EU-CERT-ICD Report Summary

Project ID: 602299
Funded under: FP7-HEALTH
Country: Germany

Periodic Report Summary 2 - EU-CERT-ICD (Comparative Effectiveness Research to Assess the Use of Primary Prophylactic Implantable Cardioverter Defibrillators in Europe)

Project Context and Objectives:
Patients for the landmark clinical trials that established the clinical treatment guidelines for primary prophylactic implantable cardioverter defibrillators (ICDs) were recruited 15-20 years ago. Over this long timespan, cardiovascular treatment significantly improved and cardiovascular patient populations have changed. Nonetheless, the guidelines remained largely unchanged for over a decade. The recently published randomised DANISH ICD study exemplified the need for overhauling the ICD guidelines. Annually, more than 100,000 ICDs are implanted in the EU-28 with huge disparities between countries (see Raatikainen et al, Europace 2015). This reflects a billion € - market but considerable socio-economic and health-care inequalities across the EU.

The European collaborative project EU-CERT-ICD (Comparative Effectiveness Research to Assess the Use of Primary Prophylactic Implantable Cardioverter Defibrillators in Europe) aims to analyse the effectiveness of prophylactic implantation of cardioverter defibrillators (ICDs) in Europe. The project features a non-randomised cohort study in candidate patients for primary prophylactic ICD therapy. A wide-ranging collection of baseline clinical characteristics and advanced electrocardiographic non-invasive diagnostics are available to be combined in multivariate models and risk scores in order to predict primary outcomes such as all-cause mortality and the occurrence of appropriate ICD therapy. We will thereby identify patients with particularly high or low risk of death from all causes, and/or particularly high or low risk of appropriate ICD therapy. As highlighted by the NEJM editorial to the recent publication of the DANISH ICD study (McMurray-JJ, ICD in Heart Failure – Time for a rethink?), a complex combination of these two primary outcomes is associated with clinical benefit of the ICD.

From retrospective data, we have already generated a large European registry of more than 5,300 patients for comparative analyses of prophylactic ICD treatment. A meta-analysis of more recently published studies on primary prophylactic ICD treatment yielded more than 46,000 patients. From all three data sources (prospective study, retrospective registry, and meta-analysis) we will estimate quality of life (QoL)-adjusted cost-effectiveness of prophylactic ICD treatment utilising actual cost comparisons and decision models. Attention will be given to individual sub-groups, including sex comparisons and regional differences. EU-CERT-ICD is expected to provide important novel information to validate or challenge current guideline indications for primary prophylactic ICD treatment.

This leads to the unchanged objectives of the project:
• To compare mortality rates between patients eligible, according to guideline-derived criteria, for primary prevention of sudden cardiac death by ICD implantation who do receive an ICD, and patients fulfilling these criteria who do not receive an ICD implantation
• To identify important patient subgroups with particularly high or low risk of the major outcomes all-cause mortality, appropriate and inappropriate ICD shock, by using dedicated diagnostic risk methods as well as primary clinical characteristics
• To determine socio-economic outcomes of primary preventive ICD implantation, including QoL, costs, and QALY-adjusted cost-effectiveness in the target population featuring sub-groups and regional comparisons within Europe
• To determine any gender-related effects on the above
• To validate or challenge current guideline indications for primary prophylactic ICD treatment
• To establish a biobank for the purpose of future risk stratification

Project Results:
In summary, EU-CERT-ICD is well under way for three years since the project start and has yielded important results from its meta-analyses and registries.

The Prospective Study WP01 is under the leadership of UMG and networked to interact with WP03 through WP12. The first patient was enrolled in month 8. Until month 36, 27 partner sites and 9 third party centres have enrolled 1436 patients towards the planned 2250 (in two non-randomised groups: 1500 ICD and 750 control). All study infrastructures such as trial office, study management office, secure database and server, central and on-site monitoring are fully functional and pivotal in data collection.

Over the first three years of the project, the Retrospective Registry WP02 was lead by UHBS and compiled data from more than 5300 patients and 14 centres. The registry was analysed in cooperation with WP10 and yielded important and novel scientific results in 2015 and 2016 (presented at ESC congresses and submitted in manuscript form). We expect that using this powerful data source, it will be statistically possible to identify factors predicting mortality and shock risk. This will enable us to define patient groups with higher or lower benefit from the primary prophylactic ICD.

WP03 Health economics and QoL is collecting incoming data from WP01 with over 90% completeness. A systematic review on QoL in ICD patients was published (Tomzik et al., Front Cardiovasc Med 2015).

WP04 Gender issues has completed two gender-related analyses as original papers, a single centre analysis of 1151 ICD patients (Seegers et al, Europace 2016), and a gender-specific meta-analysis of ICD studies (Conen et al, PLoS One 2016). The results are important and show that women receive 50% fewer appropriate shocks than men but have a similar or reduced mortality risk. Apart from gender-related analysis of the WP01, WP04 work is complete.

WP05 Beat-to-beat variability had organised an open ECG conference to discuss ECG and Holter risk stratifiers in October 2014. A QT variability consensus paper was published emerging from this conference (Baumert et al., Europace 2016).

WP06 T-wave morphology has evaluated morphological indices in the WP01 prospective study recordings and developed and tested analysis software packages. WP06 secured a common recording platform for the consortium. They are analysing all incoming WP01 ECGs. WP06 compiled an ECG database of WP02 patients, where 2041 digital ECGs were available. Preliminary analyses for all-cause mortality show that several automatically analysable 12-lead-ECG parameters are highly predictive of mortality. The data were presented at the General Assembly 2016 and are currently prepared for publication with priority.

WP07 Fractionation and early repolarisation analysed exemplary sets of WP01 prospective study patients and the complete database of digital ECGs from WP02. First results from the latter show that a number of the measured variables are highly predictive for endpoints. These results are currently under further evaluation.

WP08 Heart rate variability and heart rate turbulence is analysing all incoming Holter ECGs from WP01 with high quality and short-term after upload. Holter reports are returned to participants electronically and are updated frequently.

WP09 Biobanking is storing biosamples for more than 90% of enrolled WP01 patients in the EU-CERT-ICD biobank, it is now planned to collect samples from available WP02 patients.

WP10 Statistics and meta-analyses conducted and published a gender-specific meta-analysis in cooperation with WP04 (Conen et al., PLoS One 2016). Other co-factors are also being analysed currently. WP10 is also in charge of all other statistical calculations in the consortium including recalculation of the sample size estimates.

WP11 Dissemination improved the initial dissemination plan and oversees publications and other dissemination activities. The number of publications has increased significantly over the last year.

WP12 Prospective study management has notably supported the prospective study with eCRFs, study database, regulatory affairs, central monitoring and on-site monitoring. WP12 has also negotiated and prepared all clinical centre contracts as well as many third-party contracts.

WP13 Project management has been taken over by the UMG-EU Liaison Office for Life Sciences with effective date 01/07/2016,
they perform all consortium-wide management tasks, administrative project controlling, organize consortium finances, telephone conferences and face-to-face meetings.

Potential Impact:

Expected impact of completing the EU-CERT-ICD project and background of treatment guidelines.

The expected impact of the EU-CERT-ICD final results is unchanged and highly relevant. With the results of the DANISH ICD study being discussed since September 2016, the need for additional data has become more urgent. The EU-CERT-ICD project will provide these data in large numbers. A similar but smaller Dutch project (DO-IT, n=1500 patients) is also underway which we are already cooperating with. Experts have only now (after DANISH) considered that carefully designed randomised ICD studies have become feasible, such studies should not be planned without consulting the EU-CERT-ICD data. It is clear that the observational study design of EU-CERT-ICD was correctly chosen and should be completed.

Event rates for mortality and appropriate shock are as predicted as of August 2016. Thus, the mean follow-up of the cohort is targeted as initially planned. The initial group sizes fulfil the sample size calculation for an adequately powered study with the necessary number of events. With the tentative addition of 12 months to the prospective study we anticipate that pivotal results will be provided in 2018, by month 60. In September 2016, we have submitted the results of the WP02 registry data for publication (5033 primary prophylactic ICD patients with mortality and shock data). The WP02 data also confirm the event rates encountered in the prospective study (WP01). An additional statistical analysis of the WP02 data is underway searching for possible combinations of multivariate factors for the stratification of risk. These analyses will serve to highlight the existence of different risk groups within a primary prevention ICD cohort. We expect that the emerging risk scores will allow stratification of outcomes risk linked to ICD benefit among primary prevention patients. In patient sub-groups at high risk of non-arrhythmic mortality or at very low risk of arrhythmic mortality outcomes, ICDs may have no benefit. From the growing database of 24-hour ECG recordings, we expect novel ECG parameters to emerge as risk factors that improve on the prognostic value of known ECG indices.

Impact on changing the treatment guidelines. The consortium confirms the continued need for a revision of the current guidelines on primary prophylactic ICD device treatment. The results of the randomised DANISH study have underscored this, as these authors recently reported absence of ICD benefit in their overall cohort. In a post-hoc analysis of interacting patient characteristics, they could demonstrate ICD benefit for sub-groups (for younger patients, for patients with less heart failure). On the other hand, there were groups with absent ICD benefit (such as the elderly and patients with less heart failure), all characterised by a lower proportion of arrhythmic deaths. It follows that the decision to implant prophylactic ICDs should be individualised. This kind of sub-stratification had been predefined by the EU-CERT-ICD project to improve patient selection which will be recognized in the treatment guidelines for primary prophylactic ICD treatment. The project results will therefore help to serve the individual needs of patients. From the final results of the EU-CERT-ICD project, we also expect to plan new randomised studies. A cooperation with the research groups of our advisors in the United States (Buxton-A) and Canada (Exner-D) is pursued. The socio-economic dimensions can be determined for the EU as a whole, as well as for each individual country. Eventually, our health economics WP will be able to translate the clinical ICD benefit in important sub-groups into variations of cost-effectiveness and QoL-adjusted cost-effectiveness. The group is aware that there are scientists and clinicians who do not wish to adopt the ideas and concepts of the EU-CERT-ICD project. We expect reluctance from industry to development of stratified guidelines. The EU-CERT-ICD consortium wants to assist allocating ICD implants to patients with predictable ICD benefit, and equally in all countries. Implantations in patients who do not benefit from the device should be avoided. This could mean implanting the same number of devices in better selected patients.

The established EU-CERT-ICD biobanking module will lead to a biobank of approximately 4000 samples for future arrhythmia risk assessments of individual patients based on genetic analyses. To permit the use of these samples after the end of the EU-CERT-ICD project, a contractual framework will now be added in accordance with the pertinent EU regulations on IPR and exploitation to cover this as well as formation of a Use and Access Committee towards the end of EU-CERT-ICD.

List of Websites:

www.eu-cert-icd.eu