Figure S1

QRS-amplitude sum at diagnosis vs. Age at ECG (y)

- Solid line = mean regression line
- Dashed line = 95% confidence interval of the regression line
- Dotted line = 95% prediction limits
Figure S2. ROC-curves for the diagnosis of cardiac arrest in HCM-patients within the total HCM-cohort (all ages).

RS

TP

LP

Ri

Abbreviations:
RS = QRS-amplitude sum in limb-leads;
TP = twelve-lead amplitude x duration product;
LP = limb-lead amplitude x duration product;
Ri = Risk score; auc, area under the curve.
Figure S3. ROC-curves for the differentiation of athletes below 40 years of age against HCM-patients with cardiac arrest below 40 years of age.

- **RS**: $\text{auc} = 0.89$
- **TP**: $\text{auc} = 0.83$
- **LP**: $\text{auc} = 0.9$
- **Ri**: $\text{auc} = 0.96$

**Abbreviations:**
- RS = QRS-amplitude sum in limb-leads;
- TP = twelve-lead amplitude x duration product;
- LP = limb-lead amplitude x duration product;
- Ri = Risk score; auc, area under the curve.
Detailed Statistical Methodology

Statistical analysis was carried out using commercial software (Statgraphics Plus v5.2, GraphPad Prism 4 and R freeware version 2.7.2). Comparisons of proportions between the groups (analysis of contingency tables) were carried out by the two-tailed Fisher’s exact test, and odds ratios and their 95% confidence intervals were calculated. Comparisons of quantitative measures between groups were carried out by the non-parametric Mann-Witney U-test. Cut-off values for screening were selected using ROC-curves, with optimal cut-offs selected to prioritise sensitivity over specificity using methodology described earlier, see below for details.\textsuperscript{S1,S2} How proposed cut-off worked in different genders was further scrutinized by frequency distribution plots for each gender separately. The calculated absolute values for positive predictive value (PPV) using these cut-offs are probably overestimates, and those for negative predictive value (NPV) underestimates, since the cardiac arrest cohort is recruited from a much larger geographical base than the Gothenburg HCM-cohort, but the relative ranking in PPV and NPV between different screening measures will still be valid. Absolute values of sensitivity and false-positive rate are unaffected by this and true estimates in the Gothenburg cohort. However, like all estimates based on a single sample they may be overly optimistic. We have thus also carried out the non-parametric bootstrap to calculate the confidence intervals of the cut-off points proposed to assess their statistical accuracy, and refer to Foster et al. on how to bootstrap the statistical accuracy and confidence intervals of thresholds.\textsuperscript{S3}

To extract the cut-off point in each bootstrap sample one should define a criterion (based on some performance measure) for the optimal cut-off point.

The automatic procedure to extract the optimal cut-off point in bootstrap samples:
In this study, the optimal cut-off point is considered as the one that maximizes the function: \( f(x) = \frac{\text{prevalence}}{1-\text{prevalence}} \times r \times \text{sensitivity}(x) + \text{specificity}(x) \) where:
\( r = \frac{\text{Cfn} - \text{Ctp}}{\text{Cfp} - \text{Ctn}} \). The terms in \( r \) stand for the following:
\( \text{Cfp} \): The cost of treating a false positive
\( \text{Ctn} \): The cost of non-treating a false positive
\( \text{Cfn} \): The cost of non-treating a true positive
\( \text{Ctp} \): The cost of treating a true positive

This function is initially obtained from minimizing the overall expected cost of the test. We refer to Zweig et al. and Zhou et al (\textsuperscript{3}; section 2.11; pp48) on how optimal cut-offs may be derived from the ROC curve.\textsuperscript{S1,S2}

Interpretation and Selection of \( r \).
One can easily interpret the denominator and the numerator of \( r \) as follows:
\( \text{Cfp} - \text{Ctn} = \) The difference in costs between treating and non-treating negatives
\( \text{Cfn} - \text{Ctp} = \) The difference in costs between non-treating and treating positives
For instance, \( r=2 \) means that we assume that the difference in costs between non-treating and treating positives is 2 times the difference in costs between treating and non-treating negatives; “cost” is here used in the wider sense of clinical utility, not in the sense of financial costs.

To extract the cut-off point in each bootstrap sample (\( n=1000 \)) we defined as criterions that sensitivity should be given a greater weight than specificity. We fixed \( r = 4 \) for HCM group, where the priority is to identify the high risk individuals among a population all suffering from the disease. For the athletes, where you might use the results for screening supposedly healthy athletes, we give two sets of bootstrap results, \( r=1 \) (sensitivity and specificity given equal weight), and \( r=0.5 \) (prioritising specificity by giving it twice the weight of sensitivity). The bootstrap procedure was for each measure carried out with \( B = 1000 \) bootstrap samples to determine the 95% CI of the optimal cut-off. However the same bootstrap series provided
estimates for sensitivity, specificity etc for the range of optimal cut-offs encountered within the series. These we have documented in Tables S4 and S5 with an average, and the range by giving 2.5th and 97.5th percentile values. These values are for exploratory purpose only, and are not identical to the 95% CI of the sensitivity or specificity for the optimal cut-off obtained.

Assessing confounders and independence of risk factors.
Cox proportional hazards regression analysis, with survival time for patients diagnosed at post mortem set at time expired since the mustering ECG, was used to assess whether gender was a significant confounder for the ECG-measures advocated for screening, and whether the ECG-measures advocated for screening were independent risk factors to echocardiographic wall thickness.

References
S1. Zweig MH, Campbell G. Receiver-operating characteristic (ROC) plots: A fundamental evaluation tool in clinical medicine. Clin Chem 1993;39:561-577.
S2. Zhou X-H, Obuchowski NA, McClish DK. Statistical Methods in Diagnostic Medicine section 2.11:p 48. 2002; Wiley
S3 Foster DH, Bishop WF. Bootstrap estimates of the statistical accuracy of thresholds obtained for psychometric functions. Spatial Vision 1997;11:135-139.
**Supplementary results**

The summary statistics of all quantitative ECG-measures analyzed in normals, athletes and HCM-patients with and without cardiac arrests are given in Table S1.

**Age at ECG as a possible confounder**

In patients that were diagnosed on post mortem examination only, there has in some instances been several years between the ECG obtained at military conscription examination, and the subsequent sudden death, and it was therefore important to examine if in adulthood the chronological age influences the size of the ECG-amplitudes in HCM-patients. A plot of the ECG-amplitudes least influenced by variations in lead placements, and therefore with the smallest intra-patient variability between different examinations, namely total QRS-sum in limb leads was chosen. Limb-lead QRS-sum versus age at ECG from patients in the complete geographical Gothenburg cohort (i.e. both patients with and without cardiac arrests) is illustrated in Fig S1. As illustrated in the plot there is a very wide variability in ECG-amplitudes at all adult ages, and this variability bears no significant correlation to the age at which the ECG was taken. The slope of the plot is not different from zero, $0.024 \pm 0.19$ (SE), and the correlation coefficient is 0.014. We conclude that there is no relationship between age and ECG-amplitudes in the age range studied (15 to 79 years), and that the ECG-amplitudes reflect phenotypic characteristics independent of age. There is an obvious difference in age between those patients that have died suddenly (age $28 \pm 17$ yrs at diagnosis; cardiac arrests occurring at $36 \pm 16$ yrs of age) and the total HCM-group (age at diagnosis $42\pm17$yrs), but this relates to the well known fact that patients with the most malignant disease has a higher risk of dying at a young age from sudden arrhythmias. That is not the same thing as the age that the ECG has been recorded being a significant confounder.

**Gender as a confounder**

Many previous studies have found a higher proportion of males than females dying suddenly, but similarly most HCM-studies including young and middle-aged HCM patients have about 2/3 males and 1/3 females, and the gender proportion in our geographical cohort was 52 males 35 females, i.e 60% males. It would obviously be clinically more useful to have risk stratification measures that could be applied equally to males and females, and we have therefore performed a Cox proportional hazards analysis, using time passed since first ECG as survival time in patients which presented with sudden death. In this analysis gender does not come out as a separate independent significant risk factor for sudden death, when tested against either of the two ECG-measures advocated for screening, QRS-amplitude sum at diagnosis (QRS-sum p =0.008, gender p=0.20) or 12-lead product (12-lead product p=0.0000, gender p=0.18. Thus for neither of the two ECG-measures advocated for screening, and used in the risk score, is gender a statistically significant confounder. Likewise, including a previously known risk factor i.e wall thickness, when tested against QRS-sum, septal thickness and gender (RS-sum =0.002, septum p =0.000, gender p=0.19), gender is still not a significant confounder. And additionally, wall thickness is shown to be an independent risk factor from ECG-amplitudes.
Further Results of Bootstrapping

Bootstrapping was primarily undertaken to obtain the 95% CI for the cut-off obtained from our study populations, see Table S3. In addition we obtained bootstrapping estimates for the average sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV) for the range of optimal cut-offs encountered in the 1000 bootstrapping procedures, see Table S4. These results show that the sensitivities are very similar to the cohort estimates for limb-lead QRS-sum (90% bootstrap, 87% cohort estimate), and for the 12-lead product (90% bootstrap, 92% cohort estimate) where the bootstrap ended up with virtually identical cut-off. Thus there is no evidence that the sensitivity estimates in our cohort is unduly optimistic. For the limb-lead product the bootstrap (done on both genders together) had an average cut-off of 0.76, however as shown in Table 3 in the main text this would significantly reduce the sensitivity in male subjects (to 83%), and as we prioritise sensitivity over specificity we therefore chose the slightly lower cut-off of 0.70 which gives a sensitivity of 93% in the cohort, as against the bootstrap estimate for 92% for an average cut-off of 0.76. For the risk score the bootstrap suggests a cut-off of 6.4 or 6.5 which however is an average of integers as the point score is in integers, so we suggest to remain with the cohort cut-off of ≥6 which gives a sensitivity of 84% and a specificity of 85%, as opposed to the bootstrap cut-off of 6.7 giving a sensitivity of 81% and a specificity of 89%. Overall the bootstrap estimates give no cause to assume that the estimates of sensitivity and specificity from the cohort are unduly optimistic. The risk score did not have the greatest sensitivity in the HCM-cohort, but did have the greatest accuracy of any measure, i.e. had the greatest proportion of subjects that were correctly identified as either true positives or true negatives, both in screening for risk of cardiac arrest in the HCM-cohort, and in screening versus athletes (see Tables S4 and S5 in Supplemental Tables).

In our screening for athletes, we have recommended cut-offs for 12-lead products and limb-lead products that are slightly lower than the average bootstrap result, but within the 95% CI of the bootstrap cut-off, for reasons of optimising PPV and NPV which were not included as parameters in the bootstrap equation. The bootstrap-averages also gave substantially lower sensitivity in our cohort than the cut-offs we advocate. In any case, the risk score is substantially superior to either, as shown by the greatest area under the curve (0.96). However, for those users who want to prioritise specificity still further over sensitivity, we provide data on boot-strap estimates of cut-offs for all measures with specificity given twice the weight of sensitivity in Table S5 in Supplemental Tables.
Development of risk score

Table S2 in Supplemental Tables shows the relative frequency of abnormalities in ECG morphology. The HCM-CA group shows a significantly increased occurrence of pathological T-wave inversion in any lead (p=0.0003), precordial T-wave inversion (p<0.0001), ST-depression (p=0.0010), and a dominant S-wave in V_4 (p=0.0048) compared with the Gothenburg HCM-cohort. QRS-axis deviation is possibly increased (p=0.05). Those qualitative measures with a statistical correlation of ≥0.05 or greater were included in a risk score with those that had a frequency among cardiac arrest victims x2 or greater than that seen in the geographical HCM cohort were given a score of 2 points, and the others a score of 1 point. From the quantitative measures three were included in the score, the QRS-amplitude sum for being of high sensitivity, and completely gender neutral, and the 12-lead product, for reflecting both those individuals with a considerably broadened QRS-complex, and those with disproportionate increase in precordial ECG-amplitudes. The QTc was also included as QTc was significantly increased in HCM-patients with cardiac arrests both as compared with the Gothenburg HCM-cohort (p=0.003) and compared with normal athletes (p=0.004). For QTc a QTc ≥440 ms, which was the median value for patients with cardiac arrest, and was present in only 7% of athletes (3/43) was awarded 1 point. For QRS-sum and 12-lead product sum values greater than the cut-offs proposed by ROC-curves and bootstrapping were given 1 point, but as the risk was progressive with increasing sums the point score was increased to 2 for values that give less than 10-12% false positives, and to 3 points for values which showed no or minimal overlap with athletes, and 5-7% overlap with the Gothenburg HCM-cohort; in all instances QRS-amplitude sum had less overlap than 12-lead product.

The risk score was validated by showing with Cox proportional hazards regression analysis that when the risk score was included neither of the quantitative ECG-measures remained a significant independent risk factor. If one tests gender versus risk score on a Cox regression analysis, the results are p=0.000 for risk score, and p=0.24 for gender. Thus, there is no case for introducing gender as a separate factor in the risk score, and it is obviously more clinically useful to have a risk score that can be applied equally to males and females. Furthermore, when analysing the risk score with ROC-curves in patients with cardiac arrest versus the Gothenburg HCM-cohort, the area under the curve, 0.89, is greater than for any of the individual ECG-measures (0.84-0.87); see Figure S2 in supplemental files. In the comparison against athletes the superiority of the risk score is even clearer, with an area under the curve of 0.96 versus 0.83-0.90 for the individual ECG-measures (see Figure S3 in supplemental files).
| ECG-measure                  | Normals         | Athletes        | HCM-cohort      | HCM-CA         |
|-----------------------------|-----------------|-----------------|-----------------|----------------|
|                             | Male n=22       | Male n=20       | Male n=52       | Male n=24      |
|                             | Female n=22     | Female n=14     | Female n=35     | Female n=7     |
| Limb-lead QRS-sum (mV)      | 5.6±1.1         | 7.8±2.2         | 6.8±3.2         | 11.3±4.6       |
|                             | [5.1-6.1]       | [6.8-8.8]       | [6.0-7.7]       | [9.4-13.2]     |
|                             | 5.4±0.9         | 6.3±1.8         | 6.5±2.0         | 11.1±3.5       |
|                             | [5.0-5.7]       | [5.2-7.4]       | [5.4-7.5]       | [7.8-14.4]     |
| Chest-lead QRS-sum (mV)     | 11.8±2.1        | 16.8±3.2        | 13.0±4.4        | 17.7±5.6       |
|                             | [10.9-12.7]     | [15.3-18.4]     | [11.8-14.3]     | [15.0-20.3]    |
|                             | 8.5±1.9         | 10.1±2.7        | 10.9±3.5        | 18.8±6.0       |
|                             | [7.6-9.4]       | [8.6-12.6]      | [9.7-12.1]      | [11.3-26.2]    |
| 12-lead QRS-sum (mV)        | 17.5±2.3        | 24.5±4.8        | 19.7±6.2        | 27.5±7.3       |
|                             | [16.5-18.5]     | [22.2-26.8]     | [17.6-22.5]     | [24.1-30.9]    |
|                             | 13.9±2.3        | 16.4±4.2        | 17.4±5.5        | 33.3±11.9      |
|                             | [12.9-15.0]     | [14.0-18.8]     | [15.5-19.2]     | [18.6-48.1]    |
| 12-lead Product (mV.sec)    | 1.67±0.28       | 2.38±0.56       | 2.01±0.87       | 2.88±0.89      |
|                             | [1.55-1.80]     | [2.11-2.65]     | [1.76-2.25]     | [2.46-3.29]    |
|                             | 1.25±0.20       | 1.45±0.45       | 1.59±0.63       | 3.59±1.52      |
|                             | [1.16-1.34]     | [1.21-1.77]     | [1.36-1.80]     | [1.70-5.47]    |
| Limb-lead Product (mV.sec)  | 0.55±0.10       | 0.75±0.23       | 0.66±0.33       | 1.14±0.47      |
|                             | [0.50-0.59]     | [0.65-0.86]     | [0.57-0.76]     | [0.95-1.34]    |
|                             | 0.49±0.08       | 0.56±0.18       | 0.61±0.32       | 1.47±0.54      |
|                             | [0.45-0.52]     | [0.46-0.66]     | [0.50-0.72]     | [0.94-2.22]    |
| Sokolow-Lyon Index (mV)     | 2.8±0.5         | 3.6±0.7         | 2.8±1.0         | 4.8±1.9        |
|                             | [2.5-3.0]       | [3.3-3.9]       | [2.5-3.1]       | [3.9-5.7]      |
|                             | 2.2±0.5         | 2.4±0.6         | 2.7±1.0         | 6.1±3.2        |
|                             | [1.9-2.4]       | [2.1-2.8]       | [2.3-3.1]       | [2.7-9.4]      |
| QRS-duration (msec)         | 96±9            | 97±11           | 97±14           | 101±16         |
|                             | [92-99]         | [92-102]        | [93-101]        | [95-108]       |
|                             | 91±10           | 88±9            | 88±9            | 123±39         |
|                             | [87-96]         | [82-93]         | [85-91]         | [82-164]       |
| QTc (msec)                  | 394±13          | 402±24          | 417±38          | 446±23         |
|                             | [388-400]       | [391-413]       | [406-428]       | [435-457]      |
|                             | 404±18          | 418±17          | 425±30          | 436±30         |
|                             | [396-412]       | [410-426]       | [414-436]       | [405-468]      |
| Feature                | Proportion positive in HCM-cohort; (=false pos.) | Proportion positive Cardiac arrest; (=Sensitivity) [95% CI] | Fisher’s exact test | Odds ratio [95% CI] | Spec. (%) [95%CI] | PPV (%) [95%CI] | NPV (%) [95%CI] |
|------------------------|-------------------------------------------------|-------------------------------------------------------------|---------------------|----------------------|---------------------|------------------|------------------|
| BundB-block            | 5/83 (6%)                                       | 4/32 (13%)                                                  | n.s.                |                      |                     |                  |                  |
| Path.Q-waves           | 12/84 (14%)                                     | 6/27 (22%)                                                  | n.s.                |                      |                     |                  |                  |
| L-axis dev.            | 24/84 (29%)                                     | 15/31 (48%)                                                 | n.s.                | 2.4                  | 69                  | 38               | 79               |
|                        |                                                 |                                                             | p=0.05              | [1.02-5.5]           | [58-79]            | [24-54]         | [68-88]         |
| R-axis dev.            | 2/84 (2%)                                       | 1/31 (3%)                                                   | n.s.                |                      |                     |                  |                  |
| Any axis-dev           | 26/84 (31%)                                     | 16/31 (52%)                                                 | n.s.                | 2.4                  | 69                  | 38               | 79               |
|                        |                                                 |                                                             | p=0.05              | [1.02-5.5]           | [58-79]            | [24-54]         | [68-88]         |
| Path.T-invers.         | 50/84 (60%)                                     | 29/31 (94%)                                                 | p=0.0003            | 9.9                  | 40                  | 37               | 94               |
|                        |                                                 |                                                             |                     | [2.2-44.1]           | [30-52]            | [26-48]         | [81-99]         |
| Precord.T-inv          | 33/84 (39%)                                     | 28/31 (84%)                                                 | P<0.0001            | 8.0                  | 61                  | 44               | 91               |
|                        |                                                 |                                                             |                     | [2.8-23.0]           | [49-71]            | [31-58]         | [80-97]         |
| ST-depression          | 5/84 (6%)                                       | 5/84 (32%)                                                  | p=0.0010            | 7.5                  | 94                  | 64               | 81               |
|                        |                                                 |                                                             |                     | [2.2-24.9]           | [87-98]            | [35-87]         | [71-88]         |
| Dom. S in V4           | 18/80 (23%)                                     | 15/29 (52%)                                                 | p=0.0048            | 3.7                  | 78                  | 45               | 82               |
|                        |                                                 |                                                             |                     | [1.5-9.1]            | [67-86]            | [26-64]         | [71-90]         |
| Giant pos. T           | 8/84 (10%)                                      | 2/27 (7%)                                                   | n.s.                |                      |                     |                  |                  |
| Giant neg. T           | 4/84 (5%)                                       | 1/27 (4%)                                                   | n.s.                |                      |                     |                  |                  |

*Abbreviations:* BundB-block = bundle-branch block; Path. = pathological; dev. = deviation; T-inv = T-wave inversion; Precord. = precordial lead; Dom. = dominant (i.e.S>R); pos. = positive; T= T-wave; neg. = negative. Spec.= specificity; PPV = positive predictive value; NPV = negative predictive value
Table S3: Screening performance of ECG-measures at various cut-offs, comparing HCM cohort with HCM with cardiac arrest,[ 95% CI].

| Measure                  | Odds ratio | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) | Fisher’s (p=) |
|--------------------------|------------|-----------------|-----------------|---------|---------|---------------|
|                          |            |                 |                 |         |         |               |
|                          | Males      |                 |                 |         |         |               |
| LQRS-sum>7.7mV           | 15.0 [4.3-52.0] | 83 [63-95] | 75 [61-86] | 61 [42-77] | 91 [78-97] | <0.0001 |
| LQRS-sum>10mV           | 12.9 [3.8-44.0] | 58 [37-98] | 90 [79-97] | 74 [49-91] | 82 [70-91] | <0.0001 |
| Sokly >4.0 mV          | 15.4 [3.8-62.1] | 63 [38-84] | 90 [76-97] | 75 [48-93] | 84 [69-93] | <0.0001 |
| 12-Lsum>22.0mV         | 19.2 [3.9-93.7] | 90 [68-99] | 68 [53-81] | 55 [36-72] | 94 [80-99] | <0.0001 |
| 12-LPro >2.2mV.s       | 21.0 [4.4-100] | 90 [68-99] | 65 [50-78] | 51 [34-69] | 94 [90-99] | <0.0001 |
| LL-pro >0.70 mV.s      | 24.2 [5.0-117] | 92 [73-99] | 69 [54-80] | 60 [42-75] | 94 [81-99] | <0.0001 |
| LL-pro >0.77 mV.s      | 18.6 [5.3-65.9] | 83 [63-95] | 79 [65-89] | 65 [45-81] | 91 [79-98] | <0.0001 |
| QRS-dur>0.110 s        | 1.5 [0.4-5.6] | 21 [7-42] | 86 [73-94] | 42 [15-72] | 69 [56-70] | n.s.(0.51) |
|                          | Females    |                 |                 |         |         |               |
| LQRS-sum>7.7mV           | 15.0 [1.6-141.0] | 86 [42-100] | 71 [54-85] | 38 [15-65] | 96 [80-100] | 0.0081 |
| LQRS-sum>10mV           | 15.6 [2.2-110] | 71 [29-96] | 86 [68-96] | 56 [21-86] | 93 [76-99] | 0.0056 |
| Sokly >4.0 mV           | 10.0 [1.3-74.6] | 67 [22-96] | 83 [63-95] | 50 [16-84] | 91 [71-99] | 0.029 |
| 12-Lsum>22.0mV          | 24.9 [1.2-497] | 100 [48-100] | 70 [51-85] | 36 [13-65] | 100 [84-100] | 0.0062 |
| 12-LPro >2.2mV.s        | 41.5 [2.0-852] | 100 [48-100] | 80 [61-92] | 46 [17-77] | 100 [86-100] | 0.0014 |
| LL-pro >0.7 mV.s        | 32.2 [1.6-630] | 100 [55-100] | 72 [53-86] | 40 [16-68] | 100 [85-100] | 0.0018 |
| LL-pro >0.77 mV.s       | 42.1 [2.1-827] | 100 [54-100] | 77 [60-90] | 43 [18-71] | 100 [87-100] | 0.0007 |
| QRS-dur>0.110 s         | 57.0 [2.4-1350] | 50 [12-88] | 100 [88-100] | 100 [99-100] | 90 [74-98] | 0.0033 |
|                          | Both sexes |                 |                 |         |         |               |
| LQRS-sum>7.7mV           | 14.5 [5.0-42.2] | 84 [66-95] | 74 [66-95] | 53 [38-68] | 93 [84-98] | <0.0001 |
| Sokly >4.0 mV           | 17.0 [5.5-52.6] | 64 [43-82] | 91 [81-96] | 70 [47-87] | 88 [75-93] | <0.0001 |
| 12-Lsum>22.0mV          | 16.2 [4.4-59.4] | 88 [69-97] | 69 [57-79] | 48 [33-63] | 95 [85-99] | <0.0001 |
| 12-LPro >2.2mV.s        | 31.0 [6.7-142] | 92 [74-99] | 73 [62-82] | 50 [35-65] | 97 [89-100] | <0.0001 |
| LL-pro >0.7 mV.s        | 31.5 [6.9-143] | 93 [78-99] | 69 [58-79] | 54 [39-68] | 96 [88-100] | <0.0001 |
| LL-pro >0.77 mV.s       | 21.1 [6.6-67.8] | 87 [69-96] | 76 [66-85] | 57 [41-71] | 94 [86-98] | <0.0001 |
| QRS-dur>0.110 s         | 3.6 [1.2-11.2] | 27 [12-47] | 91 [82-96] | 53 [27-79] | 76 [66-84] | 0.029 |
| QTc>440 ms              | 3.0 [1.2-7.6] | 58 [37-77] | 69 [57-79] | 40 [24-67] | 82 [70-91] | 0.02 |
| Risk score >4           | 16.8 [5.3-53.2] | 87 [69-96] | 72 [53-86] | 52 [37-46] | 94 [85-98] | <0.0001 |
| Risk score >6           | 28.4 [9.2-87.5] | 84 [66-95] | 85 [75-91] | 67 [50-81] | 93 [85-98] | <0.0001 |

| Measure                  | Odds ratio | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) | Fisher’s (p=) |
|--------------------------|------------|-----------------|-----------------|---------|---------|---------------|
|                          | Age < 40 yrs |                 |                 |         |         |               |
| LQRS-sum>7.7mV           | 27.0 [5.0-147] | 90 [68-99] | 75 [55-89] | 72 [51-88] | 91 [72-99] | <0.0001 |
| 12-LPro >2.2mV.s        | 51.7 [2.8-957] | 100 [78-100] | 63 [42-81] | 60 [39-79] | 100 [81-100] | <0.0001 |
| LL-pro >0.7 mV.s        | 76.0 [4.1-149] | 100 [82-100] | 67 [46-83] | 68 [48-84] | 100 [81-100] | <0.0001 |
| Risk score >4           | 7.6 [1.8-31.8] | 85 [62-97] | 57 [37-76] | 59 [39-76] | 84 [60-97] | 0.0063 |
| Risk score >6           | 26.1 [5.5-124] | 85 [62-97] | 82 [63-94] | 77 [55-92] | 88 [70-98] | <0.0001 |

Abbreviations: LQRS-sum=limb-lead QRS-amplitude sum; Sokly = Sokolow-Lyon index; 12-Lsum =12-lead QRS-amplitude sum; 12-LPro = 12-lead amplitude-duration product; LL-pro = limb-lead amplitude-duration product; QRS-dur = QRS-duration; QTc = corrected QT-interval; Risk score = see Table 2 for definition.
Table S4. Bootstrap analysis of performance of suggested ECG-screening measures when comparing HCM-patients with cardiac arrest against the Gothenburg HCM-cohort. B=1000, results given as average [95% CI], or average (2.5 centile, 97.5th centile).

| Measure            | Cut-off   | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) | Accuracy (%) |
|--------------------|-----------|-----------------|-----------------|---------|---------|--------------|
| LL QRS-sum (mV)    | 7.46 [6.5, 9.7] | 90 (78,100)    | 72 (58, 88)     | 54 (40, 70) | 96 (91, 100) | 77 (67, 86)  |
| 12-lead product (mV.s) | 2.27 [1.8, 2.5] | 90 (75,100)    | 76 (61, 90)     | 54 (40, 69) | 97 (92, 100) | 80 (69, 80)  |
| LL-product (mV.s)  | 0.76 [0.7,0.89]  | 92 (80, 100)   | 76 (65, 87)     | 59 (44, 73) | 96 (91, 100) | 80 (72, 88)  |
| Risk score (points)| 6.7 [6, 8]      | 81 (64, 97)    | 89 (79, 97)     | 74 (57, 90) | 93 (87, 98) | 87 (80, 93)  |

**Abbreviations:** LL QRS-sum=limb-lead QRS amplitude sum; 12-lead product= 12-lead amplitude x duration product; LL-product= limb-lead amplitude x duration product; PPV= positive predictive value, NPV= negative predictive value; Accuracy= proportion of patients correctly identified as true positives or true negatives.
Table S5. Bootstrap analysis of performance of suggested ECG-screening measures when comparing HCM-patients with cardiac arrest against <40 yrs of age against athletes. B=1000, results given as average [95% CI], or average (2.5 centile, 97.5th centile)

| Measure          | Cut-off (mV) | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) | Accuracy (%) |
|------------------|--------------|-----------------|-----------------|---------|---------|-------------|
| **LL QRS-sum**   | 10.32        | 73 (43,100)     | 93 (69,100)     | 89 (69,100) | 86 (74,100) | 86 (78, 94) |
| **12-lead product** (mV.s) | 3.56 [2.15-4.50] | 50 (19, 95) | 96 (70, 100) | 91 (61, 100) | 84 (72, 96) | 83 (75, 94) |
| **LL-product** (mV.s) | 1.04 [0.89-1.29] | 78 (50,100) | 94 (81,100) | 89 (70,100) | 90 (79,100) | 89 (80, 96) |
| **Risk score** (points) | 6.4 [3.8] | 85 (67,100) | 100 (97,100) | 100 (94,100) | 92 (83,100) | 94 (87,100) |

**Cut-offs based on r = 0.5 (specificity given twice the weight of sensitivity)**

| Measure          | Cut-off (mV) | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) | Accuracy (%) |
|------------------|--------------|-----------------|-----------------|---------|---------|-------------|
| **LL QRS-sum**   | 10.96 [8.05, 12.1] | 64 (35, 88) | 97 (90,100) | 95 (81,100) | 83 (70,94) | 85 (76, 94) |
| **12-lead product** (mV.s) | 3.86 [2.76, 5.13] | 43 (13, 75) | 99 (94, 100) | 96 (80,100) | 81 (70,93) | 83 (77, 94) |
| **LL-product** (mV.s) | 1.12 [0.88,1.4] | 69 (38,96) | 97 (87,100) | 94 (79,100) | 87 (74,97) | 88 (78, 96) |
| **Risk score** (points) | 6.5 [6.8] | 85 (67,100) | 100 (100,100) | 100 (100,100) | 92 (83,100) | 94 (88,100) |

**Abbreviations:** LL QRS-sum=limb-lead QRS amplitude sum; 12-lead product= 12-lead amplitude x duration product; LL-product= limb-lead amplitude x duration product; PPV= positive predictive value, NPV= negative predictive value; Accuracy= proportion of patients correctly identified as true positives or true negatives.