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Endograft Treatment in Ruptured Abdominal Aortic Aneurysms Using the Talent® AUI Stentgraft System. Design of a Feasibility Study

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Objectives. *To study the outcome of patients with ruptured AAA treated by EVAR using the Talent® AUI stentgraft system.*
Design. *A multicenter prospective consecutive patient cohort of 100 patients.*
Materials. *Consecutive patients with ruptured AAA will be screened for treatment by EVAR. All patients screened, including those excluded from EVAR, will be clustered and called the study group. The study group will be compared with a historical group of patients with ruptured AAA derived from literature. The New ERA study started February 2003.*
Outcome. *Main outcome events are applicability rate and operative mortality rate of the study group.*
Conclusion. *The study rationale and design are reported here.*

Key Words: Abdominal aortic aneurysm; Rupture; EVAR; Protocol.

Background of the Study

Abdominal aortic aneurysms (AAA) larger than 5.5 cm have a significant risk of rupture, which dramatically increases with aneurysms with diameter over 6.5 cm.[1,2] Open surgical repair has typically been associated with an inhospital mortality rate of approximately 50% (40–70%).[3–5] Only a slight improvement in the outcome of ruptured (r) AAA over time was documented in a recent meta-analysis (3.5% reduction per decade), and the mortality rate as achieved in 2000 was estimated at 41%.[6] A number of non-randomised studies suggest that for elective AAA treatment, endovascular aneurysm repair (EVAR) is associated with a lower (major) morbidity and stress response than open surgery.[7–11] The reduction in major morbidity may give an improvement in outcome in patients with ruptured aneurysms given the far higher mortality in rAAA treated with conventional open surgery.

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Previous Publications

Emergency (e) EVAR has been assessed in a limited number of studies.[12–17] The mean number of patients treated by eEVAR for a documented ruptured infrarenal AAA in these reports was 15 with a range of 4–21 patients. The mean first month mortality rate in these series was 17% (range 0–45%). However, it was disconcerting that only two reports indicated that their series consisted of consecutively enrolled patients, rendering the outcomes in the other reports strongly influenced by selective patient recruitment. Patients selected for eEVAR likely constitute a lower risk category, as they would need to be stable for preoperative imaging and have a suitable anatomical configuration. Thus the good outcomes in these studies may simply reflect selection bias.

An additional point of concern was the applicability rate of eEVAR. In studies that did indicate the proportion of patients with rAAA that received eEVAR, this rate varied from 27% to 78%.[12–14,16,17] While the concept of eEVAR will lose much of its appeal if it can only be applied to the minority of patients, one must take into account that the criteria of eligibility were based on those customarily used in

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elective EVAR. However, it may be appropriate to consider less stringent anatomical criteria in patients with rAAA, in particular larger infrarenal neck diameters. Elective repair of AAAs with large neck diameters has not been associated with an increased incidence of proximal endoleak.[18] Rigid application of industry imposed criteria and overly cautious application, well justified in elective AAA-repair, seems counterproductive in emergency treatment of rAAA.

Rationale for Study Design

The New ERA study was conceived to allow an assessment of the feasibility of eEVAR. All patients presenting with rAAA within a study period and not only the subset treatable by EVAR will be included. In addition, this consecutive series with preferential eEVAR (the study group) will be compared with a comparable historical cohort that was treated by conventional open surgery.

A randomised comparative trial (RCT) to assess the value of eEVAR for rAAA would be ideal. However, in our opinion a RCT conducted at the present time, would be biased against the endo-technique. These biases include: the influence of a learning curve, an insufficiently developed infrastructure for rapid pre-operative imaging and a quick execution of an emergency endovascular procedure in hospitals, traditionally familiarity with urgent open aneurysm repair and insufficient number of endovascular specialists available for on-call rostas. A non-randomised cohort study with preferential eEVAR allows the opportunity for a comparison of the primary outcome events with the outcome of up to date meta-analysis and to resolve any organisational issues within the study centers.

Organisation of the Study

The New ERA study is a prospective, multicenter, feasibility European and Canadian study that is sponsored by Medtronic® and supported by the Medtronic® Bakken Research Centre. The objective is to evaluate applicability, clinical performance, safety and effectiveness of stentgraft placement in rAAA using the Talent® AUI stentgraft system. Vascular surgeons and interventional radiologists with considerable experience in the diagnosis and treatment of rAAA have been included as investigators in this study (list of participating investigators is reported in Appendix A). Patient data and procedural details are recorded in structured Case Report Forms (CRFs), periodically monitored by the organising company. Adverse events are reported to and evaluated by an Adverse Event Advisory Committee. Some of the members in this committee represent the Medtronic® company (AEAC, members of AEAC are reported in Appendix B). Study conduct is supervised by the Steering Committee (Appendix C) consisting of representatives of Medtronic® and clinical professionals.

An adverse event (AE) is any undesirable clinical occurrence in a patient whether or not related to the device. Any change in nature, severity, or degree of a pre-existing condition is also recorded as an AE. An SAE is recorded if the patient's hospitalization is prolonged or the patient requires re-admission, another intervention or dies. Twelve centers will participate in this study. The evaluation of the study objectives requires 100 patients, each with a follow-up of 3-months. The study has started in February 2003.

A consecutive series of patients treated for ruptured infrarenal abdominal aortic aneurysms (rAAA) is included in the study, in each of the participating institutions. The preferential treatment will be EVAR, open surgery is only selected as treatment when anatomic criteria preclude effective exclusion of the aneurysm, or if the patient is in profound hypovolemic shock that does not allow pre-operative CT scanning or the use of intravascular ultrasound to evaluate EVAR feasibility. Included in the study are patients treated by stentgraft technique or, in the case of adverse anatomy for endoluminal stentgrafting, by open surgery. Patients who are suitable for EVAR will be treated with the aorto-uni-iliac (AUI) Talent® stentgraft system (Fig. 1).

The Talent® stentgraft configuration consists of a 2-piece AUI with interchangeable proximal and distal components, for 'off-the-shelf' customisation with variable diameters and lengths. The 2-piece AUI configuration potentially reduces the complexity of the procedure compared to a bifurcated design, contributing to quicker aneurysm exclusion.

Purpose and Objectives

The purposes of the New ERA study are:

1. to assess the proportion of patients, presenting with rAAA in whom EVAR is applicable,
2. to determine operative mortality and morbidity in a cohort of patients treated with EVAR, when possible.

Study endpoints include: operative mortality, defined as death within the first 30 days or during

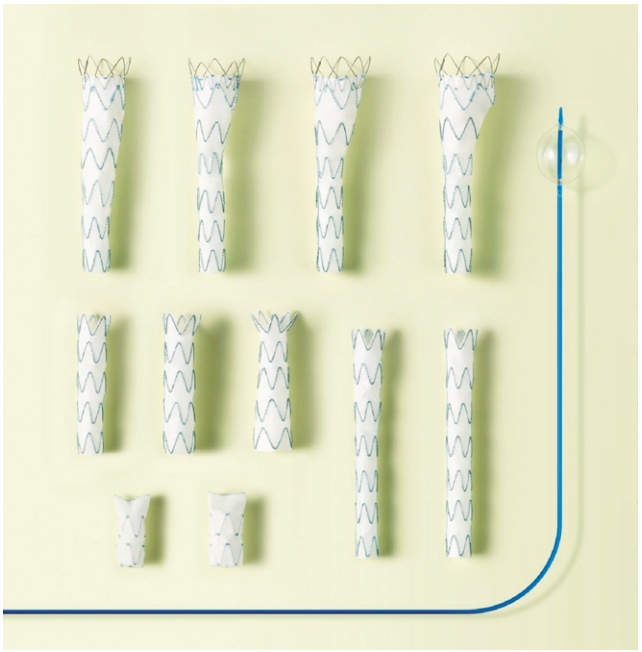

Fig. 1. The components of the Talent® aorto-uni-iliac stentgraft system used for emergency EVAR.

the same hospitalisation and major morbidity (i.e. serious adverse events). Secondary endpoints include: death from all causes and aneurysm-related death, both within three months after the procedure.

Patient Selection, Inclusion and Exclusion Criteria for the Study

During the study period each participating center will enrol a series of consecutive patients with a rAAA that meet the inclusion criteria. Rupture of the aneurysm is defined as haemorrhage outside the aortic wall, documented by preoperative CT-examination, preoperative ultrasound, or in case of a laparotomy by direct observation. In the case that there is still doubt after treatment whether the AAA was ruptured, rupture is to be confirmed by postoperative CT-scan or by autopsy. The patient, or his/her relatives are informed about the study and asked permission to participate by a written informed consent. The criteria for enrolment in the study, and after enrolment, eligibility for EVAR, are summarised in Table 1.

Triage of Patients that Meet the Inclusion Criteria

Patients in stable haemodynamic condition, or with mild to moderate haemodynamic instability (systolic blood pressure >60 mmHg and no severe cardiac arrhythmia) undergo CT-examination. Arrangements for CT-examination without any delay and short transportation time between the emergency ward, the CT-department and the operative department are prerequisites for participating institutions (Fig. 2—flow sheet).

Severely unstable patients in profound hypovolemic shock that does not allow CT-scanning (i.e. systolic blood pressure <60 mmHg and/or repeated requirement for cardiac massage due to severe cardiac arrhythmia) are taken to the operating room and clinically evaluated and if possible undergo fluoroscopic assessment to establish whether an EVAR or open surgical procedure can be performed.

The anatomic criteria determining treatment by open surgery include an infrarenal aortic neck length smaller than 10 mm and/or a diameter larger than 32 mm. In addition, an angulation of the infrarenal neck larger than 85° excludes the patient from EVAR. Bilateral iliac artery occlusions or stenosis (<6 mm diameter), not amenable to balloon angioplasty, represent exclusion criteria for EVAR. These patients are included in the study cohort, but are recorded to be ineligible for EVAR on anatomic grounds.

Table 1. Inclusion and exclusion criteria for the New ERA study

Inclusion criteria
Age >50 years
Patients with documented rupture of the infrarenal aorta (preoperative CT, preoperative ultrasound, laparotomy, postoperative CT-scan, autopsy)
Written informed consent by patient or legal representative
Exclusion criteria
No documentation of true rupture
Rupture because of endoleak of a stentgraft placed before the study has started
Severe dementia
Active infection
Malignancy with life expectancy less than one year
No consent to participate in the study
Deliberate decision of the patient (or representatives) to be treated by open surgery

Guidelines for Emergency AAA Stentgraft Procedures

The resuscitation of a patient with a ruptured AAA requires a multidisciplinary approach. It involves emergency, radiology, anaesthesiology, operating theatre and surgical staff. We prefer to maintain systolic blood pressure between 60 and 100 mmHg

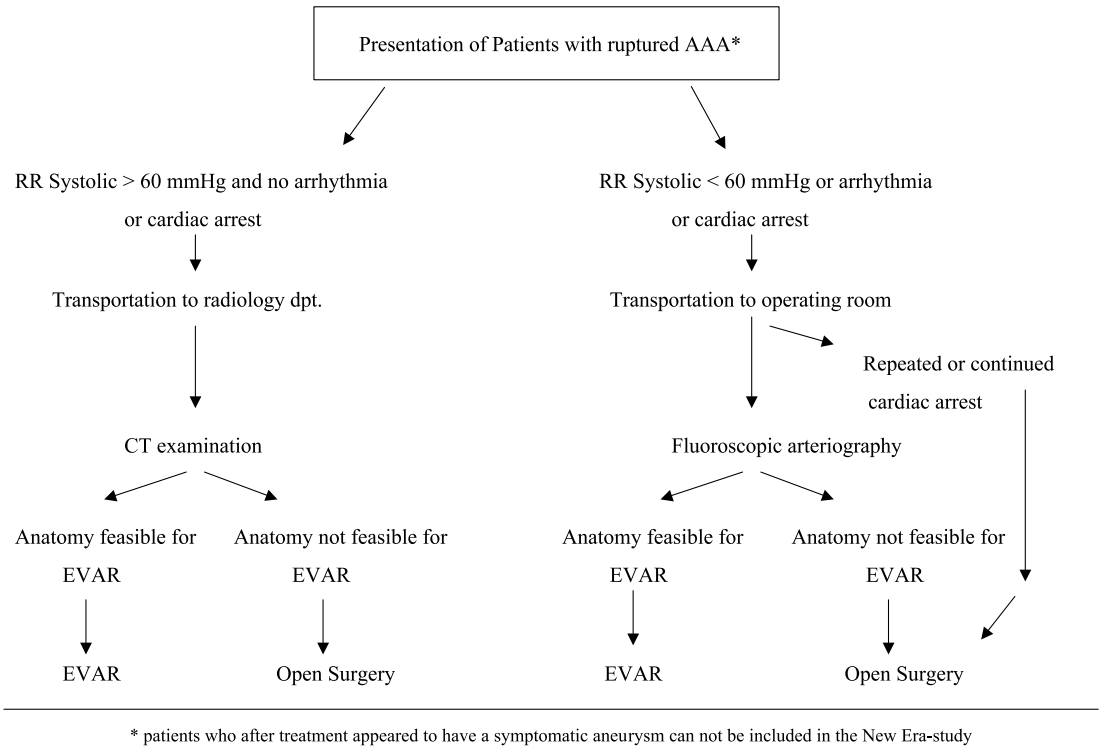

Fig. 2. Flow sheet for patients with ruptured abdominal aneurysms entering the hospital.

and avoid general anaesthesia. Emergency CT imaging should be available at all times. The responsible surgeon confirms the diagnosis of rAAA (extravasation of blood), verifies the length and diameter of the neck and then decides whether EVAR or open surgery is the appropriate treatment.

Severe hypotension (less than 60 mmHg) can be treated by blood and crystalloid transfusion. Pain and anxiety can be treated by intravenous Fentanyl administering. If the blood pressure is >100 mmHg systolic, Nitroproside or Ketansin is administered intravenously to lower the blood pressure. As soon as the decision is taken whether EVAR is possible the patient is quickly transported to the operating room for surgery.

The Talent® aorto-uni-iliac stentgraft is favoured over a bi-iliac stent graft because it is presumed to be the quickest way to exclude an aneurysm from the systemic circulation.[19] An additional advantage of using an aorto-uni-iliac (AUI) device of one single company is that no subgroups need to be formed in the analysis and therefore the study does not lose power.

Emergency EVAR starts with local anaesthesia of the groin at the selected access side. After introduction of an angiography catheter, the renal arteries are marked on the fluoroscopy-display and the proximal part of the standard aorto-uni-iliac set is deployed. Then quickly the distal component of the stentgraft to the selected iliac artery is deployed. Sealing within the common iliac arteries is preferred over extending the device into the external iliac artery. Colon ischemia from hypogastric artery inflow occlusion is a real risk.

The contralateral common femoral artery is now exposed under local anaesthesia, and this artery is used for introduction of the 'Occluder device' (Fig. 1) into the common iliac artery (if this artery is markedly aneurysmal the contralateral external iliac artery and hypogastric arteries are ligated *via* a small lower quadrant incision with retroperitoneal approach). The operation is finalised by performing a cross-over femorofemoral bypass under general anaesthesia. A completion angiogram is performed to check whether there are gross endoleaks.

Type I and III endoleaks have to be treated as soon as possible. Therefore they will be treated direct after the 'completion angiogram' in the same session, modifications are to the discretion of the participating physicians. Type II and IV endoleaks are accepted. Type II endoleaks are treated if there is growth of the aneurysm at follow-up. If Type IV endoleaks do not resolve in 30 days there should be concern that there is another type of endoleak present. All patients are postoperatively treated in the Intensive Care Unit.

Although the procedure described above is feasible, modifications are to the discretion of the participating physicians. Expedient preoperative CT-examination is

strongly recommended, and it should be performed in the large majority of patients. However, in the case of extreme haemodynamic instability (systolic blood pressure <60 mmHg or severe cardiac arrhythmia) surgeons may decide to transport a patient immediately to the operating room. Depending on the circumstances one may choose to perform an angiogram using a C-arm fluoroscopy to determine whether EVAR is a reasonable option or to proceed with open surgery without imaging.

Follow-up and Adverse Events

Clinical and imaging follow-up will be performed at 3 months after the intervention. Adverse events are documented, CT imaging results and secondary procedures are recorded.

Study Population and Statistical Analysis

Applicability

The applicability of the endovascular technique would be considered unsatisfactory if it were below 50%. Thus, the null hypothesis: applicability = 50% will be tested against the one-sided alternative of a higher applicability rate. The expected applicability rate is at least 70%. With alpha set to 0.1 and a sample size of 100 patients the power would be 93%.

Mortality

The intention is to demonstrate that the mortality rate of patients with rAAA, treated by preferential EVAR, is lower than 50%. The null hypothesis of a first-month mortality of 50% or greater will be tested against the one-sided alternative of a lower mortality, using the exact binomial test. If a mortality rate of 25% is assumed in the group of patients treated by endovascular technique, and of 50% in the open surgery group, the overall mortality adds up to 32.5%, if the applicability of the endovascular technique is 70%. Under these assumptions and an alpha of 0.1 a sample size of 100 results in a power of 87% to reject the null hypothesis.

Secondary analysis

Preferential treatment will be EVAR, and open surgery will be performed only if patients do not meet the anatomical criteria for EVAR, or if the patient is in profound hypovolemic shock that does not allow CT-scanning or the use of IVUS during the operative procedure. A comparative, secondary, descriptive analysis between patients of the study group (patients undergoing endoluminal treatment and patients undergoing open surgery) and a historical patient group, with morbidity and mortality rates derived from literature, will be performed.

All case report forms, patient informed consents, data on adverse events will be reported by the investigator and monitored by Medtronic. An Adverse Event Advisory Committee (AEAC) will review all severe or serious adverse events, device- or procedure-related, including death. Device-related and SAEs will be reported to all investigators. Each clinical participating site has obtained approval of the local ethical committee for the protocol. Data handling and analysis will be performed by the Department of Medtronic Clinical Research in co-operation with the chief clinical investigator.

Current Status

Recruitment began February 2003, and by the end of January 2004 a total of 59 patients have been included, representing 59% of the target. Final results of ERA should be available in 2005.

Conclusion

In this new era of endoluminal treatment, stentgrafting for ruptured infra-renal aneurysms has been reported in several non-consecutive, non-randomised trials with fair to good results. However, these results may be due to selection bias. The New ERA study is designed to diminish selection bias and optimise the applicability of EVAR. In the study, an international multicenter cohort of patients with rAAA will be treated preferentially by eEVAR, and the outcome of this group compared with that of patients with rAAA treated by conventional open surgery as reported in large series in the literature. If the results are again as promising as the first reports of treatment of rAAA with stentgrafting, this study may pave the way to a randomised comparative trial for patients with rAAA.

About the ERA Study

The study is sponsored and supported by Medtronic® Bakken Research Center.

The Adverse Event Advisory Committee and the Steering Committee consists of members who are affiliated to Medtronic® and members who are not

affiliated to Medtronic®. Statistical analysis will be performed by Medtronic Biostatistics and Data Management Department, Santa Rosa (CA).

Appendix Participants of the ERA-Study

J. Buth (principal investigator), P. Cuypers and N. Peppelenbosch, Eindhoven, J. Teijink, H. Odink and R. Welten, C.X. Heerlen, R.H. Geelkerken, A.B. Huisman, D.G. Gerrits, E.D.P. Volker, R. van Det and P. De Smit, Enschede, The Netherlands, J. De Letter, Brugge, F. E.G. Vermassen, and I. van Herzeele, Gent, Belgium, P. Cao, F. Verzini, and S. Mosca, Perugia, Italy, M.M. Thompson, R. Morgan, and A. Belli, London, United Kingdom, C. Soong, C. Boyd, and W. Loan, Belfast, Northern Ireland, M. Lepäntalo, P. Keto, W. Roth, and Pekka Aho, Helsinki, Finland, G. Walterbusch, N. Keck, and J. Beyer, Dortmund, Germany, G. DeRose, T.L. Forbes, and S.W. Kribs, London, Ontario, O. K. Steinmetz, K. MacKenzie, D. Obrand, and B. Montreuil, Montreal, Quebec, Canada.

Appendix Adverse Event Advisory Committee

B. Barbieri, and S. Zannetti, Medtronic Bakken Research Center, Maastricht, J. v d Berg, Nieuwegein, The Netherlands, P. Cao, Perugia, Italy.

Appendix Steering Committee Members

B. Barbieri and S. Zannetti, Medtronic Bakken Research Center, Maastricht, J.J. Jackimovicz, J. Buth, P. Cuypers and N. Peppelenbosch, Eindhoven, The Netherlands.

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