6.9	15.9	< 0.001