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with COPD
about their
mornings?



MANY PATIENTS FEEL
COPD SUCKS THE BREATH
OUT OF THEIR MORNINGS.^{1,3}

➤ Seebri® Breezhaler® is indicated as a once-daily maintenance bronchodilator treatment to relieve symptoms in adult patients with COPD.

Model is for illustrative purposes only.

INTRODUCING
ONCE-DAILY **SEEBRI BREEZHALER**
AN INHALED ANTICHOLINERGIC FOR PATIENTS WITH COPD.¹



Seebri Breezhaler 44 micrograms inhalation powder, hard capsules

▼ This medicinal product is subject to additional monitoring to allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. Refer to section 4.8 of the SmPC for how to report adverse reactions.

PRESENTATION:

Each capsule contains 63 micrograms of glycopyrronium bromide equivalent to 50 micrograms of glycopyrronium. The delivered dose (the dose that leaves the mouthpiece of the inhaler) is equivalent to 44 micrograms of glycopyrronium.

INDICATIONS: Indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD).

DOSAGE: The recommended dose is the inhalation of the content of one capsule once daily. Seebri Breezhaler is recommended to be administered, at the same time of the day each day. If a dose is missed, the next dose should be taken as soon as possible. Patients should be instructed not to take more than one dose in a day.

CONTRAINDICATIONS: ♦ Hypersensitivity to the active substance or to any of the excipients.

WARNINGS/PRECAUTIONS: ♦ Seebri Breezhaler is not indicated for the initial treatment of acute episodes of bronchospasm. ♦ Paradoxical bronchospasm has been observed with other inhalation therapy and can be life threatening. If this occurs, Seebri Breezhaler should be discontinued immediately and alternative therapy instituted. ♦ Caution in patients with narrow angle glaucoma or urinary retention. Patients should be informed about the signs and symptoms of acute narrow angle glaucoma and should be informed to stop using Seebri Breezhaler and to contact their doctor immediately should any of these signs or symptoms develop. ♦ In patients with severe renal impairment including those with end stage renal disease requiring dialysis, Seebri Breezhaler should be used only if the expected benefit outweighs the potential risk. ♦ Seebri Breezhaler should be used with caution in patients with a history of cardiovascular disease. ♦ Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine. ♦ There are no data from the use of Seebri Breezhaler in pregnant women. Glycopyrronium should only be used during pregnancy if the expected benefit to the patient justifies the potential risk to the foetus. ♦ The use of glycopyrronium by breast feeding women should only be considered if the expected benefit to the woman is greater than any possible risk to the infant. ♦ Glycopyrronium has no or negligible influence on the ability to drive and use machines.

INTERACTIONS: ♦ The co-administration of Seebri Breezhaler with other anticholinergic containing medicinal products has not been studied and is therefore not recommended. ♦ No clinically relevant drug interaction is expected when glycopyrronium is co-administered with cimetidine or other inhibitors of organic cation transport.

ADVERSE REACTIONS: ♦ Common (≥1/100 to <1/10): Nasopharyngitis, insomnia, headache, dry mouth, gastroenteritis, urinary tract infection. ♦ Uncommon (≥1/1,000 to <1/100): Rhinitis, cystitis, hyperglycaemia, hypoaesthesia, atrial fibrillation, palpitations, sinus congestion, productive cough, throat irritation, epistaxis, dyspepsia, dental caries, rash, pain in extremity, musculoskeletal chest pain, dysuria, urinary retention, fatigue, asthenia, hypersensitivity, angioedema

LEGAL CATEGORY: POM

PACK SIZES: Single pack containing 30x1 hard capsules, together with one inhaler.

MARKETING AUTHORISATION HOLDER: Novartis Europharm Limited, Wimblehurst Road, Horsham, West Sussex, RH12 5AB, United Kingdom.

MARKETING AUTHORISATION NUMBER:

Seebri Breezhaler 44 micrograms inhalation powder, hard capsules - EU/17/12/788/001-006

Please refer to Summary of Product Characteristics (SmPC) before prescribing. Full prescribing information is available on request from Novartis Pharma Services Inc., Representative Office Malta, P.O. Box 4, Marsa, MRS 1000, Malta. Tel: +356 21222872 2014-MT-SBR-1-JUL-2014

For information on Seebri Breezhaler dose expression, please refer to full prescribing information.

References: 1. Partridge MR, Karlsson N, Small IR. Patient insight into the impact of chronic obstructive pulmonary disease in the morning: an internet survey [published correction appears in Curr Med Res Opin, 2012;28(8):1405]. Curr Med Res Opin. 2009;25(8):2043-2048. 2. Barnett M. Chronic obstructive pulmonary disease: a phenomenological study of patients' experiences. J Clin Nurs. 2005;14(7):805-812. 3. Kessler R, Partridge MR, Miravittles M, et al. Symptom variability in patients with severe COPD: a pan-European cross-sectional study. Eur Respir J. 2011;37(2):264-272. 4. Novartis Europharm Ltd, Seebri® Breezhaler® Summary of Product Characteristics.

Please see SPC for full prescribing information.

NOVARTIS

Once Daily
seebri
breezhaler
glycopyrronium bromide inhalation powder



A TRIBUTE TO STEVEN SPIELBERG

Do you remember the *Minority Report*? This science fiction has been penned in 1956 by Philip Dick and adapted to the silver screen in 2002 by Steven Spielberg. The main actor was Tom Cruise. It tells the story of a future society where murders are prevented through the efforts of three mutants who can see the future. Closer to us, if you have seen *G.I. Joe: Retaliation* (2013), starring Dwayne Johnson and Bruce Willis, do you remember the scenes which depict camera-carrying flies (which could also explode)?

Notwithstanding the fact that most of us consider such film excerpts as pure science fiction, the Department of Homeland Security (US) has developed the **Future Attribute Screening Technology** (FAST) programme. Its primary aim is to detect crimes in sensitive areas, example, airports, by screening people for “psychological and physiological indicators” including heart rate, skin temperature, breathing, facial expression, body movement, pupil dilation, and other “psychophysiological/behavioral patterns” to stop “unknown terrorists”.

Indeed, security has made great advances. The development of **Hybrid Insect Micro-Electro-Mechanical Systems** (HI-MEMS) is a project of the US Department of Defense. The primary goal is to developing machine-insect interfaces by placing micro-mechanical systems inside the insects during the early stages of metamorphosis in order to exert control over the insect’s locomotion. The reason why the electronic system is attached during the early stage of metamorphosis is that the majority of tissue development in insects occurs in the

later stages of metamorphosis. Thus the renewed tissue growth around the MEMS will tend to heal and form a reliable and stable tissue-machine interface.

Skipping to the medical field, the FDA has recently given the green light to a piece of technology, which until a couple of years ago, similarly to the above technologies, was expected to hail from a *Star Trek* episode. FDA has approved the Proteus Digital Health’s new chip-embedded capsules which can report back to a sensor and your smartphone when medications have been ingested. The tiny silicon-based chips are no larger than a grain of sand. When swallowed and exposed to digestive juices, those materials produce a slight voltage which can be detected by a special skin patch and relayed to a smartphone. It not only serves as a fool-proof reminder as to if and when you’ve taken the medication, but it also allows healthcare providers to know for sure if medication has been taken by a patient who has trouble caring for themselves. Indeed, Proteus Digital Health has partnered with NHS England and the UK Trade & Investment (UKTI) to investigate further whether its ingestible sensors - taken with medications - monitor more effectively whether NHS patients follow their medicines regime.

Wishing you a peaceful Christmas & health and happiness (and reason to appreciate both) in the forthcoming year. ❄️

Pan Ellul



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NEW
The First Once-Daily
Dual Bronchodilator¹

THE FIRST ONCE-DAILY DUAL BRONCHODILATOR¹

ULTIBRO[®] BREEZHALER[®]

START A NEW CHAPTER IN COPD²⁻⁴

Once-daily ULTIBRO BREEZHALER is indicated as maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD).¹

Ultibro Breezhaler Inhalation powder, hard capsules

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. Refer to section 4.8 of the SmPC for how to report adverse reactions. **PRESENTATION:** Each capsule contains 143 µg of indacaterol maleate equivalent to 110 µg of indacaterol and 63 µg of glycopyrronium bromide equivalent to 50 µg of glycopyrronium. Each delivered dose (the dose that leaves the mouthpiece of the Inhaler) contains 110 µg of indacaterol maleate equivalent to 85 µg of indacaterol and 54 µg of glycopyrronium bromide equivalent to 43 µg of glycopyrronium. **INDICATIONS:** Ultibro Breezhaler is indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD). **DOSAGE AND ADMINISTRATION:** The recommended dose is the inhalation of the content of one capsule once daily using the Ultibro Breezhaler inhaler. Ultibro Breezhaler is recommended to be administered at the same time of the day each day. If a dose is missed, it should be taken as soon as possible on the same day. Patients should be instructed not to take more than one dose in a day. Ultibro Breezhaler can be used at the recommended dose in elderly patients (75 years of age and older). Ultibro Breezhaler can be used at the recommended dose in patients with mild to moderate renal impairment. In patients with severe renal impairment or end-stage renal disease requiring dialysis it should be used only if the expected benefit outweighs the potential risk. Ultibro Breezhaler can be used at the recommended dose in patients with mild and moderate hepatic impairment. There are no data available for the use of Ultibro Breezhaler in patients with severe hepatic impairment, therefore caution should be observed in these patients. There is no relevant use of Ultibro Breezhaler in the paediatric population (under 18 years) in the indication COPD. The safety and efficacy of Ultibro Breezhaler in children have not been established. No data are available. **Method of administration:** For inhalation use only. The capsules must not be swallowed. The capsules must be administered only using the Ultibro Breezhaler inhaler. Patients should be instructed on how to administer the product correctly. Patients who do not experience improvement in breathing should be asked if they are swallowing the medicine rather than inhaling it. **CONTRAINDICATIONS:** Hypersensitivity to the active substance or to any of the other excipients. **WARNINGS/PRECAUTIONS:** Ultibro Breezhaler should not be administered concomitantly with medicinal products containing other long acting beta adrenergic agonists or long acting muscarinic antagonists, the pharmacotherapeutic groups to which the components of Ultibro Breezhaler belong. Asthma: Ultibro Breezhaler should not be used for the treatment of asthma due to the absence of data in this indication. Long acting beta2 adrenergic agonists may increase the risk of asthma related serious adverse events, including asthma related deaths, when used for the treatment of asthma. Not for acute use: Ultibro Breezhaler is not indicated for the treatment of acute episodes of bronchospasm. Hypersensitivity related to indacaterol Immediate hypersensitivity reactions have been reported after administration of

indacaterol, one of the components of Ultibro Breezhaler. If signs suggesting allergic reactions (in particular, difficulties in breathing or swallowing, swelling of tongue, lips and face, urticaria, skin rash) occur, treatment should be discontinued immediately and alternative therapy instituted. **Paradoxical bronchospasm:** In clinical studies with Ultibro Breezhaler, paradoxical bronchospasm was not observed. However, paradoxical bronchospasm has been observed with other inhalation therapy and can be life threatening. If this occurs, treatment should be discontinued immediately and alternative therapy instituted. **Narrow-angle glaucoma:** No data are available in patients with narrow angle glaucoma, therefore Ultibro Breezhaler should be used with caution in these patients. Patients should be informed about the signs and symptoms of acute narrow angle glaucoma and should be informed to stop using Ultibro Breezhaler should any of these signs or symptoms develop. **Urinary retention:** No data are available in patients with urinary retention, therefore Ultibro Breezhaler should be used with caution in these patients. Patients with severe renal impairment: These patients should be monitored closely for potential adverse reactions. **Cardiovascular effects:** Ultibro Breezhaler should be used with caution in patients with cardiovascular disorders (coronary artery disease, acute myocardial infarction, cardiac arrhythmias, hypertension). **Hypokalaemia:** Beta2 adrenergic agonists may produce significant hypokalaemia in some patients, which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation. In patients with severe COPD, hypokalaemia may be potentiated by hypoxia and concomitant treatment, which may increase the susceptibility to cardiac arrhythmias. Clinically relevant effects of hypokalaemia have not been observed in clinical studies of Ultibro Breezhaler at the recommended therapeutic dose. **Hyperglycaemia:** Inhalation of high doses of beta₂ adrenergic agonists may produce increases in plasma glucose. Upon initiation of treatment with Ultibro Breezhaler plasma glucose should be monitored more closely in diabetic patients. Ultibro Breezhaler should be used with caution in patients with convulsive disorders or thyrotoxicosis, and in patients who are unusually responsive to beta₂ adrenergic agonists. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose galactose malabsorption should not take this medicine. **Pregnancy and Lactation:** There are no data from the use of Ultibro Breezhaler in pregnant women available. Indacaterol may inhibit labour due to a relaxant effect on uterine smooth muscle. Therefore, Ultibro Breezhaler should only be used during pregnancy if the expected benefit to the patient justifies the potential risk to the foetus. It is not known whether indacaterol, glycopyrronium and their metabolites are excreted in human milk. The use of Ultibro Breezhaler by breast feeding women should only be considered if the expected benefit to the women is greater than any possible risk to the infant. **INTERACTIONS:** Information on the potential for interactions is based on the potential for each of its two components. Beta adrenergic blockers

Therefore Ultibro Breezhaler should not be given together with beta adrenergic blockers (including eye drops) unless there are compelling reasons for their use. Where required, cardioselective beta adrenergic blockers should be preferred, although they should be administered with caution. The co administration of Ultibro Breezhaler with other anticholinergic containing medicinal products has not been studied and is therefore not recommended. Concomitant administration of other sympathomimetic agents (alone or as part of combination therapy) may potentiate the adverse events of indacaterol. Concomitant hypokalaemic treatment with methylxanthine derivatives, steroids, or non-potassium-sparing diuretics may potentiate the possible hypokalaemic effect of beta₂-adrenergic agonists, therefore use with caution. Inhibition of the key contributors of indacaterol clearance, CYP3A4 and P-glycoprotein (P gp), raises the systemic exposure of indacaterol up to two fold. The magnitude of exposure increases due to interactions does not raise any safety concerns given the safety experience of treatment with indacaterol in clinical studies of up to one year at doses up to twice the maximum recommended indacaterol dose. **ADVERSE REACTIONS:** The presentation of the safety profile is based on the experience with Ultibro Breezhaler and the individual components. Ultibro Breezhaler showed similar adverse reactions to the individual components. As it contains indacaterol and glycopyrronium, the type and severity of adverse reactions associated with each of these components may be expected in the combination. The most common adverse reactions with Ultibro Breezhaler are: Upper respiratory tract infections. Common: Pyrexia, chest pain, musculoskeletal pain, dyspepsia, dental Caries, gastroenteritis, cough, oropharyngeal pain including throat irritation, dizziness, headache, nasopharyngitis, urinary tract infections, sinusitis, rhinitis, chest Pain, oropharyngeal pain including throat irritation, Uncommon: Fatigue, peripheral oedema, muscle spasm, myalgia, pain extremity, bladder obstruction and urinary retention, dry mouth, pruritus, rash, glaucoma, myalgia, musculoskeletal pain, pruritis/rash, paradoxical bronchospasm, epistaxis, tachycardia, palpitations, hypersensitivity, diabetes mellitus and hyperglycaemia, insomnia. Please refer to SmPC for a full list of adverse events for Ultibro Breezhaler. **LEGAL CATEGORY:** POM **PACK SIZES:** Single pack containing 8x1 or 30x1 hard capsules, together with one inhaler. **MARKETING AUTHORISATION HOLDER:** Novartis Europharm Limited, Wimblehurst Road, Horsham, West Sussex, RH12 5AB, United Kingdom. **MARKETING AUTHORISATION NUMBERS:** EU/1/13/852/001 - EU/1/13/862/003 Please refer to Summary of Product Characteristics (SmPC) before prescribing. Full prescribing information is available on request from Novartis Pharma Services Inc, Representative Office Malta P.O. Box 4, Marsa, MRS 1000 Malta. Tel: +356 22983217/+35621222872 2014-MT-ULT-28-MAY-2014

References: 1. Novartis Europharm Ltd. Ultibro® Breezhaler® Summary of Product Characteristics. 2. Vogelmeier CF, Bateman ED, Pallante J, et al. Efficacy and safety of once-daily QVA149 compared with twice-daily salmeterol-fluticasone in patients with chronic obstructive pulmonary disease (ILLUMINATE): a randomised, double-blind, parallel group study. *Lancet Respir Med.* 2013;1:51-60. 3. Bateman ED, Ferguson GT, Barnes N, et al. Dual bronchodilation with QVA149 versus single bronchodilator therapy: the SHINE study. *Eur Respir J* 2013; 42(6): 1484-1494 doi: 10.1183/09031936.00200212. Epub 2013 May 30. 4. Wedzicha JA, Decramer M, Ficker JH, et al. Analysis of chronic obstructive pulmonary disease exacerbations with the dual bronchodilator QVA149 compared with glycopyrronium and tiotropium (SPARK): a randomised, double-blind, parallel-group study. *Lancet Respir Med.* 2013;1:199-209.

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breezhaler[®]
indacaterol maleate/glycopyrronium bromide
inhalation powder



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Dr Alexander Borg MD (Malta) MD (Manchester) MRCP (London) qualified from the University of Malta in 1997, underwent cardiology training in Manchester, UK, and has been working as a consultant cardiologist since 2012. His subspeciality interest is cardiovascular imaging, valvular heart disease and myocardial deformation imaging, with practical skills in advanced echocardiography, cardiac magnetic resonance imaging and cardiac CT scanning.



Dr Alfred Grech MD graduated from the University of Malta in 1985. He has been working in Primary Health (specifically at Paola Health Centre) for these last 24 years. His special interests are molecular biology and epigenetics. As a pastime he cultivates bonsai trees. The co-author of the article is Dr Sandra Baldacchino.



Brigitte Ohk MA Gestalt GPTIM MAP EAC a German national living in Malta since 1994, graduated at the Gestalt Institute in Nottingham/University of Birmingham in 2007. She has been working as a Gestalt Therapist in her private practice since 2001.



Professor Albert Cilia-Vincenti MD FRCPath is a private consultant pathologist in Malta, a scientific delegate to the European Medicines Agency (London), and Chairman of the Academy of Nutritional Medicine (London). He is a former pathology services director to the British and Maltese health services, and a former teacher of London and Malta Universities. He trained at London's Royal Marsden, Royal Free, St George's, Charing Cross and The Middlesex hospitals.



Professor Maurice Cauchi MD MSc PhD DPH FRCPA FRCPath was Professor of Pathology and Director of Pathology in Malta. He has published several monographs, including Health, Bioethics and the Law. For his services to the Maltese community in Australia he was made Member of the Order of Australia (AM), and given the Medalja għall-Qadi tar-Repubblika by the Maltese Government.



Dr Pierre Vassallo MD PhD FACA Artz fur Radiologie specialised in radiology at the Institute of Clinical Radiology at the University of Muenster, Germany and the Memorial Sloan-Kettering Cancer Center, New York, US. He is currently Consultant Radiologist and Managing Director at DaVinci Hospital, Malta.

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RECENT ADVANCES IN CARDIOVASCULAR IMAGING – PART I

ALEXANDER BORG

Cardiovascular imaging as a subspecialty field within the mother specialties of Cardiology and Radiology has become increasingly popular over the last decade. The main reasons behind this are (a) the rapidly expanding repertoire of imaging modalities, as seen with the advent of cardiovascular magnetic resonance imaging (CMR) and cardiac computed tomography (CCT), (b) the technological improvements which greatly improve the reliability of these examinations, exemplified by rapid tomographic scanning, real time 3D echocardiography and the introduction of ultrasonic contrast agents, and (c) the potential to reduce the need for invasive investigations, represented mainly by the wide choice of functional imaging modalities to detect cardiac ischaemia, and the tissue characterisation potential of CMR.

In this review, I will summarise the technological advances in cardiovascular imaging, highlighting their important clinical role. The first part of this series will deal with echocardiography, while the second part will address the role of cardiac tomographic imaging (Computed tomography and Magnetic Resonance Imaging).

CONTRAST ECHOCARDIOGRAPHY

An important technical innovation is the introduction of intravenous sonographic contrast. This is a non-iodine-containing emulsion of inert gas microbubbles encapsulated in an albumin or lipid shell, which oscillate when exposed to ultrasound, producing a strong acoustic backscattered signal. Injection of this contrast, which is very safe, highly enhances the contrast between the blood pool and the myocardium. This vastly improves the diagnostic quality, especially in patients with poor ultrasound penetration. An interesting offshoot of this technology is the use of the rate of replenishment of myocardium with contrast to assess myocardial perfusion in the assessment of suspected ischaemic heart disease. In the future, specially designed microbubbles with specific ligands attached to their shells may be used to image diseased tissue or even deliver drugs and genetic material to the targeted tissue.

The main role of contrast echocardiography is to diagnose the nature of structures within the heart which are difficult to visualise on non-enhanced scanning. Common examples are intramural thrombi, benign trabeculations and the prominent trabeculations of non-compaction cardiomyopathy, intracardiac

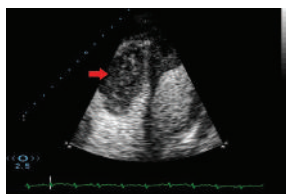


Figure 1: Contrast enhanced echocardiogram showing a tumour (arrow) in the right ventricular apex. The presence of speckles of contrast within the tumour confirms the presence of vascularity and effectively excludes an intracardiac thrombus.

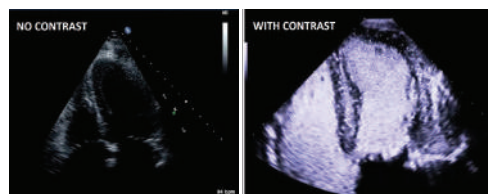


Figure 2: The effect of intravenous contrast on improving endocardial delineation in the left ventricle in a patient with poor image definition.

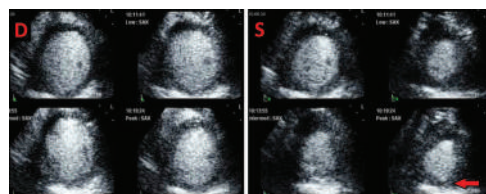


Figure 3: A dobutamine stress echo image with sonographic contrast enhancement showing short axis cuts of the left ventricle in quadrant format, acquired during baseline (top left), low dose (top right), intermediate dose (bottom left) and peak dose dobutamine infusion (bottom right). The quadrants on the left (D) are diastolic images, while those on the right (S) are systolic images. Note the systolic thinning of the inferior and inferolateral walls (red arrow) at peak dobutamine dose on the right, suggestive of ischaemia in the right coronary artery territory, becoming manifest at peak pharmacological stress.

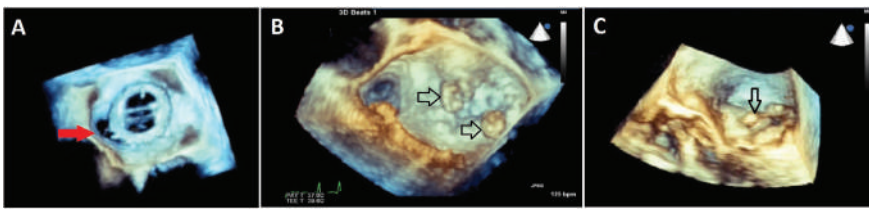


Figure 4: Examples of 3D images acquired during transoesophageal echocardiography. A. Dehiscence of a metallic valve prosthesis in mitral position (arrow) causing severe paraprosthetic leak; B. Atrial view of mitral valve endocarditis showing two vegetations (arrows) on the leaflets; C. Oblique atrial view of mitral valve showing a ruptured chord (arrow) inside left atrium.

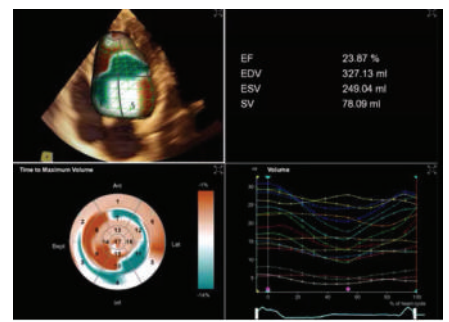


Figure 5: Multiparametric information obtained from a single 3D acquisition of the left ventricle, including a 3D colour-coded cast of regional contraction patterns (top left), volumetric data (top right), a “bull’s eye” view of regional contraction (bottom left), and regional volume-time curves (bottom right). EF - Ejection Fraction; EDV - End-diastolic volume; ESV - End-systolic volume; SV - Stroke volume.

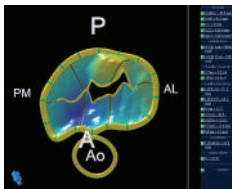


Figure 6: 3D model of the mitral valve annulus and leaflets showing prolapse of the middle scallop of the posterior mitral valve leaflet causing severe regurgitation. The model is accompanied by various automatically-derived parameters quantifying the shape of the mitral valve complex (right of image). P - posterior aspect; A - anterior aspect; PM - posteromedial aspect; AL - anterolateral aspect; Ao - aortic valve.

tumours (figure 1), the localised myocardial thickening of hypertrophic cardiomyopathy and visualisation of the right ventricle in suspected arrhythmogenic right ventricular cardiomyopathy. Contrast is often used simply to enhance the endocardial lining to facilitate quantification of left ventricular function (figure 2). Finally, the use of intravenous contrast has immensely increased the feasibility and diagnostic potential of stress echocardiography.

STRESS ECHOCARDIOGRAPHY


The main use of this technology is in the diagnosis of cardiac ischaemia in patients with chest pain. This modality is based on assessing the contractile response to inotropic drugs (dobutamine), vasodilators (dipyridamole or adenosine) or exercise stress (bicycle or treadmill). Typically, ischaemic segments manifest decreased and delayed systolic thickening at high levels of inotropic stress (figure 3). Such a response has been shown to be highly accurate in detecting significant coronary stenosis and providing prognostic information on the likelihood of cardiac events, with a performance similar to other functional imaging modalities such as nuclear imaging. Whereas the technology has been previously limited by technical problems in visualising all segments of the heart muscle, the use of contrast has eliminated this problem in more than 95% of heart segments, and significantly increased accuracy in the detection of coronary stenosis. Thus, this cheap, versatile and safe modality is considered to be one of the first line investigations for the diagnosis of suspected ischaemia in patients with moderate likelihood of coronary artery disease. Finally, routine indications for stress echocardiography have, over the years, extended beyond the diagnosis of coronary artery disease to include assessment of myocardial viability, valve disease, hypertrophic cardiomyopathy and diastolic function.

3D ECHOCARDIOGRAPHY

Probably the most impressive development in image acquisition and processing is 3D echocardiography. Whereas previously an experienced cardiologist had to mentally reconstruct a 3D appreciation of a structure from a series of

strategically acquired 2D images, modern transducers are capable of acquiring a 3D pyramidal-shaped block of data, allowing real-time visualisation of cardiac structures and their complex spatial relation with neighbouring structures. The high resolution images obtained by transoesophageal imaging (by virtue of the proximity of the probe to the structures being interrogated, allowing the use of a higher frequency probe) lend themselves nicely to 3D reconstruction, generating images which have revolutionised the approach towards heart disease. This has proved indispensable in assessing valvular heart disease (figure 4), measuring ventricular volumes (figure 5), and guiding percutaneous cardiac procedures. Providing a 3D view of a complex three-dimensional structure such as the regurgitant mitral valve facilitates communication with the surgeon (the imager can literally see what the surgeon sees) and facilitates the appreciation of disease by less experienced operators (figure 4). Complex 3D structures such as the mitral valve annulus can be quantified with commercially available software, leading to highly informative models (figure 6). There is no doubt that such models prove indispensable for understanding the mechanism of disease and guiding surgical intervention.

CONCLUSION

Echocardiography is a well-established technique, with the main advantages being its low cost, portability and lack of ionising radiation. However, ultrasound physics places some inevitable constraints on the technology. Some patients have poor image quality, and unusual cardiac anatomy can prove difficult to quantify, regardless of the operator expertise. Some structures are beyond ultrasonic interrogation, either because they lie behind bone (like the right ventricle in some patients), behind air-containing organs (such as the ascending and descending aorta) or simply because they are too far away from the transducer (as in obese patients). The use of intravenous contrast has gone a long way in improving image quality in challenging patients, but there will always be physical limits to ultrasound propagation in tissue, no matter how advanced the computing power at hand. This is where tomographic imaging, the topic of the next review, enters the scene. 



NEW PERSPECTIVES IN BARRETT'S OESOPHAGUS

MAURICE CAUCHI

Most of us have been brought up on the dogma that one important complication of reflux oesophagitis is Barrett's oesophagus which in turn is the precursor of adenocarcinoma of the oesophagus. It appears that this view gives too gloom a picture of what is actually happening.

Carcinoma of the oesophagus is not a common cancer in Malta. According to data from the Cancer Registry, between 1998 -2000 there were 27 new cases (21 males, 6 females) with a mortality of 29 (22 males, 7 females).

It has always been a worry that chronic reflux leads to irritation and inflammation of the lower part of the oesophagus, which eventually leads to intestinal metaplastic changes, dysplasia and eventually adenocarcinoma.

These concepts relating to carcinogenesis seem now to be in need of a considerable degree of revision, if not complete overhaul, following data published recently by Brian J. Reid, MD, from the Division of Human Biology and the Division of Public Health Sciences at the Fred Hutchinson Cancer Research Center in Seattle, Washington¹.

He and his colleagues studied 248 patients involving over 20,000 person-months of follow-up. They investigated the changes in chromosomes in these patients using sophisticated computerised technology to assess single nucleotide polymorphisms.

As expected, they found several changes in the DNA of these patients, including small localised deletions involving particularly chromosome 9 (9p), which occurred in either one or both of the chromosomes. These changes were found in 69%

of the patients studied, but remained more or less stable over time - involving a follow-up period of up to two decades - and therefore were of no prognostic significance from the cancer progression point of view.

On the other hand, in about a third of the patients, there were more significant changes, sometimes involved gains or losses of large chromosomal regions, or even whole chromosomes. These involved chromosomes 17, 15 and 13 but not other chromosomes.

Dr Reid believes that these changes tend to occur suddenly, a couple of years before cancer becomes manifest. He states "... we found that the cells had undergone a genome doubling, such that single surviving chromosome 17s were now being replicated. And that was occurring right before the development of cancer."

He concluded that Barrett's patients could be classified into 'progressors' and 'non-progressors.' The majority of patients were non-progressors, meaning that they were at no obvious risk of developing cancer.

These findings have considerable implications both in the understanding of the process of carcinogenesis, as well in applied clinical practice.

It has always been assumed that cancer progression is a linear process, often taking decades before clinical manifestations become obvious. These findings, on the other hand imply that the evolution of cancer is not linear but 'punctuate', namely, completely different mutations/deletions can take place relatively suddenly, producing a specific alteration in the DNA.

From the clinical point of view, Dr Reid believes that this behaviour explains why "current strategies grossly fail to detect cancer in patients diagnosed with Barrett's oesophagus." Dr Reid emphasized that less than 1% of patients diagnosed with Barrett's oesophagus develop cancer each year and concludes that doctors are scaring patients unnecessarily. His advice to doctors is this: "After you tell a patient that they have Barrett's and that only a very small minority develop cancer, just stop."

In his opinion, patients should be assessed by techniques (such as the ones described in the paper) which can select those at high risk, to avoid unnecessary panic and over-investigation of those who are at a much lesser risk.

Chromosome changes, including aneuploidy and polyploidy are a common occurrence in cancer cells. What is unique to these findings is that specific chromosome abnormalities have been detected in tissue well before cancer actually appears. If this finding is shown to occur also in more commonly occurring tumours (e.g. prostate cancer), then this could become an important tool in distinguishing tumours which have an increased likelihood of progression.

Selecting patients for special follow-up on the basis of changes in their chromosomal make-up would make sense if such techniques, as used in this study, were readily available, a project for the future, rather than for immediate application in Malta at present. ❄️

Reference

1. Li X, Galipeau PC, Paulson TG et al. Temporal and Spatial Evolution of Somatic Chromosomal Alterations: A Case-Cohort Study of Barrett's Esophagus. *Cancer Prev Res (Phila)* 2014;7(1):114-27.

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Relvar Ellipta (fluticasone furoate/vilanterol) Abridged Prescribing Information

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 on SPC how to report adverse reactions.

Please refer to the full Summary of Product Characteristics before prescribing

Trade Name: RELVAR ELLIPTA. **Active Ingredients:** 92 micrograms or 184 micrograms of fluticasone furoate and 22 micrograms of vilanterol (as trifenate). **Pharmaceutical Form:** 92 micrograms/22 micrograms or 184 micrograms/22 micrograms inhalation powder, pre-dispensed. **Indications:** The 92 micrograms/22 micrograms dose: for the regular treatment of asthma in adults and adolescents aged 12 years and older where use of a combination medicinal product (long-acting beta₂-agonist and inhaled corticosteroid) is appropriate; and for the symptomatic treatment of adults with COPD with a FEV₁<70% predicted normal (post-bronchodilator) with an exacerbation history despite regular bronchodilator therapy. The 184 micrograms/22 micrograms dose: for the regular treatment of asthma in adults and adolescents aged 12 years and older where use of a combination medicinal product (long-acting beta₂-agonist and inhaled corticosteroid) is appropriate. **Dosage and Method of Administration:** For Asthma: One inhalation of Relvar Ellipta 92/22 micrograms or 184/22 micrograms once daily. Patients usually experience an improvement in lung function within 15 minutes of inhaling Relvar Ellipta. However, the patient should be informed that regular daily usage is necessary to maintain control of asthma symptoms and that use should be continued even when asymptomatic. If symptoms arise in the period between doses, an inhaled, short-acting beta₂-agonist should be taken for immediate relief. A starting dose of Relvar Ellipta 92/22 micrograms should be considered for adults and adolescents 12 years and over who require a low to mid dose of inhaled corticosteroid in combination with a long-acting beta₂-agonist. If patients are inadequately controlled on Relvar Ellipta 92/22 micrograms, the dose

can be increased to 184/22 micrograms, which may provide additional improvement in asthma control. For COPD: One inhalation of Relvar Ellipta 92/22 micrograms once daily. Relvar Ellipta 184/22 micrograms is not indicated for patients with COPD. Relvar Ellipta is for inhalation use only. It should be administered at the same time of the day, each day. **Contraindications:** Hypersensitivity to the active ingredient or excipients. **Precautions for Use:** Fluticasone furoate/vilanterol should not be used to treat acute asthma symptoms, for which a short-acting bronchodilator is required. Caution in severe cardiovascular disease, moderate-to-severe hepatic impairment, pulmonary tuberculosis or in patients with chronic or untreated infections, history of diabetes mellitus and for paradoxical bronchospasm and pneumonia in patients with COPD. **Drug Interactions:** Beta-blockers, CYP3A4 inhibitors, P-glycoprotein inhibitors and sympathomimetic medicinal products (refer to the full Summary of Product Characteristics for list of drugs). **Fertility, Pregnancy and Lactation:** **Pregnancy:** No adequate data available. **Lactation:** insufficient information available. **Fertility:** There is no data in humans. Animal studies indicate no effect on fertility. **Effect on Ability to Drive or Use Machines:** No or negligible influence. **Undesirable Effects:** Very common side effects include headache and nasopharyngitis (refer to the full Summary of Product Characteristics for complete list of undesirable effects). **Overdose:** There is no specific antidote. Treatment of overdose should consist of general supportive measures. **Local Presentations:** Relvar Ellipta 92 micrograms/22 micrograms inhalation powder, pre-dispensed and Relvar Ellipta 184 micrograms/22 micrograms inhalation powder, pre-dispensed. **Legal Category:** POM. **Marketing Authorisation Holder:** Glaxo Group Limited, 980 Great West Road, Brentford, Middlesex TW8 9GS, United Kingdom **Marketing Authorisation Numbers:** EU/1/13/886/001-6 **DATE OF PREPARATION:** December 2013.

In order to ensure that this product information reflects the most up-to-date clinical and post-marketing surveillance data, please always refer to the latest Summary of Product Characteristics (SPC) which is available from GlaxoSmithKline (Malta) Ltd (Tel: +356 21238131).

REPORTING ADVERSE EVENTS (AEs):

Malta & Gibraltar: If you become aware of any AEs, medication errors and/or use during pregnancy in association with GSK products, please report the event promptly to: GSK (Malta) Limited, 1, De la Cruz Avenue, Qormi QRM 2458, Malta (Tel: +356 21238131).

Malta: alternatively, any suspected AEs and medication errors can also be reported via the national Adverse Drug Reactions (ADRs) reporting system:

Report forms can be downloaded from www.medicinesauthority.gov.mt/ and posted to the Malta Medicines Authority, Post-licensing Directorate, 203, Level 3, Rue D'Argens, Gzira GZR 1368, MALTA, or sent by email to postlicensing.medicinesauthority@gov.mt

Gibraltar: alternatively, any suspected AEs and medication errors can also be reported via the UK regulatory authority (MHRA): <https://yellowcard.mhra.gov.uk/>

*Patients' current or previous maintenance inhalers: HandiHaler/ DISKUS/ MDI/ HFA (COPD); DISKUS/ MDI/ HFA (asthma).⁴

References: 1. Relvar Ellipta Summary of Product Characteristics. GlaxoSmithKline; 2013. 2. Bleecker ER et al. Fluticasone furoate/vilanterol 100/25mcg compared with fluticasone furoate 100mcg in asthma: a randomized trial. *JACI In Practice* 2013 (in press). 3. Svedstater H et al. Ease of use of a two-strip dry powder inhaler (DPI) to deliver fluticasone furoate/vilanterol (FFV) and FF alone in asthma. *ERS* 2013. 4. Woepse M et al. Qualitative assessment of a two-strip dry powder inhaler (ELLIPTA™) for COPD and asthma. *EAACI* 2013.

MLT_GIB/RESP/0006/14 Date of preparation: January 2014



Theravance



ARTHROSCOPIC SHOULDER SURGERY – PART II

JOHN A CASALETTO

ROTATOR CUFF TEARS

Tears of the supraspinatus tendon occur most commonly in the 5th and 6th decade, unless in the context of significant shoulder trauma. It is not uncommon for a patient to present with an acute-on-chronic tear progression where an existing asymptomatic tear becomes decompensated as the tear enlarges.⁴ Tears are mostly commonly thought of as being an attrition rupture from both age-related tendon degeneration and mechanical impingement.⁵

The anterior edge of the supraspinatus tendon is most commonly involved with the tear gradually extending posteriorly to involve infraspinatus. The patient initially presents



Figure 4: Arthroscopic view from within the subacromial space. An arthroscopic rotator cuff tear repair using anchors.

with pain followed by weakness. In more advanced cases the patient presents with ‘pseudoparalysis’ of the shoulder, whereby the initiation of abduction and forward flexion is lost, but the passive range of movement is largely preserved.

Radiologically this situation manifests itself with subtle changes in the tuberosity and proximal humeral migration. In bigger tears, the subacromial space is decreased in dimension as the rotator cuff tendons retract medially. Other than clinically, the tear can be diagnosed on ultrasound or MRI scanning which also has the benefit of showing the degree of muscle atrophy which over time invariably accompanies the tear. Severe muscle atrophy is permanent and is associated with poor outcomes and failure of cuff healing, hence the need to intervene surgically at an early stage.

Steroid injections in this situation are not recommended as they can lead to further tear progression and deterioration of the tendon which can impair successful surgical repair.⁶

The treatment is arthroscopic rotator cuff repair (figure 4) with the use of anchors. Arthroscopic surgery avoids the damage to the deltoid muscle from open surgery, decreasing the risk of stiffness and post surgical pain enabling a faster recovery.

The success rate following cuff-repair surgery depends on the quality of the repair, the degree of muscle atrophy, preoperative extent of radiological humeral migration and the age of patient. In advanced cases where a full cuff repair is not technically possible due to retraction and poor tendon quality, a partial repair can be enough to give the patient a compensated more functional shoulder.

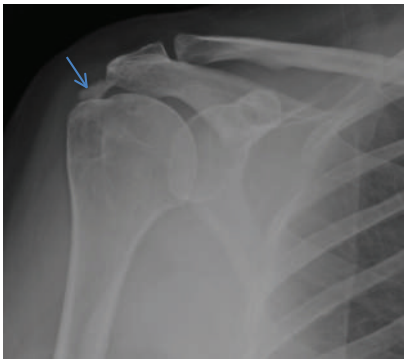


Figure 5: A large calcific deposit (blue arrow) in supraspinatus.

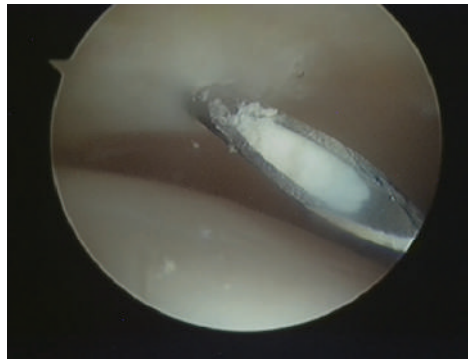


Figure 6: Arthroscopic view from within the glenohumeral joint. The calcific deposit in the cuff has been found with the use of a 16 G needle.



Figure 7: Arthroscopic view from the subacromial space. Calcium of toothpaste-like consistency is seen extruding from the cuff tendon.

ROTATOR CUFF ARTHROPATHY

Larger rotator cuff tears result in the shoulder losing its internal milieu. The accompanying synovial fluid leakage into the subacromial space, loss of control and centralization of the humeral head on the glenoid, leads to arthritis termed cuff arthropathy. The humerus migrates proximally and articulates with the undersurface of the acromion. Symptoms can be alleviated by corticosteroid injections. Pain can be ameliorated by an arthroscopic subacromial decompression and debridement even if the rotator cuff tear is found to be irreparable. In more degenerate shoulders a reverse total shoulder replacement is the ultimate treatment when more conservative measures fail. This prosthesis replaces the glenoid by a glenosphere and turns the humeral side into a socket. It has the biomechanical effect of medialising the centre of rotation, putting the deltoid at a better mechanical advantage to elevate and abduct the shoulder, compensating for the non-functional rotator cuff.

CALCIFIC TENDONITIS

Calcific tendonitis is one of the most excruciatingly painful shoulder conditions (figure 5). It is most painful during the resorptive phase when the immune system attempts to remove the calcium lesion within the tendon. Corticosteroid injections into the subacromial space often give limited pain relief by decreasing the inflammatory response, but cannot reach the intra-tendinous calcium. In some instances when the calcium is fluid in nature, it can be removed by ultrasound-guided needle barbotage. However, very often, the consistency of the calcium is that of toothpaste or chalk (figures 6 & 7) and in these cases the calcium can only be removed arthroscopically.

FROZEN SHOULDER

Frozen shoulder, sometimes termed adhesive capsulitis, can affect all age groups and tends to be recalcitrant in patients with diabetes. Despite not being directly linked to glycaemic control, it is more prevalent in Type 1 diabetes.⁷ It can also occur after ipsilateral arm trauma and following breast or chest surgery. It is a distinct entity from post-traumatic stiffness and responds very positively to appropriate treatment.

Clinical examination reveals global decreased range of movement which is easily detected when examining external

rotation with the arm by the chest. Forward flexion and abduction can be spuriously preserved if scapulothoracic movement is not blocked during examination. This can be easily done by placing one hand over the shoulder while examining the range of movement.

In suspected cases of frozen shoulder, plain radiography is essential to rule out arthritis, which is the other main cause of severe stiffness in the shoulder. The diagnosis is largely clinical as ultrasound and MRI scans are poorly diagnostic. MR imaging can show non-specific thickening of the capsule and the ligaments around the shoulder in addition to a decreased capsular volume.

The pain from frozen shoulder can respond briefly to intra-glenohumeral joint steroid injections. Physiotherapy, however, was found to have longer term effects.⁸ If the condition persists, arthroscopic release of the capsule followed by controlled manipulation restores the range of movement. Shoulder manipulation without arthroscopic release (Figure 8) has the potential of damaging structures in the shoulder.⁹ Intensive physiotherapy is required following surgery as the condition can very rapidly recur especially in patients who suffer from diabetes. ❄️

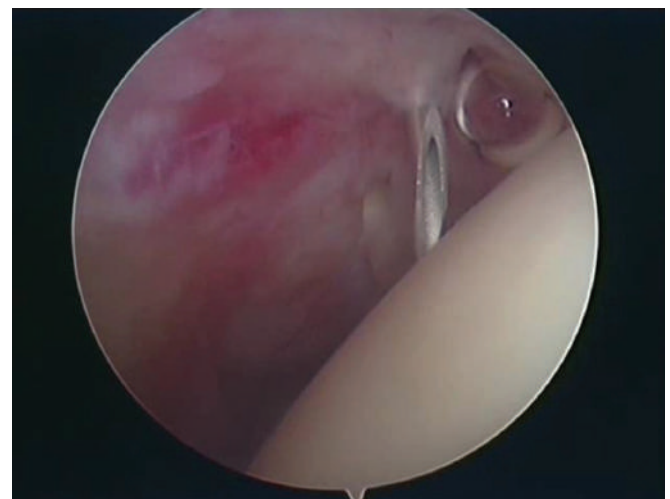


Figure 8: Arthroscopic view from within the glenohumeral joint showing the anterior of the shoulder from inside the joint. The rotator interval (penetrated by the needle) is inflamed and thickened.



THE SLIPPERY SLOPE OF MODERN MEDICAL REPORTING – PART II

ALBERT CILIA-VINCENTI

Medical literature is littered with words like “may”, “possibly”, “associated with” and “could”. These words allow indefinite conclusions, exceptions and failures, so that no one is ever “wrong”. Nutritional and conventional medicine, and the pharmaceutical industry, have a long history of issuing recommendations that are later found to be incorrect and have to be amended. Information is widely disseminated as fact, when in reality it is little more than a guess. Unproven theories are then incorporated into people’s lives under the guise of “practicing good health”. It can take decades for false information to be purged out from the “common knowledge” that is tainted with it.

Nutritional “science” has often abandoned the study of “cause and effect” in the laboratory, replacing it with “associated with”. Laboratory experiments are what medical physiology and biochemistry textbooks are based on, not mere association. This standard of requiring cause/effect relationships has often been replaced with sloppy statistical studies that reach erroneous conclusions through mere association. This practice is particularly prevalent in “epidemiology”. Some have referred to it as “desktop science vs laboratory science” – it’s a lot easier to perform desktop “studies”, but a huge price in quality is paid.

Astrophysicist/cosmologist Dr Carl Sagan warns against eager blind acceptance without personal understanding. He says, “one of the saddest lessons of history is that if we’ve been bamboozled long enough, we tend to reject any evidence of the bamboozle, and we’re no longer interested in finding out the truth. The bamboozle has captured us. It is simply too painful to acknowledge, even to ourselves, that we’ve been so credulous. So the old bamboozles tend to persist as the new bamboozles emerge”.

Stanton Glantz, professor of medicine at University of California, San Francisco, says in his book, *Primer of Biostatistics*, ‘most readers assume that when an article appears in a journal, the reviewers and editors have scrutinised every aspect of the manuscript, including use of statistics^{1,2}. Unfortunately, this is often not the case. Most journals do not provide a complete secondary statistical review of all papers, so the fraction of published papers containing statistical errors is probably still about 50% for many journals’.

Readers, including other researchers, never know of the statistical mistakes. Thus, the reported effectiveness of drugs can rarely be taken at face value, and the treatment results are often misinterpreted, either inadvertently or to push marketing goals.

The medical community doesn’t adequately understand relative risk, and physicians are forced into believing the status quo. “Absolute Risk” is a measure of occurrence. The Absolute Risk is the appropriate measure when determining the likelihood that an event will occur. Sample size is essential. An example is use of statins versus placebo and comparing the number of cardiovascular events in both legs. If the difference between the placebo and the statin is very small, then statins are highly ineffective.

“Relative Risk” is a measure of change. The Relative Risk is the appropriate measure when comparing the possibility of one event to another event, or the change between events – how much the intervention will help the patient’s disease. Sample size is irrelevant. An example is comparing a country’s skin cancer rates in 1980 vs 2010 – if the difference is significantly greater as a percentage in 2010, something is increasing skin cancer incidence.

Physician, mathematician and statistician, Dr John P.A. Ioannidis, chief of Stanford University’s Prevention Research Centre has been questioning the “massaged” pharmaceutical statistics. He claims people are being hurt and even dying because of false medical claims; not quackery, but errors in medical research. He says negative results sit in a file drawer, or the trial keeps hoping the results turn positive. With millions of dollars on the line, companies are loath to declare a new drug ineffective. As a result of the lag in publishing negative results, patients receive a treatment that is actually ineffective. He claims that from clinical trials of new drugs to cutting-edge genetics, biomedical research is riddled with incorrect findings.

The number of studies is said to be inversely proportional to the effectiveness of what is being studied. Publishing papers has become an end in itself, with the so frequent conclusion “more research is needed”. There has been little medical advancement these last 10 years compared to, say, the great advances in computers. Apart from better diagnostic equipment designed by medical physicists and electrical engineers, medical advances pale in comparison. ❖

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PRESENTATION: Each tablet contains 50 mg of Vildagliptin. **INDICATIONS:** For the treatment of type 2 diabetes mellitus in adults. As monotherapy in patients inadequately controlled by diet and exercise alone and for whom metformin is inappropriate due to contraindications or intolerance. As dual oral therapy in combination with metformin in patients with insufficient glycaemic control despite maximal tolerated dose of a sulphonylurea and for whom metformin is inappropriate due to contraindications or intolerance; a thiazolidinedione in patients with insufficient glycaemic control and for whom the use of a thiazolidinedione is appropriate. As triple oral therapy in combination with a sulphonylurea and metformin when diet and exercise plus dual therapy with these medicinal products do not provide adequate glycaemic control. Vildagliptin is also indicated for use in combination with insulin (with or without metformin) when diet and exercise plus a stable dose of insulin do not provide adequate glycaemic control. **DOSEAGE:** When used as monotherapy in combination with thiazolidinedione, in combination with metformin and a sulphonylurea or in combination with insulin (with or without metformin), the recommended daily dose of Vildagliptin is 100mg, administered as one dose of 50 mg in the morning and one dose of 50 mg in the evening. When used in combination with a sulphonylurea, a lower dose of the sulphonylurea may be considered to reduce the risk of hypoglycaemia. Galvus can be administered with or without a meal. Doses greater than 100 mg are not recommended. Galvus is not recommended for use in children and adolescents (< 18 years). The safety and efficacy of Galvus in children and adolescents (< 18 years) have not been established. No data are available. The recommended dose for patients with moderate/severe renal impairment is 50mg once daily. If a dose of Galvus is missed, it should be taken as soon as the patient remembers. A double dose should not be taken on the same day. No dose adjustments are necessary in elderly patients (≥ 65 years). The safety and efficacy of Vildagliptin as triple oral therapy in combination with metformin and a thiazolidinedione have not been established. **CONTRAINDICATIONS:** Hypersensitivity to the active substance or to any of the excipients. **WARNINGS & PRECAUTIONS:** Galvus should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis. There is limited experience in patients with ESRD on haemodialysis. Therefore Galvus should be used with caution in these patients. Galvus is not recommended in patients with hepatic impairment, including patients with pre-treatment ALT or AST >3x the ULN. Liver function tests should be performed prior to treatment initiation, at three month intervals during the first year and periodically thereafter. Should an increase in AST or ALT of ≥3xULN or greater persist, withdrawal of Galvus therapy is recommended. Patients who develop jaundice or other signs suggestive of liver dysfunction should discontinue Galvus. Clinical experience in patients with NYHA functional class III treated with Vildagliptin is still limited and results are inconclusive. Routine monitoring of diabetic patients for skin disorders such as blistering or ulsoveration is recommended. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine. Galvus should not be administered during pregnancy or breast-feeding since no studies on the effect on human fertility have been conducted for Galvus. Should be used with caution in patients with renal impairment. Sulphonylureas are known to cause hypoglycaemia. Patients receiving Vildagliptin in combination with a sulphonylurea may be at risk for hypoglycaemia. Therefore, a lower dose of sulphonylurea may be considered to reduce the risk of hypoglycaemia. Use of Vildagliptin has been associated with a risk of developing acute pancreatitis. If pancreatitis is suspected, Vildagliptin should be discontinued. If acute pancreatitis is confirmed, Vildagliptin should not be restarted. Caution should be exercised in patients with a history of acute pancreatitis. **INTERACTIONS:** Vildagliptin has a low potential for drug interactions. No clinically relevant interactions with other antidiabetic drugs (glitazones, glitazones, metformin), amiodipine, digoxin, ramipril, simvastatin, valsartan or warfarin were observed after co-administration with Vildagliptin. As with other oral antidiabetic medicines, the hypoglycaemic effect of Vildagliptin may be reduced by certain active substances, including thiazides, corticosteroids, thyroid products and sympathomimetics. **ADVERSE REACTIONS:** Rare cases (<1/10,000 to <1/1,000) angioedema, abnormal liver function tests, hepatic dysfunction (including hepatitis). Monotherapy: Common (>1/100 to <1/10): dizziness, Uncommon (>1/1,000 to <1/100): headache, constipation, arthralgia, hypoglycaemia, oedema peripheral. Very rare (<1/10,000): URTI, nasopharyngitis. Combination with metformin: Common: tremor, headache, dizziness, nausea, hypoglycaemia, hyperhidrosis, asthenia. Uncommon: fatigue. Combination with sulphonylureas: Common: tremor, headache, dizziness, asthenia, hypoglycaemia. Uncommon: constipation. Very rare: nasopharyngitis. Combination with Thiazolidinedione: Common: weight increase, oedema peripheral, Uncommon: headache, asthenia, hypoglycaemia. Combination with insulin: Common: decreased blood glucose, headache, chills, nausea, gastro-oesophageal reflux disease. Uncommon: Diarrhoea, flatulence. Frequency not known: urticaria, pancreatitis, hepatitis and abnormal liver function tests (reversible upon discontinuation of the medicinal product), bullous or exfoliative skin lesions. Combination with metformin and a sulphonylurea: Common: hypoglycaemia, dizziness, tremor, hyperhidrosis, asthenia. **LEGAL CATEGORY: POM. PACK SIZES: 7, 28 tablets. MARKETING AUTHORISATION HOLDER:** Novartis Europharm Limited, Wimshurst Road, Hirscham, West Sussex, RH12 5AB, United Kingdom. **MARKETING AUTHORISATION NUMBERS:** EU/1/02/14/001, 002. Please refer to Summary of Product Characteristics (SmPC) before prescribing. Full prescribing information is available on request from Novartis Pharma Services Inc, Representative Office Malta, P.O. Box 4, Marsa, MRS 1000, Malta. Tel +356 21222872. 2014-MT-GAL-12-JUN-2014

Eucreas®
PRESENTATION: Each 50 mg/850 mg film-coated tablet contains 50 mg of Vildagliptin and 850 mg Metformin hydrochloride. Each 50 mg/1000 mg film-coated tablet contains 50 mg of Vildagliptin and 1000 mg Metformin hydrochloride. **INDICATIONS:** Eucreas is indicated in the treatment of type 2 diabetes mellitus patients, indicated in the treatment of adult patients who are unable to achieve sufficient glycaemic control at their maximally tolerated dose of oral metformin alone or who are already treated with the combination of Vildagliptin and Metformin as separate tablets. Eucreas is indicated in combination with a sulphonylurea (i.e. triple combination therapy) as an adjunct to diet and exercise in adult patients inadequately controlled with metformin and a sulphonylurea. Eucreas is indicated in triple combination therapy with insulin as an adjunct to diet and exercise to improve glycaemic control in adult patients when insulin at a stable dose and metformin alone do not provide adequate glycaemic control. **DOSEAGE:** The dose of antihyperglycaemic therapy with Eucreas should be individualised on the basis of the patient's current regimen, effectiveness and tolerability while not exceeding the maximum recommended daily dose of 100 mg vildagliptin. Eucreas may be initiated at either the 50 mg/850 mg or 50 mg/1000 mg tablet strength twice daily, one tablet in the morning and the other in the evening. For patients inadequately controlled at their maximal tolerated dose of metformin monotherapy: The starting dose of Eucreas should provide vildagliptin as 50 mg twice daily (100 mg total daily dose) plus the dose of metformin already being taken. For patients switching from co-administration of vildagliptin and metformin as separate tablets: Eucreas should be initiated at the dose of vildagliptin and metformin already being taken. For patients inadequately controlled on dual combination with metformin and a sulphonylurea: The doses of Eucreas should provide vildagliptin as 50 mg twice daily (100 mg total daily dose) and a dose of Metformin similar to the dose already being taken. When Eucreas is used in combination with a sulphonylurea, a lower dose of the sulphonylurea may be considered to reduce the risk of hypoglycaemia. For patients inadequately controlled on dual combination therapy with insulin and the maximal tolerated dose of metformin: The dose of Eucreas should provide vildagliptin dosed as 50 mg twice daily (100 mg total daily dose) and a dose of Metformin similar to the dose already being taken. Eucreas should be taken with or just after food to reduce gastrointestinal symptoms associated with Metformin. Patients > 65 years old: Eucreas should have their renal function monitored regularly. Eucreas is not recommended for use in patients less than 18 years old. For use in renal or hepatic impairment, see contraindications and precautions below or refer to the SmPC for more information. The safety and efficacy of vildagliptin and Metformin as triple oral therapy in combination with a thiazolidinedione have not been established. **CONTRAINDICATIONS:** Hypersensitivity to Vildagliptin or Metformin hydrochloride or to any of the excipients. Diabetic ketoacidosis or diabetic pre-coma. Renal failure or renal dysfunction defined as creatinine clearance < 60 ml/min. Acute conditions with the potential to alter renal function e.g. dehydration, severe infection, shock or intravascular administration of iodinated contrast agents. Acute or chronic disease which may cause tissue hypoxia e.g. cardiac or respiratory failure, recent myocardial infarction, shock, hepatic impairment, acute alcohol intoxication, alcoholism, lactation. **WARNINGS & PRECAUTIONS:** Eucreas is not a substitute for insulin in insulin-requiring patients and should not be used in patients with type 1 diabetes. Due to the risk of lactic acidosis, renal function should be monitored at least once yearly in patients with normal renal function and at least two to four times yearly in patients with serum creatinine at the upper limit of normal and in elderly patients. Eucreas is not recommended in patients with hepatic impairment, including patients with pre-treatment ALT or AST >3x the ULN. LFT's should be performed prior to treatment initiation, at three month intervals during the first year and periodically thereafter. Should an increase in AST or ALT of ≥3xULN or greater persist, withdrawal of Eucreas therapy is recommended. Patients who develop jaundice or other signs suggestive of liver dysfunction should discontinue Eucreas. Routine monitoring of diabetic patients for skin disorders such as blistering or ulsoveration is recommended. The IV administration of iodinated contrast agents can lead to renal failure. Therefore due to Metformin active ingredient, Eucreas should be discontinued prior to and at the time of the test and not restarted until 48 hours afterwards and only after renal function has been re-evaluated and found to be normal. Eucreas should not be administered during pregnancy or lactation. Sulphonylureas are known to cause hypoglycaemia. Patients receiving Vildagliptin in combination with a sulphonylurea may be at risk for hypoglycaemia. Therefore, a lower dose of sulphonylurea may be considered to reduce the risk of hypoglycaemia. The use of Vildagliptin has been associated with a risk of developing acute pancreatitis. If pancreatitis is suspected, vildagliptin should be discontinued. If acute pancreatitis is confirmed, vildagliptin should not be restarted. Caution should be exercised in patients with a history of acute pancreatitis. **INTERACTIONS:** Vildagliptin has a low potential for drug interactions. No clinically relevant interactions with other antidiabetics (glitazones, glitazones, metformin), amiodipine, digoxin, ramipril, simvastatin, valsartan or warfarin were observed after co-administration with Vildagliptin. Interactions with Metformin hydrochloride that are not recommended include alcohol, cationic active substances e.g. cimetidine and intravascular administration of iodinated contrast media. Combinations requiring caution include metformin hydrochloride with medicines tending to produce hypoglycaemic activity e.g. glucocorticoids, beta agonists and diuretics. The dose of antihyperglycaemic medicinal products may need to be adjusted in combination with ACE inhibitors. **ADVERSE REACTIONS:** Rare cases (>1/10,000 to <1/1,000): angioedema, hepatic dysfunction (including hepatitis) have been reported with vildagliptin. Vildagliptin monotherapy: Common (>1/100 to <1/10): dizziness, Uncommon (>1/1,000 to <1/100): headache, constipation, arthralgia, hypoglycaemia, oedema peripheral, very rare (<1/10,000): URTI, nasopharyngitis. Metformin monotherapy: Very common (>1/10): nausea, vomiting, diarrhoea, abdominal pain and loss of appetite. Common: metallic taste. Combination Vildagliptin with Metformin: Common: tremor, headache, dizziness, nausea, hypoglycaemia, Uncommon: fatigue. Combination with Metformin and sulphonylurea: Common: hypoglycaemia, dizziness, tremor, hyperhidrosis, asthenia, decreased blood glucose, headache, chills. Combination with insulin: Increased blood glucose, gastro-oesophageal reflux disease. Uncommon: Diarrhoea, flatulence. Frequency not known: urticaria, pancreatitis, hepatitis and abnormal liver function tests (reversible upon discontinuation of the medicinal product), bullous or exfoliative skin lesions. Combination with metformin and a sulphonylurea: Common: hypoglycaemia, dizziness, tremor, hyperhidrosis, asthenia. **LEGAL CATEGORY: POM. PACK SIZES:** 30, 60 film-coated tablets. **MARKETING AUTHORISATION HOLDER:** Novartis Europharm Limited, Wimshurst Road, Hirscham, West Sussex, RH12 5AB, United Kingdom. **MARKETING AUTHORISATION NUMBERS:** EU/1/07/25/002-003, EU/1/07/25/008-009. Please refer to Summary of Product Characteristics (SmPC) before prescribing. Full prescribing information is available upon request from: Novartis Pharma Services Inc, Representative Office Malta, P.O. Box 4, Marsa, MRS 1000, Malta. Tel +356 21222872. 2014-MT-EUC-09-JUN-2014



1. Novartis Europharm Ltd. Galvus® Summary of Product Characteristics
 2. Novartis Europharm Ltd. Eucreas® Summary of Product Characteristics



TRULY RESTLESS & DARING SEMINAR



RACHEL GATT
FIRST YEAR
MEDICAL STUDENT

Being a fresher myself, I had no idea what to expect during the Training & Resource Development weekend (TRD) which was held between October 31st and November 2nd at Hotel San Antonio, Bugibba.

I was surprised to see a range of insightful training sessions given by the standing committees of MMSA which include the Standing Committee on Medical Education (SCOME), Standing Committee on Public Health (SCOPH), Standing Committee on Reproductive Health including Aids (SCORA) and Standing Committee on Human Rights and Peace (SCORP). Each committee had a chance to express what they do for the medical student body.

The SCOPH training session caught my attention immediately as it gave us first years the opportunity to learn how to use a sphygmomanometer. I was very eager to acquire this new skill which I then found useful for the World Diabetes Day event held on Saturday 15th November in Valletta. Another training session explored the technique of suturing, where students practiced their sutures on oranges and pig's feet – a unique experience!

Training sessions were not only about the actual techniques needed in the medical career but they were also related to interpersonal skills. Such skills were introduced through teamwork, leadership, public speaking and advocacy sessions. Furthermore, sessions on handling stress and different studying methods were given. TRD caters not only for first year students but also for more advanced students, e.g. a talk on how to present and prepare the portfolio needed for the end of 5th year was held.

One cannot forget the leisure and social side to the live-in. The Board of Directors hotseat had the scope to introduce the directors of MMSA to the students in a friendly and personal manner. There was also the chance to play laser tag and zorbing football. The famous themed parties were not to be missed with the themes being 'Twisted Disney' and 'I shouldn't be here'.

The TRD weekend turned out to be an informative yet interesting experience which helped medical students to get accustomed to the rollercoaster-ride life as a medical student. With zombified Disney princesses and emo Nemos to educational training sessions, who knows what next year's TRD will bring? 🦋

THE AIM OF THE GERMAN-MALTESE MEDICAL SOCIETY



The German-Maltese Medical Society (GMMS) was founded in 1999 under the patronage of the *German-Maltese Circle*. The aim of the institution is to promote the exchange of medical knowledge by running clinical clerkships for medical students, as well as organizing scientific symposia, seminars and workshops. Furthermore, hospitations in Germany and Malta are also organized. In 2013 and 2014 eighteen Maltese medical students took up the offer of the Red Cross Hospital in Kassel, Germany, and successfully completed a clinical clerkship in different hospital departments. The nine clinical clerkships for 2015 have already been allocated. Future offers will be expanded so that Maltese doctors can participate in longer clinical clerkships in Kassel.

Interested parties can contact
kontakt@rkh-kassel.de or access
www.rkh-kassel.de

Further information on the GMMS may be obtained
by contacting gmms@germanmaltesecircle.org or
accessing www.germanmaltesecircle.org/gmms.htm



IN THIS ISSUE WE HAVE A UK-BASED CONTRIBUTOR AS WELL AS AN AUSTRALIA-BASED CONTRIBUTOR. IDENTIFY ONE OF THESE CONTRIBUTORS

AND SEND YOUR ANSWERS TO IAN.C.ELLUL@GMAIL.COM BY 21ST JANUARY 2015.

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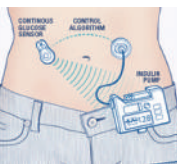
SARAH CRAUS, FIFTH YEAR MEDICAL STUDENT IS THE LUCKY WINNER OF THE MEDICAL LANGUAGE TRANSLATOR BOOK PUBLISHED BY MMSA. SHE WAS THE 5TH PARTICIPANT WHO REPLIED CORRECTLY TO THE QUESTION, 'WHO CARRIED OUT THE FIRST HUMAN HEART TRANSPLANT?' THE CORRECT ANSWER WAS DR CHRISTIAAN BARNARD.

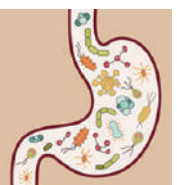


ERRATA CORRIGE

The contribution by MMSA, My Experience in the MMSA, published in Issue 5/13 has been erroneously attributed to Cheryl Cachia. The correct author was Gianluca Fava. The error is regretted.

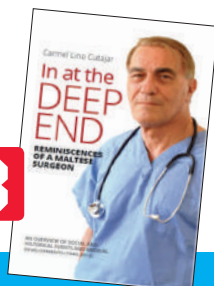
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References: 1. Mancia G, Fagard R, Narkiewicz K et al. 2013 Practice guidelines for the management of arterial hypertension of the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC): ESH/ESC Task Force for the Management of Arterial Hypertension. *J Hypertens*. 2013; 31(10):1925-38. 2. Novartis Europharm Limited. Exforge HCT® Summary of Product Characteristics. 3. Calhoun DA, Lacourciere Y, Chiang YT, Glazer RD. Triple antihypertensive therapy with amlodipine, valsartan, and hydrochlorothiazide. A randomized clinical trial. *Hypertension* 2009;54:32-39

Full prescribing information is available from the Malta M.A.H.: Novartis Europharm Ltd., Wimblehurst Road, Horsham, West Sussex, RH12 5AB, United Kingdom. Tel: +356 21222872.

Exforge® HCT (amlodipine besylate/valsartan/hydrochlorothiazide) 5/160/12.5mg and 10/160/12.5mg Film-coated tablets

PRESENTATION: Film-coated tablets containing: 5 mg amlodipine as amlodipine besylate, 160 mg valsartan and 12.5 mg hydrochlorothiazide or 10 mg amlodipine as amlodipine besylate, 160 mg valsartan and 12.5 mg hydrochlorothiazide. **INDICATIONS:** Exforge HCT is indicated for essential hypertension as a substitution therapy in adult patients whose blood pressure is adequately controlled on the combination of amlodipine, valsartan and hydrochlorothiazide (HCT) taken either as three single-component formulations or as a dual-component and a single-component formulation. **DOSEAGE:** One tablet of Exforge HCT 5/160/12.5 mg or 10/160/12.5 mg daily. No adjustment of the initial dose is required for patients with mild to moderate renal impairment due to the hydrochlorothiazide component. Exforge HCT is contraindicated for use in patients with anuria and in patients with severe renal impairment (glomerular filtration rate (GFR) <30 ml/min/1.73 m²). Amlodipine dosage recommendations have not been established in patients with mild to moderate hepatic impairment.

CONTRAINDICATIONS: Known hypersensitivity to the active substances, to other sulfonamides, to dihydropyridine derivatives, or to any of the excipients. Second and third trimesters of pregnancy. Hepatic impairment, biliary cirrhosis or cholestasis. Severe renal impairment (creatinine clearance < 30 ml/min). Anuria. Patients undergoing dialysis. Refractory hypokalaemia, Hyponatraemia, Hypercalcaemia. Symptomatic hypercalcaemia. Exforge HCT is contraindicated in patients with severe renal impairment, diabetes, anuria or underlying dialysis. Hydrochlorothiazide may raise the serum uric acid level due to reduced clearance of uric acid and may cause or exacerbate hyperuricaemia as well as precipitate gout in susceptible patients. Exforge HCT is contraindicated in patients with hypercalcaemia and should only be used after correction of any pre-existing hypercalcaemia. Exforge HCT should be discontinued if hypercalcaemia develops during treatment. Serum levels of calcium should be periodically monitored during treatment with thiazides. Severe hypotension, Shock (including cardiogenic shock), Obstruction of the outflow tract of the left ventricle (e.g. hypertrophic obstructive cardiomyopathy and high grade aortic stenosis), Haemodynamically unstable heart failure after acute myocardial infarction. Exforge HCT should not be used with alkali-containing products in patients with diabetes or renal impairment.

WARNINGS/PRECAUTIONS: The safety and efficacy of amlodipine in hypertensive crisis have not been established. In sodium-depleted and/or volume-depleted patients, such as those receiving high doses of diuretics, symptomatic hypotension may occur after initiation of treatment with Exforge HCT. Exforge HCT should be used only after correction of any pre-existing sodium and/or volume depletion. Caution is advised when administering Exforge HCT to patients with renal impairment or systemic lupus erythematosus. Exforge HCT should be used with caution to treat hypertension in patients with unilateral or bilateral renal artery stenosis or stenosis to a solitary kidney since blood urea and serum creatinine may increase in such patients. Angioedema, including swelling of the larynx and pharynx causing airway obstruction and/or swelling of the face, lips, pharynx and/or tongue, has been reported in patients treated with valsartan. Some of these patients previously experienced angioedema with other medicinal products, including angiotensin-converting enzyme (ACE) inhibitors. Exforge should be discontinued immediately in patients who develop angioedema and should not be re-administered. Calcium channel blockers, including amlodipine, should be used with caution in patients with congestive heart failure, as they may increase the risk of future cardiovascular events and mortality. Disturbance of serum electrolyte balance (monitoring recommended), glucose tolerance and serum levels of cholesterol, tryglicerides and uric acid. Not recommended in patients below 18 years of age and in patients with primary hyperaldosteronism. Beta-blocker withdrawal should be gradual. Caution in elderly and in patients with hepatic impairment or biliary obstructive disorders. Caution in patients with heart failure and coronary artery disease. As with all other vasodilators, special caution in patients suffering from aortic or mitral stenosis, significant aortic stenosis that is not high grade. If a photosensitivity reaction occurs during treatment, it is recommended to stop the treatment. Not recommended during the first trimester of pregnancy. Avoid use in women planning to become pregnant and while breast-feeding. Caution when driving or using machinery. Patients taking Exforge and driving vehicles should take into account that Exforge may cause dizziness or weariness may occasionally occur. Amlodipine can have mild or moderate influence on the ability to drive and use machines. If patients taking amlodipine suffer from dizziness, headache, fatigue or nausea the ability to react may be impaired. Treatment with Exforge HCT should only start after correction of hypokalaemia and any coexisting hypomagnesaemia. Thiazide diuretics can precipitate new onset hypokalaemia or exacerbate pre-existing hypokalaemia. As with all other diuretics should be administered with caution in patients with conditions involving enhanced potassium loss, for example salt losing nephropathies and prerenal (cardiogenic) impairment of kidney function. If hypokalaemia develops during hydrochlorothiazide therapy, Exforge HCT should be discontinued until stable correction of the potassium balance. Thiazide diuretics can precipitate new onset hyponatraemia and hypercholesterolaemia or exacerbate pre-existing hyponatraemia. Hyponatraemia, hyponatremia accompanied by neurological symptoms (nausea, progressive disorientation, apathy) has been observed. Treatment with hydrochlorothiazide should only be started after correction of pre-existing hyponatraemia. In case severe or rapid hyponatraemia develops during Exforge HCT therapy, the treatment should be discontinued until normalisation of sodium. All patients receiving thiazide diuretics should be periodically monitored for imbalances in electrolytes, particularly potassium, sodium and magnesium. Thiazide diuretics may precipitate azotaemia in patients with chronic kidney disease. When Exforge HCT is used in patients with renal impairment, periodic monitoring of serum electrolytes (including potassium), creatinine and uric acid serum levels is recommended. Hydrochlorothiazide has been associated with an idiosyncratic reaction resulting in acute transient myopia and acute angle-closure glaucoma. Symptoms are onset of decreased visual acuity or ocular pain and typically occur within hours to a week of treatment initiation. Untreated acute-angle closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue hydrochlorothiazide as rapidly as possible. Prompt medical or surgical treatment may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle closure glaucoma may include a history of sulphamide or penicillin allergy, the safety of amlodipine in human pregnancy has not been established. Use in pregnancy is only recommended when there is no safer alternative and when the disease itself carries greater risk for the mother and fetus. Evaluation of patients with heart failure or post-myocardial infarction should always include assessment of renal function. Calcium channel blockers, including amlodipine, should be used with caution in patients with congestive heart failure, as they may increase the risk of future cardiovascular events and mortality. There is evidence that the concomitant use of ACE inhibitors, ARBs or alkalis increases the risk of hypotension, hyperkalaemia and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ACE inhibitors, ARBs or alkalis is therefore not recommended. If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and should be frequently monitored for imbalances in electrolytes, particularly potassium, sodium and magnesium. ACE inhibitors and ARBs should not be used concomitantly in patients with diabetic nephropathy. **INTERACTIONS:** Monitoring recommended when used concomitantly with lithium. Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors, angiotensin II receptor antagonists including valsartan or thiazides. Since renal clearance of lithium is reduced by thiazides, the risk of lithium toxicity may presumably be increased further with Exforge HCT. Therefore careful monitoring of serum lithium concentrations is recommended during concomitant use. Caution when used concomitantly with drugs that may increase potassium levels. Caution if combined with other antihypertensives, curare derivatives, NSAIDs, corticosteroids, ACTH, amphotericin, carbamazepine, Penicillin G, salicylic acid derivatives, digoxin, CYP3A4 inhibitors and inducers, antiarrhythmic agents, allipropenolol, sulfonazoles, progestins, amantadine, amiodarone, dioxazine, cytotoxic drugs, anticholinergics, methyldopa, cholestyramine, cholestylin resins, vitamin D, calcium salts, carbamazepine and ciclosporin, alcohol, anaesthetics and sedatives. Concomitant use of amlodipine with strong or moderate CYP3A4 inhibitors (protease inhibitors, azole antifungals, macrolides like erythromycin or clarithromycin, verapamil or diltiazem) may give rise to significant increase in amlodipine exposure. The clinical translation of these pharmacokinetic variations may be more pronounced in the elderly. Caution in patients receiving amlodipine who also have a blood pressure lowering effect may potentiate orthostatic hypotension. Cisapride may decrease the bioavailability of thiazide-type diuretic. Thiazides may alter glucose tolerance, dose adjustment of the antidiabetic medicinal product may be necessary. Absorption of hydrochlorothiazide is decreased by cholestyramine or colestipol. The hypotensive effect of diuretics may be intensified by concomitant administration of medicinal products such as antihypertensives, antipsychotics, antiepileptics, etc. Caution is indicated in long-term administration of these medicinal products. Due to the risk of hypokalaemia, hydrochlorothiazide should be administered with caution when associated with medicinal products that could induce *larsades de pointes*, in particular Class Ia and Class III antiarrhythmics and some antipsychotics. Thiazides potentiate the antihypertensive action of other antihypertensive drugs (e.g. guanethidine, methyldopa, beta blockers, vasodilators, calcium channel blockers, ACE inhibitors, ARBs and Direct Renin Inhibitors). Hydrochlorothiazide may reduce the response to pressor amines such as noradrenaline. The clinical significance of this effect is uncertain and not sufficient to preclude their use. Concomitant use of thiazide type diuretics may lead to hypercalcaemia in patients pre-disposed for hypercalcaemia (e.g. hyperparathyroidism, malignancy or vitamin-D-mediated conditions) by increasing tubular calcium reabsorption. Administration of amlodipine with grapefruit or grapefruit juice is not recommended as bioavailability may be increased in some patients, resulting in increased blood pressure lowering effects. **ADVERSE REACTIONS:** Agranulocytosis, bone marrow depression, Decrease in haemoglobin and in haematocrit, Haemolytic anaemia, Leukopenia, Neutropenia, Thrombocytopenia, sometimes with purpura, Aplastic anaemia, Hypersensitivity, Hypersensitivity reactions, Hypertension, Hypokalaemia, Hyperlipidaemia, Hyperuricaemia, Hypochloroalkalosis, Hypokalaemia, Hypomagnesaemia, Hyponatraemia, Worsening of diabetic metabolic state, Depression, Insomnia/sleep disturbances, Mood swings, Confusion, Coordination abnormal, Dizziness, Dizziness postural, dizziness exertional, Dysgeusia, Extrapyramidal syndrome, Headache, Hypertonia, Lethargy, Paraesthesia, Peripheral neuropathy, neuropathy, Somnolence, Tremor, Tremor, Tinnitus, Urinary incontinence, Visual disturbances, Visual impairment, Tinnitus, Vertigo, Palpitations, Tachycardia, Arrhythmias (including bradycardia, ventricular tachycardia, and atrial fibrillation), Myocardial infarction, Flushing, Hypotension, Orthostatic hypotension, Phlebitis, thrombophlebitis, Vasculitis, Cough, Dyspnoea, Respiratory distress, pulmonary oedema, pneumonitis, Rhinitis, Throat irritation, Abdominal discomfort, abdominal pain upper, Breath odour, Change of bowel habit, Constipation, Diarrhoea, Dry mouth, Dysuria, Dyspepsia, Gastroitis, Gingivitis, Hemiparesis, Nausea, Pancreatitis, Vomiting, Hepatic enzyme elevation, including increase of serum bilirubin, Hepatitis, Intrahepatic cholestasis, jaundice, Alopecia, Angioedema, Dermatitis Bullous, Cutaneous lupus erythematosus-like reactions, reactivation of cutaneous lupus erythematosus, Erythema multiforme, Exanthema, Hyperhidrosis, Photosensitivity reaction, Pruritus, Erythema, Rash, Skin discoloration, Urticaria and other forms of rash, Vasculitis necrotising and toxic epidermal necrolysis, Exfoliative dermatitis, Stevens-Johnson syndrome, Quincke oedema, Arthralgia, Back pain, Joint swelling, Muscle spasm, Muscular weakness, Myalgia, Pain in extremity, Ankle swelling, Elevation of serum creatinine, Micturition disorder, Nocturia, Pollakiuria, Renal dysfunction, Renal failure acute, Renal failure and impairment, Impotence, Gynaecomastia, Abasia, gait disturbance, Asthenia, Discomfort, malaise, Fatigue, Non cardiac chest pain, Oedema, Pain, Paresthesia, Lips increased, Blood uric acid increased, Blood urea nitrogen increased, Glycosuria, Serum potassium decreased, Serum potassium increased, Weight increase, Weight decrease. **LEGAL CATEGORY:** POM **PACK SIZES:** Packs of 28 film-coated tablets. **MARKETING AUTHORISATION HOLDER:** Novartis Europharm Limited, Wimblehurst Road, Horsham, West Sussex, RH12 5AB, United Kingdom. **MARKETING AUTHORISATION NUMBERS:** Exforge HCT 5 mg/160 mg/12.5 mg: EU/09/559/01/2, Exforge HCT 10 mg/160 mg/12.5 mg: EU/10/569/01/1. **Please refer to Summary of Product Characteristics (SPC) before prescribing.** Full prescribing information is available on request from Novartis Pharma Services Inc., Representative Office Malta, P.O. Box 4, Marsa, MRS 1000, Malta. Tel: +356 21222872. 2014-MT-EFH-24-Sept-2014.

EPITHELIAL- MESENCHYMAL TRANSITION (EMT)- ITS THERANOSTIC ROLE IN CANCER PROGRESSION AND METASTASIS

ABSTRACT

Epithelial-mesenchymal transition (EMT) is a process by which a fully differentiated epithelial cell attains mesenchymal traits and capabilities such as motility and invasiveness. There are three types. Type 3 EMT is associated with tumour cells increasing their malignant potential and result in increased resistance to conventional chemo- and radiotherapy. Molecules involved are being used as biomarkers and therapeutic targets.

DEFINING EMT

EMT refers to the biological process by which epithelial cells become mesenchymal cells. During this transition, epithelial cells undergo several biochemical and cytoskeletal modifications. Epithelial cells are polarised cells with distinct apical, lateral and basal plasma membrane domains. They are characterised by intercellular adhesion complexes. Upon undergoing EMT, the apico-basal polarity is lost, the intercellular adhesion complexes are disrupted, and the underlying basement membrane is degraded. The resulting mesenchymal cells are nonpolarised, lack intercellular junctions, and are able to migrate away through the extracellular matrix as individual cells from the epithelial layer in which they originated^{1,2}.

EMT was first described by Elizabeth Hay³, who realised that the phenotypic conversion of epithelial cells was important during early embryo cell migration and gastrulation. She suggested that differentiated epithelial cells can “transform” into mesenchymal cells by undergoing phenotypic changes. Since then, studies have found that EMT is reversible, and mesenchymal cells can go back to epithelial cells through a reverse process of mesenchymal-epithelial transition (MET). For this reason, “transformation” has been amended to “transition”^{3,4}.

Three subtypes of EMT are encountered. Type 1 EMT is associated with implantation, embryo formation, and organ

development. Type 2 EMT is associated with organ fibrosis, tissue regeneration, and wound healing⁵⁻⁷. Type 3 EMT occurs in epithelial cancer cells that have formed solid tumours. Here, EMT is linked in the switching of epithelial cells into metastatic cells which journey in the bloodstream and then form secondaries⁸.

EMT AND ITS ROLE IN CANCER PROGRESSION AND METASTASIS

Several molecular processes are employed to initiate and complete an EMT. Some of these processes include changes in the expression of (a) specific cell-surface proteins, (b) cytoskeletal proteins, (c) extracellular proteins, (d) transcription factors, and (d) specific microRNAs.

(A) EXPRESSION OF SPECIFIC CELL-SURFACE PROTEINS

E-cadherin: E-cadherin expression has been found to decrease during EMT⁹. Indeed, the induction of EMT in cancer is promoted by a loss of function of E-cadherin¹⁰. Cell lines that lack E-cadherin are more prone to increased tumourigenicity and metastasis when transferred into mice that are immunodeficient¹¹. Mutations in the E-cadherin gene were identified in gastric cancers in patients under 35 years¹² and in the signet ring cell carcinoma of the stomach¹³. Bringuier et al showed that decreased E-cadherin correlates with a poor prognosis in bladder tumours¹⁴. A similar relationship was shown by Mattijssen et al in head and neck squamous-cell carcinoma¹⁵.

Integrins: Studies show that integrin signalling facilitates EMT^{16,17}. However, some integrins are expressed on both epithelial and mesenchymal cells, and so they have limited use as biomarkers. Still, some can be used as EMT markers, e.g. (i) $\beta 6$ integrin – in colon carcinoma, only cancer cells that have metastatic potential express high levels; normal epithelial cells and non-invasive tumour cells express low levels¹⁸; (ii) $\alpha 5$ integrin increase expression in B16F10 melanoma cells¹⁹.

Discoidin Domain Receptor 2 (DDR2): DDR2 is a marker that reflects adjustment to the changed microenvironment of the extracellular matrix as a result of EMT. Expression of this collagen-specific receptor tyrosine kinase is associated with increased invasiveness^{20,21}.

(B) EXPRESSION OF CYTOSKELETAL PROTEINS

FSP1: Fibroblast-Specific Protein-1 is used as a biomarker for the detection of Type 3 EMT^{22,23}. Indeed, as part of the molecular program of Type 3 EMT, metastatic cells express FSP1. Expression of FSP1 in tumour cells could determine the latency of tumour dispersion and it could be an appropriate therapeutic target to control metastatic progression²².

Vimentin: Vimentin is an intermediate filament expressed in mesenchymal cells. There is a positive relationship between vimentin expression and increased metastasis in infiltrating ductal breast carcinoma²⁴. In their study, Raymond and Leong state that vimentin



expression could be a marker of aggressive behaviour and such carcinomas may profit from early adjuvant therapy. This is reiterated in a review by Kokkinos et al²⁵.

α -SMA: Alpha-smooth muscle actin is used as a biomarker in breast cancers especially basal phenotype or basal-like breast cancers²⁶, which are characterised by early recurrence and decreased overall survival²⁷.

β -Catenin: In normal epithelial cells and non-invasive cancer cells, β -Catenin is found located in the cell membranes. In cells that are undergoing EMT, however, β -Catenin is located either in the cytoplasm or in the nucleus²⁸. Here, it plays a dual role – it links cadherins to the cytoskeleton, and, together with the T cell factor (TCF)/LEF, it serves as a co-transcriptional activator²⁹. In fact, the resulting complex, the β -Catenin/TCF/LEF complex, directly controls gene expression that is associated with EMT, particularly Snail³⁰. For this reason, β -Catenin is used as a biomarker of EMT in various studies of cancer. Brabletz et al investigated the nuclear overexpression of β -Catenin in colorectal cancer, and found that the nuclear translocation of β -Catenin may play a direct role in the tumour invasion processes²⁸.

(C) EXPRESSION OF EXTRACELLULAR PROTEINS

Laminins: Certain laminins have become established biomarkers. For instance, the upregulation of laminin-5 is associated with invasive cancers, such as oral squamous carcinoma³¹, hepatocellular carcinoma³², and breast carcinomas of the ductal type³³.

Fibronectin: Fibronectin is an integral constituent of the extracellular matrix associated with the desmoplastic stroma in tumours. However, its use as a biomarker is limited because it is also produced by other types of cells, such as epithelial cells³⁴. Still, some studies have found that Type 3 EMT is associated with an increase of fibronectin expression *in vitro*³⁵.

(D) ACTIVATION OF TRANSCRIPTION FACTORS

FTS-1: Fibroblast transcription site-1 is a regulatory element that is present in the promoter region of various genes associated with EMT, including those that encode α -SMA, β -Catenin, E-cadherin, FSP1, vimentin, Snail1 and Twist. In addition, FTS-1 forms a complex with CBF-A and KRAB-associated protein 1 (KAP-1)⁷; the resulting CBF-A/KAP-1/FTS-1 complex is a master regulator of EMT³⁶.

Snail: Several studies³⁷⁻⁹ have shown that the transcription factor Snail mediates EMT. Indeed, all known events occurring appear to be associated with the activation of Snail. Amongst others, Snail activation brings about the suppression of E-cadherin expression and the increased expression of mesenchymal cell markers such as fibronectin⁴⁰. A correlation between Snail activation and EMT was established in human colorectal cancer cells³⁷, in oral squamous carcinoma cells³⁸, and in thyroid cancer cells³⁹.

Studies, such as those by Medici et al⁴¹, have also demonstrated that Snail-mediated EMTs are promoted by the transforming growth factor- β (TGF- β). Separate *in vitro* studies have shown that TGF- β can induce EMT in certain types of cancers such as breast⁴², ovarian⁴³ and skin cancers⁴⁴.

Twist: Twist is a protein that is upregulated during cancer metastasis. Specifically, Twist acts independently of Snail to repress E-cadherin⁴⁵ and to upregulate fibronectin and N-cadherin³⁵.

FOXC2: Forkhead boxC2 is another transcription factor. Overexpression of any inducer of EMT (e.g. Snail, TGF- β , Twist) increases expression of FOXC2. Overexpression of FOXC2 itself induces EMT, suggesting a significant role for FOXC2 in Type 3 EMT, especially when ductal breast cancers and metastatic breast cancer cells are involved⁴⁶.

(E) CHANGES IN THE EXPRESSION OF SPECIFIC MICRORNAS

The fact that EMT is reversible, suggests that EMT can also have an epigenetic background. Non-coding microRNAs are the ones most documented and form components of the cellular signalling circuitry choreographing the EMT program⁷. miR200 was found to inhibit the transcriptional repressors of E-cadherin expression, ZEB1 (zinc finger E-box binding homeobox 1) and ZEB2, and thus helps in preserving the epithelial cell phenotype^{47,48}. miR200 have been found to be downregulated in ductal and metaplastic breast cancers, where a loss of miR200 is correlated with increased vimentin expression and a decrease in E-cadherin levels in cancer cells⁴⁷.

In addition there is also miR21 and miR-10b; TGF- β 1-induced EMT involving keratinocytes is associated with miR21⁴⁹ and Twist-induced EMT, involving breast cancer cells, is associated with miR-10b⁵⁰.

THERANOSTIC IMPLICATIONS

Many of the aforementioned molecules are being used as biomarkers to assess the presence or severity of cancer and its response to medical treatment. They are also being used to optimize therapy for individual patients. Furthermore, clinical studies based on EMT mechanisms have started.

One study by Chang et al⁵¹ showed that radio-resistance in prostate cancer is associated with EMT events and the PI3K/Akt/mTOR signaling pathway. The *in vitro* tests carried out showed that the combination of BEZ235 (PI3K/mTOR inhibitor) with radiotherapy is a promising approach to overcome radio-resistance in the treatment of prostate cancer. This modality leads to reduced expression of EMT markers and PI3K/Akt/mTOR signaling pathway proteins. Such findings have laid down a platform for *in vivo* animal studies and clinical trials.

Another showcase is the work by Cufi et al⁵² which showed that silibinin (from thistle extract) reversed levels of certain microRNAs associated with EMT and repressed mesenchymal-related markers in NSCLC (non-small cell lung cancer) refractory to erlotinib treatment. Silibinin was also found to activate a mesenchymal-to-epithelial transition (MET) and prevent the extremely migratogenic phenotype. Now clinical trials are on the way to assess how silibinin might be useful to prevent or reverse NSCLC progression after treatment with erlotinib.

CONCLUSION

Even though some insight into the mechanisms involved in EMT in cancer progression and metastasis has been achieved, more research is warranted so that the knowledge gained can be translated into coherent, clinically effective systems. ❄️



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References: 1 Terpstra IJ, Acne treatment with 4% erythromycin and 1.2% zinc acetate. Cardiff 1988; 255-259. 2 Stainforth J et al. Dermatol Treat 1993 4: 119-122. 3 Schachner L et al. J Am Acad Dermatol 1990; 22(3): 489-495.

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PSYCHOTHERAPIES

BRIGITTE OHK

Psychotherapy can help people overcome emotional problems, relationship problems, anxiety, habits like smoking, eating disorders, depression and obsessional thinking, work-related problems and much more.

There are a lot of different types of psychotherapy available. To shed some light on the choices, here are descriptions of several of the older established therapies that usually encompass a code of ethics. Professional associations also generally offer training programs on such therapies. The more recent innovative therapies may not yet involve such a structure. But this does not mean that they are not valuable therapies.

BEHAVIOURAL PSYCHOTHERAPY

This focuses on helping a person to understand how changes in behaviour can lead to changes in how he is feeling. Step by step with a set of different techniques the person learns how to increase chances for affirmative experiences when taking part in positive or socially reinforced activities.

COGNITIVE THERAPY

This assumes that much of what one thinks influences an individual's feelings. By correcting inaccurate or even false beliefs about themselves, their situation and the world around them, the patients' perception of events and their emotional state will improve. Cognitive therapy can take into account of what happened in the past, but mainly focuses on the present and future.

COGNITIVE BEHAVIOURAL THERAPY (CBT)

This is a combination of the two previous techniques. Its structure aims at changing patterns of thinking and behaviour that are behind a person's problems. By pointing out alternative ways of looking at a situation, the person's view of life will change and ultimately this will improve the way the person feels.

Several CBT treatment programs for particular disorders have been successfully evaluated for efficacy. CBT is goal oriented and fairly brief (6-25 sessions). CBT is effective for the treatment of a variety of problems, such as alcohol problems, anxiety disorders, eating disorders, mood disorders, personality disorders, substance abuse, etc.

GESTALT THERAPY

This emphasizes on personal responsibility. It is an existential form of psychotherapy that focuses upon the individual's experience in the present moment. The therapist-client relationship and the environmental and social contexts of a person's life are important tools that are used to observe the self-regulating adjustments that people adhere to as a result of their

overall situation. The goal for the individual is to become aware of what he is doing, how he is doing it and how he can change himself, and simultaneously learn to accept and value himself. In Gestalt Therapy the therapist and client are seen as equals.

PSYCHODYNAMIC (PSYCHOANALYTIC) PSYCHOTHERAPY

This is an insight-oriented therapy that focuses on unconscious processes visible in a person's current behaviour. The goal is to bring the person to self-awareness and to understand the influence of his past on this immediate behaviour. The main attention is given to the events of the first 6 years of his life. Psychodynamic psychotherapy is a long term approach that requires usually two years or more of sessions, since it takes time to change one's personality or to integrate important developmental learning that was not met in previous years.

A short-term version also exists that can focus on one main major subject that is agreed on by the therapist and client.

FAMILY AND MARITAL THERAPY

This systemic psychotherapy approach understands individuals in the context of the surroundings that influence their development, and works with people who are in a relationship. Problems can run in a marriage, relationship or family. Family and marital therapies involve everybody concerned. The therapist sheds light on the relationships involved and on past relationships and events that might influence the person's current emotional state. Communication patterns that are malfunctioning within the family or relationship system are identified and amended. The participants learn how to listen, how to ask questions and they learn how to respond in a non-defensive way.

COUNSELLING

This is usually short term and aims to help you clarify your topmost problems. It is primarily used to help someone cope with recent disturbing events and difficulties. The aim is not to help you change as a person. This is the task of the other approaches mentioned above.

CONCLUSION

Each of the above mentioned therapeutic techniques has its unique features, its practical aspects, and its shortcomings. Choosing one technique over the other is not a matter of effectiveness, it is rather a question of the individual's current difficulty and his personality. The aim of a person who seeks support is to overcome his problems and this will work best if the individual chooses a therapeutic style that he feels comfortable with. ❄

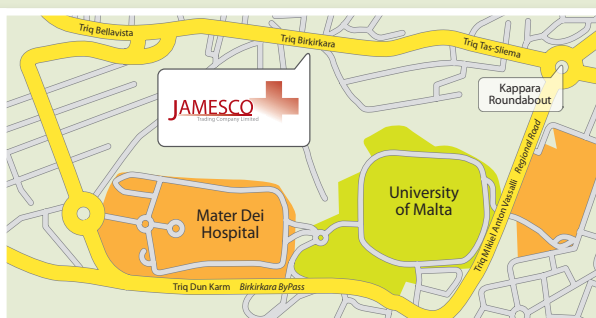
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MARIKA AZZOPARDI

BETWEEN ONE SONG AND THE NEXT

A medical student is somebody who is usually taken up completely by university studies, medicine books and the like. But Maria Angela Grima, a fifth year medical student who is just 22 years old, has something else on her plate - singing.

Meeting the petite young woman for a coffee, I get to know the story behind this love for singing. “I began singing at eight years of age, and that was as part of a children’s choir. One of my first appearances on stage was with the Cantores Sancti Juliani in St Julian’s, and one of the first performances was during the visit of Pope John Paul II. Obviously, for myself as a young child, this was a memorable and incisive experience, especially since there were over a hundred youngsters in the choir.”

Varied functions followed, both locally and abroad including in London and Naples. Her singing progressed in tandem with pianoforte studies, up until the point when she started having private singing tuition to develop her skills as a soloist. “My teacher Juliette Bisazza encouraged me to take part in various concerts and public functions, for which I am thankful since this exposure has built up my confidence towards an audience. As a classical soprano, I was eventually able to proceed in this field and have recently joined the Teatru Manoel Youth Opera, where I have taken part in two concerts held during these past months.”

Maria Angela says that her participation in the Teatru Manoel Youth Opera has allowed her to improve her theatrical skills and develop the ability to work in a team of fellow musical professionals, all with different qualities and roles to play.

She has performed in classical performances such as the concert based on Mozart’s ‘Le Nozze di Figaro’, in which she had the role of Susanna. This heralded new challenges regarding stage presence and communication with an audience.

“Being part of the TMYO thus gave me the opportunity to be a soloist in ‘Le Nozze di Figaro’, this being my first time having such an important role. The challenge was putting the audience into the story of the opera by communicating through my character of Susanna, acting as natural and as credible as possible. Another challenge was to learn the music score by heart in a very short time, since we prepared for the opera of ‘Nozze di Figaro’ in just ten weeks.”

Maria Angela’s passion for singing owes its origins to her family since her own father is a singer and her mother plays the piano and organ and teaches pianoforte studies. “I love singing and although I could have



Singing at a wedding ceremony at Dingli Parish Church

Playing the role of Suzanna in Mozart's *Le Nozze di Figaro* with the Teatru Manoel Youth Opera (far right)



taken it up as a profession, I also had a second dream in my life since I was about seven years of age - and that was medicine which fuelled my aspiration to become a doctor - a beautiful profession and vocation. Obviously, combining both singing and medicine studies means I have had to learn time management, in a big way.”

During her first year in medicine, she had to cope with studies and two concerts which were hard to handle. During the following years she learnt how to focus better, especially during stressful moments like the run-up to an opera or the run-up to exams. “All those who have studied medicine know that you have to study long hours on a daily basis, even after taxing shifts at the hospital. Coping with lack of sleep and learning to take several power naps has helped me immensely and I get a boost from jogging whenever I am able to do so.”

Apart from having attended a medicine course at the University of Manchester in 2012 and taken part in a surgery exchange in Santiago di Compostela in Spain in 2013, she has attended several medical conferences abroad. Maria Angela has also written local articles, one on diabetes, another on dehydration, with her most recently published article about oral health having appeared on the Times of Malta last September. But what are her plans post-degree? “I will take up my two years of housemanship and hopefully proceed with further studies. I would love to specialise and do have a special interest in medicine and in surgery, but I think it is a bit too early for me to decide. In the meantime I will definitely continue my singing career, hopefully having more time to dedicate to that.” ❄️



PLATELET-RICH PLASMA INJECTIONS TO PROMOTE HEALING OF SOFT TISSUE INJURIES

PIERRE VASSALLO

The healing of bone and soft tissue injuries takes place in many stages. This has been one of the most exciting areas of research in orthopedic surgery and sports medicine. The initial healing stages include inflammation and cell proliferation.

It is well known that platelet activation plays a key role in the process of wound and soft tissue healing. Platelet-rich plasma (PRP) is obtained from the patient's own blood by a simple technique that increases the platelet concentration above baseline; local injection of this PRP promotes healing of injured tendons, ligaments, muscles and joints. Platelets and the liquid plasma portion of the blood contain many factors that are essential for the cell recruitment, multiplication and specialization that are required for healing.

This technique was initially used in the 1990s in maxillofacial and plastic surgery. PRP injections are prepared under strict aseptic technique. The sample is centrifuged to obtain an increased platelet concentration and the activated platelets are injected into the abnormal tissue. The injection must be delivered as close to or preferably within the injury site. Ultrasound imaging allows identification of the injury site (Figure 1) and accurate delivery of the PRP injection (Figure 2). This results in a release of growth factors that recruit and increase the proliferation of reparative cells.

Reactions to PRP injections are very rare since the patient's own blood is being utilized. Rest from sport or

excessive exertion is advised following PRP injection for approximately one week. This is then followed by a progressive stretching and strengthening physiotherapy program.

Several clinical studies have reported that PRP injections are effective in improving function and decreasing pain in various conditions including elbow, wrist, shoulder, hip, knee and ankle tendonoses. PRP has also been show to improve healing in plantar fasciitis¹. Some studies have also reported improvement in symptoms of osteoarthritis.

The most promising early results have been seen when PRP treatment was used for chronic tendon conditions, such as lateral epicondylitis (tennis elbow) and Achilles tendinosis.

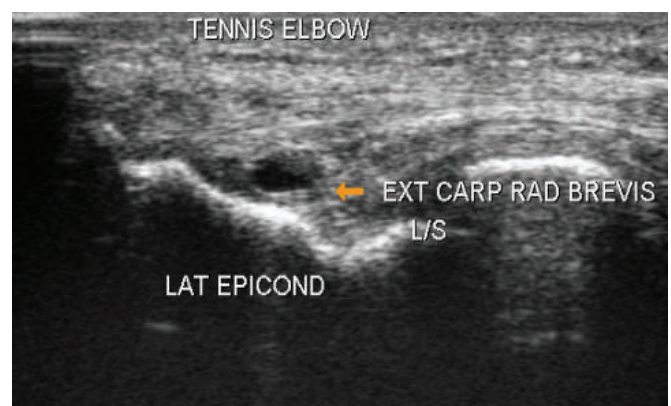
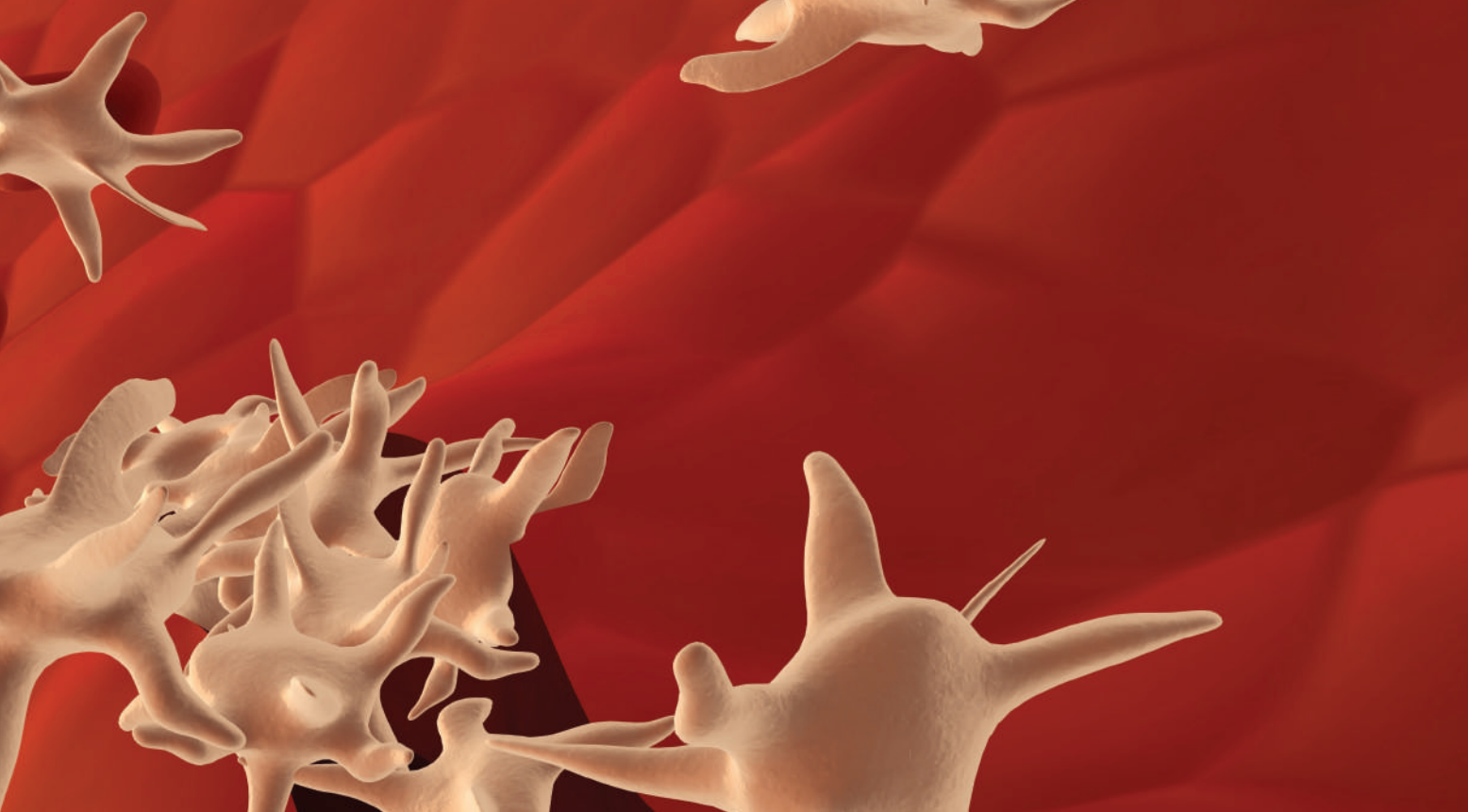


Figure 1: Coronal ultrasound scan showing lateral epicondylitis (tennis elbow) presenting with a cyst (arrow) in the deeper portion of the common extensor insertion



However, some studies were unable to prove effectiveness of PRP injection in Achilles' tendon injuries. Small studies have shown PRP treatment to be more effective than hyaluronic acid in osteoarthritis and positive results have also been seen in rotator cuff tears and medial collateral ligament knee injuries. Since it is such a safe procedure, PRP treatment can be considered for the treatment of soft tissue injuries. More research is required to optimize and standardize this mode of treatment.

Most sources recommend that anti-inflammatory medications should be stopped prior to administering a PRP injection so as not to interfere with the effect of PRP on the inflammatory response and healing. In addition, since PRP

contains endogenous growth factors, it is considered by some agencies as a performance-enhancing substance. The World Anti-Doping Agency and the United States Anti-Doping Agency forbid the use of PRP within muscles because of the possibility that growth factors may enhance the individual's performance. There is however no data to suggest that PRP truly acts as a performance-enhancing substance. Most sports agencies have not addressed the issue. ❌

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Further Reading

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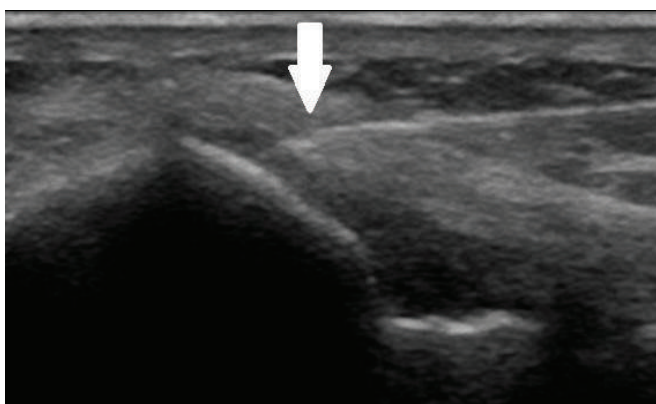


Figure 2: Needling (arrow) of lateral epicondylitis under ultrasound guidance was followed by PRP injection



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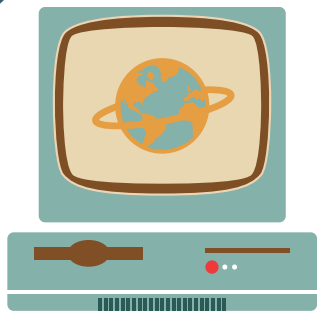


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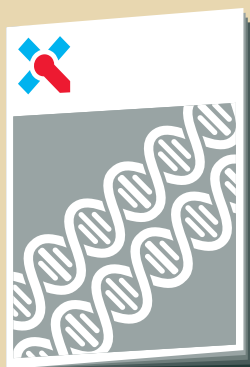
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*Season's
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THESYNAPSE TEAM

