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EMJ Cardiology

Review of ESC Congress 2022

Editor's Pick

Screening for Heart Disease in the Age of Digital Health Technologies: Who, When, and How?

Interviews

Nico Bruining and Allan Böhm

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Front cover and contents photograph: Barcelona, Spain, home of the **ESC 2022 © Biel Morro** / unsplash.com

Welcome letter

Koutsouki

Evgenia Koutsouki
Editor

Dear Readers,

It is with great pleasure that I welcome you to the 2022 issue of *EMJ Cardiology*, containing highlights from this year's European Society of Cardiology (ESC) Congress, which took place in Barcelona, Spain. This year's congress was an absolute pleasure to attend, and digital health was a recurring theme across content presented.

To this end, we are proud to offer you our latest coverage of the congress, featuring congress interviews with the Chair of the ESC Digital Health Committee, as well as the Chair of the ESC Committee for Young Cardiovascular Professionals. You will also find a selection of summaries from studies presented at the ESC, ranging from artificial intelligence-guide in single lead ECG to a summary of a study on cardiac damage staging.

Among our articles in this issue is the Editor's Pick on artificial intelligence in screening for heart disease, which discusses the usefulness of digital healthcare in disease specific groups, including atrial fibrillation and sudden cardiac death, among others. Also included is a study proposing a fuzzy interference analysis system, which could potentially be applied to help provide accurate results for the diagnosis and prevention of abdominal aortic aneurism. Of course, our issue contains a number of case reports and abstracts.

I would like to extend a big thank you to everyone who helped bring this content together: our EMJ team, as well as our authors, peer reviewers, and our Editorial Board. I do hope you enjoy reading this issue, and we look forward to seeing you next year in Amsterdam, the Netherlands.

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Foreword

Dear Colleagues,

It is my pleasure to welcome you to the latest edition of *EMJ Cardiology*. As with previous journals, this issue contains an immersive array of clinically relevant, peer-reviewed articles and case reports.

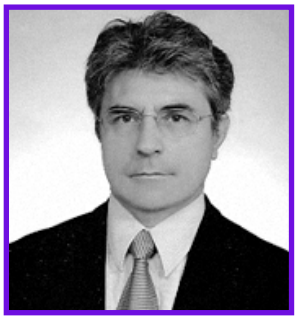
My choice for the Editor's Pick for this publication is a review summarising how the emerging field of digital health technology can aid screening for heart disease. This paper adds to an important and evolving area of investigation and will be a stimulus for the EMJ readership.

Furthermore, this issue features several insightful case reports. Of note, Palmerini et al. document a novel and interesting case of haemopericardium with cardiac tamponade during dabigatran therapy for atrial fibrillation in a patient with chronic coronary syndrome. This adds to the relatively small number of reports in the literature that describe the rare complication of dabigatran-induced haemopericardium and might help inform other practitioners when they encounter similar cases.

A spotlight is also shone on heart failure (HF). Our insightful interview with Alexander E. Berezin, Fellow of the European Society of Cardiology (ESC), is not to be missed. Berezin spoke to EMJ about the established and emerging roles of biomarkers in HF, knowledge gaps in HF diagnosis and treatment, and his previously published *EMJ Cardiology* articles, including 'Biomarker-Based Guideline-Directed Medical Therapy of Heart Failure: The Gap Between Guidelines and Clinical Practice'. This is complemented by an in-house infographic covering key messages from the 2021 ESC guidelines for medical management of HF.

For those who were unable to attend this year's ESC Congress, I highly recommend the congress review. This features research news from the meeting as well as a compelling feature and abstract review highlights.

I would like to thank all the authors, interviewees, Editorial Board members, and reviewers who contributed to successfully create the 2022 issue of *EMJ Cardiology*. I hope this journal will prove an inspiring read and assist in daily practice.



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ESC 2022

Review of the European Society of Cardiology (ESC) Congress 2022

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AFTER 2 years of virtual meetings, the European Society of Cardiology (ESC) adopted a pioneering hybrid format for its 2022 congress, allowing delegates from across the globe to meet onsite in Barcelona, Spain, and also online. Clinicians and academics came together with one common goal: to advance cardiovascular care and improve patient outcomes. This was emphasised by Stephan Achenbach, ESC President, who commented: "At ESC Congress in Barcelona, we discussed the newest science in the light of our collective clinical experience. This is how true progress in cardiovascular medicine is made." Achenbach spoke about the rapid pace of innovation and advancement since the first double-blind randomised trial in cardiovascular medicine was completed in 1971. "Numerous large trials are published every year, often practice-changing, and many are first presented at ESC Congress," he emphasised.

This year's conference was attended by more than 30,270 healthcare professionals from 174 countries, with highly anticipated clinical trial results shared during hotline sessions. Novel and impactful research was also showcased in 3,218 abstracts, presented by scientists from over 80 countries. Several standout abstracts, written by the presenters themselves, have been summarised in this edition of *EMJ Cardiology*. These cover important topics such as atrial fibrillation and the risk of stroke among veteran athletes, cardiac damage staging in patients undergoing transcatheter aortic valve repair, and artificial intelligence-guided single-lead ECG as a tool to reduce symptom-to-balloon time in ST-elevated myocardial infarction.

Digital health heavily featured at ESC Congress 2022, and EMJ had the privilege of interviewing Nico Bruining, Chair of the ESC Digital Health Committee. At this year's congress, Bruining co-chaired several sessions on e-Cardiology, artificial intelligence, and machine learning, and he provided an overview of the key take-home messages from these. EMJ also had the unique opportunity to speak with Allan Böhm, Chair of the ESC Committee for Young Cardiovascular

"Digital health heavily featured at ESC Congress 2022, and EMJ had the privilege of interviewing Nico Bruining, Chair of the ESC Digital Health Committee."

Professionals. Of note, Böhm was one of the first members of the ESC Digital Health Committee, and he talked about the importance of digital health interventions for the prevention of cardiovascular diseases, as well as actions that the ESC can undertake to ensure digital healthcare remains a priority for the cardiology community. Both interviews can be found within this journal, and are not to be missed. These are complemented by our interview with Alexander E. Berezin, a Fellow of the ESC.

Summaries of highly relevant ESC press releases have also been included in this issue of *EMJ Cardiology*, covering radial artery access for coronary angiography or percutaneous coronary intervention, the role of an invasive strategy in patents with advanced chronic kidney disease and chronic coronary disease, and the use of a polypill versus usual care to reduce cardiovascular events after a heart attack.

Looking to the future is important in any field, and Stephan Windecker, Congress Programme Chair, highlighted a particularly noteworthy session from ESC Congress 2022, "in which top experts provided their predictions for the practice of cardiovascular medicine 10 years from now." Specifically,

"EMJ also had the unique opportunity to speak with Allan Böhm, Chair of the ESC Committee for Young Cardiovascular Professionals."

this symposium looked at how the screening, prevention, and treatment of atrial fibrillation, coronary artery disease, heart disease, and heart failure might have evolved by 2033. Potential future developments in digital cardiology and artificial intelligence were also considered. This session forms the basis of our compelling in-house congress feature, and is another highlight of our independent congress review.

Whatever the future of cardiovascular medicine holds, the annual ESC Congress will remain crucial for the generation and exchange of scientific knowledge. With this in mind, we look forward to being part of the international cardiology community again at next year's conference in Amsterdam, the Netherlands. Until ESC Congress 2023 opens its doors, read on for our key insights and learnings from ESC Congress 2022. ●

Screening for Signs of Cardiovascular Disease May Reduce Risk of Morbidity and Mortality

NOVEL data has indicated that cardiovascular screening, including cardiac imaging, blood pressure measurement, and blood tests, paired with subsequent treatment when necessary, may reduce risk of heart and stroke, and lower mortality in 65–69-year-olds. The randomised trial, presented at ESC Congress 2022, investigated data from over 45,000 men with an average age of 68.8 years.

The researchers identified a total of 46,526 men between September 2014 and September 2017 from Southern and Central regions of Denmark. These men were divided into two categories: screening and intervention (n=16,736) and no screening (n=29,790), which is the current practice in Denmark. The screening and intervention group were given a cardiac and truncal non-contrast CT to detect coronary artery calcification above the sex- and age-specific medium, aortic and iliac aneurysms, and atrial fibrillation. The programme also included brachial and ankle blood pressure in both arms and legs to diagnose peripheral artery disease, and blood tests to identify high cholesterol and diabetes. When the researchers identified abnormal findings, prophylactic treatments were offered and information on medication, surgery, disease, and mortality was collected for 5 subsequent years.

“Despite remarkable reductions in mortality from cardiovascular disease, it remains the leading cause of death. More than half of cardiovascular disease is avoidable, meaning that successful prevention has a huge potential to improve public health,” stated Axel Diederichsen, Odense University Hospital, Denmark, explaining the value of this study.

"Despite remarkable reductions in mortality from cardiovascular disease, it remains the leading cause of death."

The primary outcomes from both groups were all-cause mortality, with secondary outcomes including stroke, myocardial infarction, amputation due to vascular disease, aortic dissection, and aortic rupture. When the two groups were compared over a median follow-up of 5.6 years, researchers found that 12.6% of men in the intervention group and 13.1% in the control group had died. Remarkably, the study found that the number of individuals needed to be invited to screening to prevent one death was 155. Analysis demonstrated that though an 11% decreased risk of mortality was found in those aged 65–69 years (p=0.004), no significant difference was found in men aged 70 years and older.

“We observed a substantial reduction in the combined endpoint of death, stroke or myocardial infarction in elderly men by comprehensive cardiovascular screening. Our results point quite firmly at a screening target age below 70 years,” stated Diederichsen.

Superiority of Artificial Intelligence in Assessing Cardiac Function on Echocardiograms

ARTIFICIAL intelligence (AI) technology developed by David Ouyang, Smidt Heart institute, Cedars–Sinai, Los Angeles, USA, and colleagues, shows superiority at initial echocardiographic assessment of cardiac function compared to initial sonographer assessment.

Ouyang presented these findings at ESC Congress 2022 in Barcelona, Spain, on 27th August. Having previously developed the EchoNet-Dynamic deep learning algorithm to assess cardiac function, the authors subsequently performed a randomised controlled trial to assess the algorithm against sonographer echocardiographic examination of left ventricular ejection fraction (LVEF) to determine whether EchoNet-Dynamic was non-inferior in reporting compared to sonographers, validated by a cardiologist. The study was designed to test for non-inferiority, and the primary endpoint was the frequency of a >5% change in the LVEF reporting between the initial assessor and final reporting cardiologist, with a secondary endpoint of testing for AI superiority.

Transthoracic echocardiograms from 3,495 adult patients were randomised to initial assessment by AI or initial assessment by sonographer. These initial assessments were then reviewed by a blinded cardiologist before the final report was confirmed. The percentage of assessments with >5% change in cardiologist LVEF reporting was 16.8% in the AI group versus 27.2% in the sonographer group (95% confidence interval: -13.2% to -7.7%; p=<0.001 for non-inferiority and superiority). The authors further evaluated a safety endpoint, in which they looked at the difference between an historical cardiologist report and the final cardiologist report from the current trial. They found that the mean absolute difference in LVEF reporting was 6.29% for the AI group and 7.23% for the sonographer group.

> **"These promising findings highlight how AI could be integrated into clinical work to assist with echocardiogram reporting."**

These promising findings highlight how AI could be integrated into clinical work to assist with echocardiogram reporting. AI algorithms have the potential to improve the accuracy of reporting, and therefore improve efficiency by reducing the time specialists spend altering reports. However, Ouyang stated that these algorithms will need to be "developed and integrated in the right way" to be beneficial.

Novel Data Assessing the Performance of Invasive Coronary Testing

LATE-breaking research presented at ESC Congress 2022 highlighted the value and the challenges of two myocardial perfusion imaging (MPI) tests for selecting patients with suspected coronary artery disease (CAD) for further invasive testing. Data suggested that the two MPI tests have high specificity but low sensitivity in patients who have undergone a coronary CT angiography (CTA).

Current guidelines suggest that prior to referring patients with suspected obstructive CAD to invasive coronary angiography (ICA), myocardial ischaemia should be confirmed by MPI. There is a lack of evidence about the efficacy and performance of MPI, and whether it is the most accurate choice. In a trial including 1,732 patients with obstructive CAD symptoms, the diagnostic performance of stress MPI by 3T cardiac magnetic resonance (CMR) was compared against rubidium-82 PET (Rb-PET).

The average age of patients recruited was 59 years, and 57% of the cohort was male. Overall, 445 patients had suspected stenosis and were referred for both CMR and Rb-PET. Patients also underwent ICA fractional flow reserve (FFR) as reference, with haemodynamically obstructive CAD identified in 44.1% of patients through ICA FFR.

The sensitivity of CMR was 59% (95% confidence interval [CI]: 51–67%) whereas Rb-PET had a sensitivity of 64% (95% CI: 56–71%). The specificities were 84% (95% CI: 78–89%) and 89% (95% CI: 84–93%), respectively. The overall accuracy of Rb-PET was 78% compared with 73% for CMR. Further, RB-PET correctly identified more patients as high risk of disease compared with CMR (96.8% and 77.4%, respectively).

"CMR stress and PET stress had comparably moderate sensitivities and high specificities to predict the FFR results. A perfusion test approach therefore seems safe as almost all patients with serious disease (high-grade stenoses, left main, and three-vessel disease) were diagnosed," explained Morten Bottcher, Aarhus University, Denmark.

"The accuracy of coronary CTA needs to improve so that more patients without obstructive CAD avoid further investigations. This might be achieved through better CT image quality and perhaps by more advanced image analyses like non-invasive FFR estimation and photon counting systems."

Radial Access for Coronary Procedures Improves Mortality?

RANDOMISED controlled trial (RCT) meta-analysis data presented by Giuseppe Gargiulo, Federico II University Hospital, Naples, Italy, at ESC Congress 2022 in Barcelona, Spain, on 29th August, has shown that transradial approach (TRA) for coronary angiography or percutaneous coronary intervention (PCI) resulted in improved 30-day all-cause mortality and major bleeding rates when compared with transfemoral approach (TFA).

Gargiulo stated that the data "provides definitive evidence that TRA should be considered the gold-standard for patients undergoing cardiac catheterisation with or without PCI," but also commented that the benefits associated with TRA only apply to patients experiencing acute coronary syndrome (ACS), and that the results cannot be generalised to patients undergoing elective cardiac catheterisation with or without PCI.

The meta-analysis reviewed data from seven high-quality RCTs of 21,600 patients undergoing coronary intervention who were randomised to either TRA (n=10,775) or TFA (n=10,825) against the primary outcomes of 30-day all-cause mortality and major bleeding. The median age of participants was 63.9 years, and 68.1% were male. Of the 21,600 enrolled, 95% presented with ACS and PCI was performed in 75.2%. The participants were subcategorised into several cohorts: intention-to-treat, per-protocol, as-treated, PCI, ACS, and myocardial infarction.

Primary analysis of the intention-to-treat cohort showed a 1.6% incidence of all-cause death in the TRA group compared with 2.1% in the TFA group, with a hazard ratio of 0.77 (95% confidence interval: 0.53–0.95; p=0.012). The reduction in all-cause mortality was confirmed across all the subcohorts. In addition to this, the odds of major bleeding were lower in the TRA group, at 1.5%, compared to 2.7% in the TFA group, with an odds ratio of 0.55 (95% confidence interval: 0.45–0.67; p=<0.001). Moreover, the TRA was independently associated with a relative risk reduction of 24% for 30-day all-cause mortality and 51% for major bleeding, using a multivariable model.

"These findings from the first, sufficiently powered RCT meta-analysis indicate that for patients with ACS, TRA does confer improved survival and reduced major bleeding compared to TFA."

These findings from the first, sufficiently powered RCT meta-analysis indicate that for patients with ACS, TRA does confer improved survival and reduced major bleeding compared to TFA.

No Improved Survival Rate for Patients with Kidney Disease and Ischaemia When Using an Invasive Strategy

RESEARCH has discovered that patients diagnosed with advanced chronic kidney disease and chronic coronary disease do not benefit from an invasive strategy compared to a conservative strategy, in terms of the 5-year risk of death outcome.

Late-breaking research presented at ESC Congress 2022 demonstrated that the management of chronic coronary disease has so far excluded those patients who also have advanced chronic kidney disease, or have only included a small number of such patients. Thus, optimal management for this group of patients is currently unknown.

Researchers from the ISCHEMIA-CKD study recruited 777 patients who had advanced chronic kidney disease (estimated glomerular filtration rate <30 ml/min/1.73m^2, or undergoing dialysis), and who also presented with moderate or severe ischaemia during stress testing. Median age was 63 years, and 31% of patients were female.

Patients were allocated at random to one of two groups. The first involved an initial invasive strategy (cardiac catheterisation and optimal revascularisation with percutaneous coronary intervention, or coronary artery bypass graft surgery if such a treatment proved suitable), as well as guideline-directed medical therapy. The second group consisted of an initial conservative strategy of only guideline-directed medical therapy. Cardiac catheterisation and revascularisation with percutaneous coronary intervention or coronary artery bypass graft surgery were reserved for the failure of the first-line therapy. During a median follow-up of 2.2 years, researchers discovered that the invasive strategy for patients in the first group did not reduce the outcome of death or non-fatal myocardial infarction.

The trial is following participants for a median period of 9 years. An analysis of all 777 patients after the initial 5-year period had a primary endpoint of all-cause death, and secondary endpoints of cardiovascular and non-cardiovascular death. After the 5-year follow-up, 305 deaths had occurred in the patient cohort (158 in the invasive group; 147 in the conservative group). No significant difference in death between these groups was found.

"During a median follow-up of 2.2 years, researchers discovered that the invasive strategy for patients in the first group did not reduce the outcome of death or non-fatal myocardial infarction."

Lead study investigator Sripal Bangalore, New York University School of Medicine, USA, stated: "An initial invasive management strategy did not improve survival when added to guideline directed medical therapy in patients [...] of note, the death rate was very high with close to 40% mortality at 5 years indicating a very high-risk group of patients who are in urgent need of therapies to reduce this risk."

Coronary Stenting Not Beneficial for Patients with Severe Left Ventricular Dysfunction

FINDINGS presented at ESC Congress 2022 on 27th August suggest that patients with severe left ventricular dysfunction and extensive coronary artery (CAD) disease do not benefit from percutaneous coronary intervention (PCI). CAD, which is associated with poor survival and low quality of life, is the most common cause of heart failure.

While revascularisation was long considered a treatment option, the STITCH trial showed that only highly selected, young patients showed benefit 10 years after coronary artery bypass surgery. Previously, there was no evidence to support PCI as an alternative to bypass surgery. REVIVED-BCIS2 analysed its efficacy in patients affected by the condition. The study included a total of 700 patients from 40 centres in the UK, with severe left ventricular dysfunction, extensive CAD, and demonstrable viability in at least four dysfunctional myocardial segments that could be revascularised by PCI.

They were randomly assigned to optimal medical therapy, either alone or combined with PCI. The primary outcome (all-cause death or hospitalisation for heart failure) occurred in 134 (38%) of patients in the single therapy group, and 129 (37.2%) of patients in the combined therapy group (hazard ratio: 0.99; 95% confidence interval: 0.78–1.27; p=0.96). Regarding the secondary outcomes, there was no significant difference in the left ventricular ejection fraction after 6 months and 12 months.

"PCI provided no incremental benefit over optimal medical therapy in this high-risk population, where approximately one in three patients died or were hospitalised with heart failure during follow-up."

Chief investigator Professor Divaka Perera of King's College London, UK, said: "PCI provided no incremental benefit over optimal medical therapy in this high-risk population, where approximately one in three patients died or were hospitalised with heart failure during follow-up." Furthermore, researchers concluded that PCI should not be offered to stable patients for prognostic benefit. However, PCI is still an option for patients with acute coronary syndromes and limiting angina.

Polypill Reduces Risk of Cardiovascular Events After Heart Attack

NEW research presented at ESC Congress 2022 on 26th August suggests that a polypill, containing aspirin and medication to lower lipids and blood pressure, is more effective in preventing further cardiovascular events after a heart attack than taking the drugs separately. Less than 50% of patients consistently take all of the medications prescribed post-infarction, which include an antiplatelet, lipid lowering medication, and a pressure-lowering and vascular stabilising drug. Therefore, it is suggested that combining the treatments into one polypill would improve adherence to treatment.

The first randomised trial to study the polypill, SECURE, enrolled patients having had a myocardial infarction within 6 months. In total, 2,499 patients were randomly allocated to either usual care or a polypill, which contained 100 mg of aspirin; 2.5, 5, or 10 mg of ramipril; and 20 or 40 mg of atorvastatin. The median follow-up was 3 years, during which the primary composite endpoint of death from cardiovascular causes, nonfatal myocardial infarction, stroke, or urgent revascularisation occurred in 156 (12.7%) of the usual care group and 118 (9.5%) of the polypill group. Cardiovascular death was the most notable event, occurring in 71 (5.8%) patients in the usual care group, and 48 (3.9%) patients in the polypill group. The secondary endpoint of cardiovascular death, nonfatal myocardial infarction, or stroke occurred in 144 (11.7%) patients in the usual care group and 101 (8.2%) patients in the polypill group. The adherence to treatment in the polypill group was higher than the usual care group.

"The median follow-up was of 3 years, during which the primary composite endpoint of death from cardiovascular causes, nonfatal myocardial infarction, stroke, or urgent revascularisation occurred in 156 (12.7%) of the usual care group and 118 (9.5%) of the polypill group."

Researcher Valentin Fuster from the Centro Nacional de Investigaciones Cardiovasculares (CNIC), Madrid, Spain, and Mount Sinai Health System, New York, USA, said: “The findings suggest that a polypill could become an integral part of strategies to prevent cardiovascular events in post-infarction patients. By simplifying treatment and improving adherence, this approach has the potential to reduce the risk of recurrent disease and cardiovascular death on a global scale.”

Improved Decongestion in Patients with Acute Decompensated Heart Failure

ACETAZOLAMIDE decreases congestion in patients with acute decompensated heart failure (ADHF) in 3 days, according to Wilfried Mullins, Hospital Oost-Limburg, Genk, Belgium, who presented the findings of the ADVOR trial at ESC Congress 2022.

Accounting for up to 70% of acute HF presentations, ADHF is the most common form and requires immediate evaluation and treatment. Despite the use of guideline-recommended intravenous (IV) loop diuretics to improve symptoms of fluid overload, residual congestion remains in many patients with the current drug.

Enrolling 519 adults hospitalised with ADHF across 27 centres in Belgium, the primary endpoint of the ADVOR trial was successful decongestion, with no clinical signs of fluid overload except for trace oedema. The trial investigated the use of acetazolamide as an additional drug in IV loop diuretics to improve decongestion in patients with ADHF within 3 days of randomisation, without escalating decongestive therapy. Patients were randomised 1:1, either being administered IV acetazolamide 500 mg once daily or placebo upon randomisation and for 2 days, or until successful decongestion.

In the acetazolamide group, 42.2% of patients achieved the primary outcome compared with 30.5% of patients in the placebo group (relative risk: 1.46; 95% confidence interval: 1.17–1.82; p=0.0009). The acetazolamide group also had shorter hospital stays than the placebo group (8.8 and 9.9 days, respectively; p=0.02). However, there was no difference in HF hospitalisation or all-cause mortality at 3 months.

"In the acetazolamide group, 42.2% of patients achieved the primary outcome compared with 30.5% of patients in the placebo group."

Finally, of the patients who were alive at discharge, 190 out of 241 patients (78.8%) in the acetazolamide group and 145 out of 232 patients (62.5%) in the placebo group had successful decongestion (relative risk: 1.27; 95% confidence interval: 1.13–1.42; p=0.0001).

Mullins, who was also the principal investigator for the ADVOR trial, stated: "Patients treated with acetazolamide had more diuresis and natriuresis, and were more likely to be discharged without residual signs of volume overload. There did not appear to be an increase in adverse events with the drug."

Benefits of Statins Outweigh Risk of Muscle Pain and Weakness

BREAKING research shows that the risk of muscle symptoms related to statin therapy is outweighed by its benefits, which include preventing cardiovascular disease, such as heart attacks and strokes. The research, led by Colin Baigent, Director of the Medical Research Council Population Health Research Unit at the University of Oxford, UK, was presented at ESC Congress 2022 on 29th August.

Statins typically prevent 25 major vascular events in patients with no pre-existing vascular disease, and 50 major vascular events in patients with pre-existing vascular disease; however, there have been concerns that this widely prescribed therapy may cause muscle pain or weakness. A meta-data analysis of the recorded muscle symptoms in 23 randomised, double-blinded trials of statin therapy was completed, compiling information on nearly 155,000 patients. The researchers collected adverse event data from four randomised double-blind trials of more intensive versus less intensive statin therapy, and 19 randomised double-blind trials of statin therapy versus placebo.

In the trials on statins versus placebo, 27.1% of patients reported muscle plain or weakness in the statin group versus 26.6% in the placebo group. There was a 7% relative increase in reports of muscle pain or weakness among the statin group in the first year, corresponding to an absolute excess rate of 11, and no evidence of excess risk in the remaining follow-up period. Only one in 15 of reported cases were attributed to statin therapy.

> **"The results of this research will help physicians and patients to make more informed decisions when it comes to statin therapy."**

The trials on more intensive versus less intensive therapy showed a larger relative increase in muscular pains or weakness compared with the moderate intensity regimens. Baigent said: "Statins were not the cause of muscle pain in more than 93% of patients who reported symptoms. Statin therapy marginally increased the frequency, but not the severity, of muscle-related symptoms." The results of this research will help physicians and patients to make more informed decisions when it comes to statin therapy.

The Future of Cardiovascular Medicine: From 2022 to 2033

Authors:	Janet Nzisa, Editorial Assistant
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In a session presented at this year's European Society of Cardiology (ESC) Congress, which was held in-person in Barcelona, Spain, and virtually, experts discussed their future predictions for cardiovascular health and innovations that will enter this field. The session was chaired by Roxana Mehran, Icahn School of Medicine at Mount Sinai, New York, USA, and John J. V. McMurray, Institute of Cardiovascular and Medical Sciences, University of Glasgow, UK.

ESC 2022

CARDIOVASCULAR DISEASE PREVENTION IN 2033

Brian Ference, University of Cambridge, UK, began the session by reflecting on the last two decades in cardiovascular disease prevention. "The easiest way to change the future is to shape it," they continued. Firstly, Ference emphasised the importance of having a clear and bold vision of how cardiovascular medicine should be in 2033. In their bold vision, Ference hoped that healthcare professionals would be able to completely eliminate heart attacks, strokes, hypertension, and Type 2 diabetes by 2033 by using precision medicine methodology. By accurately targeting modifiable causes of a disease that an individual may be vulnerable to due to cumulative factors, a specialist could put in place preventative measures.

Ference emphasised that cardiovascular diseases such as atherosclerosis and hypertension are completely preventable. With precision medicine methodology, they believe that cardiologists should be able to predict which patients are at risk and intervene at the right time. The prediction of a vulnerable patient, according to Ference, involves collating electronic health records of the patient, genomic data, and imaging, combined with the understanding of the biology of the disease to precisely prognosticate if the patient is at risk of developing cardiovascular disease. They proposed using a digital platform for a more personalised approach to each patient, that not only empowers the patient to manage their own health, but also provides a database that will allow the healthcare professionals to deliver the right therapy at the right dose and at the right time.

> "[It] will allow healthcare professionals to deliver the right therapy at the right dose and at the right time."

HOW WILL WE APPROACH CORONARY ARTERY DISEASE IN 2033?

Patrick W. Serruys, National University of Ireland, Galway, Ireland, began the

presentation by reiterating their belief that in 2033 lipid abnormalities will be under control. This is due to the novel, emerging low-density lipoprotein cholesterol-lowering therapies. Serruys highlighted that in 2033, conventional invasive fluoroscopic angiography will no longer be the dominant diagnostic tool and believes that a non-invasive coronary CT angiography would be the 'one-stop shop', as it can be used to detect several cardiovascular conditions.

Other remarkable innovations presented by Serruys include a 3D visualisation of a heart hologram, which his team uses to discuss strategies before heart surgery. Serruys believes that combined intravascular imaging will complement non-invasive coronary imaging in the future. Furthermore, they predict that physiological pressure-derived parameters will be replaced by physiological-derived imaging parameters. Additionally, Serruys is hopeful that biofabrication will be available in the field of cardiology, whereby stem cells could be used to recreate the heart's helical structure. "If the future is unrealistic, it will remain the future; however, if the future is realistic, it will become swiftly the past," said Serruys as they concluded their presentation.

MANAGEMENT OF VALVULAR HEART DISEASE

Martin B. Leon, Department of Cardiology, Columbia University Medical Center, New York, USA, began the presentation by highlighting the valvular heart disease growth and access to care issues. Leon and their team predict over 150 million cases of moderate or severe aortic stenosis or mitral regurgitation by 2040. Currently, there is a crisis in access to care due to either underdiagnosis or undertreatment. A study presented by Leon, which involved over 80 million people, demonstrated that over 60% of diagnosed, symptomatic patients with severe aortic stenosis went untreated in 2016. This study showed that racial and socioeconomic disparities are a factor in this, as Black and Hispanic ethnic groups are not provided with proper care and intervention compared with White ethnic groups.

"The future management of valvular heart disease includes early treatment consideration before the progression of the disease."

Leon proposed that the future management of valvular heart disease includes early treatment consideration before the progression of the disease. Some of the proposed methods for early treatment include early diagnosis through the use of emerging biomarkers, improving patient access to care, considering pre-emptive treatment before symptoms occur, and delaying calcific aortic valve disease. Leon emphasised that the current staging in moderate aortic stenosis is not accurate, as most of the patients are being treated when the disease has already progressed, meaning a higher mortality rate. In their concluding remarks, Leon stated the importance of reinventing the management of patients with aortic stenosis and highlighted that early management, in both diagnosis and treatment, and a thorough follow-up leads to optimal clinical outcomes.

DIGITAL CARDIOLOGY AND ARTIFICIAL INTELLIGENCE IN 2033

Martin R Cowie, King's College London, UK, opened their presentation by exploring the influence that the COVID-19 pandemic has had on digital health. It was clear that digital healthcare, especially remote care, boomed during the period. A number of artificial intelligence (AI) technologies such as apps and wearables were approved for medical use by regulators. Due to social distancing and isolating, most in-person events were held virtually. Therefore, healthcare professionals have become more familiar with remote consulting and with monitoring their patients.

"The importance of AI in cardiology, highlighting that machine learning would make the job of healthcare professionals easier and provide better outcomes for the patient."

Cowie presented ongoing studies on how AI is used in cardiology, including the detection of heart failure. Additionally, deep learning is currently being used to define baseline characteristics for prognosis and diagnosis in cardiovascular medicine. There are several U.S. Food and Drug Administration (FDA) machine learning products for cardiology such as the Apple Watch (Apple, Cupertino, California, USA). Some of the products are not specifically for cardiovascular medicine but provide basic information for image clarity. Cowie emphasised the importance of AI in cardiology, highlighting that machine learning would make the job of healthcare professionals easier and provide better outcomes for the patient. Furthermore, AI could be useful in managing workflow such as continuous data collection with improved quality, remote monitoring, and even pre-visit testing. "The best way of predicting the future is creating it," Cowie concluded.

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Abstract Reviews

Sharing insights from abstracts presented at the European Society of Cardiology (ESC) Congress 2022, global cardiologists and researchers have provided these overviews of their fascinating studies.

Artificial Intelligence-Guided Single-Lead ECG May Be a Game-Changer for Symptom-to-Balloon Time Reduction in ST-Elevated Myocardial Infarction

Authors: *Sameer Mehta, Daniel Vieira, Victor Guillen, David Zerpa, Aline Quintana, Madyan Al Troudy, Luis Brena-Pastor, Cynthia Whuking, Franklin Martinez, Jacques Calixte, Devarsh Desai, Surik Sedrakyan, Nataly Rendon, Gabriel Peña

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Disclosure: The authors have declared no conflicts of interest.

Keywords: Acute coronary syndrome, artificial intelligence, epidemiology, myocardial infarction, single-lead ECG, ST-elevated myocardial infarction (STEMI), symptom-to-balloon time, wearable devices.

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BACKGROUND AND AIMS

Comprehending the rate at which ischaemic myocardium succumbs to necrosis following an abrupt occlusion of a coronary artery is crucial to understand the efficacy and benefits behind the time dependency in ST-elevated myocardial infarction (STEMI) management.[1] Over decades, efforts to shave off life-saving minutes from STEMI care centred on reducing door-to-needle and door-to-balloon times.[2] Additionally, registry data have shown that between 9% and 31% of patients with STEMI present >12 hours from the symptom onset.[3,4] By shifting focus to symptom-to-balloon time and a patient's self-perception of disease and initiative to seek care, the authors aimed to empower patients and improve outcomes through an accurate, accessible, and cost-effective artificial intelligence-driven single-lead ECG STEMI detection algorithm that can be embedded into wearable devices and employed in a self-administered fashion.

MATERIALS AND METHODS

The authors examined 11,567 12-lead ECG records from Mexico, Colombia, Argentina, and Brazil from April 2014 to December 2019. These were of 10 seconds in length, with a sampling frequency of 500 Hz, and included the following balanced classes: angiographically confirmed and unconfirmed STEMI; branch blocks; nonspecific ST-T abnormalities; and normal and abnormal (200+ current procedural terminology codes, excluding those mentioned above). These were preprocessed by discarding the first and last 250 samples, which may have contained a standardisation pulse. A fifth-order digital low-pass filter with a frequency cut-off of 35 Hz was applied, and the mean was subtracted from each lead. The determined classes were STEMI (including confirmed and unconfirmed STEMI in different locations of the myocardium [anterior, inferior, and lateral]) and Not-STEMI (combination of randomly sampled branch blocks, nonspecific ST-T changes, and normal and abnormal records [25% of each]). A one-dimensional convolutional neural network was then trained and tested with a

Table 1: Accuracy, sensitivity, and specificity of the combined ST-elevated myocardial infarction and confirmed ST-elevated myocardial infarction only datasets.

Lead V2 performance	Combined STEMI	Confirmed STEMI only
Testing sample size (N)	1,156	723
Accuracy (%)	91.2	92.4
Sensitivity (%)	89.6	93.4
Specificity (%)	92.9	91.4

STEMI: ST-elevated myocardial infarction.

dataset proportion of 90% and 10%, respectively. A different model was trained and tested for each ECG lead, using the central 4,500 samples of the records. The last dense layer outputted a probability for each report of being STEMI or Not-STEMI. Lead V2 showed the best overall results. The model was further tested through the same methodology using the best lead (V2) with a subset of the previous data, excluding the unconfirmed STEMI ECG records (a total of 7,230 12-lead ECG records for confirmed STEMI only dataset) to seek potential false negative or positive sources. Performance metrics were reported for each experiment and compared.

RESULTS

The combined STEMI data had an accuracy of 91.2%, a sensitivity of 89.6%, and a specificity of 92.9%. In the confirmed STEMI only dataset, accuracy was 92.4%, sensitivity was 93.4%, and specificity was 91.4% (Table 1).

CONCLUSION

By assiduously improving the model's input data quality (confirmed only versus both confirmed and unconfirmed STEMI ECGs), the authors continue to assess their algorithm's performance and reliability for future clinical validation as a potential wearable remote monitoring and early STEMI detection device.

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Atrial Fibrillation in Veteran AthLETEs and the Risk of Stroke: AFLETES – An Online International Survey

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Keywords: Athlete's heart, atrial fibrillation (AF), stroke.

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BACKGROUND AND AIMS

Contemporary data suggest endurance athletes are at an increased risk of developing atrial fibrillation (AF) when compared with the general population.[1] Cardioembolic events such as stroke are a well-established complication of untreated AF.

The CHA_2DS_2-VASc score is used in clinical practice to risk-stratify those with AF. Due to a reduction in traditional cardiovascular risk factors associated with exercise, many athletes will have a low CHA_2DS_2-VASc score of 0–1, indicating no need for anticoagulation. However, endurance athletes demonstrate phenotypes such as atrial dilatation, which are not captured in CHA_2DS_2-VASc and are themselves associated with an increased risk of stroke in the general population.[2] It may be that athletes who develop AF are not appropriately risk-stratified by CHA_2DS_2-VASc. The aim of this study was to estimate the risk of stroke in veteran endurance athletes who develop atrial fibrillation (≥40 years).

MATERIALS AND METHODS

A questionnaire was broadcasted through social media and sports clubs. Individuals who had competed in at least one competitive event and were ≥40 years old were included. Self-reported demographic, past medical history, and training history data were collected and a CHA_2DS_2-VASc was calculated. Multivariable binary logistic regression was used to assess variables associated with AF and stroke.

RESULTS

The survey received 1,002 responses from 41 countries across Africa, Asia, Australasia, Europe, and North and South America. In total, 942 were included in the final analysis with an average age of 52.4±8.5 years and 83.7% were male. The most frequently participated sports were cycling (n=677 [71.9%]), running (n=558 [59.2%]), and triathlon (n=245 [26.0%]). There were 190 (20.2%) individuals who reported AF and 26 (2.8%) individuals who reported stroke, of which 14 (53.9%) had AF. Of those with stroke and AF, 11 were diagnosed with AF following a stroke. Lifetime exercise dose (odds ratio [OR]: 1.02; 95% confidence interval [CI]: 1.00–1.03; p=0.02) and swimming (OR: 1.56; 95% CI: 1.02–2.39; p=0.04) were associated with AF in multivariable analysis. AF (OR: 4.18; 95% CI: 1.80–9.72; p<0.01) was associated with stroke, even in individuals with a CHA_2DS_2-VASc of 0 or 1 (OR: 4.20; 95% CI: 1.83–9.66; p<0.01).

CONCLUSIONS

This survey suggests that the risk of stroke in veteran endurance athletes who develop AF is not negligible, even in those deemed to be at low risk by commonly used risk scores. Despite this, the authors found the rate of anticoagulation to be lower than expected. Longitudinal studies are needed to substantiate these findings to inform individualised decisions about anticoagulation.

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Cardiac Damage Staging in Patients Undergoing Transcatheter Aortic Valve Replacement: Incremental Value of Global Longitudinal Strain and Right Ventricular-Arterial Coupling

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Disclosure: The authors have declared no conflicts of interest.

Keywords: Aortic stenosis, aortic valve replacement, cardiac damage, staging, transcatheter aortic valve implantation, transcatheter aortic valve replacement.

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BACKGROUND AND AIMS

Staging cardiac damage in patients undergoing transcatheter aortic valve replacement (TAVR) has been proposed as a prognostic tool.[1-2] Other authors have shown that these staging systems are related with mortality.[1-3] The aim of this study was to perform an external validation of the predictive capacity of the staging system proposed by Généreux et al.[1] for 1-year mortality; and to assess the incremental value of global longitudinal strain (GLS) and right ventricular-arterial coupling (RVAc) in the prognostic performance of this cardiac damage staging model.

MATERIALS AND METHODS

There were 496 consecutive patients with severe aortic stenosis and undergoing TAVR included in a single hospital registry. According to current guidelines, baseline echocardiography was performed before TAVR. Patients were classified into the following stages of cardiac damage:[1] Stage 0: no cardiac damage; Stage 1: left ventricular (LV) damage (LV ejection fraction [LVEF]: <50%; LV mass index: >95 g/m^2 for females and >115 g/m^2 for males); Stage 2: left atrial or mitral valve damage (left atrial volume index: >34 mL/m^2, moderate-severe mitral regurgitation, or presence of atrial fibrillation); Stage 3: pulmonary vasculature or tricuspid valve damage (systolic pulmonary artery pressure ≥60 mmHg or moderate to severe tricuspid regurgitation); and Stage 4: right ventricular damage (tricuspid annular plane systolic excursion: <1.7 cm; S' <9.5 cm/sec). The area under the receiver operating characteristic curve was used to measure the discriminatory capacity of staging models to predict 1-year mortality risk. Logistic regression analysis was used to identify predictors of outcome.

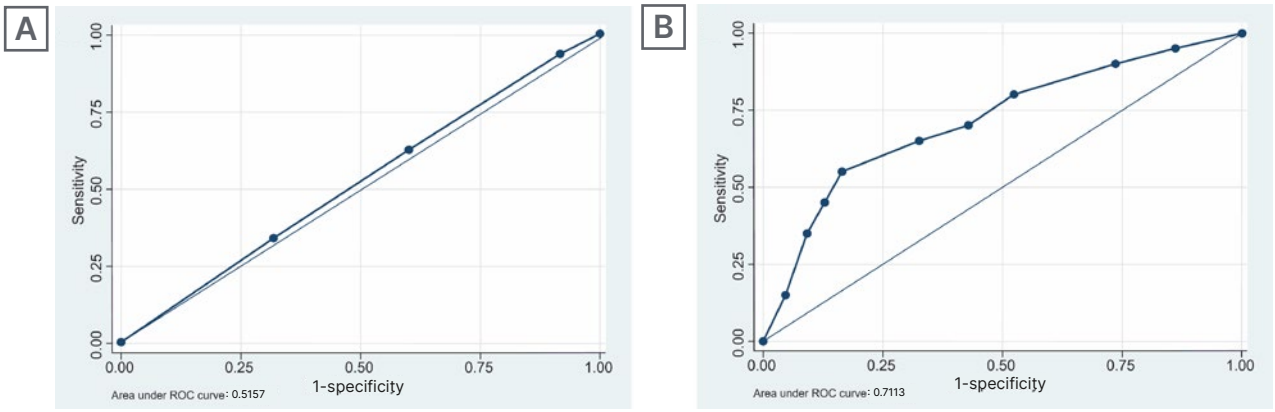
RESULTS

Regarding baseline characteristics, the mean age of the cohort was 81.9±6.2 years. In this cohort, 66.9% were males; 37.5% of patients had diabetes; 62.5% of patients had hypertension; and 62.5% of patients had dyslipidemia. The mean aortic valve area was 0.86±0.60 cm^2; the mean LVEF was 57.9±12.3%; the mean LV-GLS was -15.6±3.5%; and RVAc was 0.61±0.34. Logistic regression analysis showed that LVEF, LV-GLS, and RVAc were independent predictors of all cause 1-year mortality.

When classifying the cohort according to the cardiac damage staging system,[1] only one patient met criteria for Stage 0. Thus, patients in Stage 0 and 1 were merged in an initial stage, which included 39 patients (7.9%). Regarding the rest of the sample, 159 (32.1%) patients were in Stage 2,157 (31.7%) patients were in Stage 3, and 141 (28.4%) patients were in Stage 4.

The area under the receiver operating characteristic curve was used to predict all-cause 1-year mortality. In the authors' cohort

Figure 1: Area under the receiver operating characteristic curve for 1-year mortality.



A) Cardiac damage staging system and **B)** cardiac damage staging system after adding GLS and RVAc.

Adapted from Généreux et al.[1]

GLS: global longitudinal strain; ROC: receiver operating characteristic; RVAc: right ventricular-arterial coupling.

the staging was 0.516 (confidence interval [CI]: 0.449–0.582). The best cut-off value for LV-GLS to predict 1-year mortality was -14% with an area under the curve (AUC) of 0.634 (CI: 0.487–0.781) and for RVAc it was 0.35, with an AUC of 0.748 (CI: 0.638–0.858). By adding GLS and RVAc to the staging system, the AUC improves to 0.711 (CI: 0.584-0.839 [Figure 1]).

CONCLUSION

In conclusion, cardiac damage staging might have a fundamental role in patient selection and in the clinical outcome for patients after TAVR. However, the addition of feasible and widely available echocardiography parameters such as LV-GLS and RVAc can significantly increase its prognostic yield.

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Referrals to Palliative Care for Cardiovascular Patients: A 10-Year Longitudinal Retrospective Study

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Keywords: Cardiology, heart failure, palliative care, place of death.

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BACKGROUND AND AIMS

Globally, cardiovascular diseases remain the leading cause of death, taking an estimated 17.9 million lives each year. It is projected that the global burden of cardiovascular diseases will continue to rise.[1,2] The majority of patients with cardiovascular diseases have a significant symptom burden with comorbidities, and often have a progressive course towards end-stage disease and, ultimately, death.[2] For this reason, early integration of palliative care into the care of patients with cardiovascular diseases is recommended.[3,4] However, palliative care has not yet become an integral part of care for patients with cardiovascular diseases, as only a small proportion of patients are referred for palliative care consultations. Furthermore, referral often occurs too late in the disease course.[2,5,6] In order to improve the rate of referral to palliative care by cardiologists, there is a need to scrutinise current referral practices to palliative care from the cardiology department. Therefore, the present study aimed to examine the time between referral to palliative care and death; the clinical profile of patients referred; and the place of death of patients with cardiovascular diseases who were referred to palliative care from the cardiology department, using data from 2010–2020.

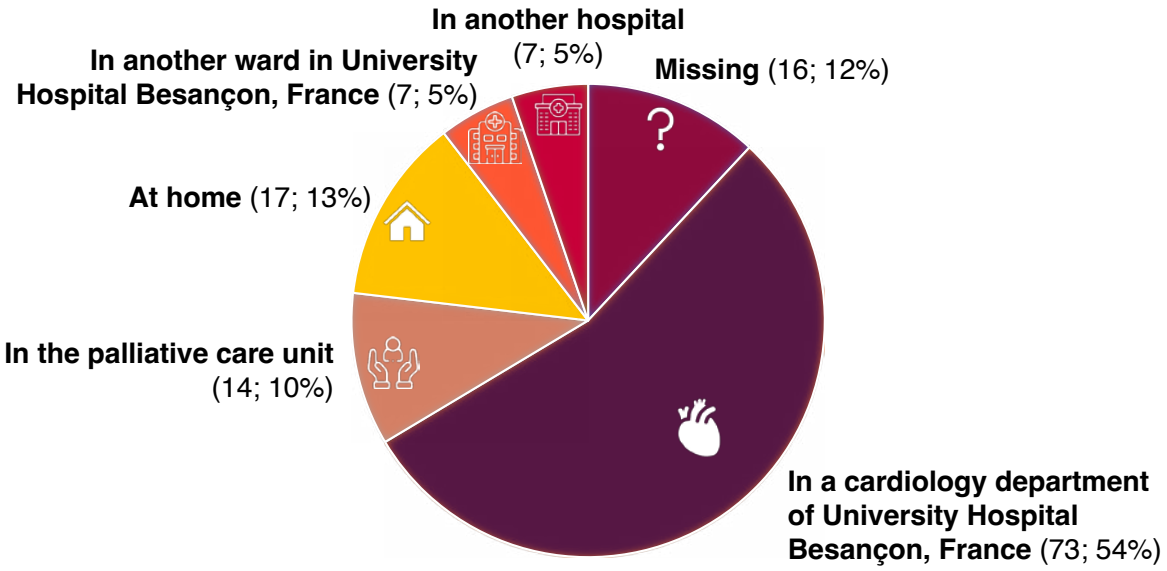
MATERIALS AND METHODS

This retrospective descriptive study included all patients who were referred to the Mobile Palliative Care Team from the cardiology unit in the large University Hospital Besançon, France, between 2010–2020. The following information was extracted from the medical hospital files: date of first referral to the palliative care team; vital status (alive/dead) at the study cut-off date (31st December 2020); sex; date of birth; main underlying disease; the motive for hospitalisation at the time the palliative care team was contacted; and for patients who died, their date of death, cause of death, and place of death.

RESULTS

Of the 142 included patients, 134 (94%) died, and eight (6%) were still alive as of July 2022. The mean age at the time of death was 75±14 years. The median time between referral to palliative care and death was 9 days (first quartile, third quartile: 2, 37.5; range: 0–5.8 years). The number of referrals from the cardiology department per year did not increase over time. As the main life-limiting disease, most patients had chronic heart failure (54%), followed by other cardiovascular diseases (valve, acute coronary syndrome, congenital, or stroke [20%]), and cancer (14%). The main motives for hospitalisation at the time the palliative care team was contacted were acute decompensation of heart failure (72%), acute coronary syndrome (11%), and infective endocarditis or pulmonary embolism (9%). The place of death was available for 118 patients

Figure 1: Visual representation of the places of death of patients with cardiovascular disease who were referred to the mobile palliative care team (n=134).



(Figure 1). The majority of patients (n=73; 54%) died in the cardiology department of University Hospital Besançon, 14 patients (10%) died in the palliative care unit, and only 17 patients (13%) died at home.

CONCLUSION

This study showed that referral of patients to palliative care from the cardiology department is suboptimal, as the referral is often only initiated very close to the time of death. In addition, a large proportion of patients still die in the hospital setting. It is noteworthy that palliative care is mainly provided to paitents with heart failure after acute decompensation. Further prospective studies are warranted to investigate whether these dispositions correspond to patients' wishes and end-of-life care needs, and future studies should investigate how the integration of palliative care into the care of patients with cardiovascular diseases can be improved.

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Congress Interview

EMJ spoke to Nico Bruining, Chair of the European Society of Cardiology (ESC) Digital Health Committee, and Allan Böhm, Chair of the ESC Committee for Young Cardiovascular Professionals, about a range of pertinent topics, including the importance of digital health approaches for the prevention and management of cardiovascular diseases.

Featuring: Nico Bruining and Allan Böhm

ESC 2022

Nico Bruining

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Q1 What does your role as Chair of the European Society of Cardiology (ESC) Digital Health Committee (DHC) entail and what have been your greatest achievements to date in this position?

To be precise, Martin Cowie, King's College London, UK, was the inaugural chair of the DHC from 2018 until earlier this year, when he changed his primary position. I covered the position until the biannual change of leadership of the ESC, which always occurs after the annual ESC Congress. I was, and will be for the 2022–2024 period, the Vice-Chair of the DHC, and I am also the Editor-in-Chief of the *European Heart Journal – Digital Health*. The new Chair from September 2022 will be Gerd Hindricks, University of Leipzig, Germany. I am very excited to be working with him and the other members of the DHC within this new mandate.

In 2016, we published a position paper on digital health (DH),[1] which led to the installation of the DHC. At the time, it was called eHealth. The position paper included a roadmap with an action plan for the ESC. The main actions were to organise a digital summit, which occurred in Tallinn, Estonia, bringing together different stakeholders, including industry, hospital information and technology departments, managers, insurance companies, patients, etc., to develop guidelines and add DH as a topic with its own sessions to the annual ESC Congress.

The Digital Summit was a great success. Unfortunately, it had to be online for the

2 years thereafter because of COVID-19. The DH sessions at the annual ESC Congress are getting more and more successful each year. Guidelines have been created and more will follow soon, such as on artificial intelligence (AI).

The last achievement I would like to mention was the addition of the *European Heart Journal – Digital Health* to the ESC's journal family. Amid the pandemic in November 2020, we launched the journal at the first online Digital Summit. I was honored to become the inaugural Editor-in-Chief.

"Remote monitoring is maturing, and developments of wearables and simpler noninvasive measurements are improving."

Q2 The goal of the ESC is to reduce the burden of cardiovascular disease. In what ways can digital health interventions help achieve this?

There are so many opportunities for digital interventions that we need to develop further in order to address challenges such as the pandemic, a shrinking workforce, and a growing elderly population, just to name a few. Remote monitoring is maturing, and developments of wearables and simpler noninvasive measurements are improving. Just look at smartwatches as an example.

In the hospitals, we mainly focus on secondary prevention with remote monitoring, but you see that the lifestyle industry is catching up and may be entering the medical market sooner or later. That could open the way for primary prevention if users adhere to the digital recommendations. Currently, this area is mainly led by big tech. However, there is a lot to gain by working together.

Q3 At ESC Congress 2022, you co-chaired several sessions on the topics of e-Cardiology, DH, AI, and machine learning. Please could you provide an overview of these sessions and the key take-home messages?

DH was prominent at the conference this year. I actually missed a lot of DH presentations because they spread across the subspecialties and there were many parallel presentations. DH is now everywhere and not just on the special stages we had before the pandemic.

DH covers a wide range of topics, and AI, remote monitoring, and risk prediction are currently the most intensively researched subtopics. A complete overview of all DH presentations would require an entire book. For those interested, the sessions can be viewed via ESC 365.[2]

Hotline session six was completely focused on DH and presented three exciting and typical studies for current DH developments, including smartphone-based screening for atrial fibrillation (eBRAVE-AF),[3] a pragmatic siteless digital randomised clinical trial by Axel Bauer, University of Innsbruck, Austria. The findings of this digital trial indicate that a scalable digital screening using ordinary smartphones provides a substantial benefit to usual care in detecting treatment-relevant atrial fibrillation.

Causal AI substantially improves the validity of estimating cardiovascular risk and benefit,[4] as presented by Brian Ference, University of Cambridge, UK. The outcome of this study was to train AI algorithms to estimate the causal effects of modifiable targets of intervention in a way that reflects the underlying biology of how disease develops. This was achieved by using randomised evidence, introducing a method to create causal AI algorithms that accurately predict risk and benefit, and prescribing specific actions to reduce risk.

"DH covers a wide range of topics, and AI, remote monitoring, and risk prediction are currently the most intensively researched subtopics."

The final presentation was by Geoffrey Strange, University of Sydney, Australia, who established a national echocardiographic database that enabled AI to develop a risk predictor capable of identifying patients with moderate-to-severe aortic stenosis with poor survival if untreated with an improved accuracy compared with traditional methods.

These three studies illustrate current developments in cardiovascular disease DH, with remote monitoring using noninvasive measurement capabilities and improved risk predictors using AI. We will soon see much more of it at conferences and in the literature.

Q4 At ESC Acute CardioVascular Care 2022, you delivered a presentation on top trends in DH research for acute care. Please could you provide a summary your talk?

Acute cardiovascular care is a young and interesting subspecialty in cardiology. It is intended to include the period from the preclinical phase to the end of the first week of hospitalisation.

After a short general introduction to DH, I focused on developments that fit in with the main aim mentioned above, including using social media as a public screening tool, which was developed to track patient-reported symptoms of COVID-19 in the first wave, filtering that from Twitter messages. I also discussed digital systems that connect first responders with the cardiac catheterisation laboratory (cath lab)

staff all the way from the home, street, and ambulance until arrival in the cath lab. I spoke about AI-supported analyses of ECGs and electronic health record systems for the detection of ST-elevation myocardial infarction, coronary artery disease, rhythm disorders, and pulmonary embolisms. This is one method of expediting clinical decision making. In addition, I considered AI-supported image analysis, smart alarms in the intensive care unit, and facilitators and barriers to DH.

So, acute cardiovascular care can very well use the support of the above-mentioned DH systems. In addition, it is important that clinicians and other healthcare professionals make their needs known to the DH developers and the developers come into the clinic to see these needs and later assess how their systems and software perform.

Q5 Please could you outline your involvement in the early developments of 3D echocardiography and discuss the wider relevance of your PhD thesis, entitled 'Quantitative 3-D echocardiography of the heart and the coronary vessels'?

I could write a book around this, but I'll try to keep it shorter. My promotor, and then Chair of the Thoraxcenter (Erasmus University Medical Center, Rotterdam, the Netherlands), the late Jos RTC Roelandt, an eminent echocardiographer, was intrigued by a 3D ultrasound system developed by a company called TOMTEC (Unterschleißheim, Germany). They introduced it to him when the system was not yet on the market. He sent me to this company to learn how to work with it and to introduce it later in the clinic. At the time, the system was complex to use and did not yet provide the high-quality four-dimensional (4D [3D plus time]) images you see today on the ultrasound machines. As an example, making a 3D reconstruction took almost an entire night.

The TOMTEC system was initially intended for 4D reconstructions of the whole heart. As I started to understand how it worked, and with my background in interventional cardiology, I conceived another use. Could we adapt it to make it suitable for 4D images of the coronary arteries as well? We succeeded by designing and building a special pullback device for intracoronary ultrasound catheters, which allowed us to acquire the image data and to visualise the coronary arteries with all their movements during the cardiac cycle, which was amazing.

In addition to imaging, quantification is especially important and in retrospect the most important part of my dissertation. By eliminating motion and deformation artefacts due to heart motion, more accurate measurements of coronary dimensions and the plaques or other structures within them could be made. This precise method of image acquisition and quantitative analysis has been used in many studies to evaluate new interventional therapies. These include the first drug-eluting stent in humans, progression–regression studies of atherosclerosis, and the bioabsorbable scaffolds. To date, this method of ECG-gated acquisition and quantification is the most accurate.

"Firstly, AI can be used to improve the accuracy of measurements applied to imaging, which is typically echocardiography and cardiac CT for patients with AS."

Q6 How important is AI in delivering precision medicine to patients with aortic stenosis (AS)?

Firstly, AI can be used to improve the accuracy of measurements applied to imaging, which is typically echocardiography and cardiac CT for patients with AS. Secondly, AI can enhance risk prediction using all available patient data. This could be performed when it is available in the electronic health record.

My belief is that this is not only true for AS but for many other pathologies, perhaps even for all. It can help with processing data as images and signals as well as data within the electronic health record system. This could provide clinical decision support and ultimately lead to precision and personalised medicine.

Q7 How has the ongoing COVID-19 pandemic influenced the development of DH and telemedicine?

We have seen lots of developments battling the adverse effects of the pandemic. Often, telemedicine and DH provided solutions. Remote monitoring and consultations were perhaps the most widely applied. Remote proctoring was also a necessity for areas where patients could not travel to a treatment centre. Instead, local physicians were able to treat the patients locally with the help of remote experts. Many of these developments have been described in the literature. Sometimes it is referred to that the pandemic caused a 'techcelleration'.

Q8 You serve as Chair of the European Association of Percutaneous Cardiovascular Interventions (EAPCI) Innovation and Digital Cardiology Committee. What are your primary duties in this role?

I was the Chair from May 2020 until last May, when the leadership in the EAPCI changed. The primary tasks were actually not different from those of the DHC in the ESC, and that was to bring together enthusiasts of digital medical technology, in this case specifically for interventional cardiology. Organising topic-specific sessions for the various conferences in which the association is involved and discussing ideas or projects were among the primary duties.

Unfortunately, it was during the middle of the pandemic, and it was difficult to organise some things in-person. However, we did get some things done, such as sessions during the ESC DH meetings. We also launched two important surveys to establish consensus on complex percutaneous cardiovascular interventions and the use of virtual reality imaging, both of which are growing topics. The results are currently being analysed, and we intend that two articles will be produced. We have handed this over to the new committee, and I wish them the best of luck in their mission.

Q9 Could you highlight the key conclusions from your 2021 review, 'Robotics, imaging, and artificial intelligence in the catheterisation laboratory'?

Interventional cardiology, including electrophysiology, relies on complex technologies for diagnostics and therapy guidance, and we described the latest technological advancements using digital technologies in a state-of-the-art review article.[5]

The possibilities to treat patients more minimally invasively have increased enormously. Besides treating coronary arteries and structural heart disease such as aortic valve replacement, it has become standard practice over the past decade. This calls for additional diagnostics and instruments, where multimodal imaging is of great importance. Many improvements are still possible here, which we hope to achieve through the use of AI. We are currently seeing many developments around improved diagnosis and risk predictors.

In terms of instruments, surgical robots have already proven their worth in other specialties, such as the Da Vinci robot (Intuitive Surgical, Sunnyvale, California, USA) for prostate cancer surgery. There are currently developments in the cath lab to perform percutaneous coronary intervention procedures remotely by a robot. This is helpful for the cardiologist and other cath lab personnel because of a reduction in X-ray exposure. Perhaps soon, given the enormous developments in the robotics industry, they might also assist with more complex interventions such as percutaneous valve replacements.

Q10 Have there been any recent innovations in the development of DH approaches for cardiovascular diseases prevention and management that you believe are particularly noteworthy? How might this field have evolved by ESC Congress 2023?

I believe we are still in the infancy of the developments in DH. With AI, we are only on the surface. Although we started working with AI around the 1990s, the hardware and software were not yet ready for applications in the complex medical field. It was too complex and difficult to explain how the AI algorithms worked. Now, we see opportunities for developments around explainable and reliable AI. We need them to generate trust among users, regulators, and patients. This is crucial for the broad acceptance of these techniques.

DH is likely to grow rapidly in remote monitoring. The pandemic has accelerated both technology and adoption. Patients with post-myocardial infarction and individuals with heart failure would probably benefit from this. Building on this year's congress, I expect many more results from randomised studies where DH technology plays a major role.

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Allan Böhm

Chair of the European Society of Cardiology (ESC) Committee for Young Cardiovascular Professionals; Chief Executive Officer and Founder of Premedix Clinic and Academy, Bratislava, Slovakia

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Q1 What does your role as Chair of the European Society of Cardiology (ESC) Committee for Young Cardiovascular Professionals (CYCP) entail, and what have you achieved so far in this position?

The CYCP emerged 2 years ago as a transformation of Cardiologists of Tomorrow. It was a very important step, leading to young cardiologists gaining official positions at the ESC with their representation on the ESC board. This allows us young cardiologists to directly shape the future of the ESC. It is a great example of the progressive and innovative character that enabled this society to achieve a leading role in the world's cardiology in the last 10 years.

The mission of CYCP is to implement ESC's activities into the young community. We started with organising surveys to learn what the needs of young cardiovascular professionals were. Afterwards, we started to develop special e-learning activities that were tailored for the young. We also developed a distant mentoring project to support mentorship for young cardiologists who can't travel. Last, but not least, we organise the best clinical case competition, an event that has already become a tradition at the annual ESC Congress. Being the Chair of the CYCP is not an easy task and it demands a lot of effort and time. Besides leading the projects of our committee, I had to attend regular ESC board meetings and participate in different activities. On the other hand, this was rewarded by a valuable experience and precious friendships.

Source: Linda Kisková Bohušová

"While in preventive cardiology we apply long-term, usually quite unpleasant lifestyle interventions to avoid the disease, in the predictive medicine we just wait and, thanks to telemonitoring and AI, we know exactly when the disease manifests itself."

Q2 You were one of the first members of the ESC Digital Health Committee (DHC). How important do you believe digital health (DH) interventions are for the prevention of cardiovascular disease?

Creating the DHC a few years ago was another display of the innovative and progressive character of the ESC. Up until then, the vast majority of cardiologists didn't know what DH was. Fortunately, there were some that understood the immense power of the digital transformation, which gave the birth to the committee. Today, we know that DH is an inseparable aspect of high-quality healthcare. Thanks to DH, especially telemedicine and artificial intelligence (AI), we can tailor various preventive strategies to the personal needs of each patient.

Furthermore, we can move from preventive cardiology to predictive cardiology. There is quite a difference between the two. While in preventive cardiology we apply long-term, usually quite unpleasant lifestyle interventions to avoid the disease, in the predictive medicine we just wait and, thanks to telemonitoring and AI, we know exactly when the disease manifests itself. It means that we have to act only at the particular moment. This enables the patient to avoid complicated and inconvenient interventions that have to be applied long-term.

Q3 In your opinion, what actions can the ESC undertake to ensure that digital healthcare remains a key priority for the cardiology community?

There are two very important activities of the ESC in the field of DH. Number one is the *European Heart Journal – Digital Health*, which was an explosion right from the start. Even though it does not have an impact factor yet, there is a huge interest in publishing in this journal. It keeps the DH research community on fire. Another priority is the Digital Summit: the annual congress of the ESC that is dedicated to the DH. The latest DH discoveries and technologies in cardiovascular medicine are presented there every year.

Q4 In 2015, you founded the Premedix Academy (Bratislava, Slovakia), which is focused on education, research, and implementation of precision medicine in Slovakia. Please could you provide an overview of the organisation's ongoing projects in precision diagnostics and personalised treatment?

Our research projects try to improve personalisation of diagnostics and treatment in the field of cardiovascular medicine. Personalisation is the cornerstone of precision medicine. To achieve this, we use methods of molecular biology (e.g., genomics and microRNA research), DH technologies (e.g., telemedicine and mobile health) and big data analysis (e.g., AI and different machine learning techniques).

A lot of our previous research was dedicated to plasmatic biomarkers of atrial fibrillation and thrombosis. Recently, we started to implement more and more machine learning and DH. For instance, in the #STOPSHOCK project (Premedix Academy) we developed a machine learning scoring system for prediction of cardiogenic shock in patients with myocardial infarction. This is also a nice example of predictive medicine that enables us to act right before the

onset of the disease. The idea is to use mechanical circulatory support in stable patients before cardiogenic shock develops. Soon we will also launch the TESTIMONY trial, which will test pure telemedicine via multifaceted mobile health system versus standard of care in the treatment of arterial hypertension. Lastly, we are also developing a machine learning photoplethysmography analysis to diagnose, monitor, and predict various cardiovascular diseases.

"Our most advanced service is probably the so-called intelligent monitoring. It is reserved for high-risk patients."

Q5 You established the Premedix Clinic (Bratislava, Slovakia) in 2021, the aim of which is to "implement precision medicine into clinical practice so that we can provide a superior health-care to our patients." How close are you to achieving this goal and what research priorities should be set to facilitate this?

In cardiology, I believe that we have reached this goal. For instance, we offer genotyping, meaning that we can identify predispositions to various diseases and assess the pharmacogenomic profile to tailor the therapy for each patient. We use a lot of DH technologies. Our most advanced service is probably the so-called intelligent monitoring.[1] It is reserved for high-risk patients (e.g., patients after myocardial infarction). They receive a set of telemedical devices to monitor their blood pressure, body temperature, heart rate, respiratory rate, and O_2 saturation, and a machine learning algorithm is continually analysing these data. It can detect severe health deterioration 24 hours before it occurs. The physician gets a notification and decides if they should examine the patient remotely or in-person. Thanks to this, we can prevent large proportion of acute hospitalisations and even deaths.

Q6 Have there been any recent technological innovations in cardiovascular prevention that you believe are particularly noteworthy?

There are many with new ones emerging every day. The important thing is that they are backed up by serious clinical trials. At the recent ESC Congress, there were some mentioned even in the hotlines. For example, the EchoNet trial showed that AI can assess left ventricular ejection fraction better than human sonographers.[2] Another trial eBRAVE-AF tested atrial fibrillation screening with a smartphone app and found it to be superior to the conventional care.[3] Additionally, research from Cambridge, UK, showed that using causal AI can substantially improve the validity of estimating cardiovascular risk and benefit.

Q7 Please could you summarise the key take-home messages from the presentation you delivered at ESC Acute CardioVascular Care 2022, entitled 'Artificial Intelligence Model for Prediction of Cardiogenic Shock in Patients with Acute Coronary Syndrome'?

It was the pilot research of our #STOPSHOCK project. We trained a machine learning algorithm on a huge database of patients with acute coronary syndrome to predict cardiogenic shock. The algorithm achieved high predictive power (area under the curve: >0.9). However, an even better achievement was our recent validation of the algorithm on an external dataset. We reached an area under the curve of 0.84 and we can't wait to publish the results.

> "I thought that I could interpret clinical trials but only in the course I learned how wrong I was."

Q8 You are studying clinical research at the University of Oxford, UK. How will you utilise the skills learnt during this course to advance the Premedix Academy and Clinic?

The MSc in clinical trials was one of my best career decisions. I'm really impressed by the whole course, the lecturers, and just everything about it. I thought that I could interpret clinical trials but only in the course I learned how wrong I was. And interpretation of clinical trials is the cornerstone of modern evidence-based medicine. I believe that one can't be a good physician without being able to understand clinical trials. And this is the skill one learns right at the beginning of the course. Finally, at the end of the course, one is able to design their own clinical trial and that's exactly the skill Premedix Academy needs in order to translate different precision medicine strategies and technologies into clinical practice.

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Interview

Alexander E. Berezin spoke to EMJ about his roles within the Ukrainian Heart Failure Association, the principal findings and key conclusions from his recent *EMJ Cardiology* publications, and the two ePosters he presented during the 2022 European Society of Cardiology (ESC) Preventative Cardiology congress.

Alexander E. Berezin

Fellow of the European Society of Cardiology (ESC); Senior Consultant, Lecturer, and Professor of Medicine, Zaporozhye State Medical University, Ukraine

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Q1 Please explain the research that led to you receiving the Award of the Cabinet of Ministers of Ukraine in 2002 and the Honor of the Ukrainian Cardiology Association in 2004.

I received both awards for developing a comprehensive strategy for biomarker-based stratification of patients at risk of heart failure (HF) and HF treatment with angiotensin II receptor antagonists as an add-on to β-blockers, prior to their routine use for this indication. I am especially proud of these achievements as they marked the completion of my long studies and the completion of my Doctor of Science degree.

Q2 Please describe the primary duties and key projects you have undertaken since becoming a member of the Ukrainian Heart Failure Association.

My main role in the Ukrainian Heart Failure Association is a co-ordination of the efforts with the aim of harmonising national clinical standards in HF management to international clinical recommendations, including the European Society of Cardiology (ESC) guidelines. I am also involved in the development and implementation of current national guidelines, initiatives, and algorithms in HF. Recently, along with my colleagues from the Working Group of the Ukrainian Association of Cardiology and Ukrainian Association of Heart Failure Specialists, I executed the national guidelines for the use of biomarkers in HF and the management of HF depending on comorbidities. The basic issues of these recommendations being harmonised with current ESC guidelines have been deeply adapted to the healthcare system in Ukraine. These documents have been incorporated into routine clinical practice in my country.

Q3 One of your principal research interests is the fundamental study of biological markers of cardiovascular diseases. Please could you summarise the established and emerging roles of biomarkers in HF.

Circulating cardiac biomarkers, mainly natriuretic peptides, high-sensitive cardiac troponins, rarely soluble suppression of tumorigenicity-2 (sST2), and galectin-3, are considered to be surrogate indicators of clinical outcomes, response to management, and undoubtedly a component of the diagnostic algorithm of HF.

However, there is a large amount of evidence regarding the lack of a universal biomarker that is unique and approachable for every phenotype of HF. For instance, cascade genetic testing offers the opportunity for early intervention in dilated cardiomyopathy-related HF. On the other hand, comprehensive adipocytokine and myokine testing encompasses ever-increasing metabolic panels with the aim of improving predictive ability of natriuretic peptides in people with diabetes, obesity, or cardiac cachexia. So far, a signature of circulating

"My main role in the Ukrainian Heart Failure Association is a co-ordination of the efforts with the aim of harmonising national clinical standards in HF management to international clinical recommendations, including the European Society of Cardiology (ESC) guidelines."

biomarkers as well as epigenetic and genetic biomarkers can relate to coexisting conditions, age, gender, and ethnicity. Unfortunately, we do not know which of these biomarkers are the best fit for monitoing in the follow-up and which are considered to be singly measured. Scientific data from large clinical trials are quite optimistic to consider cardiac biomarkers as surrogate indicators of survival and death. However, multiple biomarker models appear to be an increasingly promising tool to diagnose HF and properly predict a clinical course, including expected response on pharmacological therapy, because there is a real potential to personally adjust it to the purpose and patient.

Q4 Could you provide an overview of your 2019 *EMJ Cardiology* article, entitled 'Circulating Cardiac Biomarkers in Heart Failure: A Critical Link to Biomarker-Guided Therapy'?

Circulating cardiac biomarkers remain the most discussed topic in the field of risk stratification of patients with cardiovascular disease. Indeed, this approach seems to have shown several benefits in the personalised management of HF and prediction of short- and long-term outcomes, while biomarker-guided therapy for HF does not support the 2022 ESC guideline as it does not have strong enough evidence. The use of single and serial measures of cardiac biological markers, mainly N-terminal segment of brain natriuretic peptide (NT-proBNP) and sST2, as a surrogate endpoint to predict HF-related clinical events has been widely investigated in large clinical trials and numerous meta-analyses. Previously, it had been suggested that biomarker-guided therapy with serial biomarker measures could be a powerful means to appraise composite risk score and predict HF-related outcomes based on therapeutic adjustment. However, the results of the majority of these studies have yielded controversial issues that influenced the clinical implementation of these findings in routine practice. In fact, NT-proBNP and sST2 remained in a loop of scientific discussion around justification of an individualised strategy for HF management, whereas other biomarkers continue to be used in their combinations.

"To be honest, I am most proud of being awarded Fellow of the ESC, which became a high point in my academic career last year."

Q5 Could you highlight the principal findings and wider relevance of the recent *EMJ Cardiology* review you co-authored, entitled 'Biomarker-Based Guideline-Directed Medical Therapy of Heart Failure: The Gap Between Guidelines and Clinical Practice'?

Although there is resoundingly clear proof of natriuretic peptides, which are a crucial point in the biomarker-based strategy for the stratification of patients with HF at risk of untoward outcomes and recognition of new HF/acute decompensated HF to rule out these conditions, the new definition of HF requires an updated biomarker concept. It depends on a high variability of both diagnostic and predictive values of natriuretic peptides in patients with different HF phenotypes: their age, gender, and signature of comorbidities. To improve the discriminative ability of natriuretic peptides, including NT-proBNP, several alternative biomarkers have been proposed. They reflect biomechanical stress (adrenomedullin); inflammation and fibrosis (growth differentiation factor-15, sST2, galectin-3, and high-sensitivity C-reactive protein); cardiac damage (cardiac troponins and heart-type fatty acid binding protein); extracellular matrix remodelling (matrix metalloproteinase-2,

-6, -7, and -9); renal injury and dysfunction (cystatin C); liver fibrosis (YKL-40); neurohormonal regulators of mineral metabolism and calcification (fibroblast growth factor-23, osteonectin, and osteoprotegerin); intermediary metabolism and adipose tissue dysfunction (fatty-acid binding protein-4, apelin, irisin, and visfatin); and angiogenesis (angiopoietin-2). Please note, this is not a final list because a number of these promising molecules steadily increase. It is a big challenge to choose from it and make the biomarker strategy of HF management more predictable and personally relevant to routine clinical practice.

Another problematic issue, apart from variable discriminative ability of circulating biomarkers related to coexisting comorbidity profiles, is identifying a reasonable number of biomarkers for patients with different HF phenotypes. In fact, patients with HF with reduced ejection fraction (HFrEF) and mildly reduced ejection fraction (HFmrEF) had higher median levels of growth differentiation factor-15, high-sensitivity cardiac troponins, heart-type fatty acid-binding protein, and NT-proBNP, but not sST2, galectin-3, high-sensitivity C-reactive protein, procollagen peptides, and other abundant biomarkers of extracellular turnover, relative to those with HF with preserved ejection fraction (HFpEF). In this connection, multiple biomarker panels seem to be a more promising tool in detecting patients at higher risk of death and HF hospitalisation. Current 2022 American Heart Association (AHA)/American College of Cardiology (ACC)/Heart Failure Society of America (HFSA) and 2021 ESC guidelines recommend the use of natriuretic peptides as a prominent tool to screen, diagnose, and stratify patients with HF or at risk of HF. Furthermore, the 2022 AHA/ACC/HFSA guideline also proposes

alternative biomarkers (sST2, galectin-3, and cardiac troponins) when needed. However, large clinical trials are required to elucidate the benefits of a personal adjusted biomarker strategy for the management of HF and prediction of HF-related outcomes.

Q6 Could you share the key conclusions drawn from your 2021 paper, 'Shift of Conventional Paradigm of Heart Failure Treatment: From Angiotensin Receptor Neprilysin Inhibitor to Sodium-Glucose Co-transporter 2 Inhibitors?'

This narrative review article opens up the changes affecting the management of HFrEF, which have recently occurred, and mainly focuses on the combined use of angiotensin receptor-neprilysin inhibitors (ARNI) and sodium–glucose co-transporter 2 inhibitors (SGLT2i). It has been purported that the favourable molecular effects of ARNI and SGLT2i (e.g., attenuation of cardiac remodelling; suppression of oxidative stress, apoptosis, and inflammation; mediating repair activity; and improvement of energetic homeostasis) contribute to tissue protection and thereby dramatically decrease the risk of death and HF hospitalisation in HFrEF. The approach, which is widely known as neurohumoral modulation, results from the benefits observed in numerous large clinical trials such as PARADIGM-HF, DAPA-HF, EMPEROR-Reduced, and EMPEROR-Preserved. These studies have revealed the possibility to improve fatal and non-fatal HF events and renal outcomes among optimally treated individuals. Thus, a shift from the traditional approach of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers and β-blockers to a more effective one composed of ARNI, β-blocker, SGLT2i, and optionally mineralocorticoid receptor antagonists appears to be much more effective in this matter. Nowadays, this treatment algorithm the so-called four-pillar strategy, is approved and generally recommended by the 2022 AHA/ACC/HFSA and 2021 ESC guidelines.

Q7 Please describe the key take-home messages from the two ePosters you presented during the 2022 ESC Preventative Cardiology congress: 'Predictive Value of Both Irisin and Apelin for Health Failure with Preserved Ejection Fraction in Type 2 Diabetes Mellitus Patients' and 'Elevated Levels of Apelin Predict Favourable Clinical Course of Heart Failure in Type 2 Diabetes Mellitus Patients'.

The first ePoster, entitled 'Predictive Value of Both Irisin and Apelin for Health Failure with Preserved Ejection Fraction in Type 2 Diabetes Mellitus Patients', elucidated whether serum levels of both irisin and apelin could predict HFpEF in patients with Type 2 diabetes (T2D). Indeed, both peptides were found to play a central role in metabolic homeostasis, inflammation, immune reaction, tissue reparation, and adaptive cardiac remodeling. Irisin is skeletal muscle-derived peptide, which is produced by a proteolytic cleavage of fibronectin Type III domain-containing transmembrane protein 5, the expression of which is under close control of peroxisome proliferator-activated receptor-γ coactivator 1α. Apelin is considered to be a powerful regulatory peptide with positive inotrope ability, and acts as an autocrine regulator of cardiac and vascular reparation. One hundred and eight patients, aged 41–62 years, with HF and T2D had HFpEF (EF>50%; n=58), HFmrEF (EF<40%; n=22), and HFrEF (EF<40%; n=28). Twenty patients with T2D but without HF were enrolled in the study.

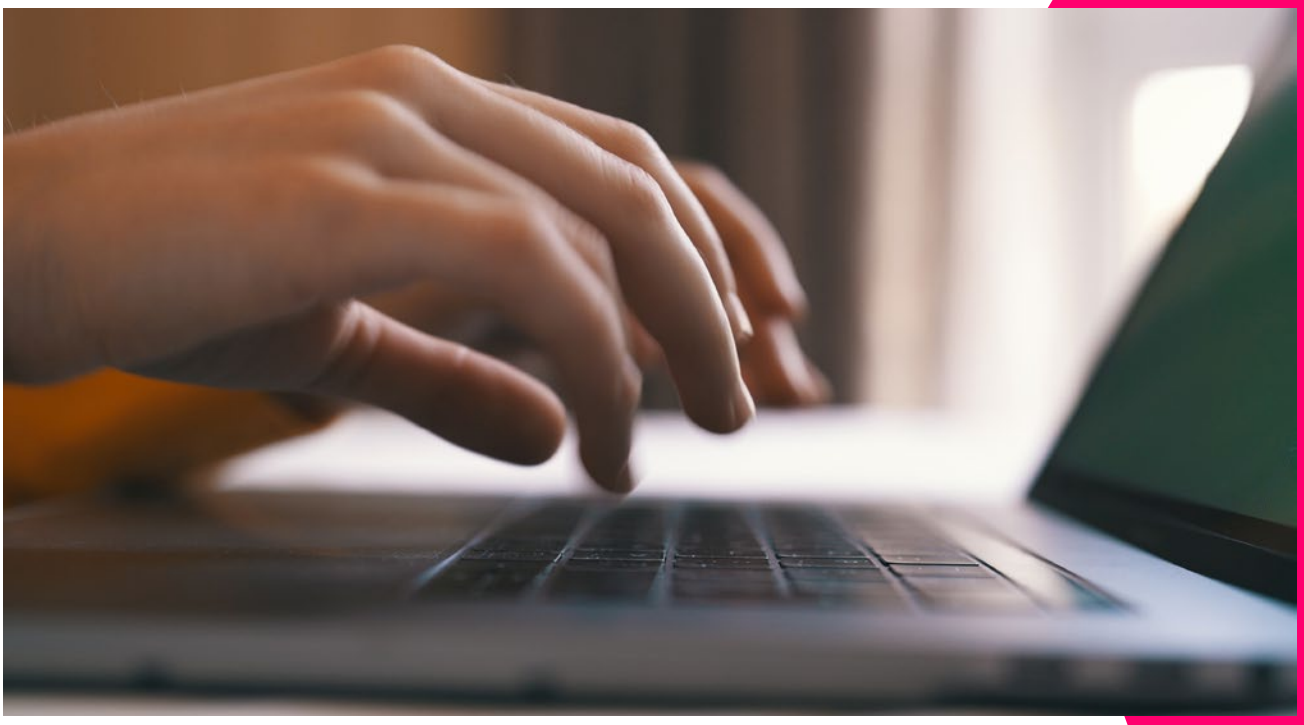
We found that the levels of irisin were significantly higher in patients with HFpEF than in people with HFrEF, whereas healthy volunteers and patients with T2D but without HF demonstrated lower concentrations of these peptides. In contrast, apelin

levels were significantly increased in patients mainly with HFrEF. Then, we divided all patients with HF having elevation of NT-proBNP >750 pmol/mL into three sub-groups, depending on the level of the biomarkers. Patients from Sub-group A had both irisin and apelin levels higher than the cut-off points; individuals from Sub-group B had higher concentrations of one of the two biomarkers; and patients from Sub-group C demonstrated levels of both peptides lower than the cut-off points. Multivariate logistic regression analysis revealed that the discriminative value of irisin and apelin to predict HFpEF in Sub-group B (hazard ratio [HR]: 2.18; 95% confidence interval [CI]: 1.26–3.14; p=0.001) was substantially higher compared with Sub-groups A and C (HR: 1.03; 95% CI: 1.00–1.05; p=0.64 and HR: 0.92; 95% CI: 0.89–1.01; p=0.62, respectively). Adding irisin and apelin to NT-proBNP as independent variables to the predictive model sufficiently improved discriminative ability of whole model for HFpEF.

The next ePoster illustrated the finding that add-on of apelin to the combined predictive model constructed from NT-proBNP (>785 ng/mL) improved the relative integrated discrimination indices by 10.5% and net-reclassification improvement of 11.5% for the combined endpoint. Moreover, the Kaplan–Meier curve showed that patients with levels of apelin >3.55 ng/mL demonstrated better clinical course of HF compared with those who had lower apelin levels (log-rank test: p=0.001). Thus, we found that apelin levels >3.55 ng/mL regardless of NT-proBNP had positive discriminative ability for clinical course of HF in patients with T2D.

Q8 You have authored more than 550 research articles. What do you believe to be the current knowledge gaps with respect to heart failure diagnosis and treatment?

Despite 2022 AHA/ACC/HFSA and 2021 ESC recommendations yielding novel strategies in HF management, we are not completely satisfied about the mortality rate in patients with HFrEF, HFmrEF, and HFpEF. I think that the new four-pillar approach to HF medical care composed of ARNI, mineralocorticoid receptor antagonist, β-blocker, and SGLT2i will allow us to make a breakthrough in it.



Conceptually, the prevention of asymptomatic HF occurrence and its turning from HFpEF to HFmrEF and finally to HFrEF seems to be more promising in this way. In addition, thorough care of comorbidities such as diabetes, chronic kidney disease, hypertension, valvular heart diseases, cardiomyopathies, arrhythmias, anaemia, etc., should be a focus in the prevention of HF manifestation and progression. In this way, biomarkers can play a pivotal role as low cost, personal, and practically useful predictive tools to identify patients at higher risk and detect a response on the treatment further.

Overall, I believe that personal adaptation of each direction of HF management; education of the patient, their family members, and caregivers; and extensive support of non-profit sectors and official institutions could reduce the total cost of management and make it more affordable for the patients at different stages of the natural evolution of HF. Last but not least, the prevention and management of acute, acutely decompensated, and advanced HF need to be justified according to the optimal algorithm of interplay between HF team members.

Q9 To date, what have been the proudest achievements of your career?

To be honest, I am most proud of being awarded Fellow of the ESC, which became a high point in my academic career last year. I am in an on-going communication with the European Union (EU) scientific community, especially with scientists from Austria, Germany, and Slovenia, but not only with them. I also have many friends from other countries, including the USA, Canada, Argentina, Brazil, and Japan, whose scientific interests overlap with my own activities. Thanks to the ESC congresses and working groups, we are able to discuss ideas together. However, it is true that nothing can replace close personal communication.

The next achievement that I especially value is my activities on the editorial boards of several highly reputed scientific journals. This gives me incredible scientific experience, which cannot be overvalued, because it allows me to be present during formation of new ideas and find out more prior to official publication. I have also had some of my proudest moments during the preparation and publication of both current national Ukrainian guidelines for biomarkers in HF and HF management, which have been successfully executed in close co-operation with my friends and colleagues from the Working Group of the Ukrainian Association of Cardiology and Ukrainian Association of Heart Failure Specialists.

Q10 Where can we expect to see your focus lie in the near future?

My most recent presentation was at the ESC's 2022 Heart Failure Congress, which was held in Madrid on 21st–24th May. I spoke about new arguments in terms of potential mechanisms by which empagliflozin, a SGLT2i, mediates cardiac protection in patients with HF and T2D. Moreover, my new research article, entitled 'Serum Levels of Irisin Predict Cumulative Clinical Outcomes in Heart Failure Patients with Type 2 Diabetes Mellitus', has been approved for production and accepted for publication.

2021 European Society of Cardiology (ESC) Heart Failure Guidelines

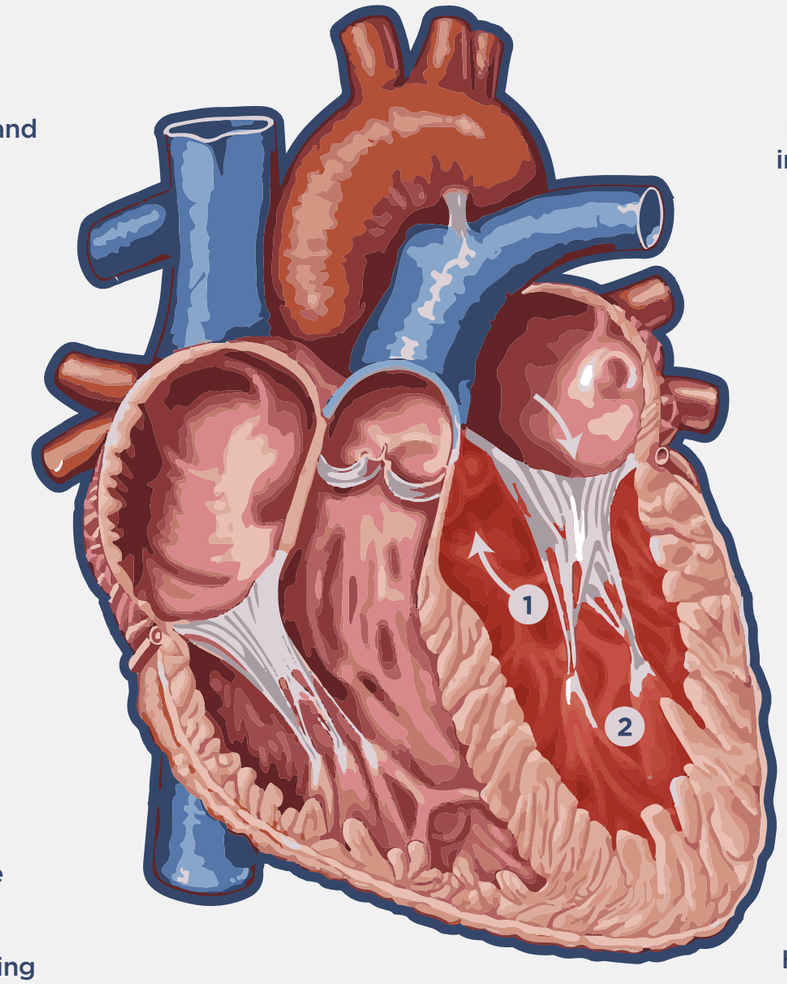
Key Messages

Natriuretic peptides, echocardiography, and MRI important for diagnosis of HF

For patients with HFmrEF, ACEi or ARNi, β-blockers, and MRA may be considered

No specific therapies shown to reduce risk of mortality in HFpEF.

Important to diagnose and treat underlying aetiology and coexisting comorbidities. Diuretics recommended in congested patients



Recommended cornerstone therapies for individuals with HFrEF are ACEIs or ARNIs, β-blockers, MRAs, and SGLT2 inhibitors

Enrolment in a multidisciplinary HF management programme recommended for all patients with HF

1 Amount of blood pumped out
2 Amount of blood in the chamber

HFmrEF characterised by LVEF of 41–49%

Clinical

Symptoms:

- Fatigue and lethargy
- Ankle swelling
- Dyspnoea
- Orthopnoea
- Paroxysmal nocturnal dyspnoea

Signs:

- Tachycardia
- Peripheral oedema
- Elevated jugular venous pressure
- Crepitations
- S3 gallop

Statistics

64 M
cases of HF worldwide

10 M
years lost because of HF-related disability

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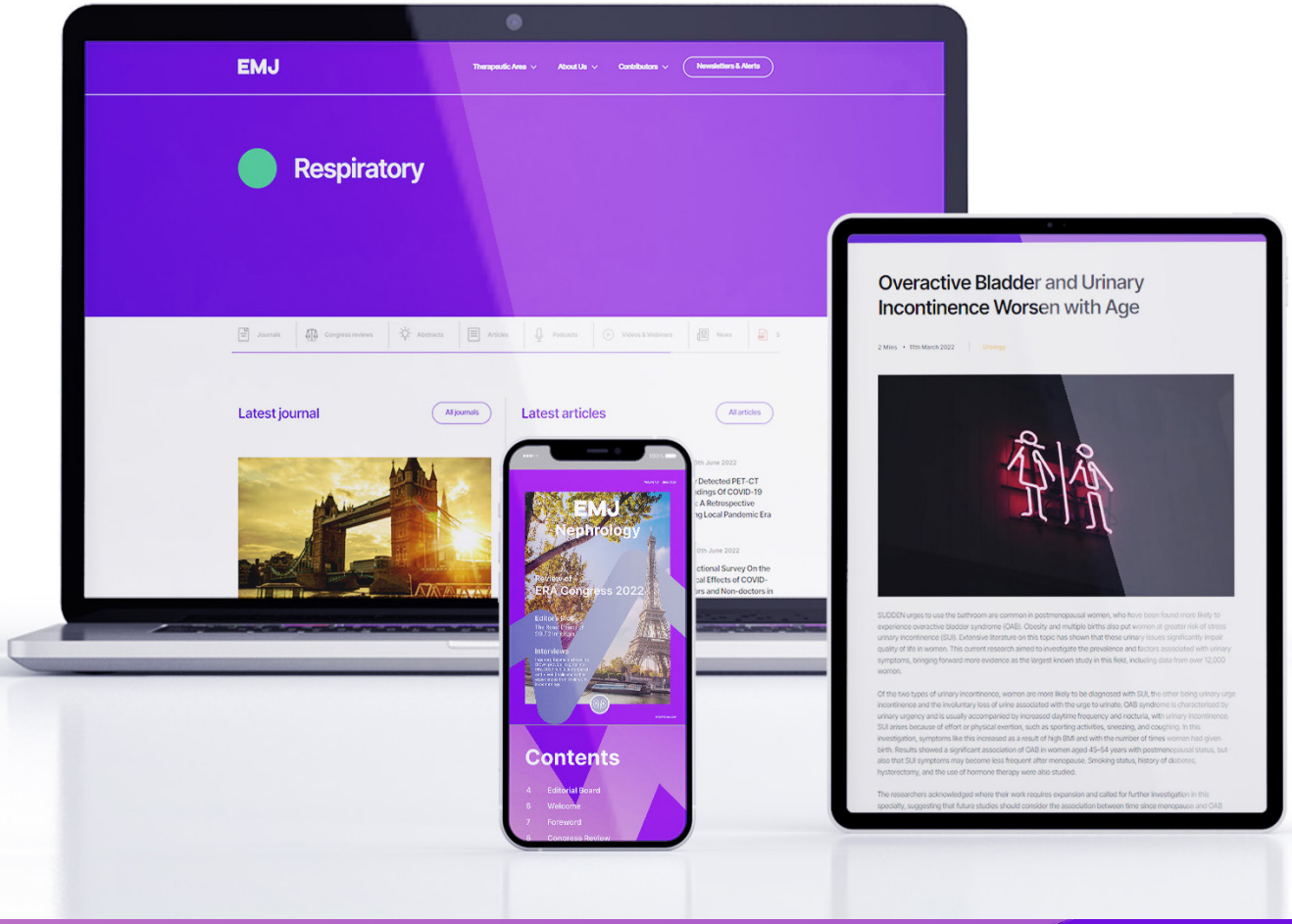

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Screening for Heart Disease in the Age of Digital Health Technologies: Who, When, and How?

Editor's Pick

Despite recent advances in diagnostic and therapeutic modalities, cardiovascular disease remains a major public health concern, and is a leading cause of morbidity and mortality throughout the world. The use of emerging digital health technologies, including artificial intelligence, big data analytics, electronic and mobile health platforms, and wearable devices is a promising way to improve primary prevention, early case detection, and disease management, which ultimately facilitates better health outcomes. In this article, the authors consider how digital technologies can be used to increase the ease, sensitivity, and specificity of screening for heart disease compared with traditional methods.

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Abstract

Heart disease affects much of the world's population, yet many people have no idea that they could have something wrong with them. An opportunity therefore exists for targeted screening for conditions such as cardiovascular disease, heart rhythm changes, valvular heart disease, structural abnormalities, and more subtle, rarer inherited heart conditions. At the same time, the rapid development of digital health technologies and clinical support systems is providing patients and their doctors access to augmented intelligence solutions to diagnose these conditions. This article will focus on how the emerging field of digital health technology can aid screening for heart disease and explore its usefulness in disease specific and population specific groups.

Key Points

1. The use of digital health technologies, including mobile devices and artificial intelligence, in screening for heart disease is a developing field, where unanswered questions include which populations or conditions might benefit from screening, as well as the role for incidental screening.

2. Digital devices can screen large population groups for multiple pathologies, and are able to provide data previously inaccessible, such as heart rhythm prior to first collapse.

3. Digital health is a rapidly expanding field with substantial ongoing developments; if these advances are evaluated properly, it is a field with great potential for screening populations for heart disease.

INCIDENCE AND PREVALENCE OF HEART DISEASE

Cardiovascular disease (CVD) is one of the leading causes of mortality and morbidity worldwide, and was the leading cause of death globally in 2019.[1] This is despite continued improvement in its management and the reduction of coronary artery disease (CAD).[2] One reason for this is the presence of undiscovered conditions in certain individuals. For instance, there are an estimated 260,000 people with familial hypercholesterolaemia in the UK, but only 6–7% of them are diagnosed. Furthermore, over 600 people under 35 years old die a year in the UK from an unrecognised heart condition.[1,3] There are particularly prominent examples of younger victims with sudden cardiac death (SCD) in professional athletes. These draw the public's attention and, whilst uncommon, are dramatic and have a high burden in terms of life-years lost.[4]

CVD also has significant economic costs, with an estimated 19 billion GBP per year impact on the UK's economy and around 106 billion EUR across the European Union (EU).[1,2] The National Institute for Health and Care Excellence (NICE) in the UK estimated that a 1% drop in cardiovascular risk would prevent 25,000 CVD cases, producing 40 million EUR a year in savings.[5]

SCREENING

The purpose of screening is to detect a disease in its early stages and treat it to reduce morbidity, mortality, and the associated societal and healthcare costs.[6] In an increasingly digital age with many innovations, there are new opportunities to utilise technology to screen for pathology. History, physical examination, ECGs, echocardiograms, CT, and genetic screening can all be utilised. The usefulness of these methods varies depending on the condition being screened. This article will focus on how the emerging field of digital health technology affects screening for CVD and explore its utility in disease- and population-specific screening.

Disease-Specific Screening

Sudden cardiac death

There remains significant debate around the optimal methods of cardiac screening for SCD in the young. The European Society of Cardiology (ESC) recommends screening of high-risk individuals, including athletes, whereas the American Heart Association (AHA) guidelines recommend just screening athletes. There are other discrepancies; the ESC endorses the use of ECGs in screening, but the AHA do not.[7,8] This is particularly interesting in the context of the leading causes of death in young competitive athletes. Additionally, a 12-lead ECG can increase the sensitivity of screening and there is good evidence supporting its cost-effectiveness.[9,10] There are papers suggesting the focus on athletes ignores the damaging effects SCD in a non-athlete can have on friends, peers, and family; especially given the number of population-wide SCDs that happen during sleep, which could be as high as 40%, and those that occur in non-athletic groups.[4,11,12]

The risk of false positives and the harm this causes is often cited as the reason more generalised screening is not recommended.[13,14]

However, screening may also be cheaper than assumed and could be employed in younger age groups. Some papers suggest relying on improving resuscitation over screening is unsatisfactory due to SCD's poor survival rate and the increased data gathered can be used to further refine screening.[11,15] The technologies mentioned later in this article show promise for collecting such data at a reduced cost and raise the possibility of being able to recover data just preceding events, such as SCD. This is without taking into account the potential for artificial intelligence (AI) to revolutionise risk prediction or early warning systems.[16]

Atrial fibrillation

Targeted screening can also assist in the detection of atrial fibrillation (AF) due to its often insidious nature and the subsequent damaging thromboembolic event.[17] The ESC recommends opportunistic screening for AF in anyone older than 65 years due to the risk of ischaemic stroke and increased mortality associated with asymptomatic AF.[18] Several studies suggest the use of a manual pulse check with supplementation from single-lead or 12-lead ECG devices due to the ESC requirements for diagnosis.[17-19]

In the 2020 ESC guidance, the sensitivity and specificity of the various AF screening tools were compared with the gold standard of a 12-lead ECG (Table 1).[18] There are two large studies, the Apple Heart study, with over 400,000 self-enrolled participants, and the Huawei Heart study, with 200,000. Both studies showed promise for the use of smartwatches and photoplethysmography (PPG) in screening for arrhythmia.[18,20,21]

A recent meta-analysis supported the systematic and opportunistic screening for AF.[22] While it did not examine smartwatches or PPG, it did find that systematic, rather than opportunistic screening, was more effective at identifying patients with AF; however, it was noted that this may not be cost-effective. Others suggest this may be achieved by lowering the age cut off to 40 years old.[22] This, combined with the Apple Heart and Huawei Heart studies not requiring in-person appointments, may increase cost-effectiveness further.[20,21] The portable single-lead ECG devices have shown promise by increasing the ease and reducing the cost of screening,[17,23,24] and could increase the potential for including wider populations.[17,22]

Coronary artery disease

CAD is one of the leading causes of death worldwide.[25] Due to its potentially silent nature there has been great interest in screening, but the optimal approach is debated. Initial screening can involve history and examination to establish risk factors for CAD, alongside blood tests and scoring systems such as the Systemic Coronary Risk Estimation 2 (SCORE2) score.[26] These take information such as blood pressure, lifestyle factors, family history, and sex into account alongside co-morbidities. The ESC recommends assessing risk in males over 40 years old and females over 50 years, unless there are known CVD risk factors. Most of the ESC recommendations discuss prevention using lifestyle and medications to adjust modifiable risk factors rather than exploring screening as an option. This makes it difficult to assess the ESC position on more generalised screening.[26]

Table 1: The sensitivity and specificity of the various atrial fibrillation screening tools.[18]

Method	Sensitivity	Specificity
Manual pulse taking	87–97%	70–81%
Automated blood pressure monitors	93–100%	86–92%
Single-lead ECG devices	94–98%	76–95%
Smartphone apps	91.5–98.5%	91.4–100.0%
Smart watches	97–99%	83–94%

In recent years, coronary artery calcium scoring and CT coronary angiography (CTCA) have come to the fore in assessing patients' CAD risk in a non-invasive manner.[27] There are also new ways to assess CAD risk using CTCA in combination with AI. One example is the CaRi-Heart® (Caristo, Oxford, UK), which uses images captured during a standard CTCA alongside traditional risk factors. By calculating the Fat Attenuation Index (FAI), which has been previously validated,[28,29] in combination with traditional risk factors, it determines an 8-year absolute risk of a fatal cardiac event, or the CaRi-Heart risk. Inflammation has long been suspected as having a key role in CAD,[30] but until FAI was established there was no straightforward way to measure this.[28] Caristo takes FAI a step further and has been demonstrated to show a significant clinical benefit over traditional CVD risk factors and has the potential to enhance the utility of CTCA in the risk stratification of CAD.[31]

Fractional flow reserve also uses CTCA and AI-powered algorithms to establish vessel-specific ischaemia and flow obstruction. It is recommended in British[32] and European[27] guidance for the risk stratification of those with stable chest pain. Not least in part due to its prognostic value and potential to increase the accuracy of assessing risk in an individual as well as helping select who undergoes invasive strategies such as direct invasive coronary angiography.[33]

In December 2021, the European Association of Cardiovascular Imaging (EACVI) and the American Society of Echocardiography (ASE) published their recommendations for non-invasive imaging in coronary syndromes.[34] This not only supported the use of fractional flow reserve, but also recommended the use of echocardiograms, especially stress echocardiography, which can also be combined with the power of AI. The EchoGo Pro (Ultromics, Oxford, UK), for instance, uses AI to automatically analyse stress echocardiograms, which it can then use to risk stratify the likelihood of severe CAD in an individual.[35] This was shown to be 10% more sensitive than a manual assessment.[35]

Valves

Due to increasing life expectancy, the prevalence of valvular heart disease (VHD) is rising. In Europe, approximately one million people over the age of 75 years suffer from severe aortic stenosis.[36] A study in 2016 screened for VHD in primary care patients over the age of 64 years and discovered just over half had previously undetected VHD. Fortunately, the majority had mild disease; however, 6.4% had clinically significant disease.[37] They also established a strong association with AF, which suggests this could be a targeted area for screening. Currently, there are no population screening programmes for VHD in adults.

Population-Specific Screening

For screening to be relevant to an individual, one must consider the disease(s) to screen for. When screening certain populations, cardiologists can screen for many cardiac diseases with the same test, being mindful that there will be different incidences in different populations.

Athlete screening

There are differences in the recommendations and methods of pre-participation cardiac screening for athletes around the world. In some countries such as Italy, this is compulsory.[7,10,14] Many other European countries have followed suit in accordance with the ESC recommendations, and several professional sporting bodies, such as the International Olympic Committee (IOC)[38] and Fédération Internationale de Football Association (FIFA),[39] recommend cardiac screening.

The incidence of sports related sudden cardiac arrest is low, 6–7/million inhabitants per year in one recent study.[40] Interestingly, it showed only 5.3% occurred in young competitive athletes, with the remaining occurring in middle-aged recreational sports participants. Only 12% had a history of heart disease.

The causes in the young, below 35 years, include cardiomyopathy, coronary artery anomalies, ion channelopathies, and acquired cardiac conditions with geographical variation in incidences.[41] In individuals who are older, CAD accounts for >80% cases with untrained individuals appearing to be at the highest risk.[42] Screening of recreational middle-aged sports participants for underlying coronary artery disease may be more beneficial in changing

behaviours and reducing the burden of sudden cardiac arrest.[42]

Risk profiling

Current NICE recommendations suggest a systematic strategy within primary care to identify individuals at the highest risk of CVD.[43] This should be reviewed regularly in those over the age of 40 years. Well-validated risk scores such as QRisk3[44] in the UK and SCORE in Europe aid this and help determine the need for primary preventative interventions. Patients with chronic kidney disease, albuminuria, Type 1 diabetes, or familial history of hypercholesterolaemia should be assumed to be high-risk and treated accordingly.[42]

The U.S. Preventive Services Task Force (USPSTF)[45] has similar recommendations. They advise against screening asymptomatic individuals with a low-risk of CVD using ECG or exercise ECG and find insufficient evidence for a recommendation in intermediate- or high-risk. Their recent review on screening for AF in asymptomatic adults aged 50 years or older found insufficient evidence to assess the benefits versus harms.[46] This is consistent with the recent LOOP study,[47] where, despite a nearly three-fold rise in AF detection and subsequent anticoagulation, there was only a non-significant trend to benefit. This was coupled with a non-significant trend to harm such as major bleeding. This suggests that the correct demographic to screen has yet to be found.

Screening of sudden cardiac arrest survivors and victims' families

A standardised approach would help phenotype and genotype individuals and has the potential to do more for our understanding of rare cardiac conditions capable of causing SCD than any whole population screening programme could ever detect. The ESC's 2015 guidelines suggest that a diagnosis could be made in 50% of families of sudden arrhythmic death victims.[48] There are guidelines from the European Society of Pathology (ESP) for autopsy investigations of victims of SCD.[49]

For survivors of sudden cardiac arrest who come under the care of cardiology, a thorough evaluation of the cause of arrest should be made before discharge to determine the need for implantation of a cardio-defibrillator and other therapies. However, some survivors never come under the care of a specialist cardiology team and the opportunity to screen family members is lost.[49]

Serendipitous Screening

With the huge rise in the use of cross-sectional radiological imaging over the last 10 years, there has been increasing recognition by radiologists that as they can see the heart, they should analyse it too. Calcification of the coronary arteries is easily visible on both unenhanced and enhanced studies and there have been several papers in recent years guiding how to best interpret and deal with these findings.[50]

The degree of coronary calcification increases with age, as does the likelihood of having a CT with at least some of the heart visible. Other signs of coronary heart disease can also be visible, such as left ventricular wall scarring, late enhancement of the myocardium, mural, and intracardiac thrombus. CT scanners are now so fast that these features are often visible on non-gated studies.

Now that Schrödinger's 'coronary cat' has been irreversibly observed, the radiologist must decide how to report it without creating unnecessary demand on cardiology services. Estimating the calcium score is feasible but should be put in the clinical context of the patient. For example, a male in their 50s with three-vessel calcification has a clear risk that might benefit from investigation and treatment. A 95-year-old male with metastatic malignancy may not.

The British Society of Cardiovascular Imaging (BSCI) published a consensus statement on this in 2020, which detailed how best to approach incidental cardiac findings.[50] They suggest interpretation should be influenced by additional available clinical information. A similar approach is made to aortic valve calcification and other incidental cardiac findings. Reports will alert the clinician to the presence of disease and having a strategy to deal with this is important. Most of the follow up should be suitable for the family physician, with symptomatic disease most likely to require onward referral. A useful pathway exists in their document referring to NICE guidelines.[50]

Digital Screening

With the worldwide increase in usage of mobile devices, there exists a basis for a digital health approach in the context of arrhythmia, be it as a diagnostic tool or for surveillance. This can be particularly beneficial in the context of AF, where the incremental costs for its use are relatively low.[51]

Several digital devices are available to diagnose and record heart rhythm changes. Among these is the MyDiagnostick (MyDiagnostick Medical, Maastricht, the Netherlands), a device equipped to record a single-lead ECG that displays a red or green light if AF or sinus rhythm is detected. AF analysis has shown 80–100% sensitivity and 93–99% specificity and a screening study during flu vaccinations found 1.1% of participants had AF.[52] The Zenicor-ECG (Zenicor Medical Systems, Stockholm, Sweden) is another hand-held device with no additional hardware. Two electrodes at each end are held and the central display shows a Lead I ECG. AF was identified in 0.9% of participants in one screening study and 3% in another study, both adopting similar protocols. Validity was high when used twice daily along with recordings during symptoms and adjudication of ECGs by a health professional.[53,54]

The RhythmPad (Cardiocity, Colchester, UK) is a mousepad-style ECG screening device[55] that offers an advantage over the single-lead view, as a third electrode can be added for enhanced image clarity. The titanium-based sensors can be placed around both arms and the right leg then attached via leads to a tablet computer that displays a six-lead ECG. Among the advantages over single-lead systems, is the existence of algorithms for the detection of arrhythmias beyond AF. A study utilising it revealed sensitivities of 97.5% for normal sinus rhythm and 95.4% for AF.[55]

The Zio Patch (iRhythm Technologies, San Francisco, California, USA) provides continuous ECG recording for 14 days with a high diagnostic yield for total arrhythmia detection when compared with Holter monitoring.[56] When 24 hours of monitoring was compared between the two methods, the Holter detected more arrhythmias; however, the time to first recorded arrhythmia often occurred after 48 hours, demonstrating the importance of longer duration monitoring. Comfort is an important consideration and impacts compliance. Both the Zio Patch and the similar S-PATCH (Wellysis, Seoul, Republic of Korea) were found to be superior in this regard when compared with traditional Holter ECG monitors.[56-58]

Commercial wearable devices measure heart rate and rhythm through ECG or PPG systems. ECG monitors can be built into belts, wristbands, adhesive patches, and mobile smartphones. PPG measures changes in microvascular blood volume that translates into pulse waves and a tachogram recording. This technology is advancing, and more arrhythmias are becoming identifiable.[59] Diagnostic clarity can be enhanced by over-reading from a competent practitioner in ECG analysis. As well as issues with sensor contact, challenges include signal correlation and patient comfort. Future developments should focus on overcoming such design barriers.

One wearable device, the Apple Watch (Apple, Cupertino, California, USA), has gone some way towards achieving both comfort and accuracy and was evaluated in the Apple Heart Study.[20] This showed that 2,161 people had an irregular rhythm, with 34% confirmed with AF on subsequent patch monitoring. Where AF was not the cause of rhythm irregularity, 40% showed other arrhythmias, mostly ectopic beats.[20,60] Adverse events were collated and anxiety was recorded most commonly, supporting findings that such devices can cause health anxiety through overuse and is worthy of consideration when considering such devices with patients.[20,61]

Perhaps the most widely adopted tool in AF screening research is the Kardia device (AliveCor, Mountain View, California, USA), a device that transmits a single-lead ECG wirelessly to a smart mobile device. The NICE recently published their guidance on the Kardia, outlining the cost-effectiveness and ability to identify significantly more AF than Holter monitoring.[62] A systematic review explored the feasibility and validity of the device.[63] Feasibility metrics, including process, resource, and management, revealed this as an effective tool. Sensitivity and specificity both reached 98% across included studies, with AF detection ranging from 0.8% to 36%, with correlation to the study demographics and screening approach.[63] Kardia has also demonstrated utility across a variety of settings, making it versatile and easy to use. Their recent

six-lead version offers advantages over the single-lead view, with the addition of more sophisticated algorithms including corrected QT interval ECG analysis.

Remote monitoring of cardiac implantable electronic devices is now recommended by major cardiology societies.[64,65] There has been an increase in use over the last few years and advantages include earlier detection of events and identification of device malfunction, permitting earlier intervention. Enhanced patient safety, reducing hospital admissions, and improving quality of care whilst proactively identifying problems contributes to the cost savings. The increasing need for monitoring patients has come at a time when there is clear evolution and improvement in the accuracy and efficacy of digital health devices.

DISCUSSION

Overall, there are multiple ways of screening for cardiac disease. In most diseases, the exact population that may benefit from screening has yet to be identified. The rapidly expanding field of smart devices and the use of AI may help identify these groups further and provide information about disease trends. Digital devices have the potential to screen large sections of the population for multiple types of pathology. It opens the possibility of examining previously impossible data, such as a patient's heart rhythm prior to their first collapse. It has the potential to reduce the cost of screening, especially in more remote areas. Various devices may also help monitor the middle-aged starting to exercise, with their potential increased risk of cardiac disease.

Personal devices such as the Apple Watch empower patients to look after their own health and to control their own data. This can occasionally be associated with increased health anxiety but, conversely, can also enable reduction of a patient's unease. For example, patients can use devices such as the Kardia whenever they get palpitations. There is also the expanding field of AI, especially in combination with imaging. This shows great promise at increasing diagnostic accuracy and assisting the risk stratification of patients.

There are of course negatives aspects to health screening, which will need to be weighed against the benefits. The wide-reaching screening that some of these digital devices might provide could be used very broadly, perhaps to identify a suitable screening target population. Digital health devices are still in adolescence with multiple unknowns; however, the future looks promising.

CONCLUSION

In conclusion, the expanding field of digital health devices has the potential to offer multiple new methods for screening for heart disease. There needs to be some caution to ensure that these technologies are properly evaluated to comply with the principles of screening, especially when comparing the potential harms and benefits of their use.

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Effect of Age on the Abdominal Aortic Aneurysm: Fuzzy Logic Analysis

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Abstract

Background: The aneurysm refers to the increase in arterial diameter in a localised position and this is characterised by the non-parallelism of the arterial wall. Despite prediction models trying to anticipate the onset of an aneurysm, the limits of their accuracy are often reached. This is due to the poor definition of the factors favouring the development of the aneurysm. In order to take into account this complex process, this study proposes a fuzzy system in the analysis of the effect of each factor.

Methods: As the variability of the diameter of the aorta is a function of several uncertain and imprecise factors, this study deals with data relating to a population of 100 patients diagnosed at the level of the service of the UFAS Setif Hospital in Algeria. This study is limited to the effect of age, which is related to the diameter of the abdominal aorta diagnosed. A fuzzy inference analysis system is proposed. As the system is very complex and in an uncertain environment, its fuzzy logic analysis compensates this uncertainty.

Results: Once the system is established from the actual values recorded, it becomes possible to introduce the input variables randomly to automatically read the result at the output with maximum precision.

Conclusions: In order to avoid the risk of rupture, it is necessary to diagnose the aneurysm according to the patient's age. The introduction of the variables relating to the patient at the entry of the system allows clinicians to have a precise idea about the aneurysm. Note that the majority of cases are diagnosed accidentally in the absence of a screening program.

Key Points

1. At present, the majority of abdominal aneurysms are accidentally discovered in the absence of a universal screening program.

2. Factors affecting abdominal aneurysm development are often difficult to detect by prediction models.

3. The authors present a study in favour of a fuzzy interference analysis system, which can be used to counteract uncertainty and provide accurate results in a highly complex system.

INTRODUCTION

The abdominal aortic aneurysm is often silent and has no visible symptoms.[1] It is necessary to take care of an abdominal aneurysm in time because it is at risk of bursting. A high percentage of aneurysm cases that are not treated in time have their chance of recovery diminished. This makes it necessary to detect aneurysms prematurely, as long as detection is rapid and reliable.[2] The problem with abdominal aortic aneurysms is to be able to act before they rupture by identifying them and defining when to treat them as they progress. A screening program is needed to prevent the development of the aortic aneurysm, and therefore to intervene before it is too late.[3]

As a preventive measure, monitoring and follow-up programs for abdominal aneurysms have been put in place. The scheduled time between two successive examinations is determined by the diameter of the aorta. When the diameter is large, the time between examinations is shortened. The goal is to monitor the critical limit of this diameter so that it does not reach 50 cm.[4]

Since the aortic aneurysm is characterised by the absence of symptoms, to be able to screen a population in a wide range it is essential to have a selection plan, taking into account the risk factors. The problem is that risk factors are distinguished by their uncertainty, complexity, and imprecision. This study deals with the analysis of these factors by artificial intelligence (AI) techniques. The principles of fuzzy inference are proposed in this analysis. A fuzzy system is established with input variables that represent the factors involved in the aortic aneurysm, a database that links inputs to output, and an output of the system that expresses the risk of occurrence of the aneurysm. As each variable is considered fuzzy, and therefore uncertain, the fuzzy analysis compensates for these uncertainties, and the result will be as precise as possible.

RISK FACTOR

Several factors are involved in the development of the aneurysm. However, some factors are much more relevant. These include smoking, high blood pressure, age, dyslipidemia, sex, atherosclerosis, and familial predispositions.[5] This study is limited to the age factor only. It is noted that this factor in itself remains a function of several other auxiliary factors such as weight, comorbidity, physiology, and intrinsic metabolism. From there emerges the complexity of the system. Also noted is that this disease is a function of geographical distribution.[6]

AGE

In addition to the race factor, the age factor is a direct function of the diameter of the abdominal aorta.[7] This is interpreted by the fact that with advanced age, other pathologies are associated such as diabetes, hyperlipidemia, or high blood pressure.[8] By considering the age factor as a fuzzy variable, the associated factors are then taken into account in an indirect way. In general, with advanced age, the risk of an aneurysm is much higher.[9] This prompted the Society for Vascular Surgery (SVS) to issue recommendations to systematically screen male patients from the age of 65 regardless of the associated factors. This remains valid for females as well. When the genetic factor is taken into account in males, this age is reduced to 55 years.[10]

METHOD

The study sample included 100 diagnosed patients. Measurements of the diameter of the abdominal aorta were performed by CT scan. This diameter was correlated with the age factor. This factor is also a function of other parameters such as smoking, blood pressure, and sex, as well as family predispositions. As these variables are imprecise and complex, the authors consider them to be fuzzy variables. These factors constitute the input variables to the analysis system. An output variable expresses the diameter of the corresponding aneurysm, and therefore its risk of possible bursting. A database is built connecting the input variables to the output variable (Figure 1). This base is established from the actual values recorded. The general form of a rule that connects inputs to output is of the form: 'If... then'. Mathematically, the resulting output variable is a function of the input variables: output = F (A,S,P,F), where A is age, S is sex, P is arterial pressure, and F is family history.

One of the techniques of AI is analysis by the principles of fuzzy inference. Like human reasoning, this technique compensates the uncertainties and inaccuracies to extract a clear decision.[11]

Fuzzy Analysis

Given the intrinsic nature of biological systems which are characterised by their uncertainty, problems of predictive control of these models can be modelled as dynamic programming problems. The information is distributed and parallel. Several factors influence the system.[12]

Sometimes classical mathematical methods are inapplicable to analyse complex phenomena. The principles of fuzzy logic applied to this study are adequate. In classical binary logic, an element either belongs to a set, or does not belong. The fuzzy analysis is based on the partial membership of a set.[13] This way of thinking has the advantage of being flexible, simple, and compatible in the analysis of complex, imprecise, and uncertain systems. The authors express the variables in degrees of truth on the membership function. Like human reasoning, they express variables in linguistic terms. For example, the variable 'age', presented in classical logic by the numeric value in years, is suppressed by a linguistic value such as 'young', 'adult', or 'old'. Belonging to the function is not binary, but belonging to the youth or adult group, for example, is.

All of the variables are considered fuzzy. Therefore, the first phase is their fuzzification. This operation allows their conversion from digital to symbolic. The variables are then expressed in linguistic language.

Fuzzification of Input Variables

Each variable must be fuzzified; this consists of their conversion from numeric to linguistic expression in human language.

The age variable

The age of the patients is fuzzified into three fuzzy triangular-type membership functions: young (0–30 years); adult (25–60 years); old: (55–100 years). There is the creation of overlap zones between two neighbouring intervals. This allows compensation for the uncertainty in the allocation of age ranges. This method is applied to all the variables to fuzzifier (Figure 2). In the same way, the other factors are fuzzified.

The sex variable

The sex variable is not fuzzified. This variable is expressed in numeric terms: male (1) and female (2).

The arterial pressure variable

The arterial pressure variable is fuzzified into three fuzzy triangular-type membership functions:

- Low (0-2; 120/80 mmHg);
- Medium (1-3; 120–129/< 80 mmHg);
- High (2-4; >130–139 mmHg systolic or 80–89 mmHg 'diastolic').

These numerical assignments translate the degree of blood pressure.

The family history variable

The family history variable is fuzzified into three fuzzy triangular-type membership functions. According to the family history, the effect of this factor and its influence is approximately estimated as absence (0–2), risky (1–3), or certain (2–4).

Figure 1: System bloc diagram.

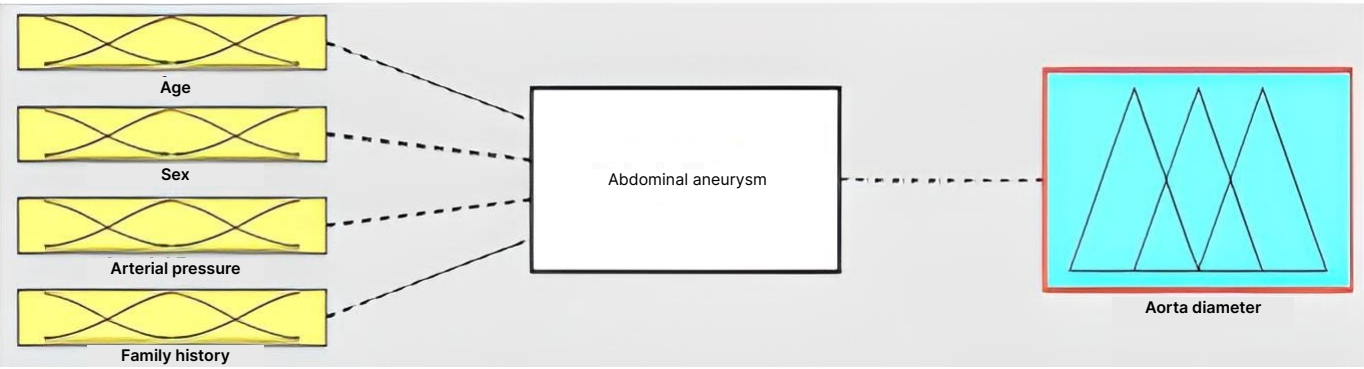


Figure 2: Fuzzification of the age variable.

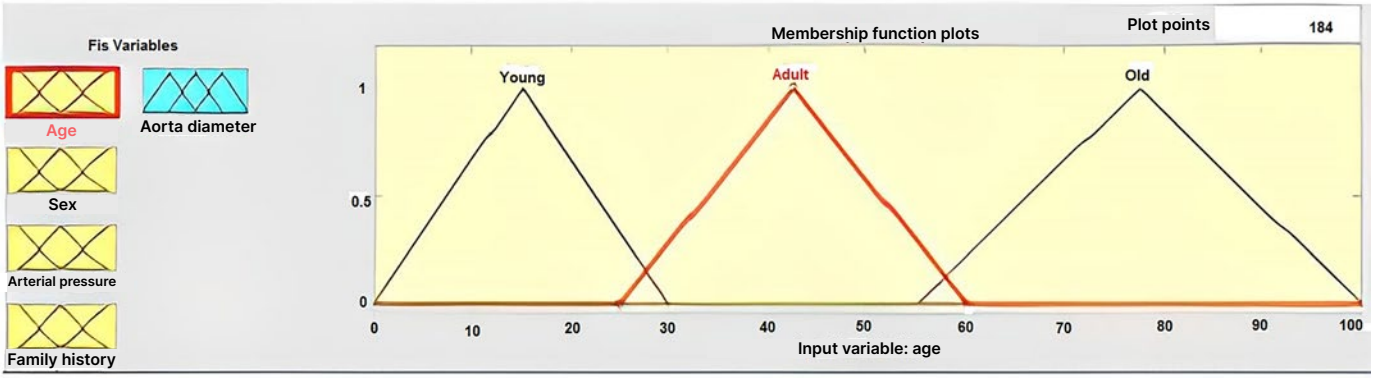
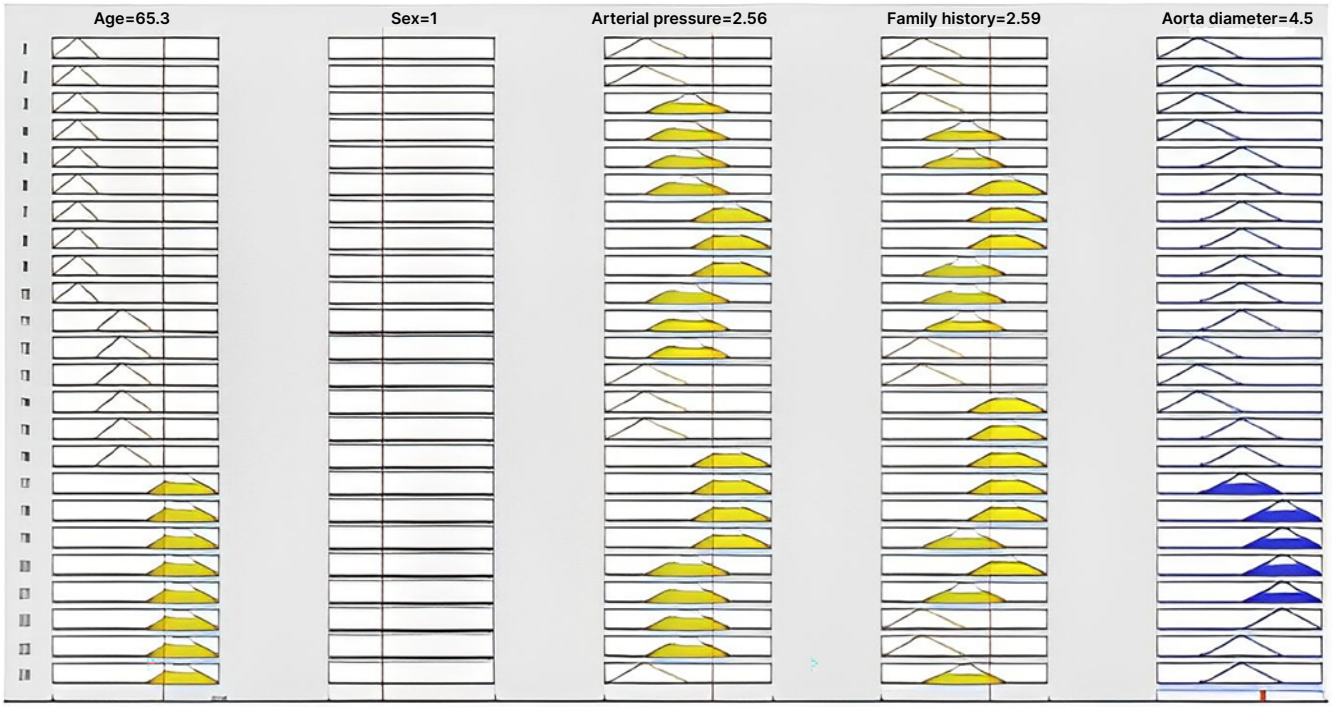


Figure 3: Example of application.



This numerical attribution expresses the probability of the effect of family history.

Output variable

People diagnosed positive according to their aorta diameter are represented by numeric values from 2.5–6 cm. The diameter of the aorta is fuzzified into three membership functions according to their recorded diameter. Again, overlapping intervals are created to compensate the imprecision of the assignment of linguistic variables: normal (2-4), risky (3-5), or severe (4-6). Matlab 2016a (MathWorks, Portola Valley, California) is used for data processing.

RESULT

The basis of the rules is established from the actual recorded values. The uncertainties of the variables age and sex, blood pressure, and the effect of family history variable are compensated by the fuzzification process. Each case mapped to the output variable, which is also fuzzified.

When the base of the rules includes all of the possible combinations, it suffices to introduce any variables at the input to read the result at the output. The result read at digital output is compared to the fuzzification function of the diameter of the aorta to be situated in linguistic terms. (Figure 3).

CONCLUSION

The factors involved in the development of the aneurysm are multiple and complex to analyse by conventional methods. This study proposes a model based on AI techniques, in particular the principles of fuzzy inference.

By the fuzzification process, the numeric variables are converted into linguistic variables in human language. It comes close to the rough reasoning that comes out with the most exact result possible. The inaccuracies are then compensated. Age as a determining factor in the appearance of the aneurysm, and is also a function of other associated factors that this study takes into account. The database established from 100 diagnosed patients makes it possible to encompass a large number of possible rule combinations that map the input variables to the diameter of the aorta recorded. When the system is complete, it is possible to read the result at the output from the random values at the input.

The output value is calculated from the aggregation of all the rules.

As there is no screening program available everywhere, this tool can be an aid in the diagnosis and prevention of abdominal aneurysm.

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Rare Association of Takotsubo Cardiomyopathy with Acquired Bartter-Like Phenotype and Colonic Stricture

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Abstract

Takotsubo syndrome is a rare entity, and the occurrence of Bartter syndrome along with Takotsubo syndrome makes it a bizarre incidence. Diagnosis of both is very crucial and important, as the signs and symptoms tend to be different for each patient. Here, the authors present a case of Takotsubo cardiomyopathy with acquired Bartter-like phenotype and colonic stricture. It was promptly diagnosed and well managed at first incidence, but failing a timely follow-up led to mortality of patient, which highlights the importance of follow-up.

Key Points

1. Takotsubo syndrome is often encountered and is mistaken as acute coronary syndrome; however, management is different in both scenarios.

2. This case report describes a rare association of Takotsubo cardiomyopathy with electrolyte imbalance, which clinically resembled Bartter syndrome. The patient's condition improved following electroylte management and conservative treatment.

3. An early rule-out of acute coronary syndrome is important because management of the two conditions differs but mortality is similar.

INTRODUCTION

Takotsubo syndrome (TTS), also known as stress-related cardiomyopathy or apical ballooning, is a transient systolic and diastolic dysfunction that is often preceded by some physical or emotional triggers. First described in Japan in 1990, it is derived from a Japanese word meaning 'octopus pot'.[1] The incidence of stress cardiomyopathy occurs in 1–2% of patients with ST-elevation myocardial infarction.[2] Bartter syndrome is a rare autosomal recessive disorder affecting the function of the thick ascending limb of the loop of Henle, which causes salt wasting and hypokalaemic metabolic alkalosis.[3] Adult-onset Bartter syndrome is rare and has been reported to be associated with chronic sialadenitis, pulmonary tuberculosis, and exposure to aminoglycosides.

CASE REPORT

This is an interesting case of a 56-year-old female diagnosed with a colonic stricture, which was likely inflammatory in nature. They presented with a history of decreased appetite, abdominal distension for the previous month, on-and-off loose motions, and vomiting for the last 10 days. The patient was admitted to the medical ward with the above symptoms, as well as generalised weakness and a confused state. Although there was no chest pain, an ECG was completed which showed acute ST elevation in the anterior leads. They were immediately referred to the cardiac centre in view of acute coronary syndrome.

On admission to the coronary care unit, the authors found marked ST elevation in V1–V6 leads (Figure 1). Cardiac biomarkers were positive, and the echocardiogram showed an akinetic apex in the anterolateral area. The patient's blood pressure on presentation was 90/70 mmHg. The arterial blood gas test showed respiratory alkalosis with severe hypokalaemia and hypocalcaemia.

The authors planned for an immediate coronary angiography and revascularisation, and unexpectedly, thrombolysis in myocardial infarction Grade 3 flow was observed in all coronaries (Figures 2 and 3). Following this observation, it was thought that the patient was displaying with either myocarditis or Takotsubo cardiomyopathy. In the absence of fever, the authors made a provisional diagnosis of Takotsubo cardiomyopathy and stopped antiplatelets, heparin, and rapidly tapered inotrops. The patient's blood pressure remained at 90/60 mmHg. The authors gave antidepressants, but persistent electrolyte disturbance occurred.

Figure 1: ECG during admission.

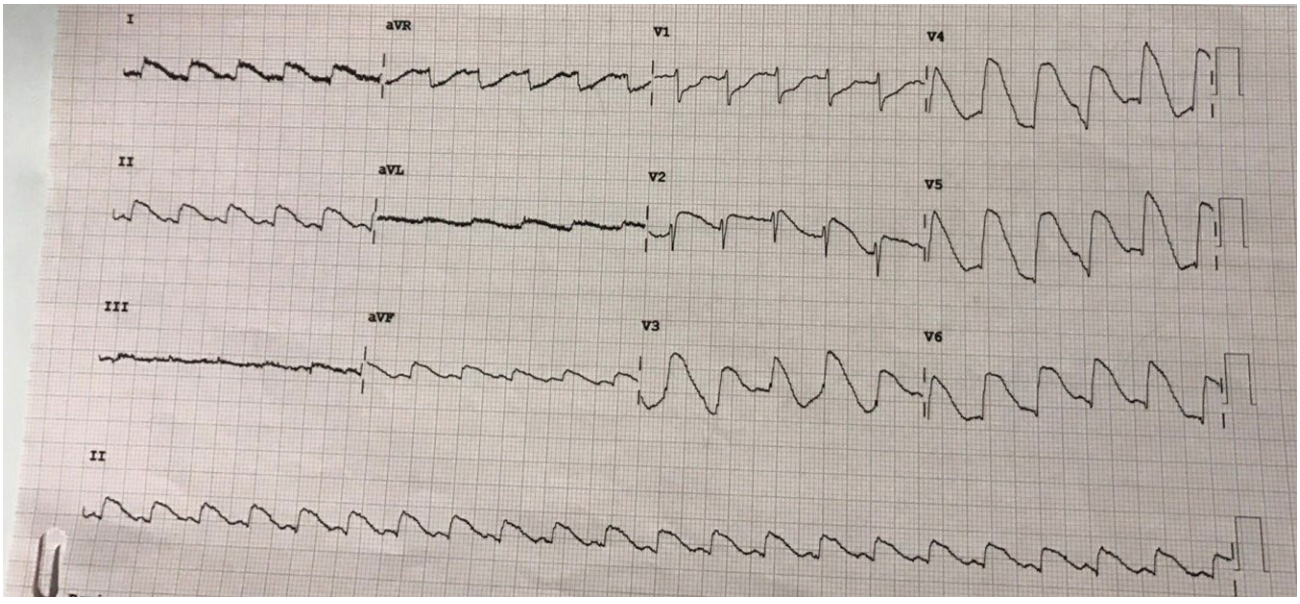


Figure 2: Normal angiogram of left anterior descending and left circumflex arteries during admission.

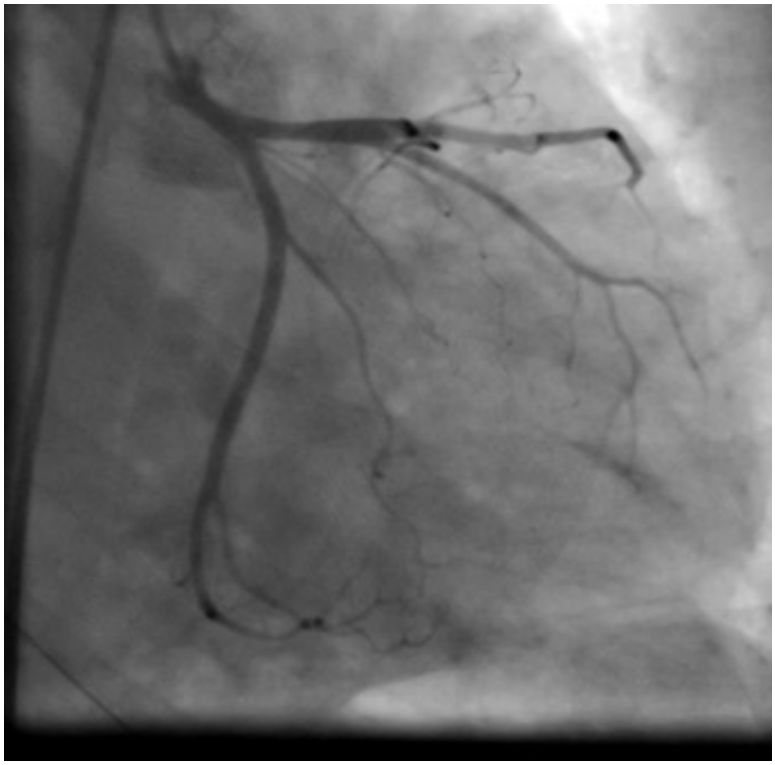
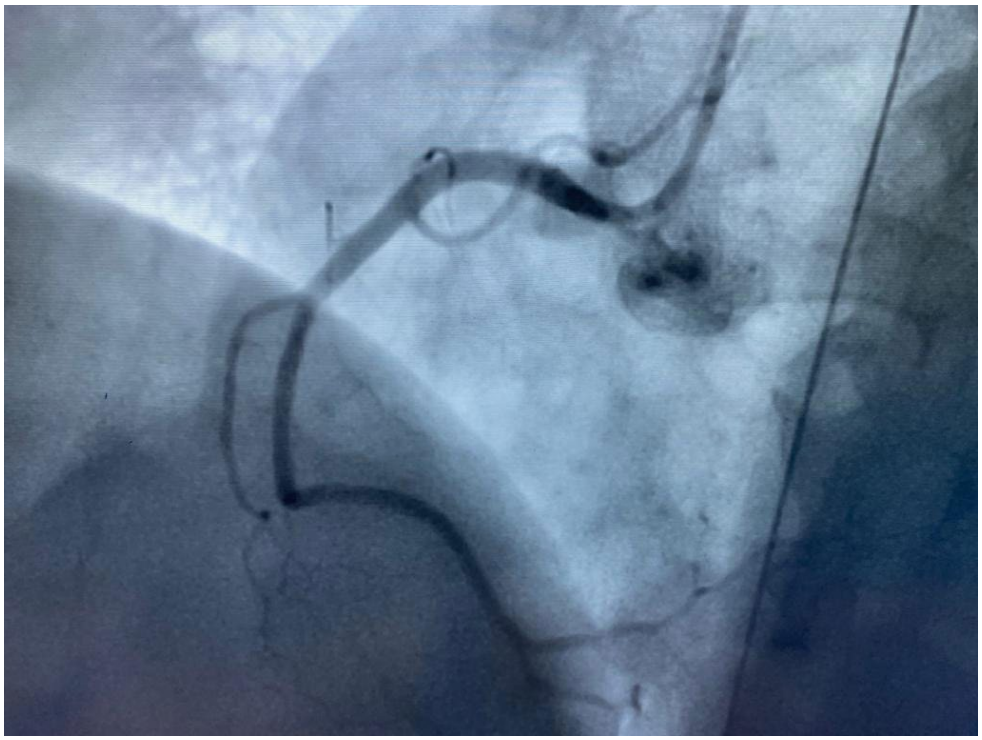


Figure 3: Normal angiogram of right coronary artery during admission.



Upon further evaluation, the patient presented with mild hypomagnesaemia, hyponatraemia, hypochloraemia, elevated renin, and elevated aldosterone, all suggesting secondary hypoaldosteronism. Following further analysis, the electrolyte abnormalities matched the Bartter phenotype. The authors' administered a potassium supplement and spironolactone, with continued monitoring and treatment. Within the next 24 hours, ECG changes began showing improvement and both the ECG (Figure 4) and echocardiogram normalised within next couple of days.

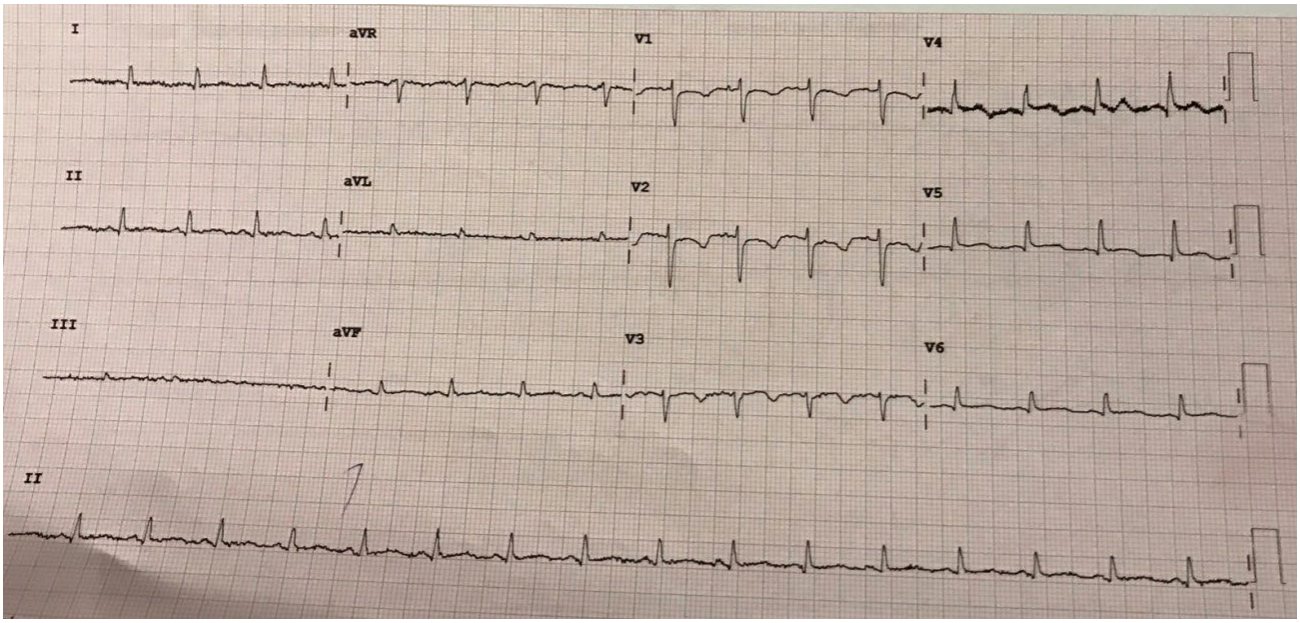
The patient was discharged and advised to attend a regular follow-up. However, the patient did not attend the planned follow-up visit, and 1 month later they developed similar symptoms and succumbed with probability of a similar disease, precipitating due to poor compliance. No autopsy was performed.

DISCUSSION

The underlying mechanism of Takotsubo cardiomyopathy remains unknown. Some studies have pointed to the pathophysiological role of catecholamine, which may cause multivessel coronary spasm or diffuse coronary vasoconstriction.[4] Post-menopausal females are most commonly affected, with clinical and ECG features indistinguishable from acute coronary syndrome. The most common complaint is often chest pain. Generally, some kind of physical or emotional trigger precedes presentation of TTS in patients.[5] It is important to differentiate primary versus secondary diagnosis of TTS, as outcomes for a secondary diagnosis reflect underlying acute medical illness and carry worse short- and long-term prognoses.

In TTS, an increase in levels of troponin and creatine kinase is low compared with the observed amount of regional wall motion abnormality and left ventricular (LV) dysfunction. Increases in brain natriuretic peptide and N-terminal pro-brain-type natriuretic peptide are also higher than that of troponin and creatine kinase.[6,7] Coronary angiography is characteristically normal, with an incidental finding of coronary disease in occasional patients. However, through LV angiography and transthoracic echocardiography, TTS can be distinguished as one of the following five types: apical, midventricular, basal, focal, and global.[8] For treatment of this entity, judicious use of

Figure 4: Normal ECG findings at Day 4.



fluids, β-blockers, and angiotensin-converting enzyme inhibitors are advised, but the use of inotropes is generally contraindicated.[9] An intra-aortic balloon pump may worsen LV outflow obstruction. There is high recurrence rate of 4%.[10]

Bartter syndrome results from the mutation of the five ion transport proteins in the thick ascending limb of the loop of Henle, resulting in hyponatraemia, hypokalaemia, hypochloraemia, metabolic alkalosis, hypocalcaemia, and mild hypomagnesaemia, as well as increased urinary prostaglandin excretion, plasma renin, and aldosterone levels.[11] Recently, a similar phenotypic picture has also been reported in adults in cases of chronic sialadenitis,[12] pulmonary tuberculosis,[13] and in those with gentamicin exposure.[14] It presents with polyuria, polydipsia, and salt craving. Treatment includes vitamin K and magnesium supplements as well as increased salt intake. The addition of spironolactone and amiloride can be appropriate.

CONCLUSION

In the authors' case, the emotional stress superimposed upon the colonic stricture may have resulted Takotsubo cardiomyopathy and acquired Bartter-like syndrome. As no diuretic abuse or persistent vomiting was noted, it was considered to be an acquired idiopathic Bartter-like phenotype. The simultaneous presence of TTS and Bartter-like phenotype has never been observed, and both may have been precipitated because of stress. The possibility of an association between the inflammatory colonic stricture and stress cardiomyopathy could not established. The authors' patient was treated with vitamin K supplements, spironolactone, and antidepressants. Dramatic improvement was noted in the clinical picture, ejection fraction, and electrolyte imbalance.

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Idarucizumab in Emergent Pericardiocentesis: A Case Report of Dabigatran-Induced Haemopericardium and Cardiac Tamponade

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Abstract

Haemopericardium has rarely been described in association with the use of a non-vitamin K antagonist oral anticoagulant. Cardiac tamponade is a life-threatening condition that usually requires urgent pericardiocentesis. Here, the authors report a case of haemopericardium with cardiac tamponade during dabigatran therapy for atrial fibrillation in a patient with chronic coronary syndrome, treated effectively with reversal agent idarucizimab before pericardiocentesis. To the authors' knowledge, this is only the third report of dabigatran-induced haemopericardium.

Key Points

1. Haemopericardium with cardiac tamponade in a patient receiving dabigatran therapy is rare; the authors have discovered only two previous cases of dabigatran-induced haemopericardium in current literature.

2. Urgent percutaneous drainage is the default strategy for resolving a pericardial effusion, but anticoagulation with dabigatran can complicate the safety of urgent surgical procedures.

3. Idarucizimab acts as a reversal agent for dabigatran, and presents a potential advantage for patients due to reducing the potential haemorrhagic risk of dabigatran and permitting urgent surgical procedures.

CASE REPORT

A 71-year-old male with atrial fibrillation (AF) was admitted to the authors' emergency department with fever, progressive dyspnoea, and chest pain spreading to the back for 2 days. They suffered from Type 2 diabetes, dyslipidaemia, obesity (BMI: 34 kg/m^2), and chronic obstructive pulmonary disease, and they were allergic to penicillin. Some years ago, they had an acute coronary event (related to non-ST elevation-acute coronary syndrome), with right coronary vessel sub-occlusion, which was treated with a percutaneous coronary intervention and insertion of a drug-eluting stent, with moderate left ventricular dysfunction (40%). They had a history of paroxysmal AF for some years, leading to treatment with dabigatran (150 mg twice daily). At the time of prescribing dabigatran, their weight was 98 kg and serum creatinine levels were 1.07 mg/dL (creatinine clearance by Cockroft-Gault formula adjusted for weight was 71 mL/min), so a dabigatran dose of 150 mg twice daily was considered appropriate. The patient's other daily medications were: aspirin (100.00 mg), due to previous coronary stent implantation; bisoprolol (1.25 mg); amiodarone (200.00 mg); potassium canrenoate (100.00 mg); sertraline (50.00 mg); furosemide (250.00 mg); atorvastatin (20.00 mg); repaglinide (1.00 mg); metformin/linagliptin (850.00/2.50 mg twice daily); and insulin glargine (14 IU).

On admission, their blood pressure was 95/65 mmHg, oxygen saturation 88%, heart rate 100 bpm, and they were anuric. Chest X-ray showed cardiomegaly, mild aortic ectasia, and signs of chronic obstructive pulmonary disease. An ECG demonstrated a low QRS voltage and incomplete left bundle branch block. Haematology results illustrated leukocytosis with neutrophilia (white blood cell count: 10.60×10^9/L; neutrophil count: 8.85×10^3/µL), low haemoglobin count (9.60 g/dL), and a high level of C-reactive protein (9.89 mg/dL). Renal injury was evident from a blood urea nitrogen level of 0.75 g/L and creatinine level of 2.07 mg/dL (creatinine clearance by Cockroft-Gault formula adjusted for weight was 36 mL/min). Serum potassium was 4.7 mmol/L and the level of sodium was 128.0 mmol/L; liver enzyme tests were normal (aspartate transaminase: 17 U/L; alanine aminotransferase: 14 U/L). Activated partial thromboplastin time (aPTT) was prolonged at 65 seconds, prothrombin time was reduced at 36%, and the international normalised ratio (INR) was measured as 2.03. Slightly elevated troponin levels were also detected (high-sensitivity cardiac troponin T: 36 pg/mL).

Right away, an echocardiogram performed in the emergency room showed a massive circumferential pericardial effusion with initial signs of cardiac tamponade (Figure 1). Regardless of the state of acute renal failure, considering the need to rapidly exclude the presence of aortic dissection, a thoracic angio-CT (Figure 2) was urgently performed. This confirmed a circumferential pericardial effusion of more than 5 cm in diastole with haemorrhagic appearance, as well as a mild dilatation of the proximal ascending aorta (40 mm; 1.72 mm/m^2) without signs of dissection. Thoracic tumoural masses were not observed. A dialysis session was scheduled to remove the contrast agent used for angio-CT, if necessary.

The patient was transferred to the intensive care unit. The last intake of dabigatran was in the morning, 4 hours before the admission. Idarucizumab (5 g) was administered intravenously; within a few minutes, a subxiphoid pericardiocentesis was performed under local anaesthesia and echo guidance. A 6 F pig-tail catheter (EasyKit®, ab medica, Milan, Italy) was inserted into the pericardium, and 1,400 mL of haemorrhagic fluid was drained. The patient was treated with intravenous fluids and a blood transfusion to increase their blood pressure, after which renal function gradually improved and anaemia slowly resolved. Doses of oral anticoagulant were temporarily stopped, while the antibiotic oral clarithromycin (500 mg once daily) and low doses of the corticosteroid oral prednisone (25 mg once daily) were administered. Fever and inflammation indices reduced (C-reactive protein: 1.50 mg/dL) within a few days, as did renal failure (creatinine: 0.98 mg/dL).

Cytology results of the pericardial fluid were negative for malignancy. Fluid microscopy revealed predominantly erythrocytes (740,000 cells/µL) and leukocytes (1,041 cells/µL), with 77% neutrophils, 5.8 g/dL total proteins, 1,492 IU/L lactate dehydrogenase, and a fluid-to-serum lactate dehydrogenase ratio >0.6. All viral serology screenings for *Chlamydia*

Figure 1: An echocardiogram at the entrance showing haemopericardium on an apical four chamber view.

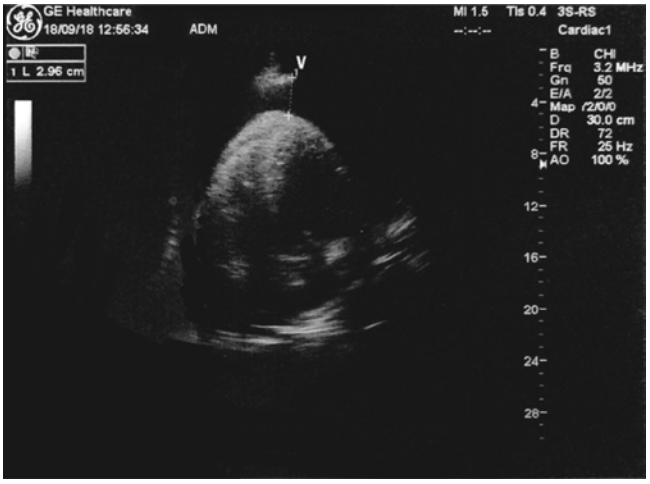
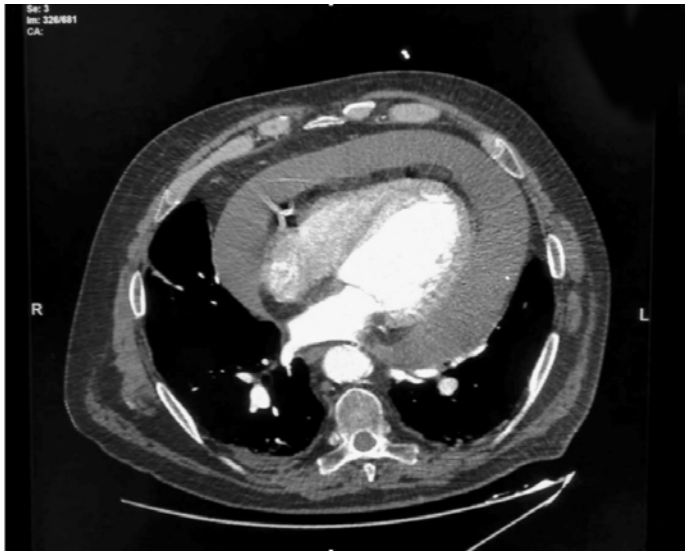


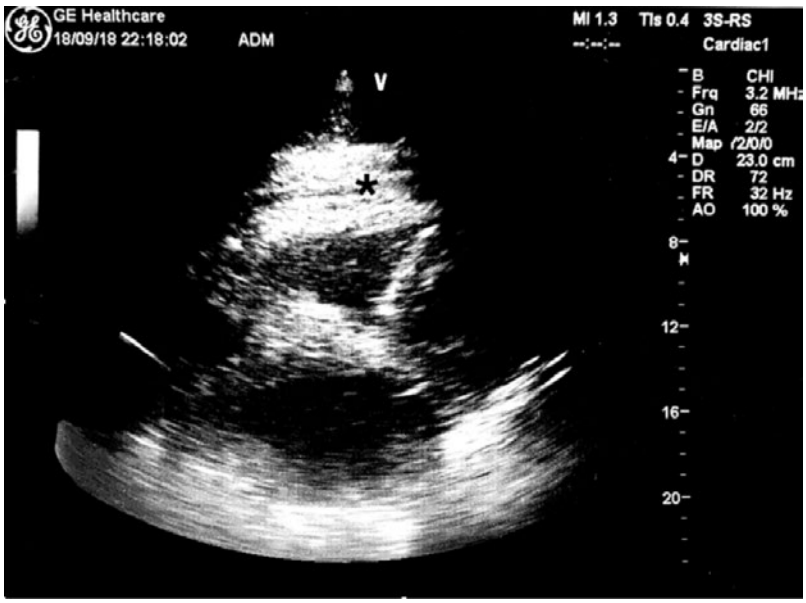
Figure 2: A thoracic angio-CT showing massive pericardial effusion.



pneumoniae, *Mycoplasma pneumoniae*, and *Legionella* antibodies; tests for specific neoplasm markers; and an autoimmune disease panel were negative. Subsequently, the echocardiogram showed a resolution of pericardial effusion with residual fibrin stratification (Figure 3).

The patient was discharged 5 days after admission. The therapy prescribed upon discharge consisted of: bisoprolol (1.25 mg), furosemide (100.00 mg), prednisone (12.50 mg), pantoprazole (20.00 mg), clarithromycin (500.00 mg), potassium canrenoate (25.00 mg), atorvastatin (20.00 mg), sertraline (50.00 mg), amiodarone (200.00 mg), dabigatran (110.00 mg twice daily), and antidiabetics, as usual. The ECG on discharge showed sinus rhythm at 70 bpm, a PR interval of 0.20 seconds, an incomplete left bundle branch block, and supraventricular premature beats. At the post-discharge 1-month follow-up, the clinical status of the patient appeared excellent, and no pericardial effusion was found in the transthoracic echocardiogram.

Figure 3: A post-pericardiocentesis echocardiogram showing a resolution of pericardial effusion with residual fibrin stratification at subcostal view.



**Site of residual fibrin stratification.*

DISCUSSION

Non-vitamin K antagonist oral anticoagulant (NOAC) therapy in patients with AF has been shown to lead to lower rates of stroke and systemic embolism compared with warfarin, as well as variable comparative rates of major bleeding.[1,2] At the admission, the patient presented with an altered coagulation status and new-onset renal failure, which might be related to various factors such as a febrile dehydration status with worsening of renal function, cardiac tamponade with obstructive shock, or peripheral hypoperfusion and acute pre-renal insufficiency causing drug accumulation and increased bleeding risk.[3] The patient was taking amiodarone, a potent P-glycoprotein inhibitor, and aspirin, which may have increased the risk of bleeding. In renal failure, bleedings are increased two-fold: the accumulation of uraemic toxins during uraemia itself can lead to bleeding episodes.[4] Moreover, renal failure contributes to increased bleeding risk because more than 80% of dabigatran etexilate is excreted via the renal pathway.[5] The detection of aPTT >90 or INR >2 in blood examination seems to be related to dabigatran overdose in several trials,[6,7] as well as in the case outlined here. This hypothetical risk was adequately considered: aspirin was withdrawn at discharge and the dabigatran dosage was reduced to 110 mg twice daily.

The side effects of NOACs are not easy to monitor. There is no laboratory test that can reliably monitor its anticoagulant effect in a similar manner to how the INR is used to monitor dicumarol drugs, or how the aPTT is used for heparin therapy.[8,9] An advantage of dabigatran compared with factor Xa inhibitors is the existence of an antidote: idarucizumab, a monoclonal antibody fragment that was approved in 2016 by the U.S. Food and Drug Administration (FDA). Idarucizumab binds to dabigatran with an affinity that is 350 times as high as that observed with thrombin, neutralising its activity within minutes.[10] In this case, the administration of idarucizumab permitted a rapid and successful pericardiocentesis after 5 minutes in the setting of haemopericardium, without clinical bleeding or other complications, and not requiring surgical intervention. To the authors' knowledge, only two cases have previously been reported to date on idarucizumab use in haemopericardium.[11,12]

The authors' recommendation for clinical practice is as follows: the use of any anticoagulant is associated with some drug–drug interactions, which may increase the risk of serious bleeding as well as diminish stroke protection.[13,14] The European Heart Rhythm Association (EHRA) recommend a structured follow-up of patients on NOACs.[15] Echo-guided pericardiocentesis is a feasible procedure for patients in therapy with dabigatran where administration of the antidote idarucizumab occurs immediately before the procedure.[16]

CONCLUSION

Percutaneous drainage is the default strategy for resolving a pericardial effusion. This case highlights the potential for dabigatran, as well as other NOACs, to cause haemorrhagic effects. However, idarucizumab presents a real advantage for patients in NOAC therapy as it reduces the potential haemorrhagic risk of dabigatran and permits urgent surgical procedures to take place, allowing for better results and fewer complications.

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Silent Myocardial Infarction in Hypereosinophilic Syndrome Overlapped with JAK2-Mediated Essential Thrombocytosis: A Case Report

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Abstract

A 61-year-old male with chronic cough, paraesthesia of the extremities, and sinusitis presented for acute worsening of symptoms despite initial treatment with antibiotics and prednisone. Emergency department evaluation revealed mild elevated troponin without ECG changes in absence of coronary symptoms, but markedly elevated eosinophil count and an abnormal chest CT. A nuclear stress test revealed basal and inferoseptal dyskinesis with fixed apical defect. Left heart catheterisation revealed multiple coronary stenosis requiring intervention. Further extensive work-up confirmed a diagnosis of hypereosinophilic syndrome complicated with respiratory, cardiac, gastroenterological, and neurological involvement. The patient was initially treated with a high dose of intravenous steroid and hydroxyurea. Flow cytometry revealed negative *FIP1L1-PDGFRA* gene rearrangement, but was positive for *JAK2* V617F mutation and perinuclear antineutrophil cytoplasmic antibodies/cytoplasmic antineutrophil cytoplasmic antibodies, indicating possible overlap of eosinophilic granulomatosis with polyangiitis.

Key Points

1. Hypereosinophilic syndrome (HES) describes a large group of disorders characterised by overproduction of eosinophils that typically infiltrate and cause damage to major organs. Only a few articles report HES in association with *JAK2* V617F mutation, and typically this is in conjunction with chronic myeloproliferative neoplasm.

2. This unique case of HES with *JAK2* V617F mutation illustrates that HES, when combined with either essential thrombocytosis or other hypercoagulable states, can lead to multi-organ involvement, including coronary artery thrombosis and stenosis.

3. Routine screening ECGs are recommended in patients with HES for evidence of acute thrombosis formation in the absence of acute cardiac symptoms. With essential thrombocytosis, antiplatelet therapy and, in more severe cases, anticoagulation therapy could be beneficial for acute coronary disease prevention; further meta-analysis is necessary for understanding clinical outcomes.

INTRODUCTION

Hypereosinophilic syndrome (HES) refers to a large group of disorders characterised by overproduction of eosinophils that typically infiltrate and cause damage to major organs. HES can be subclassified by the mechanism that leads to eosinophilic elevation. Primary HES typically occurs in the setting of a neoplastic or myeloproliferative disorder. Secondary HES is reactive and polyclonal, typically lymphocytic. Idiopathic and specific syndromes can additionally be associated with HES, such as eosinophilic granulomatosis with polyangiitis.[1] In neoplastic or myeloproliferative disorders, the most common molecular mutations are tyrosine kinase fusion genes with involvement of PDGFRA, such as FIP1L1-PDGFRA fusion. Point mutations such as JAK2 V617F constitute a relatively small proportion of HES, and are typically associated with the subtype of myeloproliferative HES.[2]

Cardiac involvement of HES is not very common as the disease itself is rare. Ogbogu et al.[3] described the staged damage of myocardium based on the chronicity of disease. Ogbogu et al.[3] observed acute myocardial necrosis within a mean time of 5.5 weeks from initial diagnosis, whereas thrombus formation was noted within 10 months and fibrosis at the 24.5 month mark.[4,5] Cardiomyopathy is theorised to be secondary to ventricular vascular damage, but subvalvular involvement has also been reported. Echocardiogram, cardiac MRI, and endomyocardial biopsy remains the mainstay of diagnosis, and treatments are usually disease-directed conventional therapy. This manuscript reports a unique case of HES in addition to JAK2 V617F-mediated essential thrombocytosis with multi-organ involvement. Most importantly, the authors report a case of myocardial infarction in the absence of acute cardiac symptoms.

CASE PRESENTATION

A 61-year-old White male presented to the emergency department complaining of chronic cough. The patient stated that the cough had begun 5 months prior and that they had been intermittently placed on azithromycin and prednisone, with the most recent course ending 1.5 weeks prior to their presentation. The patient endorsed a productive cough with white sputum, night sweats, a 5 lb weight loss, and decreased appetite over the course of the previous week. They also noted fatigue and bilateral upper and lower extremity ('glove-and-stocking') paraesthesia in the previous few days. The patient denied chest pain or shortness of breath with no fevers or chills. The patient was tested for COVID-19 a few days before their visit to the emergency department, for which they presented a negative result.

Pertinent medical history included asthma and an unprovoked deep vein thrombosis in 2019. Social history showed significant tobacco use for 5 years, with the patient quitting 10+ years ago.

Upon arrival to the emergency department, the following vitals were obtained: blood pressure of 138/87; pulse of 83 beats per minute; temperature of 36.6 °C; respiratory rate of 20 breaths per minute; and oxygen saturation of 94%. A physical exam was significant for subjective paraesthesia in hands and legs bilaterally upon neurological testing, but the remaining examination was otherwise benign. Initial lab testing included a complete blood count, which was significant for the following: white blood cell count of 25.5; platelet count of 523; absolute eosinophil count of 9.4; erythrocyte sedimentation rate elevated at 46; and troponin of 0.790. Initial diagnostic testing included ECG interpreted as sinus rhythm with a rate of 85 beats per minute, and no evidence of acute infarct. CT angiogram of the chest demonstrated patent pulmonary arteries with no central filling defect, subtle 'tree-in-bud'

opacities, mild peribronchial thickening in both lung bases, and hilar lymphadenopathy. CT angiogram additionally demonstrated a small right-sided pleural effusion.

Initial differential diagnoses included atypical pneumonia, vasculitis, pneumoconiosis, allergies, fungal and parasite infection, collagen vascular disease, HES, and potential drug side-effects.

Upon further questioning, the patient reported a chronic intermittent cough for the past 2 years, with a chronic history of sinusitis. They also noted owning a bird feeder that they changed regularly, and further stated that they had been planting trees in the fields behind their house for the past couple of weeks. Lastly, they reported new-onset dysphagia to food and wheezing. The patient was heterosexually monogamous with their wife.

It was decided to consult infectious diseases, pulmonology, and cardiology. Due to the patient's CT angiogram and previous lab results, HIV labs, antinuclear antibody, and an Ig panel were drawn, all of which were within normal limits. Folate and B12 levels in relation to the new-onset stocking-glove paraesthesia were insignificant. Due to the patient's elevated troponin levels, a heparin drip was ordered, while maximum troponin (1.7) was continuously monitored with serial ECG. An inflammatory panel revealed elevated C-reactive protein as well as a total creatine kinase of 626.

Pulmonology evaluated the patient and recommended a fungal/parasite panel, which was negative. Blood cultures showed no growth over 48 hours.

Cardiology believed the presentation could possibly be attributed to viral myocarditis and ordered the following panels: cytomegalovirus, Epstein–Barr virus, Coxsackie B, hepatitis C, parvovirus, and mycoplasma. All showed levels that were within normal limits. Cardiac lipid profile was additionally insignificant (Table 1). An echocardiogram without contrast was performed and showed no focal wall motion abnormalities; estimated ejection fraction of 55%; normal right ventricular size and function; and no left ventricular thrombus. Nuclear stress imaging demonstrated a reduced left ventricular ejection fraction of 44% with a fixed defect in the apical wall and dyskinesis of the basal inferoseptal segment (Supplementary Figure 1). At this point, the patient continued to deny experiencing any chest pain. Following the abnormal stress test, a left heart catheterisation with selective coronary angiography was performed that revealed mildly reduced left ventricular systolic function with ejection fraction of 45%. A moderate coronary atherosclerosis of 50% in the posterior lateral branch was identified. Upon second review of the study by a different cardiologist, it was deemed that the patient's posterior coronary artery was potentially severe rather than moderate, and a repeated left heart catheterisation was planned. The patient remained free of chest pain and haemodynamically stable. On Day 4, a second coronary angiography with contrast showed that the mid-left anterior descending vessel had a focal stenosis of 80%, with evidence of post-stenotic dilation. Instantaneous wave-free ratio was performed for functional testing and resulted in an abnormal value of 0.74, indicating ischaemia. Therefore, a drug-eluting stent was placed in the mid-left anterior descending vessel. The posterior left ventricular branch appeared to show moderate-to-severe stenosis up to 70%, but presented as normal on instantaneous waveform ratio, and was left for medical therapy (Supplementary Figure 2).

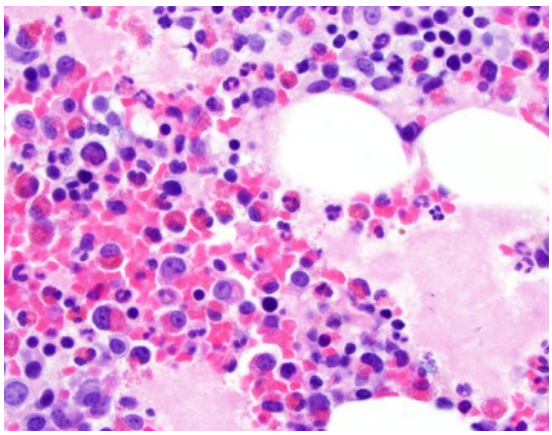
Despite elevated eosinophil levels, as the fungal, parasite, and viral panels were negative, and the patient also exhibited extensive cardiopulmonary involvement, perinuclear antineutrophil cytoplasmic antibodies and cytoplasmic antineutrophil cytoplasmic antibodies were additionally obtained. These showed elevated titres of 1:320 with a positive myeloperoxidase antibody index. Eosinophil levels continued to increase from 9.4 K/µL at admission to 11.1 K/µL on Day 3. Haematology and oncology were consulted as the combination of symptoms presented were concerning for potential HES. BCR-ABL1 and FIP1L1-PDGFRA, as well as flow cytometry of the patient's peripheral blood smear, were further obtained. Figure 1 illustrates blood smear findings that revealed leukocytosis reflecting marked eosinophilia (absolute eosinophil count approximately 11,000/µL), but no features suggestive of acute leukaemia. Fluorescence in situ hybridisation was negative for BCR-ABL and FIP1L1-PDGFRA. JAK2 testing was added due to the patient's platelet count, which continued to trend upward from admission,

Table 1: Summary of pertinent diagnostic test for new diagnosis of hypereosinophilic syndrome and essential thrombocytosis.

Diagnostic test	Result
Erythrocyte sedimentation rate	46 mm/hour
ANA, DsDNA, Rh factor	Negative
Total IgA	264 mg/dL
Total IgG	1,481 mg/dL
Total IgM	116 mg/dL
Total IgE	74.5 kU/L
Stool ova and parasite	Negative
Fungal studies	None detected
Arterial pH	7.43
Creatinine	0.969 mg/dL
Serum albumin	3.5 g/dL
Liver enzymes	AST: 35 U/L ALT: 27 U/L
Alkaline phosphatase	112 U/L
Troponin	0.790 ng/mL
Brain natriuretic peptide	94.3 pg/mL
Folate	11.43 ng/mL
Thyroid-stimulating hormone	1.933 uIU/mL
International normalised ratio	1.2
Vitamin B12	383 pg/mL
Free κ chain	3.33 mg/dL
Free λ chain	2.04 mg/dL
Complement 3	138.9 mg/dL
Urine protein electrophoresis	Small albumin band
Lipid profile	HDL: 30 mg/dL LDL: 102 mg/dL
Fluorescence in situ hybridisation	No evidence for the FIB1L1-PDGFRA gene fusion, or rearrangements of PDGFRA, PDGFRB, FGFR1, or JAK2 genes
Bone marrow biopsy	Peripheral blood or bone marrow features suggestive of chronic myeloid leukaemia, BCR-ABL1+ are not noted in the current specimens, nor are abnormal mast cell infiltrates

ANA: antinuclear antibody; ALT: alanine transaminase; AST: aspartate transaminase; DsDNA: double-stranded DNA antibody; HDL: high-density lipoprotein; LDL: low-density lipoprotein; Rh: rheumatoid.

Figure 1: Core biopsy confirming infiltration of eosinophils in the bone marrow correlated with peripheral finding of eosinophilia.



and was found to be positive for JAK2 V617F mutation. A bone marrow biopsy was obtained, which showed modest hypercellular marrow, as well as increased maturing eosinophils and mature granulocytes. Serum protein electrophoresis was remarkable for a polyclonal increase in IgG4. Urine protein plasmapheresis was negative for Bence Jones proteins.

Varas-Lorenzo et al.[6] demonstrated that use of oral corticosteroid therapy of more than 10 mg/day for 30 days increases risk of acute myocardial infarction. Since immunosuppressive benefits of steroids in the setting of acute hypereosinophilic syndrome outweighs relative increased risk of myocardial infarction, the patient was started on intravenous Solu-Medrol (Pfizer Inc., New York City, New York, USA) 125 mg daily. The patient subsequently reported feeling symptomatically better after starting steroids and showed mildly improved eosinophilia levels.

Following this, the patient was officially diagnosed with hypereosinophilia of unknown aetiology with plans to be discharged on Day 5 of admission, with prescription for prednisone 60 mg daily and an outpatient follow-up referral with haematology and oncology. The patient was also diagnosed with acute myocardial infarction and cardiac findings were suspected to be secondary to myocarditis with hypereosinophilia. The patient was started on dual antiplatelet therapy with aspirin and prasugrel, as well as a statin, angiotensin-converting enzyme inhibitor, and β-blocker.

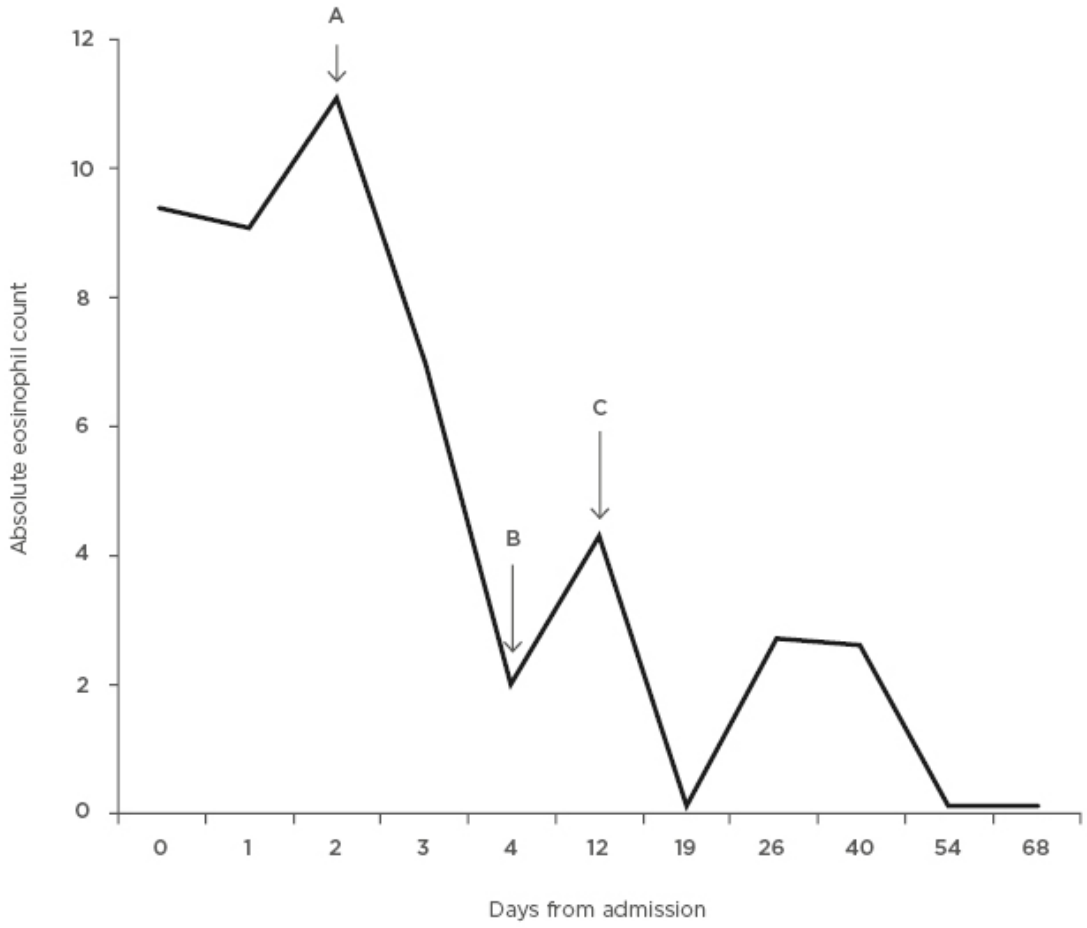
On follow-up with haematology and oncology, it was suspected that the patient had an overlap with hypereosinophilic syndrome, as well as JAK2+ essential thrombocytosis after examination of the patient's lab work. Figure 2 demonstrates the course of eosinophil response with immunosuppression therapy over time. The patient's initial complaints of cough, dysphagia, and generalised fatigue were resolved shortly with treatment. Initiation of hydroxyurea maintained long-term suppression, and no further eosinophilia or deteriorating symptoms were noted over the course of 12 months.

The patient additionally visited rheumatology, who were unable to perform a biopsy to assess eosinophilic granulomatosis with polyangiitis as the patient recently received high-dose steroids. Based on the lab findings and clinical involvement of the heart and other organs, the patient is currently being evaluated for possible monthly intravenous cyclophosphamide infusion instead of hydroxyurea in combination with steroids.

DISCUSSION

HES is a group of disorders with markedly elevated eosinophils as well as tissue infiltration. It is defined as a persistent absolute eosinophil count >1,500 cells/μL in peripheral blood on at least two examinations with the presence of eosinophil-mediated organ damage.[7] There are a variety of clinical variants of HES categorised by their causes: myeloproliferative, lymphocytic-

Figure 2: Absolute eosinophilic count trended with time and response to therapy.



Initiation of immunosuppression with steroid therapy significantly suppresses eosinophil count and improves clinical symptoms. Addition of hydroxyurea maintains long term suppression. **A)** Intravenous Solu-Medrol (Pfizer Inc., New York City, New York, USA) 125 mg started. **B)** Discharged from hospital (on prednisone 60 mg). **C)** Prednisone increased to 80 mg and hydroxyurea 500 mg daily added.

associated HES, familial, idiopathic, and specific syndromes associated with HE (overlap HES).[8] Based on previous studies and reports, venous thrombosis is a well-known complication.[7,8] It is interesting that many of these studies report venous thrombosis in regards to Budd–Chiari manifestation,[7] whereas this patient's possible major manifestation was in an unprovoked deep vein thrombosis 1 year prior.

Only a few articles report HES in association with JAK2 V617F mutation, and typically this is in conjunction with chronic myeloproliferative neoplasm.[7,9] Furthermore, it was found that in documented cases with positive JAK2 V617F and a normal karyotype lacking FIP1L1-PDGFRA, patients were more resistant to standard treatment with steroids and hydroxyurea.[9] Interestingly, this patient seemed to improve with these therapies. Peripheral neuropathy accounts for a majority of the neurologic manifestations of HES; however, the pathophysiology remains largely unexplained and should be further investigated.[10]

With multi-organ infiltration, it is well known that elevated eosinophils can cause damage to the heart, and eosinophilic myocarditis is a major cause of morbidity and mortality among patients. Loeffler's endocarditis is another

manifestation of HES, described as eosinophil degranulation causing specific toxic effects of cationic protein on the plasma membrane leading to endomyocardial disease.[11] Echocardiogram and CT imaging are initially performed to assess for left or right ventricular apical obliteration or thrombi formation, as well as evidence of restrictive cardiomyopathy. Endomyocardial biopsy remains the gold standard to diagnose Loeffler's endocarditis.[12] Interestingly, no apical obliteration, left ventricular thrombus, or clinical manifestation of restrictive cardiomyopathy were noted in this patient. Retrospectively, echocardiogram with contrast, and/or cardiac MRI with possible, if indicated, endomyocardial biopsy should have been performed to rule out atypical Loeffler's endocarditis or endomyocardial fibrosis. Further, an intracoronary imaging would have been beneficial to characterise the morphology of atherosclerotic plaques, erosion, or rupture.

In relation to multivessel coronary stenosis during eosinophilic crisis, the aetiology of sudden myocardial infarction remains unknown. Due to their advanced age, gender, mild dyslipidaemia, and smoking history, this patient is susceptible to above-average cardiovascular risk for plaque rupture. However, their troponin elevation during eosinophilic crisis raises the question as to whether coronary stenosis was acute precipitation of exaggerated plaque rupture and thrombosis due to hypercoagulable state from HES, or essential thrombocytosis, or a combination of both. Individually, it is hypothesised that toxicity from excessive eosinophils and the clotting cascade activation is one of the mechanisms of myocardial injury in HES. In the presence of JAK2 V617F, the plethora of platelets perhaps further propagates thrombosis formation at a much faster rate than either disease separately. If thrombosis is the aetiology, this can explain why acute myocardial infarction and stenosis precipitated shortly after the onset of eosinophilic syndrome. In addition to acute thrombus formation, myocarditis, endomyocardial fibrosis, and atypical Loeffler's endocarditis need to be considered in differential diagnosis. Further basic science research in vivo models can decipher signalling pathways, and likely identify key players to target for hypercoagulable state in this overlapping syndrome.

In summary, this case report describes a variant of overlapping HES with JAK2 V617F mutation presenting with asymptomatic myocardial injury, peripheral neuropathy, eosinophilic oesophagitis, pulmonary symptoms, and remote deep vein thrombosis with adequate response to corticosteroid therapy and hydroxyurea. This case illustrates HES, when combined with either essential thrombocytosis or other hypercoagulable states, lead to multiple organ involvement, especially coronary artery stenosis due to potential thrombosis. Appropriately treated patients are at increased risk for opportunistic infection and immunological complications. Table 1 summarises an extensive list of workups for new diagnosis of HES, and the respective results. Therefore, it is recommended to check ECGs routinely to screen for acute thrombosis formation in absence of myocardial injury, pericardial injury, and valvular involvement, and shows necessity to optimise modifiable cardiac disease risk factors in patients with HES despite age, gender, and ethnicity. When presented in the emergency department, regardless of cardiac symptoms, ECG and cardiac enzymes should be checked with high suspicion for myocardial infarction secondary to acute thrombosis and accelerated plaque rupture. If admitted to hospital, an echocardiogram should be performed, checking for subvalvular involvement, new wall motion abnormalities, and fibrosis evaluation. Follow-up during discharge should be monitored closely with cardiology, haematology, and rheumatology. With essential thrombocytosis, antiplatelet therapy, and, in more severe cases, anticoagulation therapy would be beneficial for acute coronary disease prevention. Further meta-analysis is necessary for understanding clinical outcomes.

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Undiagnosed Hidradenitis Suppurativa Associated with Acute Myocardial Infarction: A Case Report

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Abstract

Hidradenitis suppurativa (HS) is a chronic inflammatory disease believed to be a risk factor for cardiovascular events. Traditional cardiovascular risk factors, such as metabolic syndrome, often coexist with HS. Chronic inflammatory conditions may underlie cardiovascular events in young patients or those with few traditional risk factors. A 34-year-old female was admitted to the authors' tertiary care hospital with acute anterior ST-segment elevation myocardial infarction, and underwent a successful primary percutaneous coronary intervention to their left anterior descending artery. They were a smoker, had a high BMI, and had a positive family history of premature coronary artery disease. During their admission, the patient disclosed that they had discharging lesions under their left breast. The patient had a long-standing history of multiple discharging lesions alternating with disfiguring scars that had started in their late childhood; however, despite this leading to self-dissatisfaction, they did not seek medical advice.

Examination revealed plaques and scarring in both axillae and a chronic abscess under the left breast, the swabs from which were sterile, as is consistent with HS. The laboratory results showed a raised troponin and white cell count with mildly elevated levels of C-reactive protein. The patient was managed with standard acute coronary syndrome treatment and a course of oral doxycycline, and awaits further treatment by dermatology and plastic surgery. The morbidity of HS is grossly underestimated. This case study highlights that HS has significant cardiovascular implications, in addition to psychological impacts, and that underlying systemic inflammation may promote rapid atherosclerosis. Further research into pathogenesis and strategies to prevent adverse cardiovascular events are needed.

Key Points

1. Hidradenitis suppurativa (HS) is a chronic inflammatory skin condition that leads to development of abscesses, sinus tracts, and scars. It primarily affects young African American females and Asian males.

2. The chronic skin inflammation secondary to HS may lead to systemic and vascular inflammation and endothelial dysfunction, which can precipitate thrombus development, atherosclerosis, and plaque build-up. As a result, HS can increase risk of major adverse cardiovascular events (e.g., myocardial infarction) in young people.

3. Patients with HS should receive early and regular cardiovascular risk factor screening and clinicians should exercise a high index of suspicion for cardiovascular events in young patients presenting with cardiac symptoms.

INTRODUCTION

Hidradenitis suppurativa (HS) is a chronic inflammatory disease involving the pilosebaceous unit of the skin. It is characterised by abscesses, the development of sinus tracts, and scarring, and primarily affects the axillary, perineal, and inframammary regions.[1] The reported prevalence of HS varies from 0.03% to 4.00%, depending on geographical location.[2] HS disproportionately affects young female African Americans and male Asians.[2]

Coronary artery disease is the leading cause of death worldwide. Myocardial infarction still has a 20% mortality rate, and together with stroke contributes a significant morbidity and health cost burden.[3] Risk factor reduction has led to a reduction in the incidence of adverse cardiovascular events and associated mortality over the past 25 years.[3] Recognising the interaction of traditional risk factors with systemic inflammation in the pathogenesis of atherosclerosis is important. Cardiovascular risk factors, including obesity, metabolic syndrome, diabetes, and smoking, are prevalent in patients with HS.[1,4,5] The odds ratio of patients with HS having metabolic syndrome and central obesity is approximately 2.[4,5] Obesity causes intertriginous surface friction and increased sweat production, which are also associated with HS.[6] It is believed that nicotine may also cause increased follicular plugging; however, HS may start long before smoking.[6] Insulin resistance, relative androgen excess, and excess inflammatory markers are linked with both metabolic syndrome and HS.[6,7]

CASE PRESENTATION

A 34-year-old Black female of African descent presented to the emergency department after experiencing severe central chest pain with sweating and nausea for 2 hours. She had risk factors such as smoking, obesity, and a positive family history of premature ischaemic heart disease. An ECG showed ST-segment elevation in anterolateral chest leads and inferior limb leads (Figure 1). The patient was taken to the catheterisation lab with the intent of performing primary percutaneous coronary intervention. An emergency coronary angiogram showed a 99% occlusive thrombotic lesion in the mid-left anterior descending artery, with thrombolysis in myocardial infarction (TIMI) Grade II flow and minor plaque in right coronary artery (Figure 2). Coronary angioplasty was performed with successful restoration of TIMI Grade III epicardial flow and good myocardial blush, and ST-segment resolution was achieved.

On return to the coronary care unit, she complained of pain under her left breast, and examination revealed a discharging lesion there. On further inquiry, she declared similar lesions in both axillae for several months. She had a long history of these lesions involving her buttocks and later her armpits, which healed with unsightly scars. The location of the lesions kept her from seeking medical attention, despite causing emotional distress and self-dissatisfaction. On examination, there was a discharging abscess under the left breast and a partially healed sub-centimetric pustule under

Figure 1: An ECG presentation showing ST-segment elevation in anterolateral and inferior leads.

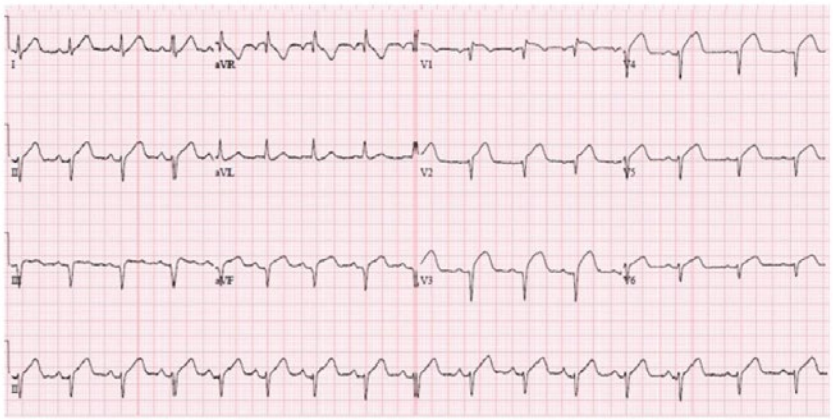


Figure 2: An angiogram from the right anterior oblique cranial projection showing a thrombotic occlusion (arrow) in the left anterior descending artery with reduced thrombolysis in myocardial infarction flow.

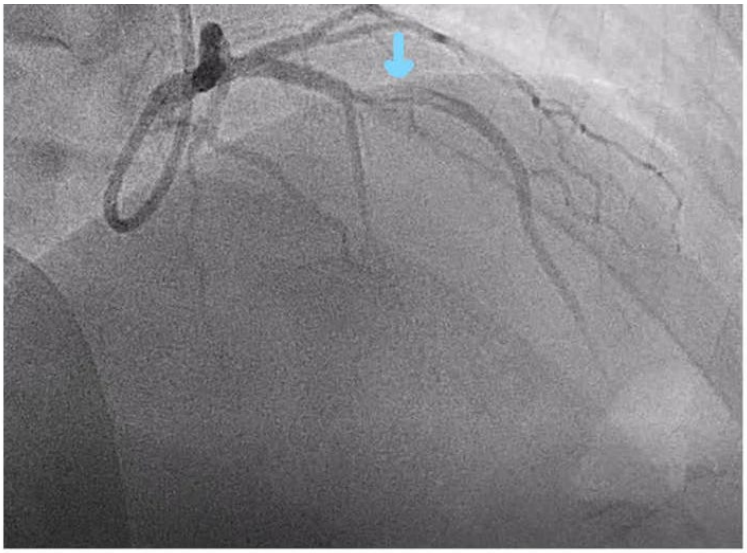
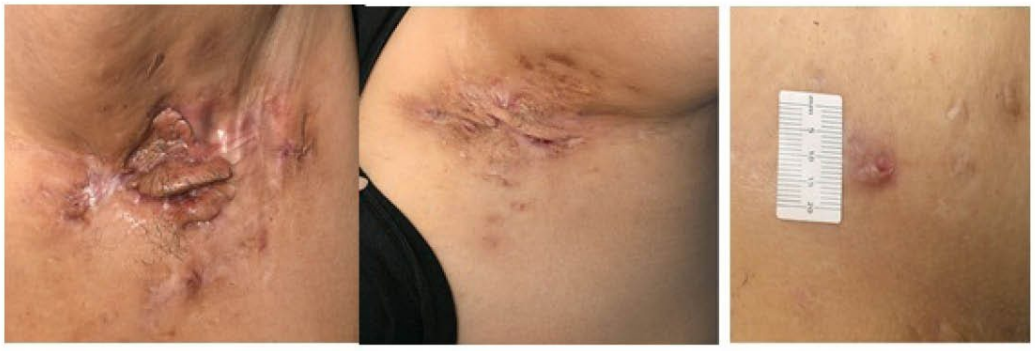


Figure 3: Chronic abscesses with tract formation and scarring lesions in both axillae (left and middle), and a small, deep abscess in the inframammary region (right).



the right breast (Figure 3). Additionally, there were scars, plaques, and sinus formation under the armpits (Figure 3). There were no signs of systemic infection, drug abuse, or diffuse skin or mucosal involvement. Swabs taken from the draining pustule did not show any bacterial growth. The opinion of dermatologists was then taken and the patient was formally diagnosed with Stage II HS.

A transthoracic echocardiogram revealed moderate left ventricular systolic impairment with regional wall motion abnormalities in the left anterior descending artery territory. The laboratory results showed a raised troponin level (9,196 ng/L), a raised white cell count of 18×10^9 /L with neutrophilia, an elevated platelet count of 817×10^9 /L, and an elevated high-sensitivity C-reactive protein level of 15 mg/L (normal range: 0–4 mg/L). The neutrophil-to-lymphocyte ratio was 3.9, the neutrophil-to-high-density lipoprotein (HDL) cholesterol ratio was 15.6, and the platelet-to-lymphocyte ratio was 227, all of which were suggestive of inflammation. The lipid profile was abnormal, with total cholesterol of 5.5 mmol/L, non-HDL cholesterol of 4.6 mmol/L, and HDL cholesterol of 0.9 mmol/L. The patient fulfilled the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) criteria for metabolic syndrome. She was managed using guideline-directed treatment, counselled for smoking cessation and weight loss, and provided with psychological support and cardiac rehabilitation. A course of oral doxycycline was prescribed by dermatologists and a follow-up was planned for the consideration of more advanced medication as needed. She was referred to plastic surgeons for possible future excision and reconstruction once active inflammation had subsided.

DISCUSSION

HS is associated with an increased risk of major adverse cardiovascular events (MACE) and related mortality.[1,4] There is a 23% increase in risk of myocardial infarction or stroke in patients with HS, which is independent and incremental of the risk from traditional cardiovascular risk factors.[1] The MACE risk is higher in younger patients with HS, and HS has also been shown to impose a higher cardiovascular risk compared with severe psoriasis.[1,4]

The inflammatory basis of HS is evidenced by the presence of inflammatory cytokines in the lesions.[6] Chronic skin inflammation in HS may be associated with systemic inflammation, as shown by elevated C-reactive protein, reactive thrombocytosis, and an increased neutrophil-to-lymphocyte ratio.[1] These inflammatory markers are related to the severity and activity of HS.[6] The accompanied vascular inflammation predisposes the body to oxidative stress, endothelial dysfunction, and thrombus formation, thus promoting the chronic progression of atherosclerosis and acute plaque change.[1,7] The most common cause of ST-segment elevation myocardial infarction is plaque rupture, and the pro-inflammatory states also increase the vulnerability of plaque to rupture.[1,8] Elevated levels of circulating inflammatory markers are associated with atherosclerosis.[1,8,9] Other inflammatory skin or systemic diseases have been independently associated with cardiovascular adverse events. As a result, inflammation appears to be paramount to the pathogenesis of HS and associated cardiovascular events. Emerging treatments targeting specific inflammatory mediators may therefore be important.[8]

The cardiovascular consequences of HS warrant taking specific steps in order to mitigate these events. Firstly, patients with HS should be informed of their increased risk of MACE, screened at an earlier stage for cardiovascular risk factors, and counselled for risk factor modification, including smoking cessation and weight loss. Secondly, a low threshold should be kept for investigating young patients with HS presenting with cardiac symptoms. Thirdly, many patients with HS suffer as a result of a considerable diagnostic delay, and increased awareness about the morbidity of HS may promote an earlier approach of patients to healthcare and an increased vigilance for diagnosis.

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