Rozen and Butt *Critical Care* (2016) 20:253
DOI 10.1186/s13054-016-1425-z

Critical Care

EDITORIAL Open Access

Rapid response teams: how are they best used?

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Never discourage anyone … who continually makes progress, no matter how slow. Plato

Many cardiac arrests in hospitalized patients are preceded by warning signs such as derangements in vital signs [1–3]. Despite advancements in many aspects of health care, in-hospital cardiac arrests continue to have a mortality of approximately 80 % [4]. Efforts to reduce mortality in hospitalized patients therefore include a focus on the deteriorating patient in order to provide earlier treatment and prevent further deterioration and ultimately cardiac arrest. Serious adverse events (SAEs) unrelated to the admission diagnosis and due to incorrect medical management may occur in up to 17 % of hospital admissions, and may result in prolonged length of hospital stay, permanent disability, or even death [5]. The rapid response team (RRT) is tasked with preventing or responding to SAEs. Two-tiered systems involving RRTs as distinct from cardiac arrest or "code blue" teams have been implemented in many hospital settings in most countries. These systems aim to identify and manage patients at high risk of further deterioration, altering their trajectory and improving morbidity and mortality outcomes.

The rapid response system describes the hospital-wide approach to recognizing and treating deterioration, and includes an afferent limb (trigger), an efferent limb (RRT), administration, and governance [6]. Ideally, the afferent limb and triggering mechanism would identify only those patients likely to benefit from intervention; however, no such criteria currently exist. "Crisis detection" therefore may be from chart-based predefined observation cutoff points in single or multiple vital signs, early warning scoring systems, computer algorithm-based warnings, or clinical concern. The efferent or responder limb may have various compositions including a critical care trained nurse and/or doctor, although a recent meta-analysis found that the presence of a physician in the rapid response system was not significantly associated with mortality reduction [7].

While multiple prior single-center studies have shown a reduction in rates of cardiac arrest, to date there has been only one large multicenter randomized controlled trial, the Medical Early Response Intervention and Therapy (MERIT) study, which failed to demonstrate an improvement in the Australian setting in cardiac arrest, unplanned ICU admission, or unexpected death despite greatly increased emergency team calling [8]. As a consequence of the significant resource requirements to function effectively, these systems are costly; and despite more than 27 published studies to date of mostly uncontrolled trials of implementation, it remains controversial whether rapid response systems are effective at preventing unexpected deaths [9]. Nevertheless, many affluent nations have begun to introduce these systems.

The Cost and Outcomes of Medical Emergency Teams (COMET) study [10] evaluated the nationwide implementation of a rapid response system in the Netherlands in 2015. This was a pragmatic before-and-after implementation study involving 12 Dutch hospitals, more than 160,000 patients, and more than a million inpatient days, with a significant improvement in the primary composite endpoint of cardiopulmonary arrests, unplanned ICU admissions, and all-cause mortality in patients in general hospital wards.

In the June issue of *Critical Care*, Brunsveld-Reinders et al. [11] present the findings of their post-hoc analysis of the COMET study [10]. Here they have substituted death without limitation of medical treatment (LOMT) or "unexpected death" for all-cause mortality, and studied the proportion of patients dying with a LOMT order and the timing and prevalence of LOMT with the introduction of a RRT.

Brunsveld-Reinders et al. report that the unadjusted OR for death without LOMT ("unexpected death") was 0.557 (95 % CI, 0.40–0.78) while the originally reported unadjusted OR for all-cause mortality was 0.865 (95 % CI, 0.77–0.97). Furthermore, in 13 % of patients who died and for whom a RRT was called, a LOMT was

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instituted or changed after consultation of the RRT. In this study, 65 % of patients who died had a LOMT placed at admission while 85 % of patients who died had some form of LOMT present at the time of death. Therefore only 15 % died without a LMOT order. There were no statistically significant differences in the overall rates of LOMT orders after introduction of the rapid response system, and both before and after RRT implementation the last change to LMOT was in the final few days of the hospital stay.

There are substantial differences internationally in withholding or withdrawing life support [12]. Cultural differences in practices relating to limiting medical treatment will affect interpretation of cardiac arrest data and overall death rates, because the actions of medical staff will differ. Hence, it is unclear whether these findings would be reproducible in other countries with different practices relating to LOMT. In an analysis of 14,488 patients from 282 ICUs in seven different geographical regions, deaths occurred after a decision to limit treatment at varying rates depending on the region [13]. These ranged from 26 % of ICU patients in Central and South America compared with 48 % in central and Western Europe, and there was an even wider variation for individual countries. Similarly, in the End-of-Life Practices in European Intensive Care Units (ETHICUS) study which assessed ICU end-of-life care in European countries, the northern European group (Denmark, Finland, Ireland, the Netherlands, Sweden, and the UK) had more limitations, less CPR use, and less time until a limitation of treatment was determined [14]. Withdrawal of life-sustaining treatments was also more common (47 % vs 18 %, $p < 0.001$) than in southern Europe (Greece, Israel, Italy, Portugal, Spain, and Turkey).

While initially intended to prevent cardiac arrests, unexpected deaths, and unplanned admissions to the ICU, emerging evidence suggests that RRTs are also used to review patients who do not have reversible deterioration and are at the end of life [15]. Brunsveld-Reinders et al. [11] highlight the impact of RRT in patients where LOMT has and has not been implemented. Clearly there is an ongoing need for the intensive care community to advocate for early discussion about appropriate limitations of therapies and compassionate end of life care prior to the point of deterioration, while simultaneously working to achieve better methods of identifying those patients most likely to benefit from ICU interventions.

Authors' contributions
Both authors contributed to the writing of this manuscript. Both authors read and approved the final manuscript.

Competing interests
The authors declare that they have no competing interests.

Consent for publication
Both authors gave final approval for manuscript publication.

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Outcomes Associated With the Nationwide Introduction of Rapid Response Systems in The Netherlands*

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Dr. Ludikhuize and Mr. Brunsveld-Reinders are primary authors and share responsibility for the logistical process together with data entry, validation, and analysis. Dr. Ludikhuize and Ms. Brunsveld-Reinders had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Drs. Ludikhuize, Dijkgraaf, and de Jonge performed the principal design of the study. Dr. Dijkgraaf performed the data analysis. Dr. Ludikhuize and Ms. Brunsveld-Reinders wrote the article under the supervision of Drs. Dijkgraaf and de Jonge. All coauthors read and acknowledge the content of this article.

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Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (http://journals.lww.com/ccmjournal).

The authors have disclosed that they do not have any potential conflicts of interest.

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DOI: 10.1097/CCM.0000000000001272

Objective: To describe the effect of implementation of a rapid response system on the composite endpoint of cardiopulmonary arrest, unplanned ICU admission, or death.

Design: Pragmatic prospective Dutch multicenter before-after trial, Cost and Outcomes analysis of Medical Emergency Teams trial.

Setting: Twelve hospitals participated, each including two surgical and two nonsurgical wards between April 2009 and November 2011. The Modified Early Warning Score and Situation-Background-Assessment-Recommendation instruments were implemented over 7 months. The rapid response team was then implemented during the following 17 months. The effects of implementing the rapid response team were measured in the last 5 months of this period.

Patients: All patients 18 years old and older admitted to the study wards were included.

Measurements and Main Results: In total, 166,569 patients were included in the study representing 1,031,172 hospital admission days. No differences were observed in patient demographics between periods. The composite endpoint of cardiopulmonary arrest, unplanned ICU admission, or death per 1,000 admissions was significantly reduced in the rapid response team versus the before phase (adjusted odds ratio, 0.847; 95% CI, 0.725–0.989; $p = 0.036$). Cardiopulmonary arrests and in-hospital mortality were also significantly reduced (odds ratio, 0.607; 95% CI, 0.393–0.937; $p = 0.018$ and odds ratio, 0.802; 95% CI, 0.644–1.0; $p = 0.05$, respectively). Unplanned ICU admissions showed a declining trend (odds ratio, 0.878; 95% CI, 0.755–1.021; $p = 0.092$), whereas severity of illness at the moment of ICU admission was not different between periods.

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Conclusions: In this study, introduction of nationwide implementation of rapid response systems was associated with a decrease in the composite endpoint of cardiopulmonary arrests, unplanned ICU admissions, and mortality in patients in general hospital wards. These findings support the implementation of rapid response systems in hospitals to reduce severe adverse events. (*Crit Care Med* 2015; 43:2544–2551)

Key Words: adult; deteriorating patients; Modified Early Warning System; multicenter trial; rapid response system; rapid response team

Patients who experience adverse events during their hospital stay, including cardiopulmonary arrest, unplanned ICU admissions, and unexpected death, show clear signs of deterioration in the hours preceding the event (1, 2). Rapid response systems (RRSs) have been developed for timely identification and treatment of patients in general wards at risk for clinical deterioration (3). RRSs are designed as a three-component system (4). The two primary components are the afferent and efferent limbs. The afferent limb comprises the early detection of the deteriorating condition by systematic measurement of vital signs using a track and trigger system (5–7). When measures reach a certain threshold, the efferent limb is activated and the medical emergency team or rapid response team (RRT) is called and responds to the patient's bedside. These teams are most often composed of ICU physicians together with ICU nurses (8). The final component is the education, data collection, and analysis limb to aid in (sustained) implementation within the institution.

Up to this moment, only two randomized studies have been performed investigating the effectiveness of RRSs. A large randomized trial from Australia, the Medical Early Response Intervention and Therapy (MERIT) study, failed to show an impact of introduction of an RRT on a composite endpoint including death, cardiac arrest, and ICU admission (9). The second study from the United Kingdom demonstrated a reduction in hospital mortality after introduction of an RRT (10). Apart from these studies, many smaller less well-controlled studies have been published generally reporting a decline in cardiac arrest rates following introduction of an RRT (11).

In 2008, implementation of RRS was mandated by the Dutch government (12). We took the opportunity to study the effects of this nationwide implementation of RRS on outcome of patients admitted to general hospital wards. Primary endpoint was the prevalence of the composite endpoint of cardiopulmonary arrest, unplanned ICU admission, or death.

METHODS

Trial Design

The study protocol has been described previously (13). In short, the Cost and Outcomes analysis of Medical Emergency Teams (COMET) multicenter study was designed as a prospective, pragmatic before-after multicenter trial enabling the analysis of clinical outcomes after sequential introduction of the RRS components. Twelve of the originally planned 14 Dutch hospitals participated throughout the study. Two hospitals were withdrawn during the study after major local reorganizations with changes in case-mix from surgical to medical patients on COMET wards. The withdrawal of study centers was performed without the knowledge of prevalence of study endpoints. Therefore, these two hospitals were excluded from final analysis.

Two large university hospitals (number of beds, 882–1,000), eight large teaching hospitals (number of beds, 359–1,070), and two smaller regional hospitals (number of beds, 290–325) completed the study. Each hospital included four study wards and two surgical and two medical wards. All patients were 18 years or above.

Patients who were readmitted to the hospital were not excluded from the analysis. These patients were considered to be a new hospital admission.

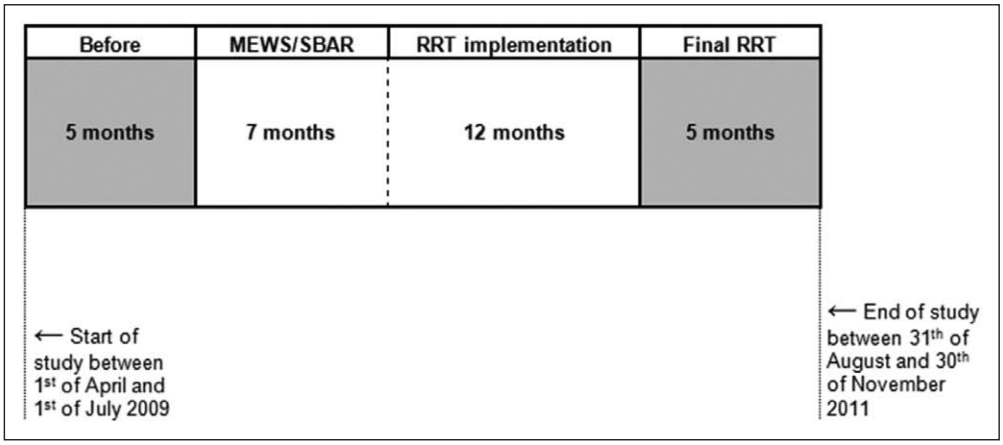

Figure 1. Design of the Cost and Outcomes analysis of Medical Emergency Teams study. Following the baseline period of 5 months, the Modified Early Warning Score (MEWS)/Situation-Background-Assessment-Recommendation (SBAR) was implemented for 7 months and subsequently followed up by 17 months in which the rapid response team (RRT) was available. Effects of the RRT on outcomes were measured during the last 5 months and compared with the 5-month baseline period. During the entire length of the study, data were collected on all the endpoints. For further clarification, hospitals were able to start with the study in a 3-month time period. The total study took 30 months, in which each hospital participated for 27 months.

The trial design was determined a priori and is shown in **Figure 1**. The before period consisted of 5 months in which baseline data were prospectively collected. The implementation of RRS was divided into two phases. Within the first phase (7 months), the MEWS (Modified Early Warning Score) and the SBAR communication tool (Situation-Background-Assessment-Response instrument) were implemented (**supplementary materials**, Supplemental Digital Content 1, http://links.lww.com/CCM/B415). In the second phase, lasting a total of 17 months, the

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RRT was introduced. The last 5 months of this phase were used to measure the effects on outcome of patients compared to the before period and will be referred to as "final RRT period." These 5 months comprise the same months of year as the before period.

Outcomes

The primary outcome is the composite endpoint of cardiopulmonary arrest, unplanned ICU admission, or death while being admitted on a COMET ward per 1,000 admitted patients. Intensive care admission did not include medium care or other high dependency units. Intensive care was defined according to the criteria from the Dutch National Intensive Care Evaluation (NICE) registry (14). The composite endpoint was chosen in accordance with previous studies (9) because of the low number of patients anticipated to reach the individual components of this endpoint.

Secondary endpoints were the individual components of the composite endpoint and the outcomes per 1,000 admissions days. Cardiopulmonary arrest was defined as an event for which the cardiopulmonary arrest team started cardiopulmonary resuscitation (CPR), using chemical resuscitation and/or manual chest compressions and/or respiratory ventilation (irrespective of type). Unplanned ICU admissions were registered according to the definitions of the Dutch NICE registry as admissions that were unscheduled and could not be delayed for at least 12 hours without risk. All hospitals had followed training in data collection and data definitions as used in the NICE registry (14).

Details of the Interventions

Within each participating hospital, all physicians and nurses working on a COMET ward were trained using standardized toolkits, including pocket cards and posters, provided by the primary investigators. Specifically, during the MEWS phase, participants were trained in using the MEWS (15) and SBAR communication tool (16). Determination of the MEWS was mandatory whenever at least one of the measured vital signs was outside its normal range or when considered necessary by the treating physician or nurse. Upon reaching the threshold of three or more points of the MEWS, the responsible physician on that ward was directly notified with communication structured using the SBAR tool. Deviation from the MEWS threshold was allowed in specific circumstances based on patient characteristics for instance in a patient with chronic hypoxemia, but should be clearly mentioned by the physician within the patient chart.

The RRT included both an ICU nurse and a physician who was at least trained in Fundamental Critical Care Support (http://www.fccs.nl). Description of activation of RRTs is presented in **Figure 2**.

During the study, no structural changes in data collection charts, medical record keeping, or treatment guidelines were introduced.

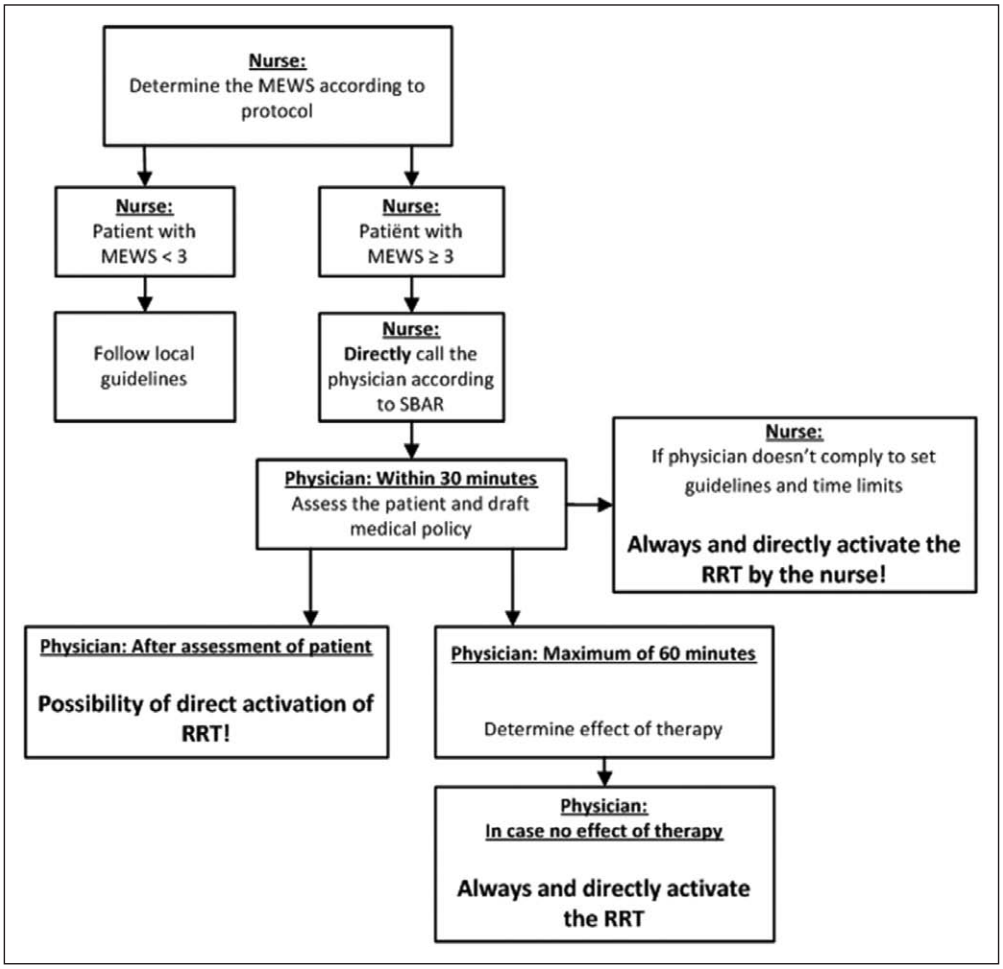

Figure 2. Algorithm for activation of rapid response team (RRT). The algorithm displays the protocol of handling positive Modified Early Warning Score (MEWS) values and all subsequent actions which either nurse or physician had to undertake together with set time limits. During the MEWS/Situation-Background-Assessment-Recommendation (SBAR) phase, the RRT was not available, and after notification of the physician by the nurse, no specified actions were protocolized. An action could include consultations to other specialties or the ICU in general, and no time frames were specified as well. For full description of the protocol, see Ludikhuize et al (13).

Sample Size

The calculation of the sample size has been described in detail previously (13). About twice the originally planned number of 27,720 admissions, equally divided over the before and RRT periods, was available for analysis. The actual analysis to detect if the RRT period would show a lower prevalence of patients experiencing the composite endpoint or its components by at least 4 (from 10 to 6) per 1,000 admissions was based on 54,479 admissions, 26,659 stemming from

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the before period and 27,820 from the final RRT period. Considering increased numbers of admissions available for analysis, the level of significance was set at a two-sided rather than the originally planned one-sided α of 0.05.

Data Acquisition

Admission data of patients who had spent time on a COMET ward at any time during the study observation period were provided by the information departments of participating hospitals. Data on cardiopulmonary arrest, unplanned ICU admission, death, and RRT activations on COMET wards were collected with clinical report forms.

Data Presentation and Statistical Analysis

Prevalences of cardiopulmonary arrest, unplanned ICU admission, and death, both as composite endpoint and each separately, are presented graphically over time for the before, MEWS, RRT implementation, and final RRT periods, respectively. Prevalences were calculated per 1,000 admissions. Admissions were counted when a patient had spent at least 1 day of his admission in a COMET ward. Inpatient days were counted when a patient had spent some part of the day in a COMET ward.

Generalized linear mixed modeling (GLMM) was applied to assess differences in outcomes per 1,000 admissions between the before and final RRT periods while correcting for potential confounding following the before-after study design.

Potential confounders were identified following 1) cross-tabulation of categorical variables (sex, emergency admission, hospital) with the before and final RRT periods or *t* testing for the difference in patients' age between the before and final RRT periods and 2) simple univariable logistic regression analyses on the composite outcome with the same variables (sex, emergency admission, hospital, age). Seasonality—reflecting differences in risk of cardiopulmonary arrests, unplanned ICU admission, or death by calendar month (17, 18)—could be ignored because in each hospital the included months of the year were identical for the before and final RRT periods.

In the GLMM, a binomial distribution was assumed for the composite primary endpoint and for deaths. For unplanned ICU admissions, a binomial distribution was assumed after recoding the original count variable into a dichotomous one, expressing whether patients were at least once admitted to the ICU or not during their stay (no convincing model fit could be achieved under the assumption of Poisson-distributed original ICU admission counts). For cardiopulmonary arrests, a Poisson distribution was assumed because of its observed (extremely) low prevalence. No offset variable was taken into account. Potential confounders were included in GLMM as fixed or random variables. Hospitals were modeled as a random variable, accounting for differences in background prevalence (level) and varying impact of the intervention (slope) while simultaneously controlling for the differentially distributed numbers of admissions by hospital during the before and final RRT periods. Age of patients was modeled as a random component, whereas patients' sex and admission type (planned vs unplanned/emergency) were modeled as fixed variables. All analyses were performed in SPSS version 20.0.0.1 (SPSS Inc, Chicago, IL).

The uncorrected odds ratios (ORs) and ORs after correction for confounding are reported along with their CIs and corresponding *p* values. In deviation from the published study protocol (13), the decision was made to simplify the analyses. We first nested admissions within hospitals rather than within the ward types as clusters because during the introduction, implementation, and maintenance of the RRSs at the local level, hospitals seemed more distinct than ward types. Second, it was decided to compare the before and final RRT periods as whole periods and to refrain from the analysis of data by successive months, because the latter approach introduced complex dependencies over time, in case admissions included two or more months.

Ethics Approval

The medical ethics committee of the Academic Medical Center in Amsterdam waived the need for formal evaluation of the study due to the obligatory nature of the intervention and the observational nature of the study. Consequently, the need for informed consent was not applicable. The trial was registered at the Dutch Trial Register (http://www.trialregister.nl) under number NTR2706. All authors hereby declare that all experiments have been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki, updated October 2008.

Funding for the primary investigators of the study was provided by the Academic Medical Center and Leiden University Medical Center. Each participating hospital provided staff for training of their personnel and acquisition of study data.

RESULTS

Characteristics of the study population from the 12 hospitals are presented in **Table 1**. Patients could be transferred during their hospital admission between non-COMET wards and COMET wards and vice versa. Therefore, the ratio of COMET admission days to the total length of hospital admissions was calculated, ranging from 0.97 to 0.98 in the different study periods.

Figure 3 shows the primary outcome, that is, the number of patients per 1,000 admissions with a cardiopulmonary arrest, unplanned admission to the ICU, or death while being admitted to a COMET ward. The number of patients who reached the primary outcome decreased from 37.14 (95% CI, 34.94–39.34) per 1,000 admissions in the before period to 32.92 (95% CI, 30.88–34.95) in the final RRT period (Fig. 3). The unadjusted OR of reaching the primary endpoint was 0.88 for the last 5 months of the RRT phase relative to the before phase. The number of patients reaching the primary endpoint in the MEWS and the RRT implementation period (Fig. 3) were 39.14 (95% CI, 37.24–41.03) and 37.28 (95% CI, 35.86–38.70), respectively. Per 1,000 COMET inpatient days, the composite endpoint was reached 5.90, 6.13, 5.98, and 5.77 times in the before, MEWS, RRT implementation phase, and final RRT periods, respectively.

The results for the individual components of the primary outcome presented per 1,000 admissions are given in **Table 2**. The number of cardiopulmonary arrests remained stable in

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TABLE 1. Characteristics of Study Population

	Before	Modified Early Warning Score	RRT Implementation	Final RRT
No. of months	5	7	12	5
No. of hospitals	12	12	12	12
No. of hospital admissions	28,298	40,499	68,212	29,560
Percentage emergency	47.2[a]	47.1[b]	47.4	49.7
Mean overall length of stay	6.42	6.57	6.34	5.81
COMET part of admissions	0.981	0.972	0.984	0.983
No. of COMET admission days	178,156	258,710	425,558	168,748
Male patients	49.2	50.1	49.9	50.1
Mean age of patients (SD)	62.2 (18)	62.3 (18)	62.4 (18)	62.3 (18)

RRT = rapid response team, COMET = Cost and Outcomes analysis of Medical Emergency Teams.
[a]Based on 26,659 admissions, excluding one hospital without provided information on emergency.
[b]Based on 37,883 admissions, excluding one hospital without provided information on emergency.

the before and MEWS periods and gradually declined in the RRT implementation and final RRT periods. The number of unplanned ICU admissions was similar in the before, MEWS, and RRT implementation periods, but dropped in the final RRT period. Mortality increased from the before to the MEWS period and fell back again to the baseline level in the RRT implementation period, before it further decreased in the final RRT period.

Interestingly, the composite endpoint was almost entirely composed of unplanned ICU admissions and deaths; cardiopulmonary arrest was a less frequent event. Per 1,000 COMET inpatient days, the point estimates for the before, MEWS, RRT implementation, and final RRT periods are 0.31, 0.30, 0.25, and 0.21 for cardiopulmonary arrests, 3.15, 3.06, 3.12, and 2.99 for unplanned ICU admissions, and 3.23, 3.52, 3.29, and 3.09 for deaths, respectively.

Table 3 shows the ORs for the primary and secondary endpoints. The unadjusted ORs of having a cardiopulmonary arrest in the final RRT period relative to the before period was 0.626 (95% CI, 0.41–0.95), of being admitted unexpectedly at least once to the ICU 0.881 (95% CI, 0.77–0.99), and of dying 0.865 (95% CI, 0.76–0.97). Adjustment for case-mix variables was performed for potential confounders, gender, age, individual hospital, and urgency of admissions, while simultaneously accounting for clustering of admissions within hospitals. Preparatory analyses revealed associations of these variables with the composite endpoint, whereas sex, hospital, and emergence level were also differentially distributed over the before and after periods (data not shown). The benefits of the RRT turned out slightly better after correcting for confounding variables while taking into account clustering of admissions within hospitals.

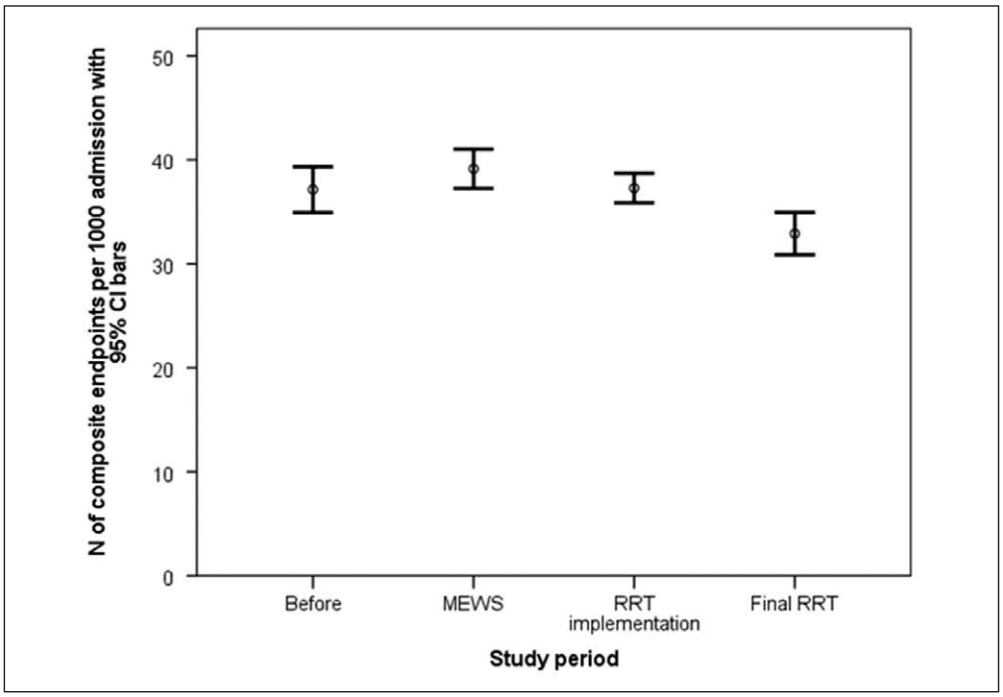

Figure 3. Composite endpoint per 1,000 admissions. The primary endpoint, that is, the number of patients per 1,000 admissions with a cardiopulmonary arrest, unplanned admission to the ICU, or death while being admitted to a Cost and Outcomes analysis of Medical Emergency Teams ward, is shown. The prevalence of the composite endpoint is shown including its 95% CI. MEWS = Modified Early Warning Score, RRT = rapid response team.

Supplementary Table 1 (Supplemental Digital Content 2, http://links.lww.com/CCM/B416) shows the characteristics of patients reaching the individual components of the primary

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TABLE 2. Secondary Outcomes per 1,000 Admissions

	Before	Modified Early Warning Score	RRT Implementation	Final RRT
Cardiopulmonary arrest, *n*/1,000 (95% CI)	1.94 (1.43–2.46)	1.93 (1.50–2.35)	1.54 (1.25–1.83)	1.22 (0.82–1.61)
ICU admission,[a] *n*/1,000 (95% CI)	19.8 (18.1–21.6)	19.6 (18.1–21.0)	19.5 (18.3–20.6)	17.1 (15.5–18.6)
Death, *n*/1,000 (95% CI)	20.4 (18.7–22.0)	22.5 (21.0–23.9)	20.5 (19.5–21.6)	17.7 (16.2–19.2)

RRT = rapid response team.
[a]Including multiple unplanned ICU admissions per patient.

TABLE 3. Odds Ratios of Composite Endpoint and Its Individual Components for the Rapid Response Team Final Period Versus the Before Period, Corrected for Sex, Age, Hospital, and Emergency of Admission

	Uncorrected OR	95% CI of Uncorrected OR	Corrected OR	95% CI of Corrected OR	*p* Corrected OR
Composite endpoint	0.882	0.807–0.964	0.847	0.725–0.989	0.036
Cardiopulmonary arrest, *n*/1,000 (95% CI)	0.626	0.411–0.953	0.607	0.393–0.937	0.018[a]
ICU admission,[b] *n*/1,000 (95% CI)	0.881	0.777–0.999	0.878	0.755–1.021	0.092
Death, *n*/1,000 (95% CI)	0.865	0.768–0.975	0.802	0.644–1.0	0.05

OR = odds ratio.
[a]A generalized linear model (GLM) based on Poisson-distributed cardiopulmonary arrest with identity link converged during its iteration and showed a *p* value of 0.018; the corrected odds ratio reported stems from a nonconverging Poisson-based GLM model with a log link which is slightly more conservative ($p = 0.024$).
[b]Odds ratio presented for being unexpectedly admitted at least once to the ICU.
Number of admissions in before period = 26,659; number of admissions in rapid response team period = 27,820.

endpoint for all study phases. Statistical comparisons were restricted to the before and RRT periods of the study only. During the before period, more patients were transferred to the coronary care unit and less patients to other hospitals or other destinations after a cardiopulmonary arrest ($p = 0.013$) when compared with the RRT period. Patients who died were younger in the RRT phase (75.0; SD, 14) compared with the before phase (76.8; SD, 12) ($p = 0.021$).

Only in the RRT implementation and final RRT phases, the RRT was available for the care providers. The call rate in the RRT implementation phase was 6.8/1,000 admitted patients and increased to 7.3/1,000 (**Supplementary Table 2**, Supplemental Digital Content 3, http://links.lww.com/CCM/B417). In this study, the RRT was primarily called by the responsible physician. However, in the RRT implementation phase, 15% of the RRT calls were initiated by a nurse, which decreased to 9% in the RRT phase with a seemingly corresponding increase of activations by the resident. Rarely, do not attempt resuscitation (DNAR) orders were instituted after an RRT was called.

DISCUSSION

The COMET study is the largest trial, which has been performed investigating the effectiveness of RRSs (9). Eventually, 12 Dutch hospitals participated in this trial in which an approximately 15% adjusted risk reduction in severe adverse events, including cardiac arrests, unplanned ICU admissions, and in-hospital mortality, was found.

Regarding the individual components of the primary endpoint, full implementation of the RRS resulted in lower rates of death and cardiac arrest and only a trend for unplanned ICU admissions. It has been argued that effective RRS may lower the rate of ICU admission by earlier detection and treatment of deteriorating patients but may also increase ICU admission if deteriorating patients are transferred to the ICU for treatment. Therefore, ICU admission rates may underestimate the beneficial effect of RRSs.

As recently reviewed, 42 studies have been published describing the effectiveness of RRSs (19). Many of these studies were relatively small and underpowered to find effects on clinically relevant endpoints. Methodological quality was suboptimal in most studies (19). In some studies, a reduction in the prevalence of cardiac arrests was reported (20–23). However, interpretation of this reduction is difficult as no adjustment was made for DNAR policies. It cannot be ruled out that institution of RRTs leads to an increase of DNAR orders and consequently to less registered CPR attempts (24, 25).

Two large, randomized, well-designed studies have been published on the effects of RRSs on outcome of in-hospital patients. The first study by Priestley et al (10) used a stepped wedge design and was performed in United Kingdom and included 7,450 patients. Introduction of an RRT lowered in-hospital

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mortality, with an OR of 0.52. By contrast, the MERIT trial randomizing 23 Australian hospitals to introduce RRS or to continue usual care did not show an improvement on a composite endpoint consisting of unexpected death, unplanned ICU admission, or cardiac arrest after introduction of an RRS (9). Several possible explanations for these negative results have been suggested, including contamination of the control group and lack of power in this cluster randomized design. Maybe more importantly, the time taken for implementation of RRSs may have been too short for optimal functioning (26–30).

Interestingly, a marked difference was present in the proportion of patients reaching the endpoints. In the Australian MERIT study, at baseline, almost 5 per 1,000 admitted patients were transferred unplanned to the ICU, whereas in the COMET study, 20 per 1,000 were admitted to the ICU. Most likely explanation for this difference is the fact that in the COMET study only patients that were admitted to four selected surgical and medical wards per hospital were included, whereas all hospital patients were included in the MERIT trial. Alternatively, we cannot exclude that differences in ICU admission policies or availability of ICU beds may account for the different ICU admission rates. Death rates were also considerably lower in the MERIT study, but this can be explained by the fact that only unexpected deaths were included in the MERIT study in contrast to all deaths in the present study. It may well be that the effects of RRSs depend on the severity of illness and other characteristics of the population it is introduced to.

In 2007, the Dutch government demanded that RRSs should be instituted in all hospitals in the Netherlands. Due to this mandatory nature of RRS in the Netherlands, any form of a randomized trial, including a stepped wedge design, was not feasible. Therefore, the COMET study was designed with a prospective before-after methodology, with the inherent risk that associations between intervention and outcome may not be causal (31). For instance, severity of illness may have changed over time, potentially influencing the rates of mortality, cardiac arrest, or ICU admission. Although baseline characteristics were very similar in the different study periods, we cannot fully rule out this possibility. Also, simultaneous interventions—which may include the SURgical Patient Safety System checklist in surgical patients (32)—or general background trends during the study could also influence our findings. Consequently, caution should be taken in this respect when interpreting the study results.

In our study, a slightly increased death rate was shown in the phase in which the MEWS data were collected but without institution of an RRT. No clear explanation can be given for this finding. It could be related to seasonal effects. In this respect, it should be emphasized that the primary comparison between baseline and full implementation of the RRS is not influenced by seasonal factors because both periods comprised the same months of year in all participating hospitals. Several arguments do support a causal interpretation of the association between the RRS and the studied severe adverse events. First, the working mechanism of RRSs makes a positive impact on prevalences of severe adverse events plausible, and proactive monitoring of patients is very likely to be beneficial (33). Second, we improved the internal validity of our before-after design by adjusting for potential confounders, including gender, age, individual hospital, and urgency of admissions. The strength of the association of the RRS with the composite endpoint increased with ORs being 0.85 (95% CI, 0.72–0.99) and 0.88 (95% CI, 0.77–0.99) with and without adjustment for confounders, respectively. Third, during the study and also in 11 of the 12 hospitals (data not shown), the effect of sequential introduction of the RRS resulted in a consistent and gradual decline of the proportion of patients reaching the endpoints over time.

Interestingly, our study was the first to perform the analysis of sequential introduction of the components of an RRS. Our data may suggest that instituting only the afferent limb of the RRS, which is the MEWS/SBAR, may not be as effective in decreasing the number of cardiac arrests, unplanned ICU admissions, or deaths. This suggestion should only be interpreted as hypothesis formulation also because these findings were not corrected for seasonal influences. It is very likely that increased utilization of the system and its components is likely to result in improved clinical outcome during the entire study period (34).

The results of the COMET study support the continuing efforts regarding implementation of RRS and optimization of current systems. A more mandatory nature of implementation and measurement of outcomes would assist in the continual optimization and research into RRS.

Based on the results of this study, introduction of an RRS with the MEWS and SBAR for early identification and an RRT for early management of patients at risk for deterioration was associated with a decrease in the prevalence of severe adverse events, including death, unplanned ICU admission, and cardiac arrest. As part of the COMET study, a budget impact analysis will be performed in further analyses.

ACKNOWLEDGMENTS

The Radboud university medical center (Bernard Fikkers, MD) is a satellite center for the Acute Life-Threatening Events Recognition and Treatment course within The Netherlands.

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