Radiation Induced DNA Damage in Operators Performing Endovascular Aortic Repair

Running Title: El-Sayed and Patel et al.; Radiation Induced DNA Damage in EVAR

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Abstract

**Background**—Radiation exposure during fluoroscopically-guided interventions such as endovascular aortic repair (EVAR) is a growing concern for operators. This study aimed to measure DNA damage/repair markers in operators performing EVAR.

**Methods**—Expression of the DNA damage/repair marker, gamma-H2AX (γ-H2AX) and DNA damage response (DDR) marker, phosphorylated ataxia telangiectasia mutated (pATM), were quantified in circulating lymphocytes in operators during the peri-operative period of endovascular (infra-renal [IEVAR], branched [BEVAR] and fenestrated [FEVAR]) and open aortic repair using flow cytometry. These markers were separately measured in the same operators but this time wearing leg lead shielding in addition to upper body protection and compared with those operating with unprotected legs. Susceptibility to radiation damage was determined by irradiating operators’ blood *in vitro*.

**Results**—γ-H2AX and pATM levels increased significantly in operators immediately after BEVAR/FEVAR (*P*<0.0003 for both). Only pATM levels increased after IEVAR (*P*<0.04). Expression of both markers fell to baseline in operators after 24hrs (*P*<0.003 for both). There was no change in γ-H2AX or pATM expression after open repair. Leg protection abrogated γ-H2AX and pATM response after BEVAR/FEVAR. The expression of γ-H2AX varied significantly when operators’ blood was exposed to the same radiation dose *in vitro* (*P*<0.0001).

**Conclusions**—This is the first study to detect an acute DNA damage response in operators performing fluoroscopically-guided aortic procedures and highlights the protective effect of leg shielding. Defining the relationship between this response and cancer risk may better inform safe levels of chronic low dose radiation exposure.

**Key Words:** radiation; aneurysm; occupational exposure, pATM, γH2AX
Clinical Perspective

What is new?

- This is the first study to detect acute radiation induced DNA damage in operators who carried out endovascular aortic repair by demonstrating an increase in the expression of DNA damage/repair markers, γ-H2AX and pATM, in their circulating lymphocytes immediately after procedures.

- *In vitro* irradiation studies demonstrated that operators had a variable susceptibility to radiation induced DNA damage.

- The use of leg lead shielding abrogated the DNA damage response in operators.

What are the clinical implications?

- Conventional dosimetry fails to account for the biological consequences of radiation exposure to operators during fluoroscopically guided procedures.

- Safe radiation exposure limits have been set without considering any inter-individual differences in susceptibility to deleterious effects.

- Wearing lower leg protective lead shielding is essential for reducing scatter radiation induced DNA damage.

- The use of cellular markers, including γ-H2AX and pATM, which readily lend themselves to high throughput sampling may facilitate individual risk-profiling, improve our understanding of the mechanisms involved in occupational radiation induced mutagensis and define optimal protection strategies.
Recent years have seen an exponential increase in the number of fluoroscopically guided cardiovascular interventions carried out by interventional cardiologists, electrophysiologists and vascular surgeons, with many of these for pathologies previously treated by open surgery. Endovascular aortic repair (EVAR), for example, has become the mainstay of treatment in many institutions and is increasingly used for patients that would have been turned down for intervention 10 years ago.\textsuperscript{1,2} The growing number and complexity of procedures means that interventionists are exposed to higher amounts of radiation, a subject that is becoming increasingly topical.\textsuperscript{3-7} A recently published 15 year follow up study of the EVAR trial, comparing endovascular and open aortic repair, reported an increased incidence of malignancy in patients treated by EVAR.\textsuperscript{8} There is, rightly so, a significant focus currently on reducing the patients’ exposure to radiation but mounting evidence suggests that recurrent low dose exposure to the practitioner is equally as important. Robust data collection to assess the risks posed to the interventionist is in its infancy, but a number of studies suggest a link to adverse health effects, including a higher risk of posterior subcapsular lens changes and malignancy.\textsuperscript{9-11} One recent study found a higher incidence of malignancy, including brain cancer, breast cancer and melanoma in interventionists who performed fluoroscopically guided procedures compared with those who had never performed these.\textsuperscript{12} A better understanding of the hazards of occupational radiation exposure requires sensitive tools to measure exposure at an individual level and clarification of the biological effects of exposure.

Circulating lymphocytes are particularly sensitive to radiation and may, therefore, offer the opportunity to study the acute biological consequences of low dose exposure.\textsuperscript{13,14} Double stranded DNA breaks (DSBs) induced by ionising radiation lead to phosphorylation of the histone protein H2AX to form γ-H2AX, with the levels of γ-H2AX in the cell peaking half an
hour after exposure to radiation.\textsuperscript{15-17} During the acute phase of exposure, DNA damage in lymphocytes also results in induction of a damage sensor known as the Mre11-Rad50-Nbs1 (MRN) complex, which causes rapid phosphorylation of ataxia telangiectasia mutated (ATM) protein.\textsuperscript{18-21} This, in turn, leads to phosphorylation of downstream targets that act as cell cycle checkpoints, resulting in DNA damage-induced arrest at G1/S, S, and G2/M as part of the DNA repair process.\textsuperscript{22-24} Expression of phosphorylated ATM (pATM), a DNA damage response (DDR) marker, and $\gamma$-H2AX, a marker of DNA repair, in circulating lymphocytes may, therefore, be a sensitive biomarker of radiation-induced DNA damage.\textsuperscript{15-17,25,26} The use of such biomarkers could facilitate a biological assessment of the effects related to radiation exposure.

The current safe limits for low dose occupational radiation exposure have been extrapolated from data obtained from individuals exposed to high doses (e.g. atomic bomb survivors) and assume a linear, no-threshold relationship between exposure and cancer risk.\textsuperscript{27} Emerging data suggest, however, that there is variability in tissue response to radiation, that the safe threshold may vary between individuals and the risk relationship is not linear.\textsuperscript{14,28}

The aims of the present study were to: (i) study the biological effect of radiation exposure in operators by measuring pATM and $\gamma$-H2AX expression in circulating lymphocytes following EVAR; (ii) to examine individual operator sensitivity to radiation exposure using $\gamma$-H2AX levels as a biomarker; and (iii) to evaluate the protective effect of wearing lower leg lead shielding.

**Methods**

**Study participants**

Blood samples were collected from vascular surgeons and interventional radiologists before, immediately after and 24hrs after they performed endovascular and open aortic repairs. All
operators had experience of endovascular aortic repair procedures and beyond their learning curve. The BEVAR/FEVAR procedures were performed by one of four operators, all of whom had experience of >100 of these procedures. Endovascular procedures consisted of standard infra-renal aortic repairs (IEVAR) and complex thoracoabdominal, branched (BEVAR) and fenestrated (FEVAR) repairs. This study was approved by the London - City & East Research Ethics Committee (16/LO/1111) following the principles of the Declaration of Helsinki and written informed consent was obtained from each participant.

**Procedural details**

All endovascular aortic repair procedures were carried out in a hybrid operating theatre equipped with the Philips Allura Xper FD20 fixed X-ray imaging system (Philips Healthcare, Eindhoven, Netherlands). Default settings used were a pulse rate of 7.5 pulses/second for background fluoroscopy and two frames/second for digital subtraction angiography (DSA) acquisitions. For both fluoroscopy and cineangiography an x-ray beam filtration of 1.5 mm Al combined with 0.4 mm Cu was used. The equipment set-up and operating staff positioning was similar for IEVAR and BEVAR/FEVAR procedures and has been described previously. The fluoroscopy equipment was controlled by a senior radiographer for each procedure. At the start of each case, the under table lead shielding was specifically checked to ensure it was in the optimal position. A ceiling-mounted lead shield was available and was positioned at the operators’ discretion for each procedure. Mobile lead shields for the radiographer and anaesthetist, lead garments (0.35 mm thickness), leaded thyroid collars, and leaded goggles were used for all endovascular cases. Leg lead shields were not routinely worn. A cohort of 6 operators (selected from the first cohort of 15 studied) were asked to wear lower leg lead shielding (0.5mm thickness, XENOLITE–TB,
DuPont Technology, Lite Tech, Inc. Norristown, PA, USA) as additional protection to separately study the effect of radiation exposure on operators when legs were protected.

**Standard dosimetry**

Electronic dosimeters (Hitachi-Aloka Medical PDM-127; Hitachi Aloka Medical Ltd, Tokyo, Japan) were used to measure direct radiation exposure. These devices recorded cumulative measurements of the “dose equivalent” of absorbed radiation in micro Sieverts (µSv) for each case. Dosimeters were attached to three different areas on the operator: (i) left breast pocket under the protective lead garment; (ii) left breast pocket over the protective lead garment; and (iii) left mid leg. The dose-area product (DAP), fluoroscopy time, and air kerma dose were recorded for all procedures.

**Flow cytometry**

Venous blood samples were collected from operators in EDTA tubes (BD Biosciences, UK). Red blood cells were lysed using Pharmlyse (BD Biosciences, UK) for 10 mins and then washed in 0.5% BSA/PBS for 5 mins at 4°C. Cells were fixed (Inside Fix, Miltenyi Biotec, UK) for 10 mins at room temperature followed by staining with FITC-conjugated mouse anti-human CD3 antibody (Miltenyi Biotec, UK) for 30 mins on ice in the dark. Cells were then permeabilised on ice (Permeabilisation Buffer A, Miltenyi Biotec, UK) and washed twice prior to staining for γ-H2AX and pATM using anti-human APC- and PE-conjugated antibodies respectively (BD Biosciences and BioLegend, UK). APC and PE conjugated IgG isotype control antibodies (BD Biosciences and BioLegend) were used in fluorescence minus one (FMO) samples for appropriate gating of γ-H2AX and pATM respectively. Samples were processed on a MACSQuant flow cytometer (Miltenyi Biotec, UK) and analysed using FlowJo software.
(FlowJo LLC, US). A more detailed analysis of γ-H2AX and pATM expression in subpopulations of CD3+ lymphocytes was also carried out (Supplemental Methods).

Samples from operators performing IEVAR were also analysed for the expression of 8-oxoguanine DNA glycosylase-1 (OGG1), a dedicated DNA repair enzyme, with its expression directly correlating with DNA damage caused by base oxidation as opposed to double stranded DNA breaks (Supplemental Methods and Supplemental Table 1 for a list of all antibodies used).

For each procedure, the opportunity was taken to collect blood samples from the patient to study γ-H2AX and pATM expression in their circulating CD3+ lymphocytes using the same methodology as outlined for operators above.

**Immunocytochemistry**

Blood samples were collected, lysed and fixed as described above. Samples were incubated with mouse anti-human CD3 immunomagnetic microbeads for 30mins following by positive selection of labelled lymphocytes using LS Columns (Miltenyi Biotec, UK). Isolated CD3+ cells were permeabilised (0.5% Triton X-100 in PBS for 20mins), washed and stained with mouse anti-human γ-H2AX (5μg/ml; BioLegend, UK), followed by secondary staining with donkey Cy3-conjugated anti-mouse (5μg/ml, Jackson ImmunoResearch Laboratories). Cells were washed and mounted using DAPI gel mount (Sigma-Aldrich, UK).

**Irradiation of blood samples in vitro**

Blood from 6 operators, randomly selected from the entire cohort of 15 operators studied, was collected in EDTA tubes and exposed to radiation doses between 100 and 1000mGy using a Darpac 2000 (Gulmay Medical, UK) x-ray unit (energy: 80kVp [half-value layer, 2.0mmAL], 6.9mA, applicator: 8cm diameter) positioned approximately 25cm from the x-ray source.

Following red blood cells lysis, γ-H2AX and pATM staining and analysis by flow cytometry (as
described above) was carried out within 30mins of irradiation. Blood was collected and irradiated on 3 separate occasions from each operator, ensuring that they had not performed any intervention involving exposure to radiation in the 48hrs prior to sampling.

Statistical Analysis

Data were analysed using GraphPad Prism 7.0a (GraphPad Software Inc., San Diego, CA, USA) and SPSS-22 (SPSS Inc., Chicago, IL, USA). Where appropriate, non-parametric Wilcoxon signed rank, Mann Whitney U and two-way ANOVA tests were used. A P value <0.05 was considered to be statistically significant.

Results

Peri-operative changes in γ-H2AX and pATM

Fifteen operators (13 males, 40years [34-49], Table 1) carried out a total of 45 procedures, including 15 IEVAR, 16 BEVAR/FEVAR and 14 open AAA repairs. BEVAR/FEVAR was associated with longer screening time and higher DAP (P<0.0001 for both) compared with IEVAR (Figure 1). Personal dosimetry showed minimal exposure under the operators’ protective lead garment, but higher exposure over the lead (P<0.0001), particularly at the lower leg level (P<0.0001, Figure 1). An optimised flow cytometric strategy was used to quantify both γ-H2AX and pATM expression in circulating lymphocytes (Figure 2). Immunohistochemistry confirmed that γ-H2AX foci, absent in both operator and patient blood samples pre-operatively, appeared in post-operative lymphocyte films (Figure 2C).

There was a significant increase in the levels of both γ-H2AX and pATM in circulating lymphocytes of operators immediately after BEVAR/FEVAR (P<0.0003 for both, Figure 3). The expression of pATM increased in operators who carried out IEVAR (P<0.04), but γ-H2AX did
not show significant changes in this cohort. The expression of both markers fell to baseline levels in all operators after 24hrs ($P<0.003$ for both, Figure 3). There was no change in $\gamma$-H2AX or pATM expression at any time point during the peri-operative period of open AAA repair.

A significant post-operative rise in $\gamma$-H2AX and pATM in both T helper and cytotoxic T cell sub-populations of CD3$^+$ lymphocytes was detected after EVAR, with the relative expression of $\gamma$-H2AX higher in T helpers compared with cytotoxic T cells ($P<0.05$ for all, Supplemental Figures 1, 2).

The deeper phenotyping strategy used to compare the relative post-operative levels of $\gamma$-H2AX and pATM in CD4$^+$ and CD8$^+$ T lymphocytes showed that the increases in levels of $\gamma$-H2AX levels were significantly higher in CD4$^+$ Naïve and Central memory cells (Supplemental Figures 1, 2).

After IEVAR, there was a significant increase in OGG1 expression in the CD3$^+$ lymphocytes that expressed elevated levels of pATM but not $\gamma$-H2AX ($P<0.03$, Supplemental Figure 3).

Changes in $\gamma$-H2AX and pATM in operators after BEVAR/FEVAR and IEVAR did not correlate with either DAP or screening time in either cohort (Figure 3).

In patients, increased expression of both $\gamma$-H2AX and pATM levels were detected in CD3$^+$ lymphocytes immediately after BEVAR/FEVAR and IEVAR procedures ($P<0.004$, for both, Supplemental Figure 4)

**Factors affecting $\gamma$-H2AX expression in operators**

A variable response ($P<0.0001$) was apparent when $\gamma$-H2AX expression in lymphocytes, sampled from six operators, was studied *in vitro* after controlled irradiation using doses ranging between 100-1000mGy (Figure 4A). At any given dose some operators mounted a consistently
exaggerated response whilst others demonstrated far lower expression of γ-H2AX on their lymphocytes.

The same six operators were asked to wear lower leg shielding during BEVAR/FEVAR procedures (n=9 cases) and blood samples were obtained prior to and after they had performed each procedure. Wearing lower leg lead protection significantly abrogated the lymphocyte γ-H2AX and pATM response in operators after BEVAR/FEVAR, with no change in the expression of either marker immediately after the procedure (Figure 4C). Comparable DAP, over the leg exposure measurements and screening times suggested that the radiation exposure associated with procedures during which the operators wore lower leg lead shielding was comparable with those carried out without leg protection (Figure 4D).

Discussion

Ionising radiation can induce different forms of DNA damage such as base pair damage, single stranded breaks (SSBs), and double stranded breaks (DSB), the latter is considered the most deleterious as these are more difficult to repair than other forms of DNA damage.30,31 Left unrepaired, DSBs can cause chromosomal instability and cell apoptosis. Incomplete repair leads to deletions and chromosomal rearrangements such as translocations and inversions that can ultimately lead to mutations.20 These types of chromosomal abnormalities have been detected in lymphocytes of both patients and hospital staff after chronic exposure to low dose radiation.13,16,17

Circulating lymphocytes are particularly sensitive to radiation exposure, mounting an acute response to radiation induced DNA damage which includes raised expression of pATM and γ-H2AX. Elevated levels of the latter marker have been demonstrated in patients’
lymphocytes after paediatric cardiac catheterisation and as a consequence of radiation exposure during diagnostic CT scanning.\textsuperscript{17,32} The present study demonstrates an upregulation of both $\gamma$-H2AX and pATM expression in interventionists’ and patients’ lymphocytes after endovascular aortic repair.

Neither $\gamma$-H2AX nor pATM have previously been studied in interventionists performing fluoroscopically guided aortic procedures. To our knowledge the present study is the first to demonstrate elevated expression of these markers of DNA damage/repair in operators exposed to radiation. This is of importance to the entire community of workers exposed to low dose radiation. A more profound effect was seen in operators performing BEVAR and FEVAR, complex and lengthy repairs that were associated with higher radiation exposure compared with standard infra-renal endovascular repairs. We, and other groups, have previously reported that DAP, flouroscopy and radiation exposure are higher for these complex procedures compared with standard IEVAR.\textsuperscript{4,33} In our experience, BEVAR/FEVAR was associated with a two-fold increase in DAP and three-fold longer flouroscopy time.\textsuperscript{5} The present study confirmed, by personal dosimetery, an almost two-fold higher exposure at leg level for the operator performing BEVAR/FEVAR as opposed to IEVAR.

Changes in $\gamma$-H2AX and pATM were not detected in operators after open repair, highlighting the fact that this is an effect directly related to radiation exposure. This effect was absent in operators who wore lower leg lead shielding during complex aneurysm repair, indicating that the majority of DNA damage occurs in lymphocytes irradiated in the lower leg tissues and long bones.

Our data also demonstrate inter-individual variability in the induction of $\gamma$-H2AX in operators’ lymphocytes when irradiated \textit{in vitro}, suggesting that susceptibility to DNA damage
may vary and that “safe” exposure limits may not apply universally. A range of doses, including some far higher than that those recorded for occupational exposure, were used to provoke an exaggerated response and help ummask differences between individuals. Although increased expression of both of these markers were detected immediately after endovascular intervention, levels fell back to normal 24hrs after the procedure in operators, a finding that has previously been reported in patients exposed to radiation. A greater understanding of this reparative response to DNA damage is needed in order to determine the influence of factors such as age, sex, co-morbidities and chronicity of exposure and whether a complete repair is achieved in damaged cells. Estimates of cancer risk from exposure to ionising radiation are based on epidemiological studies of exposed human populations, especially the atomic bomb survivors of Hiroshima and Nagasaki. These studies have provided relatively reliable estimates of risk for moderate to high radiation doses. However, risk estimates for repeated exposures to low dose radiation, are based on linear extrapolation using epidemiological data from high dose exposures, making these estimates less reliable. Traditional methods to quantify radiation risk associated with fluoroscopically guided procedures is through absorbed radiation dose or exposure indices such as DAP that estimate absorbed radiation dose. These provide theoretical risk estimate that does not factor in individual variations in susceptibility to radiation damage. Measurement of biological markers, such as γ-H2AX and pATM, provides the opportunity for individual risk profiling, but at this stage, a better understanding of the long term consequences of the raised levels of γ-H2AX and pATM during endovascular interventions is required. We found a post-operative rise in γ-H2AX and pATM in both T helper and cytotoxic cell populations, with the relative expression of post-operative γ-H2AX higher in T helper (CD4+) compared with cytotoxic T cells (CD8+). Using this deeper phenotyping strategy to compare
relative expression levels in CD4⁺ and CD8⁺ cells, we found post-operative γ-H2AX levels are significantly higher in CD4⁺ naïve and central memory cells. It appears that γ-H2AX did not rise in CD8⁺ central memory cells post-operatively.

Expanding on the biological significance of the differential expressions that we have found in T-cell subsets is beyond the scope of the present study. The effects of chronic radiation exposure on the overall health of surgical operators may only be revealed through long term investigations. Other groups have found that CD8⁺ cells are more sensitive to radiation-induced apoptosis than CD4⁺ cells.³⁹ It is possible that CD8⁺ cells are less likely to persist after being irradiated and be registered as γ-H2AX expressing cells.

After IEVAR there is a significant increase in OGG1 expression, a dedicated DNA repair enzyme that specifically excises 7,8-dihydro-8-oxoguanine (8-Oxo-G), with its expression directly correlating with DNA damage caused by base oxidation.²⁹ Our finding of higher OGG1 expression in CD3⁺ lymphocytes that demonstrate elevated levels of pATM, but not γ-H2AX, suggests that the DNA damage response marker, pATM, is activated in the lymphocytes of operators in response to DNA damage caused by base oxidation as well as DNA breaks caused by direct energy transfer.

Protective equipment available to the operator include lead aprons, thyroid shields, lead eye protection, ceiling-suspended leaded shields, rolling leaded shields, radiation-attenuating sterile surgical gloves and sterile lead-equivalent patient-mounted drapes.⁴⁰ Below table lead shielding is particularly important for minimising scatter radiation.⁴¹ The stark findings of the present study specifically highlight the importance of using leg leaded pads, by demonstrating that the markers of DNA damage detected in operators’ circulating lymphocytes were absent when the operator wore additional lower leg lead shielding. The electronic dosimeters placed
over the leg confirmed a significant amount of scatter radiation absorbed at that level - in fact, higher than the dose at chest level. The capability of modern fixed imaging systems to produce higher quality images compared with mobile c-arms is associated with a significantly higher amount of scatter radiation produced by the radiation source under the operating table. Operators often neglect to wear lower leg lead shielding, viewing its use as cumbersome and unnecessary, but the present data highlight the importance of protecting the legs.

Dose awareness and training in radiation protection are fundamental for minimising occupational radiation exposure. There is currently no mandatory requirement for training in fluoroscopic operation or mandatory radiation protection certification for vascular operators in the UK. Radiation exposed workers are encouraged, however, to attend Ionising Radiation (Medical Exposure) Regulations (IRMER) training courses. Vascular surgery was granted speciality status in the UK in 2013 and with this a new curriculum and training programme was developed. The first cohort of trainees have had instruction on radiation protection practices as part of their induction into the programme. The first sitting of the examination for these trainees will take place in 2018 and should include questions on radiation safety, reflecting the content of the new curriculum.

The current endovascular case mix exposes the vascular operator to relatively high radiation doses compared with, for example, interventional cardiologists performing percutaneous coronary intervention (PCI). In our experience the per case dose to the vascular operator is almost 6-fold higher during IEVAR compared with PCI but it should be noted that interventional cardiologists perform cases more frequently (Supplemental Table 2).

It is essential that operators adhere to “As Low As Reasonably Achievable” (ALARA) principles to minimise exposure to themselves, their team and the patient. These include wearing a
dosimeter at all times, with cumulative doses monitored regularly and leveraged use of real time dosimetry where possible.\textsuperscript{44,45} Other principles include lowering the rate of fluoroscopy where applicable, minimising use of cinefluorography (which produces 10 times more radiation compared with standard fluoroscopy), using collimation and maximising the distance between the operator and x-ray source, remembering that as distance doubles, exposure is reduced by a factor of four.\textsuperscript{46} Finally, closely monitoring the orientation and angulation of the x-ray source, particularly avoiding left anterio oblique (LAO) projection, which exposes the operating team to the highest amount of scatter radiation, is key for minimising absorbed dose.

**Limitations of this study**

The present study does not relate the effective radiation doses absorbed during each procedure, calculated by taking into account the radiosensitivity of different body tissues, to the expression of DNA damage/repair markers. We have also not established the relationship between the acute response (\(\gamma\)-H2AX and pATM levels) and cytogenetic markers of chronic low dose radiation damage and DNA misrepair, such as micronuclei and dicentric chromosomes. Finally, it is important to stress that the biomarkers of radiation exposure measured in this study demonstrate an acute cellular response, but we do not yet know how this gives rise to increased cancer risk. Relating one to the other would require longitudinal measurements in a much larger cohort of operators with long term, prospective follow up.

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Disclosures

None

References


Table 1. Details of operators participating in the study

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IEVAR indicates infra-renal endovascular aortic repair; BEVAR, branched endovascular aortic repair; FEVAR, fenestrated endovascular aortic repair; AAA, abdominal aortic aneurysm.
Figure Legends

**Figure 1. Radiation exposure to operators during EVAR procedures**

A, Screening time during BEVAR/FEVAR was significantly longer than IEVAR (P<0.0001). 
B, DAP during BEVAR/FEVAR was higher than IEVAR (P<0.0001). C, Readings from personal dosimeters placed over operators’ chest under the lead, over the lead and at the left leg. Leg doses were significantly higher during BEVAR/FEVAR compared with IEVAR (P<0.05). EVAR indicates endovascular aortic repair; IEVAR, infra-renal endovascular aortic repair; BEVAR, branched endovascular aortic repair; FEVAR, fenestrated endovascular aortic repair; DAP, dose area product (mGy.cm²); Horizontal line, median.

**Figure 2. Flow cytometric and immunohistochemistry analysis of γ-H2AX and pATM expression in operators’ lymphocytes during the peri-operative period of EVAR**

Flow cytometric dot plots of lysed, fixed and permeabilised cells from whole blood collected from an operator pre, immediately after and 24hrs post FEVAR. A, Lymphocytes are identified according to forward and side scatter profile and gated according to expression of CD3. B, Example flow cytometric dot plots showing that γ-H2AX expression in CD3⁺ lymphocytes increases in an operator immediately after a complex (fenestrated) endovascular aortic repair, and falls to pre-operative levels after 24 hours. This response is also seen with lymphocyte expression of pATM. C, Immunohistochemical staining of lymphocytes (DAPI, blue) isolated from an operator shows, compared with the pre-operative sample, an increase in γ-H2AX expression (purple foci) on these cells immediately after FEVAR. γ-H2AX indicates gamma H2AX; pATM, phosphorylated ataxia telangiectasia mutated protein; EVAR, endovascular
aortic repair, FEVAR, fenestrated endovascular aortic repair; DAPI, 4',6-Diamidino-2-Phenylindole Dihydrochloride, scale bar =10μm.

**Figure 3. Changes in expression of γ-H2AX and pATM in operators’ lymphocytes in response to radiation exposure during EVAR**

**A,** Expression of γ-H2AX in operators’ lymphocytes prior to, immediately after and 24 hours after open aortic repair (n=14) and EVAR (all IEVAR and BEVAR/FEVAR procedures grouped together, n=31).  
**B,** Expression of pATM in operators’ lymphocytes prior to, immediately after and 24 hours after open aortic repair (n=14) and EVAR (n=31).  
**C,** γ-H2AX expression during the peri-operative period of BEVAR/FEVAR (n=16) compared with IEVAR (n=15).  
**D,** pATM expression during the peri-operative period of BEVAR/FEVAR (n=16) compared with IEVAR (n=15).  
**E,** Correlation between fold change increase in γ-H2AX expression and DAP (n=31).  
**F,** Correlation between fold change increase in pATM levels and DAP (n=31).  
**G,** Correlation between fold change increase in γ-H2AX levels and fluoroscopy time (n=31).  
**H,** Correlation between fold change increase in pATM levels and fluoroscopy time (n=31). None of the operators studied wore leg shielding during these procedures. γ-H2AX indicates gamma H2AX; pATM, phosphorylated ataxia telangiectasia mutated protein, EVAR, endovascular aortic repair; IEVAR, infra-renal endovascular aortic repair; BEVAR, branched endovascular aortic repair; FEVAR, fenestrated endovascular aortic repair, *P<0.05.

**Figure 4. Factors affecting γ-H2AX expression in operators**

**A,** Variation in γ-H2AX levels in operators’ lymphocytes following in vitro irradiation of their blood samples on 3 separate occasions (bars represent standard error of means, n=6, P<0.0001).
B. An operator wearing lower leg shielding (red arrows). C, γ-H2AX and pATM expression in operators’ lymphocytes with (black bars, n=9) and without (red bars, n=16) the use of leg protection during BEVAR/FEVAR procedures (P<0.05). D, Radiation exposure, measured by DAP and personal dosimeters worn at leg levels during procedures with (n=9) and without (n=16) leg shielding. γ-H2AX indicates gamma H2AX; pATM, phosphorylated ataxia telangiectasia mutated protein; BEVAR, branched endovascular aortic repair; FEVAR, fenestrated endovascular aortic repair; DAP, dose area product; *P<0.05.
A

Fluoroscopy time (min)

IEVAR BEVAR/FEVAR

B

DAP (mGy cm²)

IEVAR BEVAR/FEVAR

C

Under lead 0 (0-3) 2 (0-13)
Over lead 11 (4-74) 27 (4-150)
Leg 92 (43-203) 145 (16-416)
A  
Fixed, lysed whole blood  
T-lymphocyte gating  
T-lymphocytes backgated

B  
\( \gamma \)-H2AX Pre  
\( \gamma \)-H2AX Post  
\( \gamma \)-H2AX 24hrs

C  
Pre  
Post
Radiation Induced DNA Damage in Operators Performing Endovascular Aortic Repair
Tamer El-Sayed, Ashish S. Patel, Jun S. Cho, James A. Kelly, Francesca E. Ludwinski, Prakash Saha, Oliver T. Lyons, Alberto Smith and Bijan Modarai
Guy's and St Thomas' Research Collaborative

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SUPPLEMENTAL MATERIAL
Supplemental Methods

Flow cytometric analysis of γ-H2AX, pATM and OGG1 expression in lymphocytes

Venous blood samples were collected from operators in EDTA tubes (BD Biosciences, UK). Red blood cells were lysed using Pharmlyse (BD Biosciences, UK) for 10mins and then washed in 0.5% BSA/PBS for 5mins at 4°C. Cells were stained with FITC-conjugated mouse anti-human CD3 antibody (Miltenyi Biotec, UK), Viogreen-conjugated mouse anti-human CD4 antibody, APC/Cy7-conjugated mouse anti-human CD8 antibody, PE/Cy7-conjugated mouse anti-human CD45RO antibody (BD Biosciences, UK) and PerCP-conjugated mouse anti-human CCR7 antibody (BioLegend, UK). Cells were fixed (Inside Fix, Miltenyi Biotec, UK) for 10mins at room temperature followed by permeabilisation on ice (Permeabilisation Buffer A, Miltenyi Biotec, UK) and washed twice prior to staining for γ-H2AX and phosphorylated ATM (pATM) using anti-human APC- and PE-conjugated antibodies respectively (BD Biosciences and BioLegend, UK). T cell subsets were divided into T Helper (CD3+CD4+) and cytotoxic (CD3+CD8+) cells. These were further phenotyped into Naïve (CD3+CD4+CD45RO− and CD3+CD8−CD45RO−), central memory (CD3+CD4+CD45RO−CCR7+ and CD3+CD8+CD45RO−CCR7+) and effector memory (CD3+CD4+CD45RO−CCR7− and CD3+CD8+CD45RO−CCR7−) helper and cytotoxic T lymphocytes respectively for further analysis of γ-H2AX and pATM expression. Samples from operators performing IEVAR were also analysed for the expression of PerCP-conjugated mouse anti-human OGG1 (Novus Biologicals, UK) in addition to γ-H2AX and pATM expression as previously described.
Appendix

**Guy's and St Thomas' Cardiovascular Research Collaborative**

From Guy’s & St Thomas’ NHS Foundation Trust, London, UK.

Supplemental Tables

Supplemental Table 1. Antibodies used for flow cytometry

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<thead>
<tr>
<th>Antibody</th>
<th>Source</th>
<th>Conjugate</th>
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<tr>
<td>CD3</td>
<td>Miltenyi Biotec</td>
<td>FITC</td>
</tr>
<tr>
<td>CD4</td>
<td>BD Biosciences</td>
<td>Viogreen</td>
</tr>
<tr>
<td>CD8</td>
<td>BD Biosciences</td>
<td>APC/Cy7</td>
</tr>
<tr>
<td>CD45RO</td>
<td>BD Biosciences</td>
<td>PE/Cy7</td>
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<tr>
<td>CCR7</td>
<td>BioLegend</td>
<td>PerCP</td>
</tr>
<tr>
<td>CD14</td>
<td>BD Biosciences</td>
<td>Vioblue</td>
</tr>
<tr>
<td>CD45</td>
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<tr>
<td>pATM</td>
<td>BioLegend</td>
<td>PE</td>
</tr>
<tr>
<td>γ-H2AX</td>
<td>BD Biosciences</td>
<td>APC</td>
</tr>
<tr>
<td>OGG1</td>
<td>Novus Biologicals</td>
<td>PerCP</td>
</tr>
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</table>
Supplemental Table 2. Radiation exposure during PCI and IEVAR

A

<table>
<thead>
<tr>
<th>Radiation Exposure</th>
<th>PCI</th>
<th>IEVAR</th>
<th>P value</th>
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<tr>
<td>DAP (mGy.cm²)</td>
<td>9940 (4440-170170)</td>
<td>82786 (53611-144257)</td>
<td>0.01</td>
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<tr>
<td>Screening Time (mins)</td>
<td>11.2 (5.21-28.57)</td>
<td>24.78 (14.06-49.39)</td>
<td>0.007</td>
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</table>

<table>
<thead>
<tr>
<th>Operator personal dosimetry (μSv)</th>
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<tbody>
<tr>
<td>Under lead</td>
</tr>
<tr>
<td>Over lead</td>
</tr>
<tr>
<td>Leg</td>
</tr>
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B

<table>
<thead>
<tr>
<th>Operator</th>
<th>Age</th>
<th>Years Performing Interventions</th>
<th>Interventional sessions/week</th>
<th>Interventional cases / session</th>
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<td></td>
<td></td>
<td>As Trainee</td>
<td>As Consultant</td>
<td>As Trainee</td>
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<tr>
<td>1</td>
<td>46</td>
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<td>9</td>
<td>3</td>
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<tr>
<td>6</td>
<td>42</td>
<td>8</td>
<td>5</td>
<td>1</td>
</tr>
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</table>

A. Direct and indirect measurement of radiation exposure during PCI and IEVAR using DAP, fluoroscopy time and personal dosimetry (n=6). B. Details of age and caseload for interventional cardiologists that were performing the monitored procedures. PCI indicates percutaneous coronary intervention; IEVAR, infrarenal endovascular aortic repair; DAP, dose area product (mGy.cm²).
Supplemental Figures
Supplemental Figure 1

A  Lymphocytes  CD4 & CD8 T cells  CD8 T cells  CD4 T cells

B  CD4 Lymphocytes

C  CD8 Lymphocytes
Supplemental Figure 1. Flow cytometric analysis of γ-H2AX and pATM expression in subpopulations of T lymphocytes in operators during the peri-operative period of FEVAR

A, Representative flow cytometric dot plots showing CD3+ lymphocytes subdivided into CD8+ (cytotoxic) and CD4+ (T helper) cells. These two cell subsets are further phenotyped into CD45RO*CCR7+ (Naïve), CD45RO*CCR7+ (Central Memory, T_{CM}) and CD45RO*CCR7− (Effector Memory, T_{EM}) cells. B, Example flow cytometric dot plots show increased γ-H2AX and pATM expression in CD3+CD4+ T helper cells and their naïve, T_{CM} and T_{EM} subpopulations from the blood of an operator immediately after FEVAR. C, Example flow cytometric dot plots show an increase in γ-H2AX and pATM expression in CD3+CD8+ cytotoxic T cells and their naïve, T_{CM} and T_{EM} subpopulations from the blood of an operator immediately after FEVAR. γ-H2AX indicates gamma H2AX; pATM, phosphorylated ataxia telangiectasia mutated protein; FEVAR, fenestrated endovascular aortic repair.
Supplemental Figure 2

A

(i) CD4

(ii) CD8

(iii) CD4

(iv) CD8

B

C

D

E

E:

- CD4
  - Pre: % γ-H2AX
  - Post: % γ-H2AX

- CD8
  - Pre: % γ-H2AX
  - Post: % γ-H2AX

D:

- CD4
  - Naive: % γ-H2AX
  - Central memory: % γ-H2AX
  - Effector memory: % γ-H2AX

- CD8
  - Naive: % γ-H2AX
  - Central memory: % γ-H2AX
  - Effector memory: % γ-H2AX

E:

- CD4
  - Naive: % pATM
  - Central memory: % pATM
  - Effector memory: % pATM

- CD8
  - Naive: % pATM
  - Central memory: % pATM
  - Effector memory: % pATM

* indicates significant difference.
Supplemental Figure 2. Comparison of changes in γ-H2AX and pATM in T helper and cytotoxic T cell subsets during the peri-operative period of FEVAR

A, The post-operative expression of γ-H2AX was significantly higher in (i) CD4\(^+\) T helper cells (n=6, \(P<0.02\)) and (ii) CD8\(^+\) T cytotoxic cells (n=6, \(P<0.02\)) of operators performing BEVAR/FEVAR. The expression of pATM was similarly raised in (iii) CD4\(^+\) T helper (n=6, \(P<0.04\)) and (iv) CD8\(^+\) T cytotoxic cells (n=6, \(P<0.04\)). B, The post-operative γ-H2AX expression was higher in CD4\(^+\) T helper cells compared with CD8\(^+\) cytotoxic T cells in operators after FEVAR (n=6, \(P<0.04\)). C, The post-operative expression of pATM in CD4\(^+\) T helper cells and CD8\(^+\) cytotoxic T cells was comparable (n=6). D, The post-operative expression of γ-H2AX was significantly higher in CD4\(^+\) Naïve and Central memory cells compared with their CD8\(^+\) counterparts (n=6, \(P<0.05\)). E, The post-operative expression of pATM in Naïve, Central Memory and Effector memory cells was comparable in CD4\(^+\) T helper cells and CD8\(^+\) cytotoxic T cells. *\(P<0.05\). γ-H2AX indicates gamma H2AX; pATM, phosphorylated ataxia telangiectasia mutated protein; FEVAR, fenestrated endovascular aortic repair.
Supplemental Figure 3. Expression of OGG1 on γ-H2AX and pATM expressing CD3+ T lymphocytes during the peri-operative period of IEVAR

A, Flow cytometric analysis of blood taken from an operator before and after IEVAR showing an increase in lymphocyte expression of pATM and OGG1, but not γ-H2AX in CD3+ lymphocytes. Selective gating of γ-H2AX and pATM positive cells indicates a greater increase in OGG1 expression in the pATM positive population. B, Analysis of CD3+ lymphocytes, isolated from 6 operators after IEVAR, co-stained for γ-H2AX, pATM and OGG1 shows a significant increase in pATM and OGG1 (P<0.03, both), but not γ-H2AX. IEVAR indicates infrarenal endovascular aortic repair; γ-H2AX, gamma H2AX; OGG1, 8-oxoguanine glycosylase; pATM, phosphorylated ataxia telangiectasia mutated protein.
Supplemental Figure 4

A, Expression of γ-H2AX in lymphocytes prior to, immediately and 24 hours after open aortic repair (n=14) and EVAR (all IEVAR and BEVAR/FEVAR procedures grouped together, n=72). B, Expression of pATM in lymphocytes prior to, immediately and 24 hours after open aortic repair (n=14) and EVAR (n=72). C, γ-H2AX expression during the peri-
operative period of BEVAR/FEVAR (n=42) compared with IEVAR (n=30). D, pATM expression during the peri-operative period of BEVAR/FEVAR (n=42) compared with IEVAR (n=30). E, Immunohistochemical staining of lymphocytes (DAPI, blue) isolated from a patient shows, compared with the pre-operative sample, an increase in γ-H2AX expression (purple foci) in these cells immediately after EVAR. *P<0.05. γ-H2AX indicates gamma H2AX; pATM, EVAR, endovascular aortic repair; IEVAR, infra-renal endovascular aortic repair; BEVAR, branched endovascular aortic repair; FEVAR, fenestrated endovascular aortic repair; phosphorylated ataxia telangiectasia mutated protein. DAPI, 4',6-Diamidino-2-Phenylindole Dihydrochloride, scale bar =10µm.
2017 AHA/ACC/HRS Systematic Review for the Guideline for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death Data Supplement

Table of Contents
Part 1. For Asymptomatic Patients With Brugada Syndrome, What is the Association Between an Abnormal Programmed Ventricular Stimulation Study and Sudden Cardiac Death and Other Arrhythmia Endpoints?............................................................................................................................................................2
Part 2. What is the Impact of ICD Implantation for Primary Prevention in Older Patients and Patients with Significant Comorbidities?.......................................................23
References..............................................................................................................................................................................................................62

Abbreviation List:
1° indicates primary; 2°, secondary; ACC, American College of Cardiology; AF, atrial fibrillation; AHA, American Heart Association; BMI, body mass index; BUN, blood urea nitrogen; CABG, coronary artery bypass graft surgery; CAD indicates coronary artery disease; CCI, charlson comorbidity index; CI, confidence interval; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; ECG, electrocardiogram; EP, electrophysiologic; ESRD, end stage renal disease; FDA, food and drug administration; HF, heart failure; HR, hazard ratio; HTN, hypertension; IHD, ischemic heart disease; ICD, implantable cardioverter defibrillator; LV, left ventricular; LVEF, ejection fraction; MI, myocardial infarction; N/A, not available; NYHA, New York Heart Association; NICM, nonischemic cardiomyopathy; PCI, primary coronary intervention; PES, programmed electrical stimulation; OR, odds ratio; RCT, randomized control trial; RR, relative risk; SBP, systolic blood pressure; SCD, sudden cardiac disease; TIA, transient ischemic attack; VA, ventricular arrhythmia; VF, ventricular fibrillation; and VT, ventricular tachycardia.
### Part 1. For Asymptomatic Patients With Brugada Syndrome, What is the Association Between an Abnormal Programmed Ventricular Stimulation Study and Sudden Cardiac Death and Other Arrhythmia Endpoints?

<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Aim of Study; Study Design; Study Size (N)</th>
<th>Patient Population</th>
<th>Study Intervention (# pts) / Study Comparator (# pts)</th>
<th>Endpoint Results (Absolute Event Rates, P values; OR or RR; &amp; 95% CI)</th>
<th>Relevant 2° Endpoint (if any); Study Limitations; Adverse Events</th>
</tr>
</thead>
</table>
| Sacher F 2006 (1)                     | **Aim:** The main objective of the present study was to assess both the clinical benefit and the complication rate at implantation and during follow-up in a group of Brugada syndrome pts implanted with an ICD for primary and secondary prevention of SCD  
**Study design:** Not Reported  
**Size:** 220 Retrospective Observational | **Inclusion Criteria:**  
- Brugada syndrome  
- Implanted with an ICD  
- Type 1 ECG at baseline on at least one occasion or after provocation with a class I antiarrhythmic drug  
**Exclusion Criteria:** Not Reported | Resuscitated  
N=18  
Syncpe  
N=88  
Asymptomatic  
N=114  
Asymptomatic Inducible  
N=95  
Asymptomatic Non-Inducible  
N=15 | Resuscitated:  
ICD, Shocks, Appropriate – Median 25.5 mo - 4 (22%) - (N=18)  
ICD, Shocks, Inappropriate - Median 25.5 mo - 3 (17%) - (N=18)  
ICD, Complications – Median 25.5 mo - 5 (28%) - (N=18)  
Syncope:  
ICD, Shocks, Appropriate - Median 39.5 mo - 9 (10%) - (N=88)  
ICD, Shocks, Inappropriate – Median 39.5 mo - 19 (22%) - (N=88)  
ICD, Complications - Median 39.5 mo - 22 (25%) - (N=88)  
Asymptomatic:  
ICD, Shocks, Appropriate – Median 31 mo - 5 (4%) - (N=114)  
ICD, Shocks, Inappropriate – Median 31 mo - 23 (20%) - (N=114)  
ICD, Complications – Median 31 mo - 35 (31%) - (N=114)  
Asymptomatic Inducible:  
ICD, Shocks, Appropriate - NR - 5 (5.3%) - (N=95)  
Asymptomatic Non-Inducible: |
<p>| ICD, Shocks, Appropriate - NR - 0 (0%) - (N=18) |</p>
<table>
<thead>
<tr>
<th><strong>Aim:</strong> We compared the clinical and ECG characteristics of symptomatic and asymptomatic pts with Brugada syndrome to identify new markers for high-risk pts.</th>
<th><strong>Aim:</strong> We report here data on the prognostic value of PES in 443 pts with Brugada syndrome, which to the best of our knowledge is the largest population collected to date.</th>
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<tbody>
<tr>
<td><strong>Study design:</strong> Retrospective Observational</td>
<td><strong>Study design:</strong> Prospective Observational</td>
</tr>
<tr>
<td><strong>Size:</strong> 188</td>
<td><strong>Size:</strong> 443</td>
</tr>
</tbody>
</table>

### Inclusion Criteria
- Brugada Syndrome
- J point amplitude >0.2mV
- Either spontaneous or drug-induced coved-type ST segment elevation (>0.1 mV) in at least two of the three right precordial leads (V1 to V3) on resting 12-lead ECG
- Normal findings on physical examination

### Exclusion Criteria
- Abnormality in right ventricular morphology demonstrated by chest radiography
- Abnormality in LV morphology demonstrated by chest radiography
- Abnormality in right ventricular function demonstrated by echocardiography
- Abnormality in LV function demonstrated by echocardiography

### Asymptomatic
- N=98

### Asymptomatic Inducible
- N=50

### Asymptomatic Non-Inducible
- N=13

<table>
<thead>
<tr>
<th>Asymptomatic</th>
<th>Asymptomatic:</th>
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<tbody>
<tr>
<td>Cardiac Event - NR - 0 (0%) (N=82)</td>
<td>Cardiac Event - NR - 0 (0%) - (N=50)</td>
</tr>
<tr>
<td>SCD - Baseline - 3 y - 0 (0%) - (N=82)</td>
<td>SCD - Baseline – 3 y - 0 (0%) - (N=50)</td>
</tr>
<tr>
<td>Ventricular Fibrillation - Baseline – 3 y - 0 (0%) - (N=82)</td>
<td>VF - Baseline – 3 y - 0 (0%) - (N=50)</td>
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</table>

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<th>Asymptomatic Inducible:</th>
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<tbody>
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<td>Cardiac Event - NR - 0 (0%) - (N=50)</td>
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<td>SCD - Baseline – 3 y - 0 (0%) - (N=50)</td>
</tr>
<tr>
<td>VF - Baseline – 3 y - 0 (0%) - (N=50)</td>
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</table>

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<thead>
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<th>Asymptomatic Non-Inducible:</th>
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</thead>
<tbody>
<tr>
<td>Cardiac Event - NR - 0 (0%) - (N=13)</td>
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<tr>
<td>SCD - Baseline – 3 y - 0 (0%) - (N=13)</td>
</tr>
<tr>
<td>VF - Baseline – 3 y - 0 (0%) - (N=13)</td>
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</table>

<table>
<thead>
<tr>
<th>Syncope:</th>
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<tbody>
<tr>
<td>Cardiac Event - NR - 3 (6%) - (N=51)</td>
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<tr>
<td>VF:</td>
</tr>
<tr>
<td>Cardiac Event - NR - 10 (30%) - (N=33)</td>
</tr>
<tr>
<td>Exclusion Criteria</td>
</tr>
<tr>
<td>--------------------</td>
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<tr>
<td>Not Reported</td>
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**Exclusion Criteria**

- Not Reported

**Inclusion Criteria**

- Brugada Syndrome, Type I, Spontaneous, ECG Diagnosis or Brugada Syndrome, Type I, Drug-Induced, ECG Diagnosis
- ICD implantation
- Continuous follow-up at UZ Brussel-VUB

**Symptomatic**

- N=180
- Arrhythmic Event - Mean 31 mo - 52 (28.9%) - (N=180)

**Aborted SCD**

- N=25
- Arrhythmic Event - Mean 31 mo - 11 (44%) - (N=25)

**Syncope**

- N=105
- Arrhythmic Event - Mean 31 mo - 8 (32%) - (N=25)

**Syncope**

- N=61
- Arrhythmic Event - Mean 31 mo - 14 (23%) N=61

**Syncope Non-Inducible**

- N=39
- Arrhythmic Event - Mean 31 mo - 2 (5.1%) - (N=39)

**Aborted SCD**

- N=25
- Arrhythmic Event - Mean 31 mo - 11 (44%) - (N=25)

**ICD**

- N=105
- Arrhythmic Event - Mean 31 mo - 8 (32%) - (N=105)

**ICD, Shocks, Inappropriate**

- N=105
- Arrhythmic Event - Mean 31 mo - 8 (32%) - (N=105)

**ICD, Shock, Appropriate**

- N=25
- Arrhythmic Event - Mean 31 mo - 11 (44%) - (N=25)

**ICD, Shock, Inappropriate**

- N=25
- Arrhythmic Event - Mean 31 mo - 11 (44%) - (N=25)

---

**Aim:** To assess the clinical features and the long-term follow-up of pts with Brugada Syndrome who underwent ICD placement and the evolution of device-based management over the past 2 decades.

**Study design:** Prospective Observational
### Exclusion Criteria
- Underlying structural cardiac abnormalities

### Inclusion Criteria
- Brugada Syndrome
- Implanted with an ICD
- Type 1 Brugada pattern on ECG at baseline on at least 1 occasion or after provocation with a class I antiarrhythmic drug

### Study Design
- Retrospective Observational

### Aim
We report the outcome of pts with Brugada syndrome implanted with an ICD in a large multicenter registry.

### Size
- 176 pts for Exclusion Criteria
- 378 pts for Inclusion Criteria

### Asymptomatic
- **ICD, Shocks, Appropriate** - Mean 83.8 mo - 6 (13%) - (N=46)
- **ICD, Shocks, Inappropriate** - Mean 83.8 mo - 7 (15.2%) - (N=46)

### Asymptomatic Inducible
- **ICD, Shocks, Appropriate** - Mean 85 mo - 12 (7%) - (N=166)
- **ICD, Shocks, Appropriate - Baseline–1 y** - 2 (1%) - (N=166)
- **ICD, Shocks, Appropriate - Baseline–2 y** - 3 (2%) - (N=166)
- **ICD, Shocks, Appropriate - Baseline–3 y** - 7 (4%) - (N=166)
- **ICD, Shocks, Appropriate - Baseline–4 y** - 10 (6%) - (N=166)
- **ICD, Shocks, Appropriate - Baseline–5 y** - 10 (6%) - (N=166)
- **ICD, Shocks, Appropriate - Baseline–10y** - 20 (12%) - (N=166)
- **ICD, Shocks, Inappropriate** - Mean 85 mo - 47 (28%) - (N=166)

### Asymptomatic Non-Inducible
- **ICD, Shocks, Appropriate** - NR - 1 (5%) - (N=20)

### Aborted Sudden Cardiac Arrest
- **ICD, Shocks, Appropriate** - NR - 11 (8.5%) - (N=130)

### Lead Failure
- **ICD, Shocks** - Mean 85 mo - 28 (17%) - (N=166)

### Syncope
- **ICD, Shocks, Appropriate** - Mean 85 mo - 7 (4%) - (N=166)
ICD, Removal without Reimplantation - Mean 67 mo - 0 (0%) - (N=31)
Lead Failure - Mean 85 mo - 3 (10%) - (N=31)
ICD, Shocks, Appropriate - Mean 85 mo - 12 (39%) - (N=31)
ICD, Shocks, Appropriate - Baseline-1 y - 8 (25%) - (N=31)
ICD, Shocks, Appropriate - Baseline-2 y - 9 (30%) - (N=31)
ICD, Shocks, Appropriate - Baseline-3 y - 11 (36%) - (N=31)
ICD, Shocks, Appropriate - Baseline-4 y - 13 (41%) - (N=31)
ICD, Shocks, Appropriate - Baseline-5 y - 15 (48%) - (N=31)
ICD, Shocks, Appropriate - Baseline-10 y - 15 (48%) - (N=31)
ICD, Shocks, Inappropriate - Mean 67 mo - 6 (19%) - (N=31)

Syncope:
ICD, Removal without Reimplantation - Mean 71 mo - 3 (1.7%) - (N=181)
Lead Failure - Mean 85 mo - 29 (16%) - (N=181)
ICD, Shocks, Appropriate - Mean 85 mo - 22 (12%) - (N=181)
ICD, Shocks, Appropriate - Baseline-1 y - 5 (3%) - (N=181)
ICD, Shocks, Appropriate - Baseline-2 y - 11 (6%) - (N=181)
ICD, Shocks, Appropriate - Baseline-3 y - 13 (7%) - (N=181)
ICD, Shocks, Appropriate - Baseline-4 y - 18 (10%) - (N=181)
ICD, Shocks, Appropriate - Baseline-5 y - 20 (11%) - (N=181)
| Aim: To investigate the clinical characteristics, management, and long-term prognosis of asymptomatic Brugada syndrome pts. | Study design: Prospective Observational Size: 363 |
| Inclusion Criteria | Asymptomatic N=363 |
| - Brugada Syndrome, Type I, Spontaneous, ECG Diagnosis or Brugada Syndrome, Type I, Drug-Induced, ECG Diagnosis | Asymptomatic Inducible N=32 |
| Exclusion Criteria | Asymptomatic Non-Inducible N=289 |
| - Underlying structural cardiac abnormalities - Brugada Syndrome, Symptomatic - Syncope, History of - SCD, History of | |
| Asymptomatic: Fracture of Ventricular Electrode - Mean 73.2 mo - 5 (8.2%) - (N=61) |
| ICD, Complications - Mean 73.2 mo - 6 (9.8%) - (N=61) |
| Infection, Any - Mean 73.2 mo - 1 (1.6%) - (N=61) |
| Arrhythmic Event - Mean 73.2 mo - 9 (3%) - (N=303) |
| ICD, Shocks, Appropriate - Mean 73.2 mo - 5 (15.6%) - (N=32) |
| ICD, Shocks, Inappropriate - Mean 34.2 mo - 9 (14.8%) - (N=61) |
| SCD - Mean 73.2 mo - 2 (0.7%) - (N=303) |
| SCD, Aborted - Mean 73.2 mo - 1 (0.3%) - (N=303) |
| Asymptomatic Inducible: Arrhythmic Event - Mean 73.2 mo - 5 (15.6%) - (N=32) |
| ICD, Shocks, Appropriate - Mean 73.2 mo - 5 (15.6%) - (N=32) |
| SCD - Mean 73.2 mo - 0 (0%) - (N=32) |
| SCD, Aborted - Mean 73.2 mo - 0 (0%) - (N=32) |
| Asymptomatic Non-Inducible: Arrhythmic Event - Mean 73.2 mo - 3 (1%) - (N=289) |
| ICD, Shocks, Appropriate - Mean 73.2 mo - 1 (0.3%) - (N=289) |
| SCD - Mean 73.2 mo - 1 (0.3%) - (N=289) |
Sieira J 2015 (7)  
25904495

**Aim:** The purpose of this study was to analyze our single-center experience of PES VA inducibility in pts with BS gathered in the last 20 y, since the first description of the syndrome.

**Study design:** Retrospective Observational

**Size:** 404

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Asymptomatic</th>
<th>Asymptomatic Non-Inducible</th>
<th>Aborted Sudden Death</th>
<th>Aborted Sudden Death Non-Inducible</th>
<th>Syncope</th>
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</thead>
<tbody>
<tr>
<td>- Brugada Syndrome</td>
<td>N=273</td>
<td></td>
<td>N=17</td>
<td></td>
<td>N=114</td>
</tr>
<tr>
<td>- Brugada Syndrome, Type I, Drug-Induced, ECG Diagnosis or Brugada Syndrome, Type I, Spontaneous, ECG Diagnosis</td>
<td>Asymptomatic Non-Inducible</td>
<td>N=241</td>
<td>Aborted Sudden Death Non-Inducible</td>
<td>N=13</td>
<td>Syncope</td>
</tr>
<tr>
<td>- Follow-up longer than 1 y achieved</td>
<td>Asymptomatic</td>
<td>N=32</td>
<td>Aborted Sudden Death</td>
<td>N=17</td>
<td>Aborted Sudden Death</td>
</tr>
<tr>
<td>- PES VT induction protocol performed</td>
<td>Asymptomatic</td>
<td>N=32</td>
<td>Aborted Sudden Death</td>
<td>N=17</td>
<td>Aborted Sudden Death</td>
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</tbody>
</table>

- Underlying structural cardiac abnormalities, found by noninvasive methods, including echocardiogram
- Underlying structural cardiac abnormalities, found by noninvasive methods, including stress tests
- Underlying structural

<table>
<thead>
<tr>
<th>Exclusion Criteria</th>
<th>Asymptomatic:</th>
<th>Asymptomatic Non-Inducible:</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Underlying structural cardiac abnormalities, found by noninvasive methods, including echocardiogram</td>
<td>SCD, Aborted - Mean 74.3 mo - 1 (0.4%) - (N=273)</td>
<td>Arrhythmic Event - Mean 74.3 mo - 2 (0.8%) - (N=241)</td>
</tr>
<tr>
<td>- Underlying structural cardiac abnormalities, found by noninvasive methods, including stress tests</td>
<td>Arrhythmic Event - Mean 74.3 mo - 2 (0.8%) - (N=241)</td>
<td>ICD, Shocks, Appropriate - Mean 74.3 mo - 1 (0.4%) - (N=241)</td>
</tr>
<tr>
<td>- Underlying structural</td>
<td>SCD, Aborted - Mean 74.3 mo - 1 (0.4%) - (N=273)</td>
<td>Arrhythmic Event - Mean 74.3 mo - 2 (0.8%) - (N=241)</td>
</tr>
<tr>
<td>- Underlying structural cardiac abnormalities, found by noninvasive methods, including stress tests</td>
<td>ICD, Shocks, Appropriate - Mean 74.3 mo - 1 (0.4%) - (N=241)</td>
<td>ICD, Shocks, Appropriate - Mean 74.3 mo - 1 (0.4%) - (N=241)</td>
</tr>
<tr>
<td>- Underlying structural</td>
<td>Arrhythmic Event - Mean 74.3 mo - 2 (0.8%) - (N=241)</td>
<td>Arrhythmic Event - Mean 74.3 mo - 2 (0.8%) - (N=241)</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th></th>
<th>Syncope Non-Inducible</th>
<th>Aborted Sudden Death Inducible</th>
<th>Syncope Inducible</th>
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<tbody>
<tr>
<td>N=77</td>
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<td></td>
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<tr>
<td>Syncope:</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>SCD, Aborted</td>
<td>Mean 74.3 mo</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>(N=114)</td>
<td></td>
<td></td>
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<tr>
<td>Syncope Non-Inducible:</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Arrhythmic Event</td>
<td>Mean 74.3 mo</td>
<td>4 (5.2%)</td>
<td></td>
</tr>
<tr>
<td>(N=77)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Syncope Inducible:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SCD, Aborted</td>
<td>Mean 74.3 mo</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>(N=37)</td>
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</table>
**Aim:** The PRELUDE prospective registry was designed to assess the predictive accuracy of sustained VT/VF inducibility and to identify additional predictors of arrhythmic events in Brugada syndrome pts without history of VT/VF

**Study design:** Prospective Observational

**Size:** 308

<table>
<thead>
<tr>
<th><strong>Inclusion Criteria</strong></th>
<th><strong>Asymptomatic</strong></th>
<th><strong>Asymptomatic Non-Inducible</strong></th>
<th><strong>Syncope</strong></th>
<th><strong>Syncope Inducible</strong></th>
<th><strong>Syncope Non-Inducible</strong></th>
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</thead>
<tbody>
<tr>
<td>- Brugada Syndrome</td>
<td>N=244</td>
<td>N=NR</td>
<td>N=64</td>
<td>N=NR</td>
<td>N=NR</td>
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<tr>
<td>- Age &gt;18 y</td>
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<tr>
<td>- Spontaneous or a pharmacologically induced type I ECG pattern</td>
<td></td>
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<tr>
<td>- Coved ST-segment elevation &gt;2mm in at least 2 right precordial leads</td>
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</table>

<table>
<thead>
<tr>
<th><strong>Exclusion Criteria</strong></th>
<th><strong>Asymptomatic:</strong></th>
<th><strong>Asymptomatic Non-Inducible:</strong></th>
<th><strong>Syncope:</strong></th>
<th><strong>Syncope Inducible:</strong></th>
<th><strong>Syncope Non-Inducible:</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>- Experienced cardiac arrest</td>
<td>Arrhythmic Event - Mean 36 mo - 7 (2.9%) - (N=244)</td>
<td>Arrhythmic Event - Mean 36 mo - 4 (NR%) - (N=NR)</td>
<td>Cardiac Arrest, Resuscitated - Mean 36 mo - 1 (0.4%) - (N=244)</td>
<td>ICD, Shocks, Appropriate - Mean 36 mo - 3 (NR%) - (N=NR)</td>
<td>SCD - Mean 36 mo - 0 (0%) - (N=NR)</td>
</tr>
<tr>
<td>- Experienced sustained VT</td>
<td>Cardiac Arrest, Resuscitated - Mean 36 mo - 0 (0%) - (N=244)</td>
<td>Cardiac Arrest, Resuscitated - Mean 36 mo - 0 (0%) - (N=NR)</td>
<td>ICD, Shocks, Appropriate - Mean 36 mo - 3 (NR%) - (N=NR)</td>
<td>SCD - Mean 36 mo - 0 (0%) - (N=NR)</td>
<td></td>
</tr>
<tr>
<td>- Structural cardiac abnormalities verified by echocardiography</td>
<td>Cardiac Arrest, Resuscitated - Mean 36 mo - 0 (0%) - (N=244)</td>
<td>Cardiac Arrest, Resuscitated - Mean 36 mo - 0 (0%) - (N=NR)</td>
<td>ICD, Shocks, Appropriate - Mean 36 mo - 3 (NR%) - (N=NR)</td>
<td>SCD - Mean 36 mo - 0 (0%) - (N=NR)</td>
<td></td>
</tr>
<tr>
<td>- Structural cardiac abnormalities verified by exercise stress test</td>
<td>Cardiac Arrest, Resuscitated - Mean 36 mo - 0 (0%) - (N=244)</td>
<td>Cardiac Arrest, Resuscitated - Mean 36 mo - 0 (0%) - (N=NR)</td>
<td>ICD, Shocks, Appropriate - Mean 36 mo - 3 (NR%) - (N=NR)</td>
<td>SCD - Mean 36 mo - 0 (0%) - (N=NR)</td>
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</tr>
<tr>
<td>- Previous MI, verified by echocardiography</td>
<td>Cardiac Arrest, Resuscitated - Mean 36 mo - 0 (0%) - (N=244)</td>
<td>Cardiac Arrest, Resuscitated - Mean 36 mo - 0 (0%) - (N=NR)</td>
<td>ICD, Shocks, Appropriate - Mean 36 mo - 3 (NR%) - (N=NR)</td>
<td>SCD - Mean 36 mo - 0 (0%) - (N=NR)</td>
<td></td>
</tr>
<tr>
<td>- Cardiomyopathies, verified by echocardiography</td>
<td>Cardiac Arrest, Resuscitated - Mean 36 mo - 0 (0%) - (N=244)</td>
<td>Cardiac Arrest, Resuscitated - Mean 36 mo - 0 (0%) - (N=NR)</td>
<td>ICD, Shocks, Appropriate - Mean 36 mo - 3 (NR%) - (N=NR)</td>
<td>SCD - Mean 36 mo - 0 (0%) - (N=NR)</td>
<td></td>
</tr>
<tr>
<td>- Angina, verified by echocardiography</td>
<td>Cardiac Arrest, Resuscitated - Mean 36 mo - 0 (0%) - (N=244)</td>
<td>Cardiac Arrest, Resuscitated - Mean 36 mo - 0 (0%) - (N=NR)</td>
<td>ICD, Shocks, Appropriate - Mean 36 mo - 3 (NR%) - (N=NR)</td>
<td>SCD - Mean 36 mo - 0 (0%) - (N=NR)</td>
<td></td>
</tr>
<tr>
<td>- LV hypertrophy, verified by echocardiography</td>
<td>Cardiac Arrest, Resuscitated - Mean 36 mo - 0 (0%) - (N=244)</td>
<td>Cardiac Arrest, Resuscitated - Mean 36 mo - 0 (0%) - (N=NR)</td>
<td>ICD, Shocks, Appropriate - Mean 36 mo - 3 (NR%) - (N=NR)</td>
<td>SCD - Mean 36 mo - 0 (0%) - (N=NR)</td>
<td></td>
</tr>
<tr>
<td>- Previous MI, verified by exercise stress test</td>
<td>Cardiac Arrest, Resuscitated - Mean 36 mo - 0 (0%) - (N=244)</td>
<td>Cardiac Arrest, Resuscitated - Mean 36 mo - 0 (0%) - (N=NR)</td>
<td>ICD, Shocks, Appropriate - Mean 36 mo - 3 (NR%) - (N=NR)</td>
<td>SCD - Mean 36 mo - 0 (0%) - (N=NR)</td>
<td></td>
</tr>
<tr>
<td>- Cardiomyopathies, verified by exercise stress test</td>
<td>Cardiac Arrest, Resuscitated - Mean 36 mo - 0 (0%) - (N=244)</td>
<td>Cardiac Arrest, Resuscitated - Mean 36 mo - 0 (0%) - (N=NR)</td>
<td>ICD, Shocks, Appropriate - Mean 36 mo - 3 (NR%) - (N=NR)</td>
<td>SCD - Mean 36 mo - 0 (0%) - (N=NR)</td>
<td></td>
</tr>
<tr>
<td>- Angina, verified by exercise stress test</td>
<td>Cardiac Arrest, Resuscitated - Mean 36 mo - 0 (0%) - (N=244)</td>
<td>Cardiac Arrest, Resuscitated - Mean 36 mo - 0 (0%) - (N=NR)</td>
<td>ICD, Shocks, Appropriate - Mean 36 mo - 3 (NR%) - (N=NR)</td>
<td>SCD - Mean 36 mo - 0 (0%) - (N=NR)</td>
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<tr>
<td>- LV hypertrophy, verified by exercise stress test</td>
<td>Cardiac Arrest, Resuscitated - Mean 36 mo - 0 (0%) - (N=244)</td>
<td>Cardiac Arrest, Resuscitated - Mean 36 mo - 0 (0%) - (N=NR)</td>
<td>ICD, Shocks, Appropriate - Mean 36 mo - 3 (NR%) - (N=NR)</td>
<td>SCD - Mean 36 mo - 0 (0%) - (N=NR)</td>
<td></td>
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<tr>
<td>- Cardiac diseases, verified by echocardiography</td>
<td>Cardiac Arrest, Resuscitated - Mean 36 mo - 0 (0%) - (N=244)</td>
<td>Cardiac Arrest, Resuscitated - Mean 36 mo - 0 (0%) - (N=NR)</td>
<td>ICD, Shocks, Appropriate - Mean 36 mo - 3 (NR%) - (N=NR)</td>
<td>SCD - Mean 36 mo - 0 (0%) - (N=NR)</td>
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</tbody>
</table>

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|                  | Cardiac diseases, verified by exercise stress test | (NR%) - (N=NR)
Cardiac Arrest, Resuscitated - Mean 36 mo - 0 (0%) - (N=NR)
ICD, Shocks, Appropriate - Mean 36 mo - 2 (NR%) - (N=NR)
SCD - Mean 36 mo - 0 (0%) - (N=NR)

Syncope Non-Inducible:
Arrhythmic Event - Mean 36 mo - 5 (NR%) - (N=NR)
Cardiac Arrest, Resuscitated - Mean 36 mo - 0 (0%) - (N=NR)
ICD, Shocks, Appropriate - Mean 36 mo - 5 (NR%) - (N=NR)
SCD - Mean 36 mo - 0 (0%) - (N=NR) |
**Aim:** The aim of this study was to prospectively evaluate the incidence of arrhythmic events and the prognostic role of clinical presentation, ECG, and of a standardized PES protocol in consecutive cases from a community-based population.

**Study design:** Prospective Observational

**Size:** 166

### Inclusion Criteria
- Brugada Syndrome
- Brugada type 1 ECG spontaneously or after pharmacological testing with class 1 C drugs

### Exclusion Criteria
Not Reported

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<th>Asymptomatic Inducible</th>
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<tr>
<td>Asymptomatic Non-Inducible</td>
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<tr>
<td>Asymptomatic</td>
<td>N=103</td>
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<tr>
<td>Syncope Inducible</td>
<td>N=26</td>
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<tr>
<td>Syncope Non-Inducible</td>
<td>N=24</td>
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<tr>
<td>Aborted Sudden Death Inducible</td>
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<td>Aborted Sudden Death Non-Inducible</td>
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<td>Syncope</td>
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<td>Aborted Sudden Death</td>
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<td>Symptomatic</td>
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<table>
<thead>
<tr>
<th>Asymptomatic Inducible: Arrhythmic Event</th>
<th>Mean 30 mo - 0 (0%) - (N=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCD</td>
<td>Mean 30 mo - 0 (0%) - (N=17)</td>
</tr>
<tr>
<td>Ventricular Arrhythmias, Sustained</td>
<td>Mean 30 mo - 0 (0%) - (N=17)</td>
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<table>
<thead>
<tr>
<th>Asymptomatic Non-Inducible: Arrhythmic Event</th>
<th>Mean 30 mo - 0 (0%) - (N=64)</th>
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</thead>
<tbody>
<tr>
<td>SCD</td>
<td>Mean 30 mo - 0 (0%) - (N=64)</td>
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<tr>
<td>Ventricular Arrhythmias, Sustained</td>
<td>Mean 30 mo - 0 (0%) - (N=64)</td>
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<table>
<thead>
<tr>
<th>Asymptomatic: Arrhythmic Event</th>
<th>Mean 30 mo - 1 (1%) - (N=103)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICD, Shocks, Appropriate</td>
<td>Mean 30 mo - 1 (1%) - (N=103)</td>
</tr>
<tr>
<td>SCD</td>
<td>Mean 30 mo - 1 (1%) - (N=103)</td>
</tr>
<tr>
<td>Ventricular Arrhythmias, Sustained</td>
<td>Mean 30 mo - 0 (0%) - (N=103)</td>
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</table>

<table>
<thead>
<tr>
<th>Syncope Inducible: Arrhythmic Event</th>
<th>Mean 30 mo - 0 (0%) - (N=26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICD, Shocks, Appropriate</td>
<td>Mean 30 mo - 5 (19.2%) - (N=26)</td>
</tr>
<tr>
<td>SCD</td>
<td>Mean 30 mo - 0 (0%) - (N=26)</td>
</tr>
<tr>
<td>Ventricular Arrhythmias, Sustained</td>
<td>Mean 30 mo - 5 (19.2%) - (N=26)</td>
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</table>

<table>
<thead>
<tr>
<th>Syncope Non-Inducible: Arrhythmic Event</th>
<th>Mean 30 mo - 0 (0%) - (N=24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCD</td>
<td>Mean 30 mo - 0 (0%) - (N=24)</td>
</tr>
<tr>
<td>Ventricular Arrhythmias, Sustained</td>
<td>Mean 30 mo - 0 (0%) - (N=24)</td>
</tr>
</tbody>
</table>
Aborted Sudden Death Inducible:
Arrhythmic Event - Mean 30 mo - 0 (0%) - (N=3)
ICD, Shocks, Appropriate - Mean 30 mo - 2 (66.7%) - (N=3)
SCD - Mean 30 mo - 0 (0%) - (N=3)
Ventricular Arrhythmias, Sustained - Mean 30 mo - 2 (66.7%) - (N=3)

Aborted Sudden Death Non-Inducible:
Arrhythmic Event - Mean 30 mo - 0 (0%) - (N=1)
SCD - Mean 30 mo - 0 (0%) - (N=1)
Ventricular Arrhythmias, Sustained - Mean 30 mo - 0 (0%) - (N=1)

Syncope:
Arrhythmic Event - Mean 30 mo - 5 (8.6%) - (N=58)
ICD, Shocks, Appropriate - Mean 30 mo - 5 (8.6%) - (N=58)
SCD - Mean 30 mo - 0 (0%) - (N=58)
Ventricular Arrhythmias, Sustained - Mean 30 mo - 5 (8.6%) - (N=58)

Aborted Sudden Death:
Arrhythmic Event - Mean 30 mo - 3 (60%) - (N=5)
ICD, Shocks, Appropriate - Mean 30 mo - 3 (60%) - (N=5)
SCD - Mean 30 mo - 0 (0%) - (N=5)
Ventricular Arrhythmias, Sustained - Mean 30 mo - 3 (60%) - (N=5)
**Aim:** From a large cohort of Brugada syndrome pts, we present data at variance with the current view and propose that in analogy with the long-QT syndrome, the Brugada syndrome is characterized by incomplete penetrance and heterogeneous clinical phenotype (S.G.P., unpublished data, 1999).

**Study design:** Prospective Observational

**Size:** 60

<table>
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<tr>
<th>Inclusion Criteria</th>
<th>Asymptomatic</th>
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<th>Asymptomatic Non-Inducible</th>
<th>Symptomatic</th>
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<td>N=30</td>
<td>N=13</td>
<td>N=6</td>
<td>N=30</td>
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<tr>
<td>Brugada Syndrome, Clinical Diagnosis</td>
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<tr>
<td>Brugada Syndrome, ECG Diagnosis</td>
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</table>

**Exclusion Criteria**

- Structural heart disease, defined by evaluation of blood enzymes
- Structural heart disease, defined by evaluation of electrolytes
- Structural heart disease, defined by Holter monitoring
- Structural heart disease, defined by echocardiogram with careful evaluation of the right ventricle
- Structural heart disease, defined by stress test
- Structural heart disease, defined by nuclear MR

- Structural heart disease, defined by evaluation of blood enzymes
- Structural heart disease, defined by evaluation of electrolytes
- Structural heart disease, defined by Holter monitoring
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- Structural heart disease, defined by evaluation of electrolytes
- Structural heart disease, defined by Holter monitoring
- Structural heart disease, defined by echocardiogram with careful evaluation of the right ventricle
- Structural heart disease, defined by stress test
- Structural heart disease, defined by nuclear MR

- Structural heart disease, defined by evaluation of blood enzymes
- Structural heart disease, defined by evaluation of electrolytes
- Structural heart disease, defined by Holter monitoring
- Structural heart disease, defined by echocardiogram with careful evaluation of the right ventricle
- Structural heart disease, defined by stress test
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- Structural heart disease, defined by evaluation of electrolytes
- Structural heart disease, defined by Holter monitoring
- Structural heart disease, defined by echocardiogram with careful evaluation of the right ventricle
- Structural heart disease, defined by stress test
- Structural heart disease, defined by nuclear MR
### Aim
To investigate the long-term prognosis of probands with noncoved type ST-elevation in leads V1–V3, prospectively, and compared it with that of probands with the type 1 ST-elevation.

### Study design
Prospective Observational

### Size: 330

### Inclusion Criteria
- Brugada Syndrome
- Normal findings on physical examination
- Probands
- J-point (QRS-ST junction) amplitude of ≥0.1 mV (1 mm) with either coved or saddle back type ST-segment elevation in at least 2 of the 3 precordial leads (V1–V3) on resting standard 12-lead ECG

### Exclusion Criteria
- Abnormality in right ventricular morphology demonstrated by chest radiography
- Abnormality in LV morphology demonstrated by chest radiography
- Abnormality in right ventricular function demonstrated by echocardiography
- Abnormality in LV function demonstrated by echocardiography
- Vasospastic angina
- Vasovagal syncope
- Abnormality in right ventricular function demonstrated by chest radiography
- Abnormality in LV function demonstrated by chest radiography

### Table

<table>
<thead>
<tr>
<th>Group</th>
<th>Asymptomatic</th>
<th>Arrhythmic Event, Fatal - Mean 47.7 mo</th>
</tr>
</thead>
<tbody>
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<td>Symptomless</td>
<td>N=207</td>
<td>3 (1.4%) - (N=207)</td>
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<tr>
<td>Symptomless Inducible</td>
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<td>1 (1.6%) - (N=61)</td>
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<td>N=62</td>
<td>2 (3.2%) - (N=62)</td>
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<tr>
<td>Type 1 Spontaneous</td>
<td>N=108</td>
<td>3 (2.8%) - (N=108)</td>
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<td>Type 1 Spontaneous Inducible</td>
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<td>1 (3.1%) - (N=32)</td>
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<td>2 (8%) - (N=25)</td>
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<tr>
<td>Type 1 Drug-Induced</td>
<td>N=46</td>
<td>0 (0%) - (N=46)</td>
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<tr>
<td>Type 1 Drug-Induced Inducible</td>
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<td>0 (0%) - (N=20)</td>
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<tr>
<td>Asymptomatic Non-Type 1 Non-Inducible</td>
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<td>VF</td>
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<td>Syncope</td>
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<td>VF Non-Inducible</td>
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<td>4 (22.2%)</td>
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<tr>
<td>VF Inducible</td>
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<tr>
<td>VF Type 1 Spontaneous</td>
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<td>12 (34.3%)</td>
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</tbody>
</table>

- Abnormality in right ventricular morphology demonstrated by echocardiography
- Abnormality in LV morphology demonstrated by echocardiography
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<tr>
<th>Spontaneous Inducible N=22</th>
<th>VF Type 1 Spontaneous Inducible: Arrhythmic Event, Fatal - Mean 51.9 mo - 8 (36.4%) - (N=22)</th>
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<tbody>
<tr>
<td>VF Type 1 Spontaneous Non-Inducible N=10</td>
<td>VF Type 1 Spontaneous Non-Inducible: Arrhythmic Event, Fatal - Mean 51.9 mo - 3 (30%) - (N=10)</td>
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<tr>
<td>VF Type 1 Drug-Induced Non-Inducible N=4</td>
<td>VF Type 1 Drug-Induced Non-Inducible: Arrhythmic Event, Fatal - Mean 51.9 mo - 0 (0%) - (N=4)</td>
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<tr>
<td>VF Non-Type 1 Inducible N=7</td>
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<tr>
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<td>VF Non-Type 1 Non-Inducible: Arrhythmic Event, Fatal - Mean 51.9 mo - 1 (25%) - (N=4)</td>
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<tr>
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<tr>
<td>Syncope Type 1</td>
<td>Syncope Type 1 Spontaneous:</td>
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<td>Category</td>
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<td>VF Type 1</td>
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<td>Syncope Type 1:</td>
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<tr>
<td>Type</td>
<td>N</td>
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<td>Syncope Type 1</td>
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<td>VF Non-Type 1</td>
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<td>Syncope Non-type 1</td>
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</table>
Aim: Brugada et al very recently reported on a large number of individuals with an ECG diagnostic of Brugada syndrome and no previous cardiac arrest. During a mean follow-up of 2 y, 8% of these pts suffered SCD or had documented VF. In contrast, Priori et al. demonstrated that asymptomatic individuals and in particular individuals with only transient ECG abnormalities are at low risk of SCD. Therefore, our goal was to verify these 2 opposite standpoints and to present long-term follow-up data on clinical and EP parameters in a large number of individuals with a so-called type 1 ECG compatible with Brugada syndrome.

**Study design:** Prospective Observational

**Size:** 212

**Inclusion Criteria**
- Brugada Syndrome, ECG Diagnosis
- Type 1 ECG at baseline or after provocation with a class I antiarrhythmic drug

**Exclusion Criteria**
- Underlying structural heart disease confirmed by echocardiography
- Underlying structural heart disease confirmed by cardiac catheterization
- Underlying structural heart disease confirmed by chest x-ray
- Underlying structural heart disease confirmed by exercise testing
- Acute ischemia confirmed by laboratory tests
- Metabolic disturbances confirmed by laboratory tests
- Electrolyte disturbances confirmed by laboratory tests
- Only saddle-type ECG changes not changing to a type 1 pattern after drug testing with a class I agent

<table>
<thead>
<tr>
<th>Symptom Group</th>
<th>Arrhythmic Event</th>
<th>SCD</th>
<th>VF</th>
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</table>

Asymptomatic: Arrhythmic Event - Mean 33.7 mo - 1 (0.8%) - (N=123)
SCD - Mean 33.7 mo - 0 (0%) - (N=123)
VF - Mean 33.7 mo - 1 (0.8%) - (N=123)

Asymptomatic Inducible: Arrhythmic Event - NR - 1 (2.6%) - (N=38)
SCD - NR - 0 (0%) - (N=38)
VF - NR - 1 (2.6%) - (N=38)

Asymptomatic Non-Inducible: Arrhythmic Event - NR - 0 (0%) - (N=60)
SCD - NR - 0 (0%) - (N=60)
VF - NR - 0 (0%) - (N=60)

Aborted SCD: Arrhythmic Event - Mean 83.2 mo - 4 (17%) - (N=24)

Syncope: Arrhythmic Event - Mean 38.9 mo - 4 (6%) - (N=65)
### Aim
The aim of the present study was to evaluate the prognosis and risk factors of SCD in Brugada syndrome pts in the FINGER Brugada syndrome registry.

### Study design
Prospective Observational

### Inclusion Criteria
- Brugada Syndrome
- Type 1 ECG

### Exclusion Criteria
- Diseases that mimic Brugada Syndrome
- Children <16y old

### Size: 1029

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<th>Asymptomatic Non-Inducible</th>
<th>Cardiac Arrest</th>
<th>Cardiac Arrest Inducible</th>
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## Part 2. What is the Impact of ICD Implantation for Primary Prevention in Older Patients and Patients with Significant Comorbidities?

<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Aim of Study; Study Design; Study Size (N)</th>
<th>Patient Population</th>
<th>Study Intervention (N (# pts) / Study Comparator (# pts))</th>
<th>Endpoint Results (Absolute Event Rates, P values; OR or RR; &amp; 95% CI)</th>
<th>Relevant 2° Endpoint (if any); Study Limitations; Adverse Events</th>
</tr>
</thead>
</table>
| MADIT II  
Moss AJ 2002 (14)  
11907286 | **Aim:** To evaluate the effect of an ICD on survival in pts with reduced LV function after MI.  
**Study type:** RCT  
**Size:** 1,232 | **Inclusion Criteria:**  
- Age ≥21 y  
- EF ≤0.30 within 3 mo before entry, as assessed by angiography, radionuclide scanning, or echocardiography  
- MI ≥1 mo before entry  
- Documented finding of an abnormal Q wave on electrocardiography, elevated cardiac-enzyme levels on laboratory testing during hospitalization for suspected MI, a fixed defect on thallium scanning, or localized akinesis on ventriculography with evidence of obstructive coronary disease on angiography  

**Exclusion Criteria:**  
- Indication approved by the FDA for an ICD.  
- NYHA functional class IV at enrollment  
- Undergone coronary revascularization within the preceding 3 mo  
- MI within the past mo, as evidenced by measurement of ICD N=742  
Conventional Therapy N=490 | ICD:  
Mortality, All-Cause - 20 mo - 105 (14.2%) - (N=742)  
Conventional Therapy: Mortality, All-Cause - 20 mo - 97 (19.8%) - (N=490) | The 1° endpoint was death from any cause.  
Results adjusted for sequential monitoring  

ICD:  
ICD, Complications, Lead Problems, Requiring Surgical Intervention - Mean 20 mo – 13 (1.8%) - (N=742)  
ICD, Complications, Infection, Nonfatal, Requiring Surgical Intervention - Mean 20 mo – 5 (0.7%) - (N=742) |
- Cardiac enzyme levels
- Advanced cerebrovascular disease
- Childbearing age and not using medically prescribed contraceptive measures
- Any condition other than cardiac disease that was associated with a high likelihood of death during the trial

<table>
<thead>
<tr>
<th>Study</th>
<th>Aim</th>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
<th>ICD; Age &lt;75y N= 614</th>
<th>ICD; Age ≥75y N=128</th>
<th>Conventional Therapy; Age &lt;75y N=414</th>
<th>Conventional Therapy; Age ≥75y N=76</th>
<th>Not Reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>MADIT II</td>
<td>To evaluate the mortality benefit from ICD therapy in eligible elderly pts.</td>
<td>Prior MI &gt;1 mo before enrollment - LVEF ≤30 %</td>
<td>Advanced cerebrovascular disease - Undergone coronary revascularization within the preceding 3 mo from the time of enrollment - Preexisting indications for an ICD - NYHA functional class IV - Any other condition that was associated with a high likelihood of death during the trial</td>
<td>ICD; Age &lt;75y N= 614</td>
<td>ICD; Age ≥75y N=128</td>
<td>Conventional Therapy; Age &lt;75y N=414</td>
<td>Conventional Therapy; Age ≥75y N=76</td>
<td>Not Reported</td>
</tr>
<tr>
<td>Huang DT 2007 (15)</td>
<td>17537209</td>
<td>ICD, Complications, Difficult Lead Position - Mean 20.8 mo – 4 (0.7%) - (N=599)</td>
<td>ICD, Complications, Elevated Defibrillation Threshold - Mean 20.8 mo – 1 (0.2%) - (N=599)</td>
<td>ICD, Complications, Lead Dislodgement - Mean 20.8 mo – 9 (1.5%) - (N=599)</td>
<td>ICD, Complications, Difficult Lead Position - Mean 17.2 mo – 0 (0%) - (N= 121)</td>
<td>ICD, Complications, Elevated Defibrillation Threshold - Mean 17.2 mo – 1 (0.8%) - N=121</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Aim:** The present investigation was an analysis of the relation among the severity of renal dysfunction, risk of arrhythmic mortality, and ICD benefit in pts enrolled in the prospective MADIT-II

**Study type:** RCT

**Size:** 1232

**Inclusion Criteria:**
- MI, History of
- LVEF ≤30%

**Exclusion Criteria:**
- HF, NYHA Class IV
- Renal Failure
- Coronary revascularization within the previous 3 mo
- Elapsed interval from their most recent MI of <1 mo
- Advanced medical comorbidity

| ICD | N=738 |
| Conventional Therapy | N=485 |

- ICD; eGFR <35 mL/min/1.73 m² |
  - N=41 |

- ICD; eGFR ≥35 mL/min/1.73 m² |
  - N=227 |

- ICD; eGFR ≥60 mL/min/1.73 m² |
  - N=470 |

- ICD; eGFR ≥35 mL/min/1.73 m² |
  - N=697 |

- ICD; eGFR ≥35 mL/min/1.73 m² |
  - N=107 |

**Not Reported**

| ICD: |
| SCD - Mean 20 mo - NR |
| (N=742) |

- Conventional Therapy: |
  - SCD - Mean 20 mo - NR |
  - (N=490) |

- ICD; eGFR <35 ml per min per 1.73 m²: |
  - SCD - Mean 20 mo - NR |
  - (N=41) |

- ICD; eGFR 35–59 mL/min/1.73 m² |
  - SCD - Mean 20 mo - NR |
  - (N=227) |

- ICD; eGFR ≥60 mL/min/1.73 m² |
  - SCD - Mean 20 mo - NR |
  - (N=470) |

- ICD; eGFR ≥35 mL/min/1.73 m² |
  - SCD - Mean 20 mo - NR |
  - (N=697) |

- ICD; eGFR 35–49 mL/min/1.73 m² |
  - SCD - Mean 20 mo - NR |
  - (N=107) |
<table>
<thead>
<tr>
<th>eGFR Category</th>
<th>Group</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>50–59 mL/min/1.73 m²</td>
<td>ICD</td>
<td>120</td>
</tr>
<tr>
<td>60–89 mL/min/1.73 m²</td>
<td>ICD</td>
<td>338</td>
</tr>
<tr>
<td>≥90 mL/min/1.73 m²</td>
<td>ICD</td>
<td>132</td>
</tr>
<tr>
<td>&lt;35 mL/min/1.73 m²</td>
<td>Conventional Therapy</td>
<td>39</td>
</tr>
<tr>
<td>35–59 mL/min/1.73 m²</td>
<td>Conventional Therapy</td>
<td>160</td>
</tr>
<tr>
<td>≥60 mL/min/1.73 m²</td>
<td>Conventional Therapy</td>
<td>286</td>
</tr>
<tr>
<td>≥35 mL/min/1.73 m²</td>
<td>Conventional Therapy</td>
<td>446</td>
</tr>
<tr>
<td>35–49 mL/min/1.73 m²</td>
<td>Conventional Therapy</td>
<td>77</td>
</tr>
<tr>
<td>50–59 mL/min/1.73 m²</td>
<td>Conventional Therapy</td>
<td>83</td>
</tr>
<tr>
<td>60–89 mL/min/1.73 m²</td>
<td>Conventional Therapy</td>
<td>160</td>
</tr>
<tr>
<td>90–109 mL/min/1.73 m²</td>
<td>Conventional Therapy</td>
<td>286</td>
</tr>
<tr>
<td>≥110 mL/min/1.73 m²</td>
<td>Conventional Therapy</td>
<td>446</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Study</th>
<th>Aim</th>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
<th>Outcome</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MADIT II</strong></td>
<td>To determine the efficacy of ICD therapy in preventing SCD in post-infarction pts with advanced LV dysfunction.</td>
<td>Previous MI, LVEF ≤30%</td>
<td>NA</td>
<td>The 1° endpoint was total mortality.</td>
<td>ICD: Mortality, All-Cause - NR - 105 (14.2%) - (N=742) Conventional Therapy: Mortality, All-Cause - NR - 97 (19.8%) - (N=490)</td>
</tr>
<tr>
<td><strong>Greenberg H 2004 (17) 15093884</strong></td>
<td>N=742</td>
<td>N=490</td>
<td></td>
<td>ICD:</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>ICD</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Conventional Therapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>SCD, Clinical Classification Scheme</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td><strong>SCD, LV Dysfunction, Severe, modified Hinkle-Thaler Scheme</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>SCD, LV Dysfunction, Severe, modified Hinkle-Thaler Scheme, None</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>SCD, Primary Arrhythmia, Clinical Classification Scheme</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>SCD, Secondary Arrhythmia, Clinical Classification Scheme</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

© 2017 by the American Heart Association, Inc. and the American College of Cardiology Foundation.
| Razak E 2010 (18) | **Aim:** To examine the effect of the ICD on total mortality in pts with COPD and depressed LVEF who otherwise have an indication for ICD implantation for the primary prevention of SCD according to published guidelines.  
**Study type:** Retrospective Observational  
**Size:** 100 | **Inclusion Criteria:**  
- COPD  
- LVEF ≤ 35%  
- Cardiomyopathy | ICD  
N=30  
No ICD  
N=70 | The 1° endpoint was all-cause mortality.  
Results adjusted for:  
1. Covariates incorporated into the multivariate model including pts’ LVEF and the QRS interval on surface ECG as continuous variables and for race, the use of β-blockers and steroids as categorical variables. These covariates were examined for interactions and were found to be independent.  
2. Presence of comorbidities using the CCI. | **SCD, LV Dysfunction, Severe, modified Hinkle-Thaler Scheme - NR - 15 (3.1%) - (N=490)**  
**SCD, LV Dysfunction, Severe, modified Hinkle-Thaler Scheme, None - NR - 34 (6.9%) - (N=490)**  
**SCD, modified Hinkle-Thaler Scheme - NR - 49 (10%) - (N=490)**  
**SCD, Primary Arrhythmia, Clinical Classification Scheme - NR - 41 (8.4%) - (N=490)**  
**SCD, Secondary Arrhythmia, Clinical Classification Scheme - NR - 7 (1.4%) - (N=490)**  
**Not Reported** |
3. Predictors of ICD implantation using the propensity score method, as previously described.

ICD:
Mortality, All-Cause - Mean 3.1y - 11 (36.7%) - (N=30)
Mortality, All-Cause - Mean 3.1y - NR - (N=30); Adjusted for QRS interval etc.
Mortality, All-Cause - Mean 3.1y - NR - (N=30); Adjusted for Charlson Comorbidity
Mortality, All-Cause - Mean 3.1y - NR - (N=30); Adjusted for Propensity Score

Conventional Therapy:
Mortality, All-Cause - Mean 3.1y - 35 (50%) - (N=70)
Mortality, All-Cause - Mean 3.1y - NR - (N=70); Adjusted for QRS interval etc.
Mortality, All-Cause - Mean 3.1y - NR - (N=70); Adjusted for Charlson Comorbidity
Mortality, All-Cause - Mean 3.1y - NR - (N=70); Adjusted for Propensity Score
<table>
<thead>
<tr>
<th>Study</th>
<th>Aim</th>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
<th>Study Type</th>
<th>Size</th>
<th>Results</th>
</tr>
</thead>
</table>
| MADIT II | To determine the efficacy of ICD therapy in high-risk subgroups defined by NYHA functional class, EF, and BUN levels. | *HF*  
*MI within 1 mo*  
*LVEF≤ 30 %* | *Undergone recent revascularization procedures*  
*NYHA class IV at enrollment*  
*Major comorbidities* | RCT | 1232 | Not Reported |
| GWTG-HF & OPTIMIZE-HF | We conducted a retrospective cohort study of the clinical effectiveness of ICD therapy in older pts with HF by using data from the OPTIMIZE-HF registry, the GWTG-HF registry, and long-term outcome data from Medicare claims files. | *Age ≥65 y*  
*Eligible for an ICD*  
*LVEF ≤35 %*  
*Discharged alive from hospitals participating in the OPTIMIZE-HF and GWTG-HF quality-improvement programs during the period January 1, 2003, through December 31, 2006*  
*Hospitalized with a diagnosis of HF* | *Discharged to a skilled nursing facility*  
*Died before discharge*  
*New-onset HF* | Retrospective Observational | 4685 | The 1° endpoint was all-cause mortality within 3 y of the index hospitalization for HF.  
Results adjusted for the probability of treatment, other prognostic variables, and medical therapy at discharge. |

ICD:  
Mortality, All-Cause - Baseline – 3 y - 101 (26.9%)  
(N=376)  
No ICD:  
Mortality, All-Cause - Baseline – 3 y - 1771  
(N=4309)
- LVEF > 35%
- Transferred to another acute care hospital
- Left hospital against medical advice
- Discharged to hospice
- Unknown discharge status
- ICD at admission
- Documented contraindication, defined as a specific contraindication or any reason documented by a physician for not using ICD therapy
- Not receiving optimal medical therapy
- Acute MI within 40 d
- Life-threatening illness that would compromise 1 y survival with good functional status
- Economic reasons for not using ICD therapy
- Social reasons for not using ICD therapy
- Religious reasons for not using ICD therapy
- Compliance-related reasons for not using ICD therapy
- Admitted to hospital that did not provide ICD therapy
- Aged ≥85 y
- Admitted electively for ICD therapy

<table>
<thead>
<tr>
<th>ICD; Age 65–74:</th>
<th>Mortality, All-Cause - Baseline - 3 y - NR - (N=188)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No ICD; Age 65–74:</td>
<td>Mortality, All-Cause - Baseline - 3y - NR - (N=1851)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ICD; Age 75–84:</th>
<th>Mortality, All-Cause - Baseline - 3 y - NR - (N=188)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No ICD; Age 75–84:</td>
<td>Mortality, All-Cause - Baseline - 3y - NR - (N=2458)</td>
</tr>
</tbody>
</table>

(41.1%) - (N=4309)

Mortality, All-Cause - Baseline – 3 y - NR - (N=188); Adjusted using Inverse Probability Weighted model

Mortality, All-Cause - Baseline – 3 y - NR - (N=188); Adjusted using Inverse Probability Weighted model

Mortality, All-Cause - Baseline – 3 y - NR - (N=1851); Adjusted using Inverse Probability Weighted model

Mortality, All-Cause - Baseline – 3 y - NR - (N=2458)
### GWTG-HF & NCDR

- Al-Khatib SM 2014 (21)
- 24893088

**Study type:** Retrospective Observational

**Size:** 816

<table>
<thead>
<tr>
<th>Aim: To characterize pts with LVEF between 30% and 35% and compare the survival of those with and without ICDs</th>
</tr>
</thead>
</table>

**Inclusion Criteria:**
- Age ≥ 65 y
- Prophylactic ICD received between January 1, 2006 through December 31, 2007 in those pts from the NCDR
- Hospitalized for HF from January 1, 2005, through December 31, 2009, in those pts from the GWTG-HF database
- Primary insurance was Medicare
- LVEF 30%–35%

**Exclusion Criteria:**
- Recent MI
- Potential contraindication to an ICD
- Recent-onset of HF
- CABG
- New-onset HF, in those pts from the GWTG-HF database
- Left hospital against medical advice, in those pts from the GWTG-HF database
- Transferred to another acute care facility, in those pts from the GWTG-HF database
- Discharged to hospice, in those pts from the GWTG-HF database
- Discharged to skilled nursing facility, in those pts from the GWTG-HF database

<table>
<thead>
<tr>
<th>ICD</th>
<th>No ICD</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=408</td>
<td>N=408</td>
</tr>
</tbody>
</table>

(N=2458): Adjusted using Inverse Probability Weighted model.

The 1° endpoint was all-cause mortality.

Results adjusted using Cox models which include age, sex, race, LVEF, IHD, prior atrial arrhythmia, SBP, diabetes, hypertension, and baseline use of angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, calcium channel blocker, digoxin, diuretic, or statin.

**ICD:**
- Mortality, All-Cause - Median 4.4 y - 248 (60.8%) - (N=408)
- Mortality, All-Cause - Baseline – 1 y - 97 (23.8%) - (N=408)
- Mortality, All-Cause - Baseline – 3 y - 196 (48%) - (N=408)

**No ICD:**
- Mortality, All-Cause - Median 2.9 y - 249 (61%) - (N=408)
- Mortality, All-Cause - Baseline – 1 y - 99 (24.3%) - (N=408)
- Mortality, All-Cause - Not Reported
- Discharged to a rehabilitation center, in those pts from the GWTG-HF database
- NYHA class IV HF symptoms (entered as a reason for not receiving an ICD), in those pts from the GWTG-HF database
- No reasonable expectation of survival to at least 1 year, in those pts from the GWTG-HF database
- Received an ICD, in those pts in the Get With the Guidelines-Heart Failure (GWTG-HF) database
- Physician-documented reason for not receiving an ICD
- NYHA class IV HF symptoms, in those pts from the National Cardiovascular Data Registry (NCDR)
- Received a secondary prevention ICD, in those pts from the National Cardiovascular Data Registry (NCDR)
- Received an ICD with cardiac resynchronization therapy, in those pts from the NCDR
- Received ICD device replacements, in those pts from the NCDR

Baseline – 3 y - 204 (50%) - (N=408)
**Aim:** To examine the effect of ICDs, age, and multiple co-morbidities on survival in elderly pts who otherwise meet implantation criteria for primary prevention of SCD

**Study type:** Retrospective Observational

**Size:** 152

**Inclusion Criteria:**
- LVEF ≤ 35%
- Age ≥ 80y

<table>
<thead>
<tr>
<th>Group</th>
<th>Size</th>
<th>Criteria</th>
<th>Results adjusted for the following confounding variables:</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICD</td>
<td>N=99</td>
<td></td>
<td>(1) age only; (2) age and CCI; (3) age, CCI, and LVEF; (4) age, CCI, and GFR; and (5) age, CCI, LVEF, and GFR.</td>
</tr>
<tr>
<td>No ICD</td>
<td>N=53</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**ICD:**
Mortality, All-Cause - Mean 2.3y - 58 (59%) - (N=99)

**No ICD:**
Mortality, All-Cause - Mean 2.3y - 35 (66%) - (N=53)
<table>
<thead>
<tr>
<th>Aim: To investigate the association between primary prevention ICDs and mortality among Medicare, racial and ethnic minority pts in clinical practice. Study type: Retrospective Observational Size: 2922</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusion Criteria: - Age ≥65 y - Fee-for-service Medicare beneficiaries - Hospitalized for a diagnosis of HF</td>
</tr>
<tr>
<td>Exclusion Criteria: - Recent MI - LVEF &gt;35% - No documented LVEF - Recent CABG - Class IV HF symptoms</td>
</tr>
<tr>
<td>ICD; Minority N=426</td>
</tr>
<tr>
<td>ICD; White, Non-Hispanics N=1035</td>
</tr>
<tr>
<td>No ICD; Minority N=426</td>
</tr>
<tr>
<td>No ICD; White, Non-Hispanics N=1035</td>
</tr>
</tbody>
</table>

The 1st endpoint for this analysis was all-cause mortality. Results adjusted for race (white versus other), age, past medical history (previous atrial arrhythmia, IHD, HTN, and diabetes mellitus), concomitant medications (beta blocker, calcium channel blocker angiotensin converting enzyme inhibitor, angiotensin receptor blocker, statin, digoxin, and diuretic), and clinical characteristics (SBP and LVEF). NYHA class and QRS duration were not available in the GWTG-HF database.

ICD; Minority:
Mortality, All-Cause - Baseline - 5.9y - 234 (54.9%) - (N=426)
Mortality, All-Cause - Baseline - 1y - 67 (22.4%) [CI 95%: 21.9-22.9] - (N=297)
Mortality, All-Cause - Baseline - 3y - 80 (44.9%) [CI 95%: 44.2-45.7] - (N=179)

ICD; White, Non-Hispanics: Not Reported
| Mortality, All-Cause - Baseline - 6y - 637 (61.5%) - (N=1035) |
|--------------------------|--------------------------|
| Mortality, All-Cause - Baseline - 1y - 185 (24.2%) [CI 95%: 23.9-24.5] - (N=766) |
| Mortality, All-Cause - Baseline - 3y - 234 (47.8%) [CI 95%: 47.3-48.3] - (N=490) |

<table>
<thead>
<tr>
<th>No ICD; Minority:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality, All-Cause - Baseline - 6.7y - 239 (56.1%) - (N=426)</td>
</tr>
<tr>
<td>Mortality, All-Cause - Baseline - 1y - 79 (28.4%) [CI 95%: 27.9-29] - (N=279)</td>
</tr>
<tr>
<td>Mortality, All-Cause - Baseline - 3y - 66 (54.3%) [CI 95%: 53.4-55.1] - (N=121)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>No ICD; White, Non-Hispanics:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality, All-Cause - Baseline - 6.8y - 646 (62.4%) - (N =1035)</td>
</tr>
<tr>
<td>Mortality, All-Cause - Baseline - 1y - 203 (30.6%) [CI 95%: 30.2–31] - (N=663)</td>
</tr>
<tr>
<td>Mortality, All-Cause - Baseline - 3y - 174 (57.3%) [CI 95%: 56.8–57.9] - (N=303)</td>
</tr>
</tbody>
</table>
**Aim:**
We analyzed 2 large national registries linked with Medicare claims to examine the characteristics and outcomes of HF pts aged $\geq 65$ y in clinical practice who received an ICD for primary prevention compared with eligible pts who did not receive an ICD. We also examined the associations between mortality and comorbidities and between mortality and HF burden to better inform clinical decision making in this population.

**Study type:**
Retrospective Observational

**Size:** 2974

<table>
<thead>
<tr>
<th>Inclusion Criteria:</th>
<th>ICD</th>
<th>No ICD</th>
</tr>
</thead>
<tbody>
<tr>
<td>- HF</td>
<td>N=1487</td>
<td>N=1487</td>
</tr>
<tr>
<td>- Age $\geq 65$ y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Enrolled in fee-for-service Medicare for at least 12 mo before the index admission</td>
<td>ICD; $\leq$ 3 Comorbidities N=1202</td>
<td>N=978</td>
</tr>
<tr>
<td>- Discharged alive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- LVEF $\leq 35$ %</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Exclusion Criteria:**
- Discharged to a skilled nursing facility
- Discharged to a hospice
- Left hospital against medical advice

**ICD:**
- Mortality, All-Cause - Baseline - 6y - 876 (58.9%) - (N=1487)
- Mortality, All-Cause - Baseline - 1y - 348 (23.4%) [CI 95%; 23.1–23.7] - (N=1487)

<table>
<thead>
<tr>
<th>≤3 Comorbidities</th>
<th>&gt;3 Comorbidities</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=1202</td>
<td>N=283</td>
</tr>
<tr>
<td>N=978</td>
<td>N=278</td>
</tr>
</tbody>
</table>

The 1st endpoint was all-cause mortality.

Results were adjusted for the following covariates: patient demographic characteristics (age, sex, race), medical history IHD, prior atrial arrhythmia, diabetes, HTN, chronic renal disease, chronic lung disease, cerebrovascular disease), laboratory tests and vital signs (LVEF, SBP), and discharge medications (angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, beta-blocker, diuretic, calcium channel blocker, digoxin, statin). NYHA class and QRS duration were not available in the GWTG-HF database.
<table>
<thead>
<tr>
<th>Comorbidity Level</th>
<th>Baseline - 3y</th>
<th>Baseline - 3y</th>
<th>Baseline - 3y</th>
<th>Baseline - 3y</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>694 (46.7%)</td>
<td>[CI 95%: 46.2–47.2]</td>
<td>(N=1487)</td>
<td><strong>Mortality, All-Cause - Baseline - 3y - NR</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(N=1487)</td>
</tr>
<tr>
<td>No ICD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>896 (60.3%)</td>
<td>[CI 95%: 60.0–61.0]</td>
<td>(N=1487)</td>
<td><strong>Mortality, All-Cause - Baseline - 3y - NR</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(N=1487)</td>
</tr>
<tr>
<td>ICD; ≤3 Comorbidities</td>
<td>830 (55.8%)</td>
<td>[CI 95%: 55.3–56.3]</td>
<td>(N=1487)</td>
<td><strong>Mortality, All-Cause - Baseline - 3y - NR</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(N=1487)</td>
</tr>
<tr>
<td>ICD; &gt;3 Comorbidities</td>
<td>830 (55.8%)</td>
<td>[CI 95%: 55.3–56.3]</td>
<td>(N=1487)</td>
<td><strong>Mortality, All-Cause - Baseline - 3y - NR</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(N=1487)</td>
</tr>
</tbody>
</table>

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ICD; >3 Comorbidities:
Mortality, All-Cause - Baseline - 5.9 y - 198 (70%) - (N=283)
Mortality, All-Cause - Baseline - 1y - 84 (29.8%) [CI 95%: 29.2–30.5] - (N=283)
Mortality, All-Cause - Baseline - 3y - 162 (57.2%) [CI 95%: 56.2–58.1] - (N=283)
Mortality, All-Cause - Baseline - 5y - NR - (N=283)

No ICD; ≤3 Comorbidities:
Mortality, All-Cause - Baseline - 6.7 y - 566 (57.9%) - (N=978)
Mortality, All-Cause - Baseline - 1y - 266 (27.2%) [CI 95%: 26.8–27.6] - (N=978)
Mortality, All-Cause - Baseline - 3y - 516 (52.8%) [CI 95%: 52.2–53.4] - (N=978)
Mortality, All-Cause - Baseline - 5y - NR - (N=978)

No ICD; >3 Comorbidities:
Mortality, All-Cause - Baseline - 6y - 200 (71.9%) - (N =2 78)
Mortality, All-Cause - Baseline - 1y - 102 (36.8%) [CI 95%: 36–37.6] - (N=278)
| ● **GWTG** | Aim: To examine clinical practice data to compare survival rates among women with HF with or without a primary prevention ICD. **Study type:** Retrospective Observational **Size:** 2578 | **Inclusion Criteria:**  
- Primary insurance was Medicare  
- Linked to Centers for Medicare data  
- Linked to Centers for Medicaid Services data  
- LVEF ≤ 35%  
- At least 65y old  
- In the GWTG-HF registry  
- Discharged from the hospital to home  
- Reasonable expectation of survival to 1 year  
**Exclusion Criteria:**  
- Class IV HF symptoms  
- Received comfort care only  
- Missing medical history data  
- Contraindication to ICD | ICD; Women N=430  
ICD; Men N=859  
No ICD; Women N=430  
No ICD; Men N=859 | Mortality, All-Cause - Baseline - 3y - 185 (66.4%) [CI 95%: 65.5–67.4] - (N=278)  
Mortality, All-Cause - Baseline - 5y - NR - (N=278) | All-cause mortality was the 1° endpoint of this analysis.  
Results adjusted for Age, White race, LVEF, SBP, IHD, Prior atrial arrhythmia, Diabetes mellitus, HTN, Chronic renal insufficiency, Depression, COPD, Anemia, Previous cerebrovascular attack or transient ischemic attack, Angiotensin-converting enzyme-inhibitor or angiotensin receptor blocker, Beta-blocker, Calcium channel blocker, Digoxin, Diuretic, Statin, Sodium, Blood urea nitrogen, Creatinine, Hemoglobin | ● Not Reported |
- MI within 40d
- Coronary Revascularization
- PCI within 90d
- Coronary artery bypass grafting within 90d
- Received cardiac resynchronization therapy
- Records of subsequent hospitalizations
- Missing LVEF data
- Recent onset of HF (i.e., HF diagnosis not predating the index admission)
- Died during hospital admission
- Already had an ICD in place

ICD; Women:
Mortality, All-Cause - Baseline - 1y - 79 (18.3%) [CI 95%; 17.6–19] - (N=430) (Propensity-matched and propensity-adjusted analysis)
Mortality, All-Cause - Baseline - 3y - 168 (39.1%) [CI 95%; 38–40.3] - (N=430) (Propensity-matched and propensity-adjusted analysis)
Mortality, All-Cause - Baseline - 1y - 73 (17.3%) [CI 95%; 13.9–21.3] - (N=422) (Propensity-matched 30d landmark analysis)
Mortality, All-Cause - Baseline - 3y - 169 (40.1%) [CI 95%; 35.3–45.3] - (N=422) (Propensity-matched 30-d landmark analysis)

ICD; Men:
Mortality, All-Cause - Baseline - 1y - 183 (21.3%) [CI 95%; 20.7–21.8] - (N=859) (Propensity-matched and propensity-adjusted analysis)
Mortality, All-Cause - Baseline - 3y - 380 (44.2%) [CI 95%; 43.3–45] - (N=859) (Propensity-matched and propensity-adjusted analysis)
<table>
<thead>
<tr>
<th>Propensity-adjusted analysis</th>
<th>Mortality, All-Cause - Baseline - 1y - 163 (19.4%) [CI 95%: 16.8–22.3] - (N=839) (Propensity-matched 30-d landmark analysis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality, All-Cause - Baseline - 3y - 363 (43.3%) [CI 95%: 39.9–47] - (N=839) (Propensity-matched 30d landmark analysis)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>No ICD; Women:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality, All-Cause - Baseline - 1y - 99 (23.1%) [CI 95%: 22.3–23.9] - (N=430) (Propensity-matched and propensity-adjusted analysis)</td>
</tr>
<tr>
<td>Mortality, All-Cause - Baseline - 3y - 203 (47.1%) [CI 95%: 45.9–48.3] - (N=430) (Propensity-matched and propensity-adjusted analysis)</td>
</tr>
<tr>
<td>Mortality, All-Cause - Baseline - 1y - 100 (23.6%) [CI 95%: 19.8–28.1] - (N=422) (Propensity-matched 30d landmark analysis)</td>
</tr>
<tr>
<td>Mortality, All-Cause - Baseline - 3y - 205 (48.6%) [CI 95%: 43.6–54] - (N=422) (Propensity-matched 30d landmark analysis)</td>
</tr>
</tbody>
</table>
| Nakhoul GN 2015 (26) | **Aim:** To examine the survival benefits of ICDs placed for primary prevention in those with CKD not on dialysis (estimated glomerular filtration rate <60 mL/min per 1.73 m²). | **Inclusion Criteria:**
- CKD
- Echocardiogram at the Cleveland Clinic (between 2001 and October 2011)
- At least one face-to-face outpatient encounter with a Cleveland Clinic health care provider
- Two estimated glomerular filtration rate (27) values <60mL/min/1.73m², calculated using the CKD Epidemiology | **ICD**
N=631

No ICD
N=631

ICD; eGFR, 45–59 mL/min/1.73m²
N=303

ICD; eGFR, 30–44 mL/min/1.73m² | The 1st endpoint of interest was all-cause mortality. Results adjusted for demographics, comorbid conditions, use of cardioprotective medications, eGFR, LVEF, and ventricular arrhythmia. | **Not Reported** |
Collaboration (CKD-EPI) equation >90d apart

**Exclusion Criteria:**
- Aged <18y
- Diagnosed with ESRD needing dialysis before CKD diagnosis
- Diagnosed with ESRD needing renal transplantation before CKD diagnosis

| No ICD; eGFR, <30 mL/min/1.73m² | N=227 |
| ICD; eGFR, 45–59 mL/min/1.73m² | N=101 |
| ICD; eGFR, 30–44 mL/min/1.73m² | N=305 |
| No ICD; eGFR, 30–44 mL/min/1.73m² | N=219 |
| No ICD; eGFR, <30 mL/min/1.73m² | N=107 |

Median 2.9y - NR - (N=631)
Mortality, All-Cause - Median 2.9y - NR - (N=631); Adjusted
No ICD:
Mortality, All-Cause - Median 2.9y - NR - (N=631)
Mortality, All-Cause - Median 2.9y - NR - (N=631); Adjusted
ICD; eGFR, 45–59 mL/min/1.73m²:
Mortality, All-Cause - Median 2.9y - NR - (N=303)
Mortality, All-Cause - Median 2.9y - NR - (N=303); Adjusted
ICD; eGFR, 30–44 mL/min/1.73m²:
Mortality, All-Cause - Median 2.9y - NR - (N=227)
Mortality, All-Cause - Median 2.9y - NR - (N=227); Adjusted
ICD; eGFR, <30 mL/min/1.73m²:
Mortality, All-Cause - Median 2.9y - NR - (N=101)
Mortality, All-Cause - Median 2.9y - NR - (N=101); Adjusted
No ICD; eGFR, 45–59 mL/min/1.73m²:
| GWTG-HF & NCDR | **Aim:** To assess the benefit of primary prevention ICDs in women. | **Inclusion Criteria:** | ICD  
N=1473  
No ICD  
N=1473  
ICD; Female  
N=490  
ICD; Male  
N=983  
No ICD; Female  
N=490  
No ICD; Male  
N=983 | Mortality, All-Cause - Median 2.9y - NR - (N=305)  
Mortality, All-Cause - Median 2.9y - NR - (N=305); Adjusted  
No ICD; eGFR, 30–44 mL/min/1.73m²:  
Mortality, All-Cause - Median 2.9y - NR - (N=219)  
Mortality, All-Cause - Median 2.9y - NR - (N=219); Adjusted  
No ICD; eGFR, <30 mL/min/1.73m²:  
Mortality, All-Cause - Median 2.9y - NR - (N=107)  
Mortality, All-Cause - Median 2.9y - NR - (N=107); Adjusted  
Not Reported |
| **Study type:** Retrospective Observational  
**Size:** 2946 | **Exclusion Criteria:**  
- Age ≥65 y  
- LVEF ≤35%  
**ICD**  
N=1473  
**No ICD**  
N=1473  
**ICD; Female**  
N=490  
**ICD; Male**  
N=983  
**No ICD; Female**  
N=490  
**No ICD; Male**  
N=983 | The 1° endpoint was all-cause mortality.  
Results adjusted for Age, White race, LVEF, SBP, IHD, Prior atrial arrhythmia, Diabetes mellitus, HTN, Chronic renal insufficiency, Depreession, COPD, Anemia, Previous cerebrovascular attack or TIA, Angiotensin-converting enzyme-inhibitor or angiotensin receptor blocker, Beta-blocker, Calcium channel blocker, Digoxin, Diuretic, |
<table>
<thead>
<tr>
<th>Statin, Sodium, BUN, Creatinine, Hemoglobin</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICD:</td>
</tr>
<tr>
<td>Mortality, All-Cause - Median 4.6y - 868 (58.9%) - (N=1473)</td>
</tr>
<tr>
<td>No ICD:</td>
</tr>
<tr>
<td>Mortality, All-Cause - Median 3.2y - 874 (59.3%) - (N=1473)</td>
</tr>
<tr>
<td>ICD; Female:</td>
</tr>
<tr>
<td>Mortality, All-Cause - Baseline - 1y - 106 (21.7%) [CI 95%: 21.2–22.2] - (N=490)</td>
</tr>
<tr>
<td>Mortality, All-Cause - Baseline - 3y - 217 (44.3%) [CI 95%: 43.5–45.1] - (N=490)</td>
</tr>
<tr>
<td>Mortality, All-Cause - Median 4.6y - 286 (58.4%) - (N=490)</td>
</tr>
<tr>
<td>ICD; Male:</td>
</tr>
<tr>
<td>Mortality, All-Cause - Baseline - 1y - 231 (23.5%) [CI 95%: 23.2–23.9] - (N=983)</td>
</tr>
<tr>
<td>Mortality, All-Cause - Baseline - 3 - 465 (47.3%) [CI 95%: 46.7–47.9] - (N=983)</td>
</tr>
<tr>
<td>Mortality, All-Cause - Median 4.4y - 582 (59.2%) - (N=983)</td>
</tr>
</tbody>
</table>
Aim: To compare the mortality of dialysis pts receiving a primary prevention ICD with matched controls.  

Study type: Retrospective Observational  

Size: 172  

Inclusion Criteria:  
- Age ≥65y  
- Dialysis  
- LVEF ≤35%  
- Cardiomyopathy  
- Renal Failure  

Exclusion Criteria:  
- Class IV HF symptoms  
- MI within 40 d prior to implant  
- CABG surgery within 90 d prior to implant  
- New-onset HF (<3 mo)  

ICD N=86  
No ICD N=86  

The 1° endpoint was all-cause mortality.  

Results adjusted for demographic characteristics, LVEF, comorbid conditions (history of IHD and arrhythmias), blood pressure readings, cardiovascular medication use and serum creatinine values.  

Not Reported
<table>
<thead>
<tr>
<th></th>
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<th></th>
<th>ICD:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mortality, All-Cause - Baseline – 1 y - 37 (43.4%) - (N=86)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mortality, All-Cause - Baseline – 3 y - 64 (74%) - (N=86)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No ICD:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mortality, All-Cause - Baseline – 1 y - 34 (39.7%) - (N=86)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mortality, All-Cause - Baseline – 3 y - 66 (76.6%) - (N=86)</td>
</tr>
</tbody>
</table>
**Aim:** To investigate possible mechanisms underlying the lack of mortality benefit in the DINAMIT.

**Study type:** RCT

**Size:** 653

**Inclusion Criteria:**
- Age 18–80 y
- MI 6–40 d before randomization
- Evidence of impaired cardiac autonomic function
- LVEF ≤ 35%
- SD of N-N intervals ≤ 70 ms or average heart rate > 80 bpm on a 24 h Holter monitor performed ≥ 3 d after the index MI

**Exclusion Criteria:**
- NYHA class IV HF symptoms at the time of randomization
- CABG
- 3-vessel PCI immediately after the acute MI
- 3-vessel percutaneous coronary intervention planned at the time of randomization
- Prior ICD therapy

<table>
<thead>
<tr>
<th>ICD</th>
<th>No ICD</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=311</td>
<td>N=342</td>
</tr>
</tbody>
</table>

The 1° endpoint in DINAMIT was death resulting from any cause.

The analysis adjusted for treatment effect by taking into account potentially differential effects of the risk factors for the different causes of death.

**ICD:**
- SCD, Presumed Arrhythmic - Mean 30 mo - 10 (3.2%) - (N=311)
- No ICD:
- SCD, Presumed Arrhythmic - Mean 28 mo - 29 (8.5%) - (N=342)
**Aim:** To evaluate the benefit of primary prevention with an ICD during an extended 8 y follow-up of the MADIT-II population

**Study type:** RCT  
**Size:** 1232

**Inclusion Criteria:**  
- Ischemic LV dysfunction  
- EF ≤ 30%  
- MI ≥ 1 mo before entry

<table>
<thead>
<tr>
<th>Group</th>
<th>Size</th>
<th>Inclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICD</td>
<td>630</td>
<td>Age &lt; 65 N = 309</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Age ≥ 65 N = 321</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Age &lt; 65 N = 200</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Age ≥ 65 N = 190</td>
</tr>
<tr>
<td>No ICD</td>
<td>390</td>
<td></td>
</tr>
</tbody>
</table>

The 1° endpoint of the present study was the occurrence of all-cause mortality during 8y after enrollment.

Results were adjusted for covariates in the multivariate models, including age (as a continuous variable), NYHA functional class II, QRS duration 120ms, EF 25%, gender, and blood urea nitrogen levels 25mg/dL.

**ICD:**  
Mortality, All-Cause - Baseline - 8y - NR - (N=630); Adjusted  
Mortality, All-Cause - Baseline - 4y - NR - (N=630)  
Mortality, All-Cause - 5 y - 8y - NR - (N=630)  
Mortality, All-Cause - Baseline - 8y - NR - (N=630); ITT & Adjusted  
Mortality, All-Cause - Baseline - 8y - NR - (N=630); Adjusted moA & Follow-up time was censored

**No ICD:**  
Mortality, All-Cause - Baseline - 8y - NR - (N=630)
<table>
<thead>
<tr>
<th>ICD; Age &lt;65y</th>
<th>Mortality, All-Cause - Baseline - 8y - NR - (N=309); Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICD; Age ≥65y:</td>
<td>Mortality, All-Cause - Baseline - 8y - NR - (N=321); Adjusted</td>
</tr>
<tr>
<td>No ICD; Age &lt;65y:</td>
<td>Mortality, All-Cause - Baseline - 8y - NR - (N=200); Adjusted</td>
</tr>
<tr>
<td>No ICD; Age ≥65y:</td>
<td>Mortality, All-Cause - Baseline - 8y - NR - (N=190); Adjusted</td>
</tr>
<tr>
<td>Aim: To evaluate the impact of an ICD on survival in ESRD pts.</td>
<td>Inclusion Criteria: Renal Failure</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Study type: Retrospective Observational</td>
<td>Size: 100</td>
</tr>
</tbody>
</table>

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**Aim:** The present study used data from the second MADIT II to characterize the mortality experience of a contemporary diabetic cohort with a depressed LVEF after MI and to evaluate the relative benefit of ICD therapy in this group compared with nondiabetic pts enrolled in the trial.

**Study type:** RCT  
**Size:** 1231

<table>
<thead>
<tr>
<th>Inclusion Criteria:</th>
<th>ICD</th>
<th>Conventional Therapy</th>
<th>The 1st endpoint: was death from any cause.</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI &gt;1 mo before entry</td>
<td>N=742</td>
<td>N=489</td>
<td>Results are adjusted for adjustment for renal insufficiency, NYHA class, and BMI.</td>
</tr>
<tr>
<td>LVEF ≤0.30 documented within 3 mo before entry</td>
<td>ICD; Diabetes N=249</td>
<td>ICD; No Diabetes N=493</td>
<td>ICD; Diabetes: Mortality, All-Cause - Baseline - 2 y - NR - (N=249)</td>
</tr>
<tr>
<td></td>
<td>Conventional Therapy; Diabetes N=184</td>
<td></td>
<td>ICD; No Diabetes: Mortality, All-Cause - Baseline - 2 y - NR - (N=493)</td>
</tr>
<tr>
<td></td>
<td>Conventional Therapy; No Diabetes N=305</td>
<td></td>
<td>Conventional Therapy; Diabetes: Mortality, All-Cause - Baseline - 2 y - 46 (25%) - (N=184)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Conventional Therapy; No Diabetes: Mortality, All-Cause - Baseline - 2 y - 61 (20%) - (N=305)</td>
</tr>
</tbody>
</table>

**ICD; Diabetes:**
- Mortality, All-Cause - Baseline - 2 y - NR - (N=249)

**ICD; No Diabetes:**
- Mortality, All-Cause - Baseline - 2 y - NR - (N=493)

**Conventional Therapy; Diabetes:**
- Mortality, All-Cause - Baseline - 2 y - 46 (25%) - (N=184)

**Conventional Therapy; No Diabetes:**
- Mortality, All-Cause - Baseline - 2 y - 61 (20%) - (N=305)
**Aim:** To test the hypothesis that an ICD will reduce the risk of death in pts with nonischemic cardiomyopathy and moderate-to-severe LV dysfunction.  

**Study type:** RCT  

**Size:** 458

### Inclusion Criteria
- History of symptomatic HF  
- LVEF <36%  
- Ambient arrhythmias defined by an episode of NSVT on Holter or telemetric monitoring (3–15 beats at a rate of more than 120 beats per minute) or an average of at least 10 premature ventricular complexes per hour on 24h Holter monitoring  
- NICM

### Exclusion Criteria
- NYHA class IV HF  
- CHD  
- Acute myocarditis  
- Clinically significant CAD as the cause of the cardiomyopathy  
- Not candidates for the ICD  
- Underwent EP testing within the prior 3 mo  
- Cardiac transplantation appeared to be imminent  
- Familial cardiomyopathy associated with sudden death  
- Permanent pacemakers

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Standard Therapy</th>
<th>ICD</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICD (Age &lt;65 y)</td>
<td>229</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICD (Age ≥65y)</td>
<td>NR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard Therapy (Age &lt;65 y)</td>
<td>229</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard Therapy (Age ≥65 y)</td>
<td>NR</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The 1st endpoint of the study was death from any cause.

Results Adjusted for duration of HF

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Standard Therapy</th>
<th>ICD</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICD</td>
<td>229</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard Therapy</td>
<td>229</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Cardiac Tamponade
- Implantation of ICD - 1 (0.4%) - (N=229)
- Hemothorax - Implantation of ICD - 1 (0.4%) - (N=229)
- ICD, Complications - Mean 29 mo - 10 (4.4%) - (N=229)

### Cardiac Complications
- Lead Dislodgement or ICD, Complications, Lead Fractures - Mean 29 mo - 6 (2.6%) - (N=229)
- Infection, Any - Mean 29 mo - 1 (0.4%) - (N=229)
- Pneumothorax - Implantation of ICD - 1 (0.4%) - (N=229)
- Venous Thrombosis - Mean 29 mo - 3 (1.3%) - (N=229)
- SCD - Mean 29 mo - 3 (1.3%) - (N=229)

### Standard Therapy
- SCD - Mean 29 mo - 14 (6.1%) - (N=229)

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<table>
<thead>
<tr>
<th></th>
<th>Mortality, All-Cause - Mean 29 mo - NR - (N=NR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard Therapy (Age &lt;65 y)</td>
<td>Mortality, All-Cause - Mean 29 mo - NR - (N=NR)</td>
</tr>
<tr>
<td>Standard Therapy (Age ≥65 y)</td>
<td>Mortality, All-Cause - Mean 29 mo - NR - (N=NR)</td>
</tr>
</tbody>
</table>
Aim: To evaluate the hypothesis that amiodarone or a conservatively programmed shock-only, single-lead ICD would decrease the risk of death from any cause in a broad population of pts with mild to-moderate HF. **Study type:** RCT  
**Size:** 2521

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>ICD</th>
<th>Amiodarone</th>
<th>Placebo</th>
<th>Amiodarone (Age &lt;65 y)</th>
<th>Placebo (Age &lt;65 y)</th>
<th>Amiodarone (Age ≥65 y)</th>
<th>Placebo (Age ≥65 y)</th>
<th>ICD (Diabetes, Type Unknown)</th>
<th>Amiodarone (Diabetes, None)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=829</td>
<td>N=845</td>
<td>N=847</td>
<td>N=NR</td>
<td>N=NR</td>
<td>N=NR</td>
<td>N=NR</td>
<td>N=253</td>
<td>N=576</td>
</tr>
<tr>
<td>NYHA class II or III chronic</td>
<td>ICD (Age &lt;65 y)</td>
<td>N=NR</td>
<td>Amiodarone (Age &lt;65 y)</td>
<td>Placebo (Age &lt;65 y)</td>
<td>Amiodarone (Age ≥65 y)</td>
<td>Placebo (Age ≥65 y)</td>
<td>ICD (Diabetes, Type Unknown)</td>
<td>Amiodarone (Diabetes, None)</td>
<td></td>
</tr>
<tr>
<td>Stable HF due to ischemic or nonischemic causes</td>
<td>ICD (Age ≥65 y)</td>
<td>N=NR</td>
<td>Amiodarone (Age &lt;65 y)</td>
<td>Placebo (Age &lt;65 y)</td>
<td>Amiodarone (Age ≥65 y)</td>
<td>Placebo (Age ≥65 y)</td>
<td>ICD (Diabetes, Type Unknown)</td>
<td>Amiodarone (Diabetes, None)</td>
<td></td>
</tr>
<tr>
<td>LVEF ≤35 %</td>
<td>ICD (Diabetes, None)</td>
<td>N=576</td>
<td>Amiodarone (Age ≥65 y)</td>
<td>Placebo (Age ≥65 y)</td>
<td>ICD (Diabetes, None)</td>
<td>Amiodarone (Age ≥65 y)</td>
<td>Placebo (Age ≥65 y)</td>
<td>ICD (Diabetes, None)</td>
<td>Amiodarone (Age ≥65 y)</td>
</tr>
</tbody>
</table>

The primary end point was death from any cause.  
Results adjusted for the NYHA class and the cause of CHF.

ICD Mortality, All-Cause - Median 45.5 mo - 182 (22%) - (N=829)
Amiodarone Mortality, All-Cause - Median 45.5 mo - 237 (28%) - (N=845)
Placebo Mortality, All-Cause - Median 45.5 mo - 246 (29%) - (N=847)

ICD Mortality, All-Cause - Median 45.5 mo - NR - (N=NR)
Amiodarone Mortality, All-Cause - Median 45.5 mo - NR - (N=NR)

ICD Complications - Median 45.5 mo - 75 (9%) - (N=829)
<table>
<thead>
<tr>
<th></th>
<th>Amiodarone (Diabetes, Type Unknown) N=243</th>
<th>Amiodarone (Diabetes, None) N=602</th>
<th>Placebo (Diabetes, Type Unknown) N=271</th>
<th>Placebo (Diabetes, None) N=576</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality, All-Cause</td>
<td>Median 45.5 mo - NR - (N=NR)</td>
<td>Placebo (Age &lt;65 y) Mortality, All-Cause - Median 45.5 mo - NR - (N=NR)</td>
<td>Placebo (Age ≥65 y) Mortality, All-Cause - Median 45.5 mo - NR - (N=NR)</td>
<td>ICD (Diabetes, Type Unknown) Mortality, All-Cause - Median 45.5 mo - NR - (N=253)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ICD (Diabetes, None) Mortality, All-Cause - Median 45.5 mo - NR - (N=576)</td>
<td>ICD (Diabetes, None) Mortality, All-Cause - Median 45.5 mo - NR - (N=576)</td>
<td>Amiodarone (Diabetes, Type Unknown) Mortality, All-Cause - Median 45.5 mo - NR - (N=243)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Amiodarone (Diabetes, None) Mortality, All-Cause - Median 45.5 mo - NR - (N=602)</td>
<td>Amiodarone (Diabetes, None) Mortality, All-Cause - Median 45.5 mo - NR - (N=602)</td>
<td></td>
</tr>
</tbody>
</table>
### Study Details

**Aim:** To evaluate benefit of primary prevention ICD among pts with CKD

**Study type:** Meta-analysis of RCT

**Size:** 2867

**Inclusion criteria:**
- Symptomatic HF NYHA class <IV
- LVEF ≤35%
- Assignment to either an ICD or usual care.
- Kidney function was determined by calculating estimated GFR (27) at study enrollment. CKD-EPI (CKD Epidemiology Collaboration) creatinine equation was used.

<table>
<thead>
<tr>
<th>Arm</th>
<th>Inclusion criteria</th>
<th>Results adjusted for demographic characteristics, LVEF, comorbid conditions (history of IHD and arrhythmias), blood</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICD</td>
<td>- Symptomatic HF NYHA class &lt;IV</td>
<td>The 1° endpoint was mortality, re-hospitalizations, and effect modification by eGFR.</td>
</tr>
<tr>
<td>Usual Care</td>
<td>- LVEF ≤35%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Assignment to either an ICD or usual care.</td>
<td></td>
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<td></td>
<td>- Kidney function was determined by calculating estimated GFR (27) at study</td>
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<tr>
<td></td>
<td>enrollment. CKD-EPI (CKD Epidemiology Collaboration) creatinine equation was used,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ICD; eGFR&lt; 60 N=1533</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Usual Care; eGFR&lt; 60 N=541</td>
<td></td>
</tr>
<tr>
<td></td>
<td>N=499</td>
<td></td>
</tr>
<tr>
<td>Placebo (Diabetes, Type Unknown) Mortality, All-Cause - Median 45.5 mo - NR - (N=271)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo (Diabetes, None) Mortality, All-Cause - Median 45.5 mo - NR - (N=576)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
which uses age, race, and sex in addition to serum creatinine concentration to determine eGFR. For consistency with prior literature and for simplicity, the cohort was dichotomized into 2 strata of eGFR:

1. eGFR < 60 (CKD stages 3–5)
2. eGFR ≥ 60 mL/min1.73m².

They also examined outcomes by finer categories of eGFR (eGFR <45, 45–59, 60–89, and ≥ 90 mL/min1.73m²).

**Exclusion criteria:**
- Patients without HF symptoms or with NYHA class IV symptoms
- Patients with LVEF > 35%
- Patient who were missing data on prior MI
- Patients who had a MI in the 40 days preceding randomization
- Patients whose time from randomization was unknown were excluded

<table>
<thead>
<tr>
<th>ICD; eGFR ≥ 60 N=992</th>
<th>ICD; eGFR ≥ 60 N=835</th>
<th>pressure readings, cardiovascular medication use and serum creatinine values.</th>
</tr>
</thead>
</table>
| Kaplan-Meier estimate of the probability of death during follow-up was: | - 43.3% for 1,334 pts receiving usual care  
- 35.8% for 1,533 ICD recipients |
| ICD and Sudden Death in CKD: | |
| GFR <45 HR (Adjusted) – 0.77; 95% CI= 0.36–1.32 |
| GFR 45–60 HR (Adjusted) – 0.8; 95% CI= 0.38–1.48 |
| GFR 60–90 HR (Adjusted) – 0.46; 95% CI = 0.22–0.83 |
| GFR 90+ HR (Adjusted) – 0.45; 95% CI = 0.19–0.89 |
Aim: The aim of this study was to determine if the benefit of ICDs is modulated by medical comorbidity.

Study type: Meta-analysis of RCT

Size: 3,348

**Inclusion criteria:**
- LVEF ≤35%
- Either no prior MI or time from MI to randomization >40 d
- Availability of data on important covariates.

Seven comorbidities were selected for assessment:
- Smoking
- IHD
- CKD
- Diabetes
- Pulmonary disease
- AF
- Peripheral vascular disease

**Exclusion criteria:**
- Patients with NYHA functional class IV HF were excluded.

ICD
N=1771
Control
N=1527

ICD, <2 Comorbidities
N=442

Control, <2
Comorbidities
N=388

ICD, ≥2 Comorbidities
N=1329

ICD, ≥2 Comorbidities
N=1189

The 1° endpoint was all-cause mortality at last follow-up.

Adjusted (Mean) Survival Difference Between ICD and Control at 5y:
- 0 Comorbidity: 0.13; 95% CI = 0.06 – 0.19
- 1 Comorbidity: 0.13; 95% CI = 0.07 – 0.19
- 2 Comorbidity: 0.13; 95% CI = 0.08 – 0.18
- 3 Comorbidity: 0.11; 95% CI = 0.06 – 0.15
- 4 Comorbidity: 0.06; 95% CI = 0.00 – 0.14
- 5 Comorbidity: 0.00; 95% CI = -0.10 – 0.12
- 6 Comorbidity: -0.05; 95% CI = -0.18 – 0.09

- Use of an ICD resulted in significant improvement in survival in pts:
  - low comorbidity (unadjusted HR: 0.59; 95% CI: 0.40–0.87)
  - Patients with extensive comorbid illness (unadjusted HR: 0.71; 95% CI: 0.61–0.84)

2° endpoint included all-cause re-hospitalization and cause-specific mortality.

- The proportion of deaths due to arrhythmia were higher for pts in the control group (40% and 37% of deaths with <2 and ≥2 comorbidities, respectively) compared with pts in the ICD group (12% and 22% of deaths with <2 and ≥2 comorbidities, respectively).

- Hospitalization rates were lowest in pts with <2 comorbidities who did not receive an ICD (54%) and highest for pts with ≥2 comorbidities who received an ICD (74%).

- Adverse event rates were lowest in pts with low comorbidity not receiving an ICD (0%) and highest in pts with high comorbidity receiving an ICD (21%).
Aim: The aim was to assess the impact of patient age on the risks of death or re-hospitalization after 1° prevention ICD placement.

Study type: Meta-analysis of RCT

Size: 3530

Inclusion criteria:
- HF (NYHA I-III)
- LVEF of ≤35%
- Availability of important covariates.

Exclusion criteria:
- Patients without HF symptoms or with NYHA IV symptoms
- LVEF of >35%
- Time from MI to randomization <40 d
- Those missing values for variables that define the inclusion criteria

ICD
N=1837

Conventional Medical Therapy
N=1693

ICD, age <55 y
N=527

Conventional Medical Therapy, age <55 y
N=483

ICD, age 55–64 y
N=529

Conventional Medical Therapy, age 55–64 y
N=526

ICD, age 65–74 y
N=555

Conventional Medical Therapy, age 65–74 y
N=520

ICD, age >75 y
N=226

Conventional Medical Therapy, age >75 y
N=164

The 1° endpoint: was all-cause mortality.

No. of events (death)
ICD, age <55 y
N=43

Conventional Medical Therapy, age <55 y
N=84

ICD, age 55–64 y
N=97

Conventional Medical Therapy, age 55–64 y
N=139

ICD, age 65–74 y
N=127

Conventional Medical Therapy, age 65–74 y
N=174

ICD, age >75 y
N=56

Conventional Medical Therapy, age >75 y
N=66

- ICD benefit in older pts:

DEFINITE HR 0.48; 95% CI: 0.30–0.79
MADIT-I HR 0.37; 95% CI: 0.22–0.61

The 2° endpoint was re-hospitalization for any reason.
MADIT-II HR: 0.44; 95% CI: 0.31–0.59
MUSTT HR: 0.27; 95% CI: 0.14–0.49
SCD-HeFT HR: 0.58; 95% CI: 0.45–0.74
Overall HR: 0.41; 95% CI: 0.21–0.71

References:


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