Prevalence and Prognostic Significance of Negative U-waves in a 12-lead Electrocardiogram in the General Population

Arttu Holkeri MD , Antti Eranti MD , M. Anette Haukilahti BM , Tuomas Kerola MD , Tuomas V. Kenttä PhD , Kai Noponen MSc , Tapio Seppänen PhD , Harri Rissanen MSc , Markku Heliövaara MD , Paul Knekt PHD , M. Juhani Junttila MD , Heikki V Huikuri MD , Aapo L. Aro MD

PII: S0002-9149(18)31964-7
DOI: https://doi.org/10.1016/j.amjcard.2018.10.010
Reference: AJC 23574

To appear in: *The American Journal of Cardiology*

Received date: 30 July 2018
Revised date: 1 October 2018

Prevalence and Prognostic Significance of Negative U-waves in a 12-lead Electrocardiogram in the General Population

Arttu Holkeri, MD[a]; Antti Eranti, MD[b]; M. Anette Haukilahti, BM[c]; Tuomas Kerola, MD[b]; Tuomas V. Kenttä, PhD[c]; Kai Noponen, MSc[d]; Tapio Seppänen, PhD[d]; Harri Rissanen, MSc[e]; Markku Heliövaara, MD[e]; Paul Knekt PHD[e]; M. Juhani Junttila MD[c]; Heikki V Huikuri MD[c]; Aapo L. Aro MD[a]

Affiliations:

[a] Division of Cardiology, Heart and Lung Center, Helsinki University Hospital, Helsinki, Finland. Postal address: Meilahti Tower Hospital, PL 340, 00029 HUS, Finland.

[b] Department of Internal Medicine, Päijät-Häme Central Hospital, Lahti, Finland. Postal address: Päijät-Hämeen keskussairaala, Keskussairaalankatu 7, 15850, Lahti, Finland.

[c] Research Unit of Internal Medicine, Medical Research Center, Oulu University Hospital and University of Oulu, Oulu, Finland. Postal address: Faculty of Medicine, P.O. Box 5000, FI-90014, University of Oulu, Finland.

[d] Center for Machine Vision and Signal Analysis, University of Oulu, Oulu, Finland. Postal address: Center for Machine Vision and Signal Analysis, P.O Box 4500, FI-90014, University of Oulu, Finland.

[e] National Institute for Health and Welfare, Helsinki, Finland. Postal address: P.O. Box 30, FI-00271 Helsinki, Finland.

Short title:

Prognostic Significance of Negative U-waves

Declarations of interest:

None

Funding:

This work was supported by Ida Montin's Foundation (A.H.); Finnish Medical Foundation (A.H./A.E./A.L.A.); Paavo Nurmi's Foundation (A.E.); Onni and Hilja Tuovinen's Foundation (A.E.); the Orion Research Foundation (A.E./T.V.K.); the Aarne Koskelo Foundation (T.V.K.); the Paulo Foundation (T.V.K.); the Sigrid Juselius Foundation (M.J.J./H.V.H./A.L.A); Academy of Finland (M.J.J./H.V.H.); Finnish Foundation of Cardiovascular Research (M.J.J./H.V.H.); and the Veritas Foundation (A.E.).
Funding sources had no involvement in the study design, in the collection, analysis and interpretation of data, in the writing of the report, or in the decision to submit the article for publication.

Corresponding author:
Arttu Holkeri, arttu.holkeri@gmail.com, +358505992179, Heart and Lung Center, Meilahti Tower Hospital, PL 340, 00029 HUS, Finland. Fax number 09 471 75600 (HUS hospitals)

Manuscript revised October 1, 2018.

Abstract

Negative U-waves are a relatively rare finding in an electrocardiogram (ECG), but are often associated with cardiac disease. The prognostic significance of negative U-waves in the general population is unknown. We evaluated 12-lead ECGs of 6518 adults (45% male, mean age 50.9±13.8 years) for the presence of U-waves, and followed the subjects for 24.5±10.3 years. Primary endpoints were all-cause mortality, cardiac mortality and sudden cardiac death (SCD); secondary endpoint was hospitalization due to cardiac causes. Negative U-waves (amplitude ≥0.05mV) were present in 231 (3.5%) subjects, minor negative (amplitude <0.05mV) or discordant U-waves in 1,004 (15.4%) subjects, normal positive U-waves in 3,950 (60.6%) subjects, and no U-waves were observed in 603 (9.3%) subjects. In 730 (11.2%) subjects U-waves were unassessable. When adjusted for age and sex, negative U-waves were associated with all endpoints ($p<0.01$). In an analysis adjusted for multiple demographic and clinical factors, among men negative U-waves were associated with increased risk of all-cause mortality (Hazard Ratio [HR] 1.60; 95% Confidence Interval [CI] 1.26–2.03; $p<0.001$), cardiac mortality (HR 1.74; 95% CI 1.26–2.39; $p=0.001$) and cardiac hospitalization (HR 1.67; 95% CI 1.27–2.18; $p<0.001$), but not with SCD, whereas women did not show a significant association to any of the endpoints ($p>0.30$). In conclusion, negative U-waves are associated with adverse events in the general population. Among men, this association is independent of cardiovascular risk factors.

Keywords

U-wave, Electrocardiography, Prognosis, General Population

Introduction

Although first described over 100 years ago [1], the U-wave has received much less attention than other components of the ECG, and the mechanisms underlying the genesis of the U-wave are still not fully understood [2]. Normally, U-waves are concordant with the preceding T-wave and are best seen in the leads V2–V4 [3]. U-wave's amplitude is inversely proportional to heart rate, and it is visible in more than 90% of ECGs with heart rate under 60 beats per minute (bpm) [4]. However, negative U-waves are a much less frequent phenomenon [5], and are often associated with cardiac diseases [6–9]. The prognostic significance of U-wave morphologies has been studied mostly in specific cardiac patient populations [10]. However, data are lacking on the prognostic significance of different U-wave manifestations in the general population. In the present study, we investigated the prevalence and prognostic significance of negative U-waves and other U-wave morphologies in a large general population sample with a follow-up of 25 years.

Methods

The study population consists of participants of the Mini-Finland Health Survey which was part of the Social Insurance Institution's Finnish Mobile Clinic Survey. The survey included health interviews and examinations. Detailed study protocol and methods are published elsewhere [11]. Briefly, a total of 8,000 subjects representing the Finnish population aged over 30 years received invitation to the survey in 1978–80. Of those, 7,217 participated in health examinations. The health interviews included a detailed questionnaire on known diseases, medications, symptoms, and tobacco consumption. Health examinations included measuring of heart rate, blood pressure, body mass index, and serum cholesterol level. In addition, plasma potassium levels were obtained from a subgroup of subjects. A resting paper ECG was recorded in supine position from all subjects with Kone Oy's Olli 308 ECG device with a paper speed of 50 mm/s and calibration of 10 mm/mV. After a few months, an additional ECG was recorded from a subgroup of subjects based on the presence of signs of cardiovascular disease. Assessment of baseline diagnoses and the list of diagnoses included as cardiac disease are described in the Supplementary Material. When the original survey was conducted, no institutional review committees existed and universal practice was that subjects gave their consent by participating in the study.

After exclusion of missing ECGs, a total of 6,969 ECGs were digitized and analyzed, as described previously [12]. In brief, examiners digitized and digitally measured the ECGs, with concurrently manually assessing the presence, deflection and amplitude of U-waves in each lead. Subjects (n=442) with bundle branch block, incomplete bundle branch block, atrial fibrillation or flutter, or with rare pathological ECG findings, and subjects (n=9) with missing data were excluded. The remaining 6,518 subjects underwent classification into 4 groups: 1) Normal U-waves (positive $\geq$0.05mV U-wave in $\geq$1 leads and no negative U-waves), 2) No U-waves in any leads (or only minor positive <0.05mV U-waves), 3) Negative

U-waves (amplitude ≥0.05mV) in ≥1 leads, and 4) Minor negative U-waves (amplitude <0.05mV) or discordant U-waves (positive U-wave with negative preceding T-wave) in ≥1 leads. The rationale behind the classification and assessment of U-waves is presented in detail in the Supplementary Material.

The follow-up phase continued from the baseline examination until December 31st, 2011. Nationwide health registries (Statistics Finland and National Hospital Discharge Register) were the source for the follow-up information. Sudden cardiac deaths (SCD) were identified by using the modified CAST-criteria [13] (detailed description is provided in the Supplementary Material). An autopsy was performed on 1077 cases (27% of all deceased), of which 194 were SCD cases (48% of all SCD cases). The primary endpoints were all-cause mortality, cardiac mortality, and SCD. The secondary endpoint was hospitalization due to cardiac causes.

The general linear model was used for the comparison of the age and sex adjusted mean values for continuous variables, and the prevalence of categorical variables. We used the Cox proportional hazards model to estimate hazard ratios (HR) and their 95% confidence intervals (95% CI) between categories of U-waves. The Kaplan-Meier estimator was used to estimate survival function. The multivariate models were adjusted for age, sex, body mass index, systolic blood pressure, serum cholesterol, smoking, heart rate, diabetes, baseline cardiac disease with or without myocardial infarction, and left ventricular hypertrophy (LVH) according to the Sokolow-Lyon ECG criteria. The statistical significance of effect modification by sex and baseline cardiac disease was tested using the Wald test by entering an interaction term of U-waves and sex, and U-waves and cardiac disease, respectively. P-value of <0.05 was considered to be statistically significant. IBM SPSS version 24 served for statistical analysis.

Results

Of the 6,518 subjects (mean age 50.9±13.8, 45% male), 3,950 subjects (60.6%) had normal U-waves, 231 subjects (3.5%) presented with negative U-waves, and 1,004 subjects (15.4%) presented with minor negative or discordant U-waves; in 603 subjects (9.3%) no U-waves were present. In 730 subjects (11.2%), U-waves were not assessable, which was generally due to the fusion of U-wave and P-wave due to sinus tachycardia. Examples of different U-wave morphologies are presented in Figure 1. The distribution of U-waves in different ECG leads is presented in Figure 2. In 16% of subjects with negative U-waves T-wave inversion preceded the negative U-wave.

The baseline characteristics of subjects with different U-wave morphologies are presented in Table 1. Subjects with negative U-waves were older and more likely female, than subjects with normal U-waves (p<0.001 for both). When adjusted for age and sex, subjects with negative U-waves had higher systolic and diastolic blood pressure, higher heart rate, and were more likely to have a history of hypertension, cardiac disease and LVH, compared to subjects with normal U-waves (p<0.001 for all). Overall, 89% of the subjects with negative U-waves had systolic blood pressure > 140 mmHg or had a cardiac disease.

Serum potassium was obtained from a total of 2,637 subjects (40%), with a mean level of 4.5 ± 0.4 mmol/l, with no statistically significant difference between subjects with negative U-waves and normal U-waves. A repeat ECG was recorded after a few months from 78 of the 231 subjects with negative U-waves according to the study design. After exclusion of 3 ECGs with unassessable U-waves, a negative U-wave was again observed in 47 (63%) of these subjects.

During the follow-up of 24.5 ± 10.3 years, 3,488 subjects (53.5%) died, of which 1,509 due to cardiac causes (43.3% of all deaths), and 358 due to SCD (10.3% of all deaths). Kaplan-Meier curves for overall mortality according to the U-wave morphology are demonstrated in Figure 3. Table 2 shows the unadjusted and adjusted HRs for all-cause mortality, cardiac death, SCD, and cardiac hospitalization associated with different U-wave morphologies, in comparison with normal positive U-waves. In the age and sex adjusted analysis negative U-waves were associated with increased risk for all of the endpoints, compared to subjects with normal U-waves ($p<0.01$ for all). In the multivariate analysis, negative U-waves remained independently associated with increased risk for all-cause mortality. Statistically significant effect modification of negative U-waves by baseline cardiac disease was not found on adjusted analyses for all-cause mortality, cardiac death, and cardiac hospitalization.

The baseline characteristics of male and female subjects with negative U-waves were largely similar. After adjusting for age, male and female subjects differed significantly only in heart rate (males 66±9 vs. females 70±9 bpm), serum cholesterol (males 6.7±1.3 vs. females 7.6±1.4 mmol/l), body mass index (males 23.8±3.4 vs. females 26.0±4.3 kg/m^2), and smoking (males 43.2% vs. females 6.7%) ($p<0.01$ for all). No statistically significant differences were found on age, blood pressure, the prevalence of cardiac disease, LVH, or diabetes. Negative U-wave lead distribution did not differ between genders.

The prognostic significance of negative U-waves stratified by sex, and interaction between sex and negative U-waves are presented in Table 3. Significant sex interaction was noted in overall mortality, cardiac mortality, and cardiac hospitalizations. When male and female subjects were analyzed separately, women with negative U-waves did not show statistically significant increase in the risk of any of the endpoints in multivariate analysis compared to normal U-waves. On the contrary, among men, negative U-waves were associated with an increase in the risk for all-cause mortality, cardiac death, and hospitalization due to cardiac causes. Furthermore, negative U-waves remained associated with all-cause mortality, cardiac death and hospitalization due to cardiac causes in a subanalysis of male subjects without cardiac disease (presented in the Supplementary Material). Neither male nor female subjects with negative U-waves showed statistically significant increase in the risk of SCD compared to subjects with normal U-waves.

Discussion

The present study is the first to directly address the prevalence, characteristics and prognostic significance of different U-wave morphologies and negative U-waves in the general population. We found that negative U-waves are a relatively rare ECG finding in the general population often associated with older age, female gender and cardiac diseases. Negative U-waves are in general a marker of poor prognosis; however, among men they are also independently associated with overall mortality, cardiac death, and cardiac hospitalizations.

Overall, the prevalence and distribution of U-waves and negative U-waves in the present study were similar with earlier reports [3,4,14]. Our study population had slightly higher prevalence of negative U-waves, 3.5%, compared to some published reports with prevalences of 1 – 2% [5,14], although prevalence as high as 14 % have been reported [15].
18/10/2018 17:57:00

In the present study, subjects with negative U-waves were on average over 15 years older than those with normal U-waves. Similar association of negative U-waves and older age have been demonstrated previously [15,16]. The presence of negative U-waves is also shown to be a specific marker for cardiac diseases [5,6], e.g. hypertension [9,17] and CAD [6,17–19]. Concordantly, in our study subjects with negative U-waves had almost 20 mmHg higher systolic blood pressure and were much more likely to have cardiac disease compared to those with normal U-waves.

Although the definite origin of the U-wave has remained unresolved [3], according to the prevailing mechanoelectrical hypothesis, U-wave originates from afterpotentials caused by the mechanical stretch during ventricular relaxation [2,20]. Consequently, myocardium relaxation abnormalities caused by cardiac diseases could be the mechanism behind negative U-waves [21,22], which would also explain the adverse prognosis associated with negative U-waves.

The prognostic significance of negative U-waves has been studied only in special patient populations. In hypertensive subjects negative U-waves have been associated with higher morbidity and mortality [23], and among patients with recent myocardial infarction, negative U-waves have been associated with reduced left ventricular ejection fraction, more advanced disease and increased infarction recurrence rates [10]. However, the prognostic significance of negative U-waves has not been studied in the general population. In the present study, we demonstrated that negative U-waves in the general population were associated with an increased risk of all-cause mortality. Although much of this risk was explained by traditional cardiovascular risk factors, negative U-waves in the ECGs should prompt investigation of underlying cardiac diseases.

We observed a clear female predominance in subjects with negative U-waves, contrary to previous studies [15,16], not explained by blood pressure or the prevalence of cardiac diseases. However, when adjusted for risk factors, negative U-waves seemed to be a relatively benign finding among women. In contrast, among men negative U-waves were independently associated with increased mortality, cardiac death, and cardiac hospitalizations. A possible explanation for these sex differences may be different etiologies for negative U-waves in different subpopulations, somewhat similarly to anterior T-wave inversions, which are more often observed among women and carry a benign prognosis in this population [24]. For example, in normal aging diastolic function decreases more quickly in women compared to men [25]. As negative U-waves are hypothesised to result from myocardial relaxation abnormalities, this difference might explain the higher prevalence and better prognosis associated with negative U-waves in women compared to men.

Although the subjects underwent comprehensive health examinations, echocardiography was not performed; consequently, no data was available on the cardiac structure, or on the left ventricular systolic and diastolic function. In addition, coronary heart disease mortality in Finland, especially in the eastern parts of Finland, was one of the highest in the world in the 1960s and 1970s [26]. As the study population was representative of the Finnish population, with approximately one sixth of the subjects from Eastern Finland, there may be limitations in applying the results of our study to other populations.

In conclusion, negative U-waves are a relatively rare finding in the standard 12-lead ECG in the general population, and are often associated with older age and cardiovascular risk factors and may also be markers of underlying cardiac disease. In addition, negative U-waves are associated with increased cardiac mortality, and especially among men, this association is not fully explained by traditional cardiovascular risk factors, warranting further research.

Acknowledgements

We thank the National Institute for Health and Welfare for their important contribution. This work was supported by Ida Montin's Foundation, Finnish Medical Foundation, Paavo Nurmi's Foundation, Onni and Hilja Tuovinen's Foundation, the Orion Research Foundation, the Aarne Koskelo Foundation, the Paulo Foundation, the Sigrid Juselius Foundation, Academy of Finland, Finnish Foundation of Cardiovascular Research, and the Veritas Foundation.

References

1. Einthoven W. The Different Forms of the Human Electrocardiogram and Their Signification. *Lancet* 1912;179:853–861.

2. Eyer K. Support for a mechanico-electrical source of the "U" wave. *J Electrocardiol* 2015;48:31–32.

3. Perez Riera AR, Ferreira C, Filho CF, Ferreira M, Meneghini A, Uchida AH, Schapachnik E, Dubner S, Zhang L. The enigmatic sixth wave of the electrocardiogram: the U wave. *Cardiol J* 2008;15:408–421.

4. Surawicz B. U wave: facts, hypotheses, misconceptions, and misnomers. *J Cardiovasc Electrophysiol* 1998;9:1117–1128.

5. Fisch C. The clinical electrocardiogram: Sensitivity and specificity. *ACC Curr J Rev* 1997;6:71–75.

6. Kishida H, Cole JS, Surawicz B. Negative U wave: a highly specific but poorly understood sign of heart disease. *Am J Cardiol* 1982;49:2030–2036.

7. Duke M. Isolated U wave-inversion in acute myocardial infarction. *Cardiology* 1975;60:220–225.

8. Fisch, C. Y. The electrocardiogram in the early diagnosis of myocardial infarction. *ACC Curr J Rev* 1995;4:25–28.

9. Twidale N, Gallagher AW, Tonkin AM. Echocardiographic study of U wave inversion in the electrocardiograms of hypertensive patients. *J Electrocardiol* 1989;22:365–371.

10. Kishida H, Hata N, Nejima J, Suzuki T, Otsu F, Saito T, Kusama Y. Prognosis of patients with persistent negative U wave following myocardial infarction. *Jpn Heart J* 1987;28:15–25.

11. Anon. Mini-Finland Health Survey - THL. *Natl Inst Health Welf THL Finl*. Available at: http://www.thl.fi/en/web/thlfi-en/research-and-expertwork/population-studies/finnish-mobile-clinic/mini-finland-health-survey. Accessed December 13, 2017.

12. Holkeri A, Eranti A, Kenttä TV, Noponen K, Haukilahti MAE, Seppänen T, Junttila MJ, Kerola T, Rissanen H, Heliövaara M, Knekt P, Aro AL, Huikuri HV. Experiences in digitizing and digitally measuring a paper-based ECG archive. *J Electrocardiol* 2018;51:74–81.

13. Pratt CM, Greenway PS, Schoenfeld MH, Hibben ML, Reiffel JA. Exploration of the precision of classifying sudden cardiac death. Implications for the interpretation of clinical trials. *Circulation* 1996;93:519–524.

14. Palmer JH. Isolated U wave negativity. *Circulation* 1953;7:205–210.

15. Watanabe N. Clinical significance of the negative U wave in the electrocardiogram. *Jpn Circ J* 1967;31:9–31.

16. Kishida H, Cole JS, Surawicz B. Negative U wave: the clinical significance and the consideration of pathogenesis. In: *Frontiers of Cardiac Electrophysiology*. Springer; 1983:100–119.

17. Gerson MC, McHenry PL. Resting U wave inversion as a marker of stenosis of the left anterior descending coronary artery. *Am J Med* 1980;69:545–550.

18. Kodama K, Hiasa G, Ohtsuka T, Ikeda S, Hashida H, Kuwahara T, Hara Y, Shigematsu Y, Hamada M, Hiwada K. Transient U wave inversion during treadmill exercise testing in patients with left anterior descending coronary artery disease. *Angiology* 2000;51:581–589.

19. Chikamori T, Kitaoka H, Matsumura Y, Takata J, Seo H, Doi Y. Clinical and electrocardiographic profiles producing exercise-induced U-wave inversion in patients with severe narrowing of the left anterior descending coronary artery. *Am J Cardiol* 1997;80:628–632.

20. Schimpf R, Antzelevitch C, Haghi D, Giustetto C, Pizzuti A, Gaita F, Veltmann C, Wolpert C, Borggrefe M. Electromechanical coupling in patients with the short QT syndrome: further insights into the mechanoelectrical hypothesis of the U wave. *Heart Rhythm* 2008;5:241–245.

21. Bernardo D di, Murray A. Origin on the electrocardiogram of U-waves and abnormal U-wave inversion. *Cardiovasc Res* 2002;53:202–208.

22. Choo MH, Gibson DG. U waves in ventricular hypertrophy: possible demonstration of mechano-electrical feedback. *Br Heart J* 1986;55:428–433.

23. Bellet S, Bettinger JC, Gottlieb H, Kemp RL, Surawicz B. Prognostic significance of negative U waves in the electrocardiogram in hypertension. *Circulation* 1957;15:98–101.

24. Aro AL, Anttonen O, Tikkanen JT, Junttila MJ, Kerola T, Rissanen HA, Reunanen A, Huikuri HV. Prevalence and prognostic significance of T-wave inversions in right precordial leads of a 12-lead electrocardiogram in the middle-aged subjects. *Circulation* 2012;125:2572–2577.

25. Carvalho J-C, Farand P, Do HD, Brochu M-C, Bonenfant F, Lepage S. Effect of age and sex on echocardiographic left ventricular diastolic function parameters in patients with preserved ejection fraction and normal valvular function. *Cardiol J* 2013;20:513–518.

26. Jousilahti P, Laatikainen T, Salomaa V, Pietilä A, Vartiainen E, Puska P. 40-Year CHD Mortality Trends and the Role of Risk Factors in Mortality Decline: The North Karelia Project Experience. *Glob Heart* 2016;11:207–212.

Figure Legends

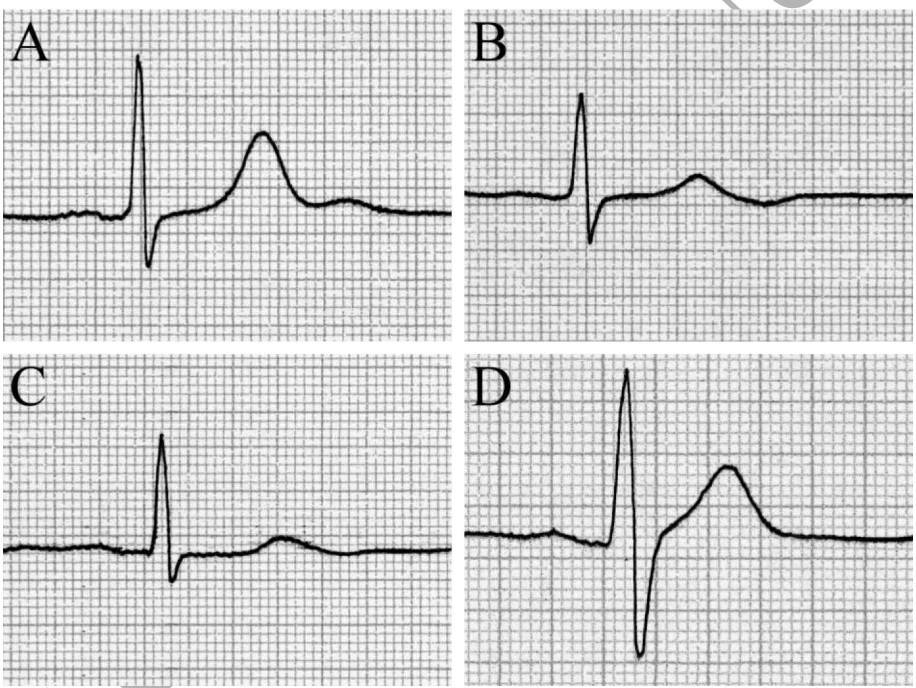

Figure 1 Legend

Demonstration different U-wave morphologies.

(A) Normal U-wave (amplitude ≥0.05mV), (B) negative U-wave (amplitude ≥0.05mV), (C) minor negative U-wave (amplitude <0.05mV), (D) no U-wave.

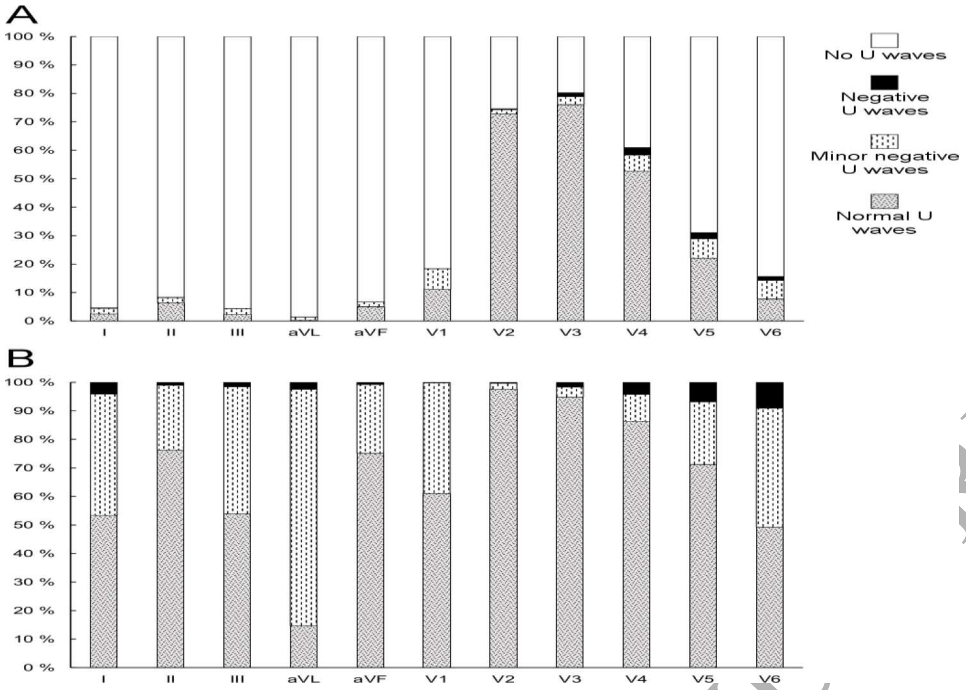

Figure 2 Legend

Distribution of U-wave morphologies in the 12-lead ECG.

Picture A demonstrates the prevalence of U-waves in the ECG. Picture B demonstrates the distribution of U-wave morphologies in leads in which U-waves were present. “Minor negative or disc. U-waves” includes subjects with minor negative U-waves (amplitude <0.05mV) or U-waves discordant with preceding T wave. “No U-waves” includes subjects with no U-waves or only minor (amplitude <0.05mV) positive U-waves.

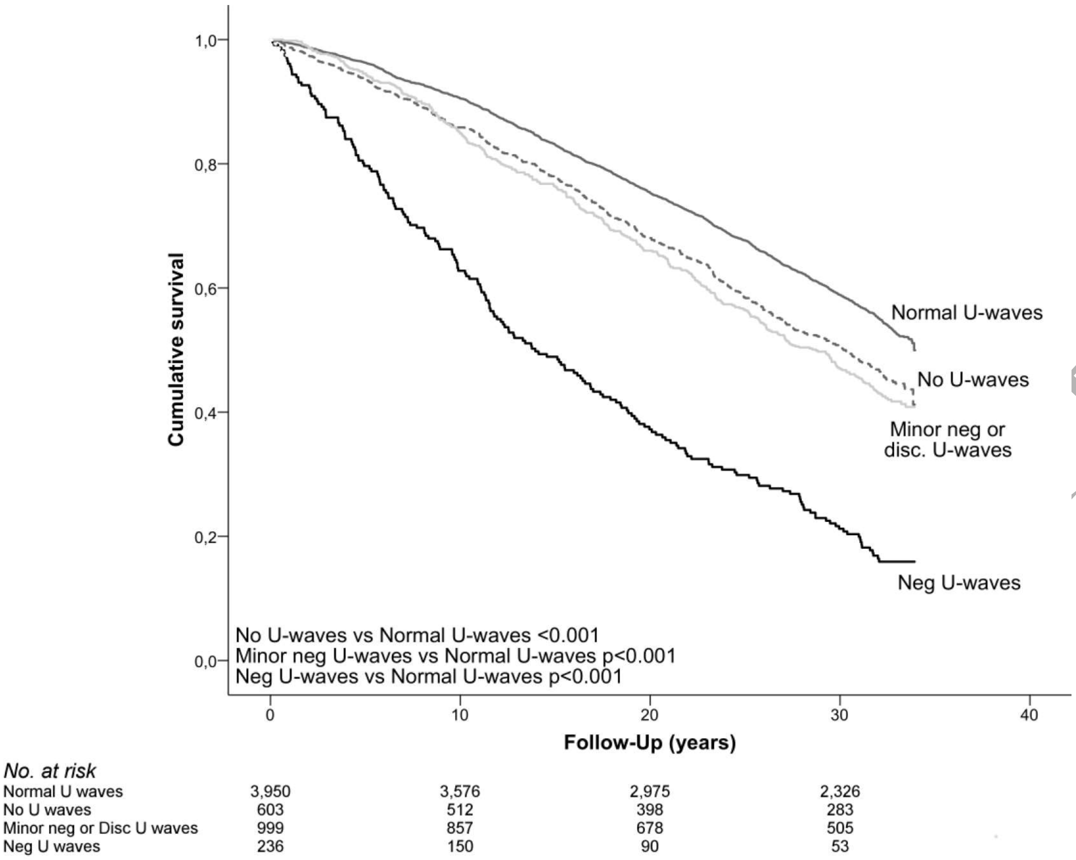

Figure 3 Legend

Kaplan-Meier survival plots for overall mortality according to the U-wave morphology. “Minor neg or disc. U-waves” stands for minor negative (amplitude <0.05mV) U-waves or U-waves discordant with the preceding T-wave. “Neg U-waves” stands for negative (amplitude ≥0.05mV) U-waves. “No U-waves” includes subjects with no U-waves or only minor (amplitude <0.05mV) positive U-waves.

Table 1. Baseline characteristics

Table 1
Baseline characteristics

Variable	Normal U-waves (n=3,950)	Negative U-waves (n=231)	Minor negative or discordant U-waves (n=1,004)	No U-waves (n=603)	Negative U-waves vs normal U-waves p-value

Men *	2,094 (53.0%)	81 (35.1%)	354 (35.3%)	173 (28.7%)	<0.001
Age (years) +	47.9±12.7	63.7±12.7	52.6±14.0	54.0±13.0	<0.001
Systolic blood pressure (mmHg) §	138.3±20.1	167.3±25.9	148.4±24.6	139.9±20.4	<0.001
Diastolic blood pressure (mmHg) §	85.3±11.1	92.8±12.8	87.8±11.0	86.9±10.6	<0.001
Hypertension diagnose §	460 (11.6%)	84 (36.4%)	173 (17.2%)	99 (16.4%)	<0.001
Heart rate (bpm) §	64±10	69±10	65±9	72±12	<0.001
Total serum cholesterol (mmol/l, *mg/dl*) §	6.9±1.3 *265±50*	7.3±1.4 *283±56*	7.1±1.5 *276±58*	6.9±1.4 *269±53*	0.63
Body mass index (kg/m^2) §	25.7±3.8	25.2±4.1	25.5±3.9	26.9±4.5	<0.001
Cardiac disease §	557 (14.1%)	95 (41.1%)	208 (20.7%)	104 (17.2%)	<0.001
Cardiac disease without myocardial infarction §	455 (11.5%)	81 (35.1%)	163 (16.2%)	77 (12.8%)	<0.001
Cardiac disease with myocardial infarction §	102 (2.6%)	14 (6.1%)	45 (4.5%)	27 (4.5%)	0.69
Diabetes mellitus §	150 (3.8%)	16 (6.9%)	45 (4.5%)	35 (5.8%)	0.15
Left ventricular hypertrophy §	318 (8.1%)	46 (19.9%)	97 (9.7%)	18 (3.0%)	<0.001
Smoking §	1061 (26.9%)	45 (19.5%)	193 (19.2%)	134 (22.2%)	0.19
Beta blocker medication §	236 (6.0%)	25 (10.8%)	79 (7.9%)	52 (8.6%)	0.43

In 730 subjects U-waves were not assessable. Left ventricular hypertrophy according to the Sokolow-Lyon criteria. Diagnoses included as cardiac disease are listed in the Supplementary Material.

Statistical test for difference: * adjusted for age, + adjusted for sex, and § adjusted for age and sex.

Table 2. Prognostic significance of U-waves

Table 2
Prognostic significance of U-waves

Variable	Normal U-waves (n=3,950)	Negative U-waves (n=231)	Minor negative or discordant U-waves (n=1,004)	No U-waves (n=603)
All-cause mortality				
No. of deaths	1,844 (46.7%)	194 (84.0%)	551 (54.9%)	350 (58.0%)
Unadjusted HR (95% CI)	1	3.18 (2.74-3.69)	1.29 (1.17-1.42)	1.40 (1.25-1.57)
Age and sex adjusted HR (95% CI)	1	1.49 (1.28-1.73)	1.04 (0.95-1.15)	1.01 (0.90-1.13)
Multivariate adjusted HR (95% CI)	1	1.26 (1.08-1.47)	1.01 (0.92-1.12)	1.00 (0.89-1.13)
Cardiac death				
No. of deaths	803 (20.3%)	90 (39.0%)	235 (23.4%)	126 (20.9%)
Unadjusted HR (95% CI)	1	3.41 (2.74-4.24)	1.26 (1.09-1.46)	1.16 (0.96-1.40)
Age and sex adjusted HR (95% CI)	1	1.55 (1.24-1.93)	1.01 (0.88-1.18)	0.82 (0.68-0.99)
Multivariate adjusted HR (95% CI)	1	1.15 (0.91-1.44)	0.94 (0.81-1.09)	0.86 (0.71-1.05)
SCD				
No. of deaths	190 (4.8%)	21 (9.1%)	50 (5.0%)	29 (4.8%)
Unadjusted HR (95% CI)	1	3.17 (2.02-4.98)	1.12 (0.82-1.54)	1.11 (0.75-1.64)
Age and sex adjusted HR (95% CI)	1	2.18 (1.37-3.47)	1.12 (0.81-1.53)	1.06 (0.71-1.58)
Multivariate adjusted HR (95% CI)	1	1.41 (0.87-2.28)	1.00 (0.72-1.37)	1.05 (0.70-1.57)
Hospitalization due to cardiac causes				
No. of hospitalizations	1,723 (43.6%)	157 (68.0%)	481 (47.9%)	293 (48.6%)
Unadjusted HR (95% CI)	1	2.96 (2.51-3.49)	1.23 (1.11-1.36)	1.25 (1.11-1.42)

Age and sex adjusted HR (95% CI)	1	1.47 (1.25-1.74)	1.03 (0.93-1.14)	0.93 (0.82-1.06)
Multivariate adjusted HR (95% CI)	1	1.14 (0.96-1.35)	0.97 (0.87-1.07)	0.95 (0.84-1.08)

SCD = sudden cardiac death.

Hazard ratios (HR) and 95% confidence intervals (CI) were calculated using the Cox proportional hazards model. Variables included in the multivariate analyses were age, sex, systolic blood pressure, heart rate, total serum cholesterol, body-mass index, cardiac disease (with or without myocardial infarction), diabetes, left ventricular hypertrophy, and active smoking.

Table 3. Prognostic significance of negative U-wave in males and females

Table 3
Prognostic significance of negative U-wave in males and females

	Negative U-waves		
	Male	Female	P-value for sex interaction
Overall mortality			
Univariate HR (95% CI)	4.89 (3.88-6.18)	2.97 (2.45-3.61)	0.001
Age adjusted HR (95% CI)	2.06 (1.63-2.61)	1.24 (1.02-1.50)	0.001
Multivariate HR (95% CI)	1.60 (1.26-2.03)	1.09 (0.89-1.33)	0.01
Cardiac death			
Univariate HR (95% CI)	6.22 (4.57-8.47)	2.91 (2.13-3.96)	0.001
Age adjusted HR (95% CI)	2.42 (1.77-3.31)	1.12 (0.82-1.53)	0.001
Multivariate HR (95% CI)	1.74 (1.26-2.39)	0.85 (0.62-1.17)	0.002

SCD			
Univariate HR (95% CI)	4.94 (2.67-9.13)	3.99 (2.01-7.92)	0.65
Age adjusted HR (95% CI)	2.41 (1.29-4.49)	1.94 (0.98-3.87)	0.65
Multivariate HR (95% CI)	1.51 (0.79-2.87)	1.28 (0.64-2.58)	0.73
Hospitalization due to cardiac causes			
Univariate HR (95% CI)	4.69 (3.60-6.11)	2.83 (2.29-3.50)	0.003
Age adjusted HR (95% CI)	2.06 (1.58-2.69)	1.26 (1.02-1.56)	0.004
Multivariate HR (95% CI)	1.67 (1.27-2.18)	0.96 (0.77-1.19)	0.001

SCD = sudden cardiac death. Hazard ratios (HR) and 95% confidence intervals (CI) were calculated using the Cox proportional hazards model. Negative U-waves were compared to normal U-waves. Variables included in the multivariate analyses were age, sex, systolic blood pressure, heart rate, total serum cholesterol, body-mass index, cardiac disease (with or without myocardial infarction), diabetes, left ventricular hypertrophy, active smoking, and interaction term of U-waves and sex.