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THE SYNAPSE

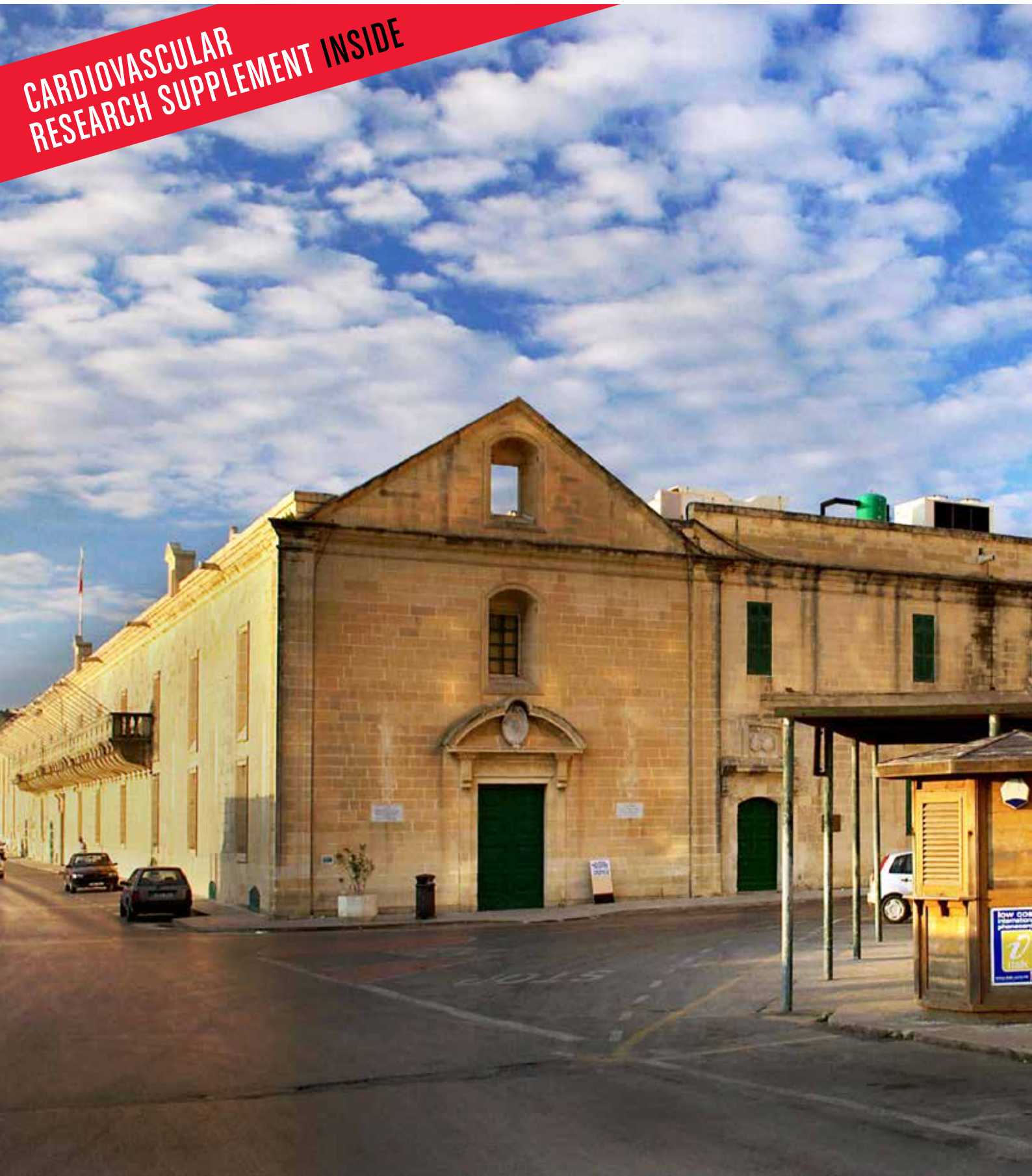
THE MEDICAL PROFESSIONALS' NETWORK

- The Decline and Fall of the Sacra Infermeria
- Cardiac surgery in Malta: past, present and future
- Developments in the management of acute coronary syndromes
- The Value of Troponin assays in modern medical practice

Volume 15, 2016 Issue 02

ISSN number 2313-8084

CARDIOVASCULAR RESEARCH SUPPLEMENT INSIDE



Actifed*

Actifed* oral solutions and tablets provide symptomatic relief of upper respiratory tract disorders [1-7]

Actifed* DM COUGH LINCTUS

- relieves dry cough and nasal congestion [3,6]

Actifed* SYRUP AND TABLETS

- clears blocked and runny noses [2,5]

Actifed* EXPECTORANT

- clears chesty cough and nasal congestion [4,7]

DOSAGE		
LIQUIDS	children aged 2 to 5 years [2-4]	2.5ml every 4-6hrs as required
	children aged 6 to 11 years [2-4]	5ml every 4-6hrs as required
	adults (including the elderly) and children aged 12 years and over [5-7]	10ml every 4-6hrs as required
TABLETS	adults (including the elderly) and children aged 12 years and over [1]	1 tablet every 4-6hrs as required

OTC legal status applies for oral solutions in adults and children aged 12 years and over.

ACTIFED ABRIDGED PRESCRIBING INFORMATION: *Please refer to full Summary of Product Characteristics (SPC) before prescribing.* **TRADE NAME:** ACTIFED. **ACTIVE INGREDIENT:** *Actifed DM Cough Linctus:* Each 5ml contains Dextromethorphan Hydrobromide 10mg, Pseudoephedrine Hydrochloride 30mg and Triprolidine Hydrochloride 1.25mg; *Actifed Syrup:* Each 5ml contains Pseudoephedrine Hydrochloride 30mg and Triprolidine Hydrochloride 1.25mg; *Actifed Expectorant:* Each 5ml contains Triprolidine Hydrochloride 1.25mg, Pseudoephedrine Hydrochloride 30mg and Guaiphenesin 100mg; *Actifed Tablets:* Each tablet contains Pseudoephedrine Hydrochloride 60mg; Triprolidine Hydrochloride 2.5mg. **PHARMACEUTICAL FORM:** Oral Solution and Tablets. **INDICATIONS:** Symptomatic relief of upper respiratory tract disorders which are benefited by a combination of: Actifed DM Linctus: a nasal decongestant, an anti-histamine and an antitussive; Actifed Syrup: a nasal decongestant, and an anti-histamine; Actifed Expectorant: a nasal decongestant, an anti-histamine and an expectorant; Actifed Tablets: a nasal decongestant, and an anti-histamine. **DOSAGE:** *please refer to full SPC. Actifed DM Cough Linctus, Actifed Syrup and Actifed Expectorant* are authorised for use without the need of a medical prescription in Adults and Children over 12 years. In Children between 2-11 years of age, these products are authorised for use only against a medical prescription as recommended by your doctor. **CONTRAINDICATIONS:** Previous intolerance to any of the active substances; use of MAOI's in the preceding two weeks; severe hypertension or heart disease; concomitant use of pseudoephedrine can cause a rise in blood pressure. **PRECAUTIONS:** May cause drowsiness; avoid the concomitant use of alcohol or other centrally active sedatives; use with caution in patients with liver impairment or moderate to severe renal impairment. **INTERACTIONS:** Sympathomimetics; MAOI's. **ADVERSE EVENTS:** Central nervous system depression or excitation with drowsiness being reported most frequently; sleep disturbance and rarely hallucinations have also been reported; skin rashes, tachycardia, dryness of mouth, nose and throat and urinary retention have occasionally been reported especially in men with prostatic enlargement. **PREGNANCY AND LACTATION:** Administration should only be considered if the expected benefits to the mother outweigh the potential risks to foetus or child. **PRESENTATION:** *DM Cough Linctus, Expectorant, Syrup:* Amber glass bottle x 100ml; Tablets: Pack x 24 tablets. Marketing Authorisation Holder: Glaxo Wellcome UK Limited, **Marketing Authorisation Number:** MA 167/00101-7 **Legal category:** POM – Actifed Tablets, POM – Actifed DM Cough Linctus, Actifed Syrup, Actifed Expectorant in Children between 2-11 years, OTC – Actifed DM Cough Linctus, Actifed Syrup, Actifed Expectorant in Adults and Children over 12 years. **For further information and full prescribing information contact GlaxoSmithKline (Malta)** Ltd: Tel. 21238131. **Date of preparation:** January 2015

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): **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)

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References: 1. Actifed Tablets SPC (Apr 2014); 2. Actifed Syrup SPC (Mar 2015); 3. Actifed DM Cough Linctus SPC (Jan 2015); 4. Actifed Expectorant SPC (Jan 2015); 5. Actifed Syrup SPC OTC (Mar 2015); 6. Actifed DM Cough Linctus SPC OTC (Jan 2015); 7. Actifed Expectorant SPC OTC (Jan 2015)

Job No: MLT_GIB/PDH/0005/16 Date of preparation: February 2016

BREXIT

THE PHARMA INDUSTRY & MALTA'S AVAILABILITY OF MEDICINES

Twenty-third June 2016. This is the referendum date when British, Irish and Commonwealth citizens living in the UK and Gibraltar, as well as UK nationals who have lived overseas for less than 15 years will decide whether the UK will withdrawal from the EU or not. Although EU citizens living in the UK and Gibraltar will not have a vote, citizens from the Commonwealth countries of Malta and Cyprus can vote. The reason for this is that, apart from the UK, only these two European countries are in Commonwealth.

Those in favour of UK's withdrawal from the EU, or Brexit as it is commonly referred to, are mainly Eurosceptics who argue that such move would allow for better control of irregular migration, as well as gain more control on UK's own trade negotiations and reduce unnecessary EU bureaucracy. However, those arguing against a possible Brexit claim that this would risk the UK's current prosperity, undermine current employments, as well as increase trade barriers with the EU.

A possible Brexit also would undoubtedly impinge on the healthcare sector. According to a letter published last February in the Financial Times the UK receives more EU funding per capita for health research than any other EU country. The letter, penned by the *UK life sciences sector* also states that *"Not only would an exit from the EU negatively impact the life sciences sector, but changing the current arrangement would lead to disruption, expense, and significant regulatory burdens for a new authorization system."* This would possibly translate into less funding for innovative research projects stemming from the various European funding programs such as Horizon 2020.

Another concern relates to the issue of patents, including pharmaceutical ones. Currently, different authorities can decide on the validity and infringement of European patents. However, this may give rise to various challenges - when either a patent proprietor seeks to enforce a patent or when a third party seeks to revoke a patent in different countries - such as high costs and possible divergent decisions. This is all set to change with the establishment of a new Unitary Patents Court of Europe, part of which is set to open in the forthcoming months in London. This will have exclusive jurisdiction for litigation relating to European patents. Obviously, if a Brexit materialises, this Court would have to re-locate outside the UK.

Apart from the European Banking Authority, London also houses the European Medicines Agency which is the regulatory body responsible for the scientific evaluation, supervision and safety monitoring of medicines developed by pharmaceutical companies for use in the EU. It is Europe's equivalent of the US Food and Drug Administration. Obviously, if a Brexit materialises, the Agency would have to move as well. This transition would definitely slow the approvals of pharmaceuticals across Europe. It also goes without saying that if Britain were to exit Europe it would produce a lacuna in the technical capability of EMA since British experts are renowned to be the biggest contributor to its drug evaluation system.

Another aspect is that Malta has over 1400 medicines licensed in Malta which are sourced from the UK market through various European procedures. Most notably, parallel importation licences, and authorisations in accordance with article 126(a) of Directive 2001/83/EC [for justified public health reasons] are issued in Malta specifically on the premise that they are licensed in another EU /EEA country; the regulatory lifecycle of these medicines shadows that of the source country. So, if indeed, the UK leaves the EU [and possibly the EEA, negotiating a separate trading relationship with the EU], would this lead to a revocation of these licences by the Maltese authorities?

FRONT COVER

Cover: The Sacra Infermeria, the 'Holy Infirmery', or the Mediterranean Conference Centre as we know it today was a state-of-the-art hospital at the time of its establishment by the Order of the Knights of St John

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The magazine is distributed free of charge to all Maltese doctors, pharmacists & dentists, as well as students of the aforementioned professions, with a print run of 3500 copies.

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A maintenance bronchodilator treatment for patients with COPD who are breathless

Anoro® Ellipta® (umeclidinium bromide/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.

Kindly consult the full Summary of Product Characteristics (SmPC) before prescribing

Trade Name: Anoro® Ellipta® **Active Ingredients:** 55 micrograms umeclidinium bromide and 22 micrograms vilanterol (as trifenatate). **Pharmaceutical Form:** 55 micrograms/22 micrograms inhalation powder, pre-dispensed. **Indications:** Maintenance bronchodilator treatment to relieve symptoms in adult patients with Chronic Obstructive Pulmonary Disease (COPD). **Dosage and administration:** Inhalation only. One inhalation once daily of Anoro® Ellipta® at the same time of the day. **Contraindications:** Hypersensitivity to the active substances or to any of the excipients (lactose monohydrate and magnesium stearate). **Precautions:** Anoro® Ellipta® should not be used in patients with asthma. Treatment with Anoro® Ellipta® should be discontinued immediately in the event of paradoxical bronchospasm and alternative therapy initiated if necessary. Cardiovascular effects may be seen after the administration of muscarinic receptor antagonists and sympathomimetics therefore Anoro® Ellipta® should be used with caution in patients with severe cardiovascular disease. Anoro® Ellipta® should be used with caution in patients with urinary retention, narrow angle glaucoma, convulsive disorders, thyrotoxicosis, hypokalaemia, hyperglycaemia and severe hepatic impairment. No dosage adjustment is required in the elderly, in renal impairment or mild to moderate hepatic impairment. **Acute symptoms:** Anoro® Ellipta® is not indicated for acute episodes of bronchospasm. Warn patients to seek medical advice if use of short-acting inhaled bronchodilator increases. A re-evaluation of the patient and of the COPD treatment regimen should be undertaken. **Interactions with other medicinal products:** Interaction studies have only been performed in adults. Avoid beta- adrenergic blockers since this may weaken or antagonize the effect of $beta_2$-adrenergic agonists. Caution is advised when co-administering with strong CYP3A4 inhibitors (e.g. ketoconazole, clarithromycin, itraconazole, ritonavir, telithromycin). Anoro® Ellipta® should not be used in conjunction with other long-acting muscarinic antagonists, long-acting $beta_2$-adrenergic agonists or medicinal products containing either of these agents. Caution is advised with concomitant use with methylxanthine derivatives, steroids or non-potassium-sparing diuretics as it may potentiate possible hypokalaemic effect of $beta_2$-adrenergic agonists. **Fertility, pregnancy, and breast-feeding:** No available data. Balance risks against benefits. **Side effects:** Common: Urinary tract infection, sinusitis, nasopharyngitis, pharyngitis, upper respiratory tract infection, headache, cough, oropharyngeal pain, constipation and dry mouth. Uncommon: Atrial fibrillation, supraventricular tachycardia, rhythm idioventricular, tachycardia, supraventricular extrasystoles and rash. **Legal category:** POM. **Presentation:** Anoro® Ellipta®. 1 inhaler x 30 doses. Anoro® Ellipta® 55/22mcg. **Marketing authorisation (MA) nos:** 55/22mcg 1x30 doses [EU/1/14/898/002]; **MA holder:** Glaxo Group Ltd, 980 Great West Road, Brentford, Middlesex, TW8 9GS, UK. **Last date of revision:** October 2014. Anoro® and Ellipta® are registered trademarks of the GlaxoSmithKline group of companies. All rights reserved. Anoro® Ellipta® was developed in collaboration with Theravance, Inc.

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)

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

ANORO ELLIPTA was developed in collaboration with Theravance

Theravance

MLT_GIB/UCV/0004/15 Date of preparation: March 2014

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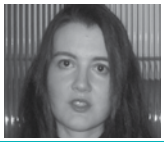

Dr Michelle Muscat MD MRCS(Ed) MSc
is currently in her third year reading for a PhD. In 2012 she obtained associateship of the Royal College of Pathologists (in chemical pathology). She harbours a strong interest in biochemical laboratory science.

ISSUE GUIDE

TheSynapse

Augmentin® ES

600 mg/42.9 mg/5 ml

Amoxicillin/Clavulanate Potassium

Powder for oral suspension

- ✓ Provides extended antibacterial coverage to include the most penicillin-resistant strains.[1]
- ✓ Recommended by leading Guidelines as first line treatment in AOM.[2,3]
- ✓ Most common adverse effects are diarrhoea, nausea, vomiting and mucocutaneous candidiasis.[4]
- ✓ Indicated for children <40 kg and older than 3 months; dosed at 90/6.4 mg/kg/day in 2 divided doses.[4]

Spreading infectious energy!

Mini Abridged Prescribing Information: *Please refer to full Summary of Product Characteristics (SPC) before prescribing.* **TRADE NAME:** Augmentin ES. **ACTIVE INGREDIENTS:** Amoxicillin (as trihydrate) and potassium clavulanate. **PRESENTATION:** 600 mg/42.9 mg/5 ml powder for oral suspension. Supplied in 100 ml glass bottle with a dosing spoon. **INDICATION:** treatment of acute otitis media and community acquired pneumonia infections in children aged at least 3 months and less than 40 kg body weight, caused or thought likely to be caused by penicillin-resistant *Streptococcus pneumoniae*. **POSOLOGY & ADMINISTRATION:** Oral use. Recommended dose is 90/6.4 mg/kg/day in two divided doses. To minimise potential gastrointestinal intolerance, administer at the start of a meal. **CONTRAINDICATIONS:** Hypersensitivity (and past history of) to the active substances, to any penicillins or to any of the excipients. **SPECIAL WARNINGS & PRECAUTIONS:** Before initiating therapy careful enquiry of previous hypersensitivity reactions to beta-lactams. Where an infection is proven to be due to an amoxicillin susceptible organism, a switch to an amoxicillin-only preparation should be considered. Convulsions may occur in patients receiving high doses or who have impaired renal function. Concomitant use of allopurinol increase likelihood of allergic skin reactions. Prolonged use may occasionally result in overgrowth of non-susceptible organisms. Contains aspartame (E951), a source of phenylalanine. The suspension also contains maltodextrin (glucose). **INTERACTIONS:** Penicillins may reduce the excretion of methotrexate causing a potential increase in toxicity. Concomitant use of probenecid is not recommended. If co-administration with oral anticoagulants is necessary, the prothrombin time or international normalised ratio should be carefully monitored with the addition or withdrawal of amoxicillin. Moreover, adjustments in the dose of oral anticoagulants may be necessary. Clinical monitoring should be performed during the combination with mycophenolate mofetil and shortly after antibiotic treatment. **PREGNANCY & LACTATION:** Use should be avoided unless considered essential by the physician. **UNDESIRABLE EFFECTS:** Very common (≥1/10): diarrhoea. Common (≥1/100, <1/10): mucocutaneous candidosis, nausea, abdominal pain. *Refer to SPC's for full list of undesirable effects*. **AUTHORISATION NUMBER:** AA 1051/00101. **MARKETING AUTHORISATION HOLDER:** GlaxoSmithKline Bulgaria EOOD. **LEGAL CATEGORY:** POM. **DATE OF PREPARATION:** July 2014. **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):*** **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). **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/adrportal and posted to the Malta Medicines Authority, Post-licensing Directorate, 203, Level 3, Rue D'Argens, Gżira GŻR 1368, MALTA, or sent by email to postlicensing.medicinesauthority@gov.mt.

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Prepared: September 2015
Job No: MLT_GIB/AES/0001/15(2)

THE DECLINE AND FALL OF THE SACRA INFERMERIA

GIOVANNI BONELLO

Visitors to Malta who recorded their experiences of the island during the rule by the Order (1530 – 1798) may not have agreed about everything. But on one view they appear unanimous: the outstanding excellence of the main hospital of the knights of St John. Very likely, the most important and advanced hospital in Europe. What distinguished the Order of Malta from other chivalric institutions existing in Europe was its hospitaller character and mission. By the fourteenth century the other knightly Orders had mostly turned into vanity institutions that responded to a purely military vocation: to provide aristocratic militias to defend the Christian faith from the might of the Infidels. The Templars, the Teutonic Order, that of Calatrava, and, later, the Orders of the Golden Fleece, of St Stephen, of the Holy Spirit and several others fell in these categories. The knights of St John, on the other hand, added a unique, rming dimension to their mission: the care of the sick and the infirm.

And they took this vocation very seriously. In many of their commanderies in Europe they established clinics, dispensaries and nursing homes for the *malades*. In Malta they had free hospitals running in Birgu from the very beginning, managed and financed by the Order and manned by local and foreign physicians and surgeons. The popular Maltese word for health centre, *Berġa*, comes from the public clinic in the Italian auberge, *l'albergia d'Italia* in Birgu. Probably the very first public building constructed in the new city of Valletta after the Great Siege was the Sacra Infermeria complex, today the Mediterranean Conference Centre. The seven national 'langues' in which the Order subdivided took it in turn to provide nursing personnel. Each day of the week a different langue sent its younger knights to tend and serve the patients in the infermeria. Hospital duty once a week remained one of the incumbencies no knight in Malta escaped. Through their nursing and religious training, the knights saw the sick patient as "their Lord and Master".

In 1582, seven years after the building of the Infirmary, Giovanni Battista Leoni had seen it as a *macchina meravigliosa* and superlative ornament of the new city. The anonymous *Nouvelle Relation* of 1679 called it "one of the most beautiful

ONLY SOLID SILVER PLATES, VESSELS AND CUTLERY WERE GOOD ENOUGH FOR THE PATIENTS' MEALS

[AT THE SACRA INFERMERIA] "ALMOST THE SAME NUMBER OF PATIENTS DIE FROM BAD NUTRITION AS DIE FROM DISEASES"

in the world".[1] An English traveller would not be outdone "The very glory of Malta" he called it in 1739.[2]

Earlier, another Englishman had described the Infermeria thus: "The hospital is a vaste structure, wherein the sick and wounded lye. This so broade that twelve men may with ease walke abreast up the misdst of it, and the beddes are on each side, standing on four yron pillars, with white curtains and vallands and covering, extremely neate and kept cleane and sweete; the sick served all in sylver plate; and it contains above 300 beddes below, besides many spacious roomes in other quadrangles with it, for the chiefe Cavaliers and Knights with pleasant walks and gardens and a stately house for the chiefe doctor and other his attendants".[3]

"This asylum, noted a historian, is constantly open for the reception of the sick of all countries who are treated with every possible attention and furnished with medicines and comforts of every kind. The utensils used are almost all silver".[4]

A good overview of the Sacra Infermeria in its "splendid" heyday is provided by Elizabeth Schermerhorn: "Separate wards for surgical and medical cases, fever and dysentery patients isolated; ample accommodation for convalescents; a special guardian and ward for the insane (whom the cruel superstition of that day generally condemned to confinement in prisons); the luxury of single beds at a time when in most hospitals the sick lay two or three to a bed; and higher standards of comfort and cleanliness than could be found in any of the large hospitals of Europe; these were some of the points of excellence in which the Hospitallers claimed pre-eminence, quite as jealously as on the sea. They had been pioneers in hospital nursing; they had been the first to extend their ministrations irrespective of creed or nationality; the fame of their Sacred Infirmary attracted strangers to Malta, not only to study its organization and methods but to profit by them – to be nursed by knights of sixteen quarterings, and to be fed off silver".[5]

I have reproduced but a few of the glowing testimonials left by those who observed closely the Malta scene: they admired the building, the medical services and treatments provided, the sumptuousness (only solid silver plates, vessels and cutlery were good enough for the patients' meals); the fact that it was one of the very few hospitals in Europe where patients lay one to a bed; that the sons of the finest nobility in Europe attended the patients; that the hospital only employed the most highly trained physicians and surgeons, the fact that everything was extremely clean and perfumed and that the Order never skimped on nourishment and medicaments. All this went to make the Infermeria the most advanced hospital in Europe.

This positive image persisted for most of the Order's rule over Malta. Additions to the structures and improvement to the management continuously featured on the books. But towards the end of the era of the knights, the rot started setting in. There was widespread moral decadence, there was a blurring of ideals and loss of faith, there was an erosion of the very raison d'etre of the chivalric and hospitaller Order. To compound the oppressive sense of futility and anachronism, the French revolution virtually bankrupted the finances of the Order which before had always been investing massively in the hospital. All this, cumulatively, reflected on the rather abrupt decline of the Infermeria and of anything connected with it.

The evidence of this dramatic deterioration is to be found mainly in two records, both detailed, both conceived with an agenda, but overall, credible.

The first comes from a British philanthropist and reformer who visited Malta between March and April 1786. John Howard (1726 – 1790) toured various hospitals, prisons and plague lazarettos in Europe and left a detailed report on each.[6] His account of what he saw in Malta was anything but flattering.

In the long ward of the Infermeria, the ceiling had turned black "the walls hung round with dusty pictures, this noble hall makes but a gloomy appearance". All the halls were "so dirty and offensive as to create the necessity of perfuming them". The physician, while doing the rounds, was obliged to press a handkerchief to his face. This struck him even more forcibly when he opened some "private closets" next to each bed. The large ward at basement level "is nothing but a dark and damp arched cellar". The physician on duty does not visit it. The kitchen of the hospital "is darker and more offensive than even the lower hall, which it adjoins". Food is served from dirty kettles into silver bowls for the higher class patients, and into pewter ones for the poorer inmates.

There were about 520 patients when Howard visited "served by the most dirty, ragged, unfeeling and inhuman persons I ever saw. I once found eight or nine of them highly entertained with a delirious dying patient". Many of the nurses were debtors or criminals who had taken refuge in the hospital to escape justice as the building enjoyed criminal immunity. Howard noticed that only 22 nurses had to cope with all the hospital, while there were 40 grooms to take care of the 50 horses and mules of the Grand Master, whose stables were noticeably clean. Running water flowed in the stables, but not in the hospital.

The women's hospital, close by, was no better "a more offensive and dirty hospital for women I never visited".

Shortly later, another source confirms all this, in even more lurid detail. The publication of the two volumes of 'Carasi's' *L'Ordre de Malthe dévoilé*, printed in Lyons in 1790 and in German translation in Leipzig in 1793, had only one motivation driving it: to discredit and destroy the autocratic and aristocratic Order of Malta after the assertion of enlightened and democratic government thought to be a natural consequence of the French

GALVUS and EUCREAS

COMPREHENSIVE POWER TO ADVANCE TYPE 2 DIABETES TREATMENT

GALVUS is a DPP-4 inhibitor that improves glycemic control through powerful islet enhancement[1]

EUCREAS is the combination of a DPP-4 inhibitor, GALVUS, and metformin[2]

Galvus®
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 metformin alone, or with a sulphonylurea 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. **DOSAGE:** 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 ulceration 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 antidiabetics ogliyuretic, pioglitazone, metformin, amlodipine, 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. There may be an increased risk of angioedema in patients concomitantly taking ACE-inhibitors. **ADVERSE REACTIONS:** Rare cases (>1/10,000 to <1/1,000) angioedema, sinonimal 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 sulphonylurea: 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, Frimley Business Park Camberley GU16 7SR United Kingdom. **MARKETING AUTHORISATION NUMBERS:** EU/1/07/414/001, 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 3000, Malta. Tel +356 21222872. 2015-MT-GAL-16-DEC-2015

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 when 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. **DOSAGE:** 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 dose 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 triple 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 taking 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 (see) be monitored at least once yearly in patients with normal renal function and at least two to four times/year 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 3x ULN 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 ulceration is recommended. As Eucreas contains metformin, treatment should be discontinued 48 hours before elective surgery with general anaesthesia and not usually restarted earlier than 48 hours afterwards. The IV administration of iodinated contrast agents can lead to renal failure. Therapy due to metformin active ingredient. Eucreas should be discontinued prior to or at the time of the test and not reinstituted 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. There may be an increased risk of angioedema in patients concomitantly taking ACE-inhibitors. **INTERACTIONS:** Vildagliptin has a low potential for drug interactions. No clinically relevant interactions with other antidiabetics glibenclamide, pioglitazone, metformin, amlodipine, 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 hyperglycaemic 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). 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: Decreased blood glucose, headache, chills, nausea, gastro-oesophageal reflux disease, diarrhoea, flatulence. For a full list of adverse reactions, please refer to the SmPC. **LEGAL CATEGORY:** POM. **PACK SIZES:** 30, 60 film-coated tablets. **MARKETING AUTHORISATION HOLDER:** Novartis Europharm Limited, Frimley Business Park, Camberley GU16 7SR, United Kingdom. **MARKETING AUTHORISATION NUMBER:** EU/1/07/420/020-023, EU/1/07/420/030-033. **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. 2015-MT-EUC-16-DEC-2015

GAL Ad1 03/16 MT

NOVARTIS PHARMACEUTICALS

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

Galvus vildagliptin

Eucreas vildagliptin/metformin

"YOUNG MALTESE [DOCTORS] WHO HAVE SERVED TWO OR THREE YEARS IN THE HOSPITALS OF MARSEILLES RETURN TO THEIR NATIVE COUNTRY WITH EMPTY HEADS BUT FULL OF PRIDE AND ARROGANCE."

Revolution. All the two books say is coloured by massive bias, weighted by resentment, ridicule and hate. It is still uncertain who the author or authors were, though a Masonic Lodge in Marseilles has been credibly, if not compellingly, suggested as its promoter and publisher, to disseminate the ideals of the Revolution.[7] All it says about the political state of Malta, its government and its institutions is to be taken with a pinch of salt. But, saving some obvious exaggerations in style and message, everything Carasi writes that the autho could double check against other sources, proved surprisingly accurate in substance. This is, in translation, the desolating picture it paints of the once-splendid Sacra Infermeria.

The first impact the hospital made on Carasi was highly negative. From the building's basement he could only hear the clinking of chains. He thought to be near a prison, only to discover it was a hospital. Inside, how scruffily dressed the nursing attendants were struck him instantly.

Carasi approached a patient in bed and asked about his condition. "The patient complains about the inhumanity of the physicians, the bad treatment of the attendants, the bad meals and the negligence of the commander on duty. Since such complaints come from many patients in many European hospitals, one is not too surprised to hear them here as well. But still it is strange to hear them in Malta as the hospital of the knights is famous and praised all over Europe for its unique service, its rich equipment and its perfect service".

In the basement he asked the first patient he encountered why he was chained in iron. "I am chained because I complained against an attendant. I was accused by this attendant to have ordered tobacco not through him but through his comrade. Before, I had been in the big hall upstairs, but then I was transferred down here, together with vagabonds, slaves and galley rowers. I wanted to speak to the commander of the hospital, but he did not even look at me". The patient in the bed opposite had a bad fever and had been in a different hall before. Then, suffering one of his fever attacks, he stood up and walked around. "Immediately the attendants jumped on him and gave him some lashes with the whip, hit him until he could not walk anymore and brought him down here. Then they chained his feet and arms to his bed. In every other place where an attendant would have behaved like that to his patients, he would be punished severely and instantly dismissed from his service. But over here mercy and mildness towards the sick is unknown".

Carasi then mentions his own experience as a patient at the Infermeria. He spent eight days there following an attack of fever. A physician came to bleed him, put a bandage round his arm and ordered a boy between eight and ten year old to cut him with a lancet. In fear and anger Carasi complained loudly. The hospital commander happened to be passing by and asked what was going on. He told him that the doctor was using him to teach the boy medicine. The commander ordered the doctor to perform the bleeding himself: "the physician now took the lancet and stuck it much deeper than was necessary. He complained again loudly to the commander who just turned his back and walked out. The patient shouted at the physician in anger and pain, but the latter calmly and cold-bloodedly bandaged his arm and left without uttering a word".

They did not skimp on medicines – in fact Carasi received a lot; "what was lacking was attentive service and good food." The doctors only visited the patient in the morning. If after that the patient suffers an attack or becomes paralysed, he has to wait until the next visit in the evening. The food served was minimal "it is a fact that here in the hospital of Malta almost the same number of patients die from bad nutrition as die from diseases".

The evening before his release, a patient in a neighbouring bed was caught adding some salt to his soup. The bowl was snatched from his hands and he was chained to his bed, and carried downstairs to the confinement hall. The same treatment is reserved for anyone who questions the treatment given or when the medicine did not result in a cure. "Sometimes these attendants – or should one say, hangman's assistants – go so far with their barbaric behaviour as to give the patients the bastinado".

The main hall where Carasi lay was the one where the patients received the best treatment: "one can imagine the situation in the other halls and rooms". Then Carasi puts in some comments on Maltese doctors: "To this bad treatment of the sick, one has to add the ignorance and incompetence of the physicians. It is just enough to listen to their comments to know that they have no idea of their profession. Young Maltese who have served two or three years in the hospitals of Marseilles return to their native country with empty heads but full of pride and arrogance. Many of these young local medics and physicians do not even make the effort to go abroad, but just stay at home and repeat the mistakes and errors of their superiors." Carasi characterised the Sacra Infermeria as "a place of pain, of chains and of tombs".[8]

So fade the glories of the world.

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4. Louis de Boisgelin, Ancient and Modern Malta, London, 1805, Vol 1, p.38-9.
5. Elizabeth W. Scermerhorn, Malta of the Knights, Hienemann, 1924, p.193.
6. John Howard, An Account of the Principal Lazzarettos in Europe, London 1789, p.58-61.
7. Alain Blondy «Un pamphlet scandaleux» in Melita Historica, 1992, XI, 1, p.59-76.
8. Carasi, translated by Thomas Freller as The Order of Malta Exposed, Malta 2010, p. 144-9. Original Fench edition, 1790, Vol. 2, p.100-9.

Augmentin® SR

1000 mg/62,5 mg

Amoxicillin/Clavulanic Acid

Prolonged release tablets

- ✓ Unique bilayer tablet with immediate and sustained release delivery of amoxicillin provides superior efficacy against resistant pathogens[1,2]
- ✓ Recommended by leading Guidelines in the treatment of Community Acquired Pneumonia[3,4]
- ✓ Most common adverse effects are diarrhoea, nausea, vomiting and mucocutaneous candidiasis[5]
- ✓ Indicated for use in adults & adolescents aged ≥16 years; 2 tablets BD for 7-10 days[5]

Spreading infectious liveliness!

Mini Abridged Prescribing Information: *Please refer to full Summary of Product Characteristics (SPC) before prescribing.* **TRADE NAME:** Augmentin SR. **ACTIVE INGREDIENTS:** Amoxicillin (as trihydrate) and potassium clavulanate. **PRESENTATION:** 1000 mg/62.5 mg prolonged-release tablets. Supplied in 28 tablet packs. **INDICATION**: Treatment of community acquired pneumonia in adults and adolescents aged at least 16 years, caused or thought likely to be caused by penicillin-resistant *Streptococcus pneumoniae.* **POSOLOGY & ADMINISTRATION:** Oral use. Recommended dose of two tablets twice daily for seven to ten days. To minimise potential gastrointestinal intolerance, administer at the start of a meal. **CONTRAINDICATIONS:** Hypersensitivity (and past history of) to the active substances, to any penicillins or to any of the excipients. **SPECIAL WARNINGS & PRECAUTIONS:** Before initiating therapy careful enquiry of previous hypersensitivity reactions to beta-lactams. Where an infection is proven to be due to an amoxicillin susceptible organism, a switch to an amoxicillin-only preparation should be considered. Convulsions may occur in patients receiving high doses or who have impaired renal function. Concomitant use of allopurinol increase likelihood of allergic skin reactions. Prolonged use may occasionally result in overgrowth of non-susceptible organisms. Contains 29.3 mg (1.3 mmol) of sodium per tablet. *Refer to SPC's for full list of precautions.* **INTERACTIONS:** Penicillins may reduce the excretion of methotrexate causing a potential increase in toxicity. Concomitant use of probenecid is not recommended. If co-administration with oral anticoagulants is necessary, the prothrombin time or international normalised ratio should be carefully monitored with the addition or withdrawal of amoxicillin. Moreover, adjustments in the dose of oral anticoagulants may be necessary. Clinical monitoring should be performed during the combination with mycophenolate mofetil and shortly after antibiotic treatment. **PREGNANCY & LACTATION:** Use should be avoided unless considered essential by the physician. **UNDESIRABLE EFFECTS:** Very common (≥1/10): diarrhoea. Common (≥1/100, <1/10): mucocutaneous candidosis, nausea, abdominal pain. *Refer to SPC's for full list of undesirable effects*. **AUTHORISATION NUMBER:** AA 1051/00102. **MARKETING AUTHORISATION HOLDER:** GlaxoSmithKline Bulgaria EOOD. **LEGAL CATEGORY:** POM. **DATE OF PREPARATION:** July 2014. **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):*** **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). **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/adrportal and posted to the Malta Medicines Authority, Post-licensing Directorate, 203, Level 3, Rue D'Argens, Gżira GŻR 1368, MALTA, or sent by email to postlicensing.medicinesauthority@gov.mt.

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Prepared: September 2015
Job No: MLT_GIB/AES/0002/15(2)

1903. The Wright brothers made the very first flight[1]

AUGMENTIN®
Amoxicillin+clavulanic acid
OVER 30 Years
EXPERIENCE

1981. Augmentin® – The first clavulanate-potentiated amoxicillin was launched for oral use[2]

LEADERS WALK IN FRONT

1. "The Wright Brothers - First Flight, 1903", EyeWitness to History, www.eyewitnesstohistory.com (2003) accessed on 28 May 2014. **2.** White AR *et al.* Augmentin™ (amoxicillin/clavulanate) in the treatment of community-acquired respiratory tract infection: a review of the continuing development of an innovative antimicrobial agent; Journal of Antimicrobial Chemotherapy 2004; 53:S1 i3-i20.

Mini Abridged Prescribing Information: *Please refer to full Summary of Product Characteristics (SPC) before prescribing.*
Trade Names: Augmentin ES 600 mg/42.9 mg/5 ml powder for oral suspension; Augmentin-Duo 400 mg/57 mg/5 ml Powder for Oral Suspension. Active Ingredients: Amoxicillin (as trihydrate) and potassium clavulanate. **Pharmaceutical Form:** Powder for oral suspension. **Augmentin ES:** Each 1 ml of oral suspension contains amoxicillin trihydrate equivalent to 120 mg amoxicillin and potassium clavulanate equivalent to 8.58 mg of clavulanic acid; **Augmentin-Duo:** Each 1 ml of reconstituted product contains amoxicillin trihydrate equivalent to 80 mg amoxicillin and potassium clavulanate equivalent to 11.4 mg of clavulanic acid. **Indications: Augmentin ES/Augmentin Duo:** For the treatment of acute otitis media and community acquired pneumonia infections caused or thought likely to be caused by penicillin-resistant *Streptococcus pneumoniae*. *Refer to SPCs for more details and a comprehensive list of sensitive organisms.* **Posology and Method of Administration:** Oral use. **Augmentin ES:** Children ≥ 40 kg: No experience with Augmentin suspension in adults and children ≥ 40 kg, and therefore no dose recommendation can be given. Children < 40 kg (aged ≥ 3 months): Recommended dose of is 90/6.4 mg/kg/day in two divided doses. There are no clinical data on Augmentin in children under 3 months of age. **Augmentin-Duo:** Children ≥ 40 kg should be treated with the adult formulations of Augmentin. Children < 40 kg: Recommended doses: 25 mg/3.6 mg/kg/day to 45 mg/6.4 mg/kg/day given as two divided doses; up to 70 mg/10 mg/kg/day given as two divided doses may be considered for some infections (such as otitis media, sinusitis and lower respiratory tract infections). There are no clinical data regarding doses higher than 45 mg/6.4 mg per kg per day in children under 2 years. There are no clinical data for patients under 2 months of age. Caution in patients with hepatic impairment and monitor hepatic function at regular intervals. In patients with renal impairment dose adjustments are based on the maximum recommended level of amoxicillin. For both products, to minimise potential gastrointestinal intolerance, administer at the start of a meal; absorption is optimised when taken at the start of a meal. *Refer to SPCs for further administration and dosage guidance.* For both products, treatment should not be extended beyond 14 days without review. **Contraindications:** Hypersensitivity (and past history of) to the active substances, to any penicillins or to any of the excipients; to beta-lactam agents (e.g. a cephalosporin, carbapenem or monobactam); jaundice/hepatic impairment due to amoxicillin/clavulanic acid. **Special Warnings and Precautions:** Before initiating therapy careful enquiry of previous hypersensitivity reactions to beta-lactams. Where an infection is proven to be due to an amoxicillin susceptible organism, a switch to an amoxicillin-only preparation should be considered. Convulsions may occur in patients receiving high doses or who have impaired renal function. Concomitant use of allopurinol increase likelihood of allergic skin reactions. Prolonged use may occasionally result in overgrowth of non-susceptible organisms. **Augmentin ES/Augmentin Duo:** Contains aspartame (E951), a source of phenylalanine. The suspension also contains maltodextrin (glucose). **Interactions with other medicaments:** Penicillins may reduce the excretion of methotrexate causing a potential increase in toxicity. Concomitant use of probenecid is not recommended. If co-administration with oral anticoagulants is necessary, the prothrombin time or international normalised ratio should be carefully monitored with the addition or withdrawal of amoxicillin. Moreover, adjustments in the dose of oral anticoagulants may be necessary. Clinical monitoring should be performed during the combination with mycophenolate mofetil and shortly after antibiotic treatment. **Fertility, Pregnancy and Lactation:** Use should be avoided unless considered essential by the physician. **Effect on Ability to Drive or Use Machines:** No studies, however, undesirable effects may occur such as dizziness. **Side Effects:** Very common (≥1/10): diarrhoea. Common (≥ 1/100, < 1/10): mucocutaneous candidosis, nausea, abdominal pain, & vomiting. *Refer to SPC's for full list of undesirable effects.* **Overdose:** Gastrointestinal symptoms may be treated symptomatically, with attention to the water/electrolyte balance. Amoxicillin/clavulanic acid can be removed from the circulation by haemodialysis. **Local Presentations: Augmentin ES:** Supplied in 100 ml glass bottle with a dosing spoon. **Augmentin Duo:** Supplied in 35 ml & 70 ml bottles. **Marketing Authorisation Holders: Augmentin ES:** GlaxoSmithKline Bulgaria EOOD; **Augmentin Duo:** SmithKline Beecham Ltd trading as: GlaxoSmithKline UK. **MA Numbers: Augmentin ES:** AA 1051/00101; **Augmentin Duo:** MA 172/00101. **Legal category:** POM. **Date of preparation:** December 2015.

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:**

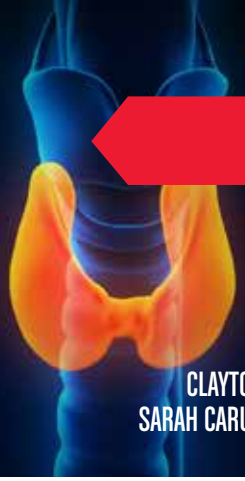
Report forms can be downloaded from www.medicinesauthority.gov.mt/adrportal and posted to the Malta Medicines Authority, Post-licensing Directorate, 203, Level 3, Rue D'Argens, Gżira GŻR 1368, MALTA, or sent by email to postlicensing.medicinesauthority@gov.mt

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

Date of Preparation: December 2015
Job No: MLT_GIB/CAM/0012/15

MONITORING OF THYROID FUNCTION TESTS

IN HYPOTHYROID PATIENTS ON LEVOTHYROXINE



CLAYTON J. FSADNI
SARAH CARUANA GALIZIA

ABSTRACT

The study aims to identify and recommend ways of improving thyroid function monitoring. Over a three month period, eighty-eight patients with clinical and subclinical primary hypothyroidism on long-term levothyroxine therapy were seen by GPs at the Chronic Disease Managment Clinic. The monitoring intervals of thyroid function tests for patients with controlled and uncontrolled primary hypothyroidism were benchmarked with the American Association of Clinical Endocrinologists guidelines.
The overall average compliance for clinical hypothyroid cases was 69% (n=15) and 40% (n=9) for the subclinical hypothyroid cases. In the clinical hypothyroid cases compliance was 71% (n=15) and 67% (n=14) for controlled and uncontrolled cases, respectively. In the subclinical hypothyroid cases compliance was 43% (n=10) and 35% (n=8) for controlled and uncontrolled cases, respectively. Knowledge of the guidelines amongst GPs should be increased especially when it comes to the management of subclinical hypothyroidism, and in cases of uncontrolled hypothyroidism in general. This is possible through better dissemination, availability and reinforcement of such guidelines.

INTRODUCTION

Primary hypothyroidism results from under-secretion of thyroid hormones from the thyroid gland. The most common cause of primary hypothyroidism is chronic autoimmune thyroiditis (Hashimoto's Disease). Other causes include throidectomy, thyroid gland ablation with radioactive iodine, external irradiation, a biosynthetic defect in iodine organification, thyroid lymphoma and drug-induced. Signs and symptoms are generally related to the duration and severity of hypothyroidism, the rapidity with which hypothyroidism occurs, and the psychological characteristics of the patient. Hypothyroid patients usually present dry skin, cold sensitivity, fatigue, muscle cramps, voice changes and constipation.[1]

Increased thyroid stimulating hormone (TSH) values usually indicate hypothyroidism whilst decreased values usually indicate hyperthyroidism. This test has proved to be both sensitive and specific for hypothyroidism. An elevated TSH level with a normal free T_4 level is referred to as subclinical hypothyroidism. It is important to note that patients with subclinical hypothyroidism may still have clinical symptoms.[2] In general, hypothyroidism can be adequately treated with a constant daily dose of levothyroxine, usually with a single maintenance dose of 100-200 mcg.[3,4]

TSH levels are the best indicator of thyroid function and the best test for monitoring response to levothyroxine therapy.[5] It has been found that adverse events related to replacement therapy with levothyroxine are more common in patients who do not receive the recommended monitoring.[6] Therefore, monitoring of thyroid function tests (TFTs) has a role to gauge the thyroid function response to levothyroxine, ensuring the minimum effective dose at the least adverse drug effects.

AIMS

- To evaluate the adequacy of thyroid function test (TFT) monitoring in patients with primary hypothyroidism that are on levothyroxine therapy.
- To recommend ways in which TFT monitoring can be improved.

METHOD

SETTING AND SAMPLING

An audit was conducted in a Primary Care setting at Qormi Health Centre from July till September 2015. The reason for conducting the study solely at the Qormi Health Centre was that during the study period, the only Chronic Disease Management Clinic (CDMC) was located at that centre. All patients with clinical and subclinical primary hypothyroidism, that were on long term levothyroxine (for more than 3 months), were identified from the CDMC by the ten GPs that practice in this clinic. The cohort amounted to eighty-eight patients. The study excluded hypothyroid patients that had disturbances of hypothalamic-pituitary function and females that were pregnant. With regards to subclinical hypothyroid patients, only those with TSH levels > 10 micro IU/ml were considered, as data for patients with mildly raised TFTs is controversial.[1]

Hypothyroid patients, including those diagnosed with subclinical hypothyroidism, were identified by the GPs that regularly follow patients at the CDMC. For each patient, the ID number and date of visit of the patient were recorded by the GPs on a data sheet which was distributed prior to the commencement of the study. For each patient, iSOFT clinical manager was then used to identify the TFT results over the previous year. The time interval between TFT monitoring for controlled and uncontrolled thyroid function for both clinical and subclinical hypothyroid patients was recorded.

STANDARDS

The standard criteria established by the AACE (last updated in 2012) are as follows:

1. Well-controlled subclinical hypothyroid patients (normal TSH) should have their TFT monitored every 48 weeks.
2. Patients with uncontrolled subclinical hypothyroidism or patients who experienced a change in levothyroxine dose should have their TFT checked every 6-8 weeks.
3. Well-controlled clinical hypothyroid patients (normal TSH levels) should have a TFT repeated at 24 weeks and the 2nd TFT at 48 weeks.
4. Patients with uncontrolled clinical hypothyroidism, or patients who experienced a change in levothyroxine dose should have the TFT repeated at least 6 weeks after a deranged TSH level, or dose adjustment, respectively.

DATA ANALYSIS

All data were processed using Microsoft Excel 2013. The data were then analysed by recording the TSH monitoring intervals for patients with subclinical/clinical hypothyroidism with normal/abnormal TFTs. Compliance with AACE guideline criteria was recorded for each category.

ETHICAL APPROVAL AND CONSENT

The study was approved by the Audit Committee and the Data Protection Act Committee. Consent was achieved from the Principal General Practitioner and Clinical Director of Primary Health Care.

RESULTS

48% (42 from 88 patients) studied had clinical hypothyroidism, whilst 52% (n=46) had subclinical hypothyroidism (Figure 1).

In controlled clinical hypothyroid cases 71% (n=15) compliance to the recommended TFT monitoring interval, as per AACE guidelines, was observed (Figure 2) whilst for uncontrolled cases compliance was 67% (n=14) (Figure 3).

In controlled subclinical cases there was 43% (n=10) compliance to the recommended TFT monitoring interval, whilst for those with abnormal TFTs there was 35% (n=8) compliance to the recommended monitoring interval (Figures 4 and 5 respectively).

When considering both controlled and uncontrolled cases, the overall average compliance for clinical and subclinical hypothyroid cases were 69% (n=15), and 39% (n=9) respectively. This was achieved by calculating the mean of the compliance for controlled and uncontrolled cases in both clinical ((71% + 67%)/2) and subclinical hypothyroid ((43% + 35%)/2) cases.

DISCUSSION

In this study all patients with hypothyroidism were on levothyroxine treatment. Since downward dose adjustment or even cessation of levothyroxine therapy may be required, T4 and TSH monitoring is necessary for the management of both clinical and subclinical hypothyroidism.

For both controlled and uncontrolled hypothyroid cases compliance to the thyroid monitoring guidelines was noted to be greater for patients with clinical hypothyroidism (69%)

Figure 1: Total number of clinical and subclinical hypothyroid cases

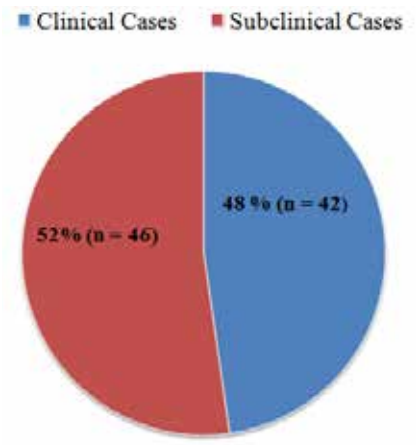


Figure 2: Compliance to recommended TFT monitoring interval in clinical cases with controlled thyroid function

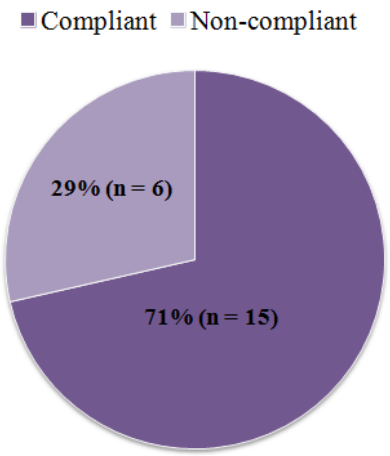


Figure 3: Compliance to recommended TFT monitoring interval in clinical cases with uncontrolled thyroid function

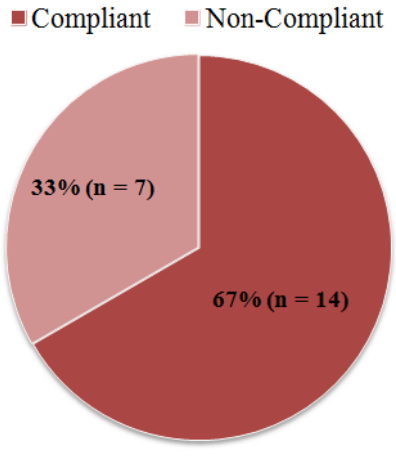


Figure 4: Compliance to recommended TFT monitoring interval in subclinical cases with controlled thyroid function

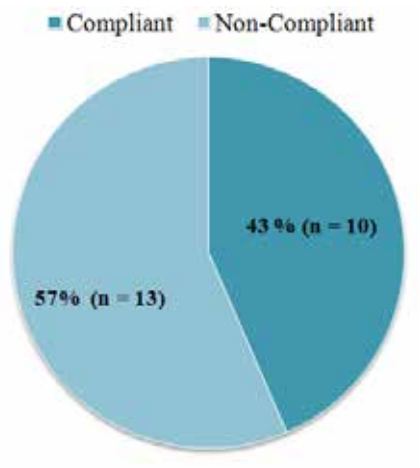
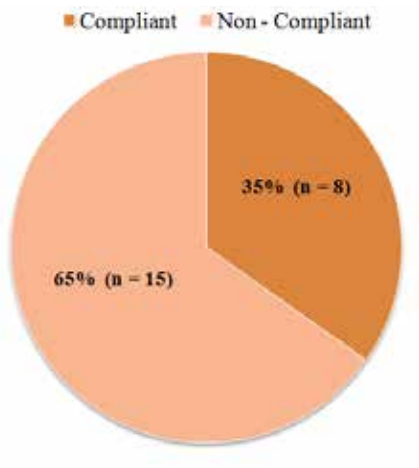


Figure 5: Compliance to recommended TFT monitoring interval in subclinical cases with uncontrolled thyroid function



than for those with subclinical hypothyroidism (40%). The most probable reason for this is that physicians are more aware of thyroid monitoring frequency guidelines for clinical hypothyroid cases. Furthermore, physicians may have experienced difficulties in interpreting subclinical hypothyroid biochemical derangements and thereby in differentiating it from clinical hypothyroidism. Delayed monitoring was noted whenever physicians showed non-compliance in both patient categories with normal and abnormal TFT results. This is contrary to what is normally expected since uncontrolled hypothyroid cases require shorter interval monitoring times, hence a stricter monitoring approach.

The results show that physicians are not aware of the clinical importance of adequately monitoring subclinical hypothyroidism, with more importance being given to clinical hypothyroidism. Regular monitoring of TSH levels in primary care patients can be ensured through a computer-generated recall system with written notification to patients.[7]

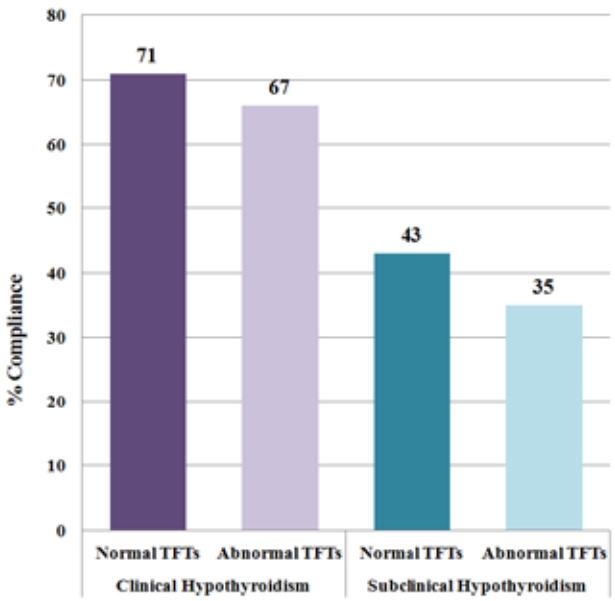
LIMITATIONS

The main limitation of the audit was the small sample size which may have led to inaccuracies in the interpretation of the results. In most cases no documentation was found with regards to changes in levothyroxine dose, hence it was assumed that a change in dose was made with every deranged TFT result. Data was only collected by GPs working at the Qormi Health Centre, and hence the data may not truly represent compliance to the guidelines in patients attending other health centres. The audit did not assess the possible reasons for abnormal TSH levels, for example pregnancy, medication interactions and compliance to levothyroxine therapy.

CONCLUSION AND RECOMMENDATIONS

This audit has shown that there is room for improvement when it comes to thyroid function monitoring, especially in cases of subclinical hypothyroidism. Physicians should be more aware of the biochemical derangements that correlate to subclinical hypothyroidism which will enable them to differentiate it from

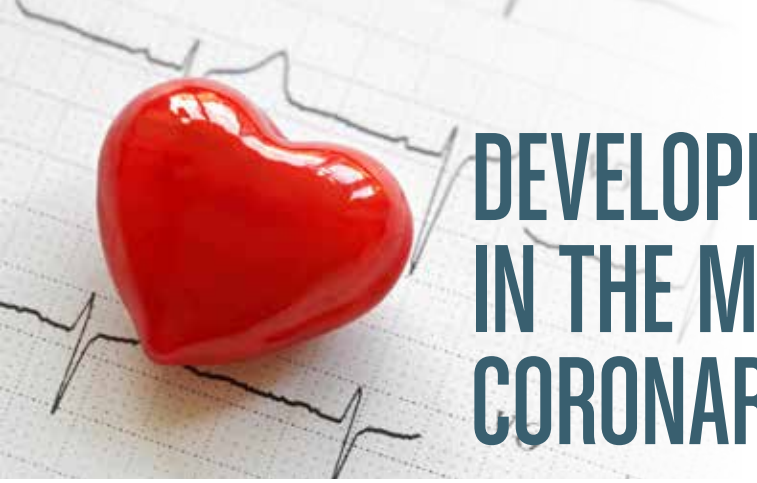
Figure 6: Percentage compliance to recommended intervals for TFT monitoring in controlled and uncontrolled clinical and subclinical hypothyroidism



clinical hypothyroidism. Whilst excessive monitoring leads to unnecessary visits by patients and increased expenditure, on the other hand, delayed monitoring may lead to inaccurate dosing of levothyroxine and hence possibly increased adverse effects and/or ineffective thyroid function control.

In order to improve compliance to the AACE guidelines, it is recommended that they should be well-disseminated both at Mater Dei Hospital medical outpatients clinic and at health centres (where many patients have their thyroid function monitored). Knowledge of the guidelines especially amongst GPs can be increased by means of seminars and conferences given by endocrinologists. A downloadable PDA version and availability of the guidelines on KURA would also help to improve compliance.

REFERENCES CAN BE ACCESSED ON THESYNAPSE.NET



DEVELOPMENTS IN THE MANAGEMENT OF ACUTE CORONARY SYNDROMES

AMY CHRISTINE CHIRCOP

Cardiovascular mortality remains one of the leading causes of death across the globe, accounting to a total of 27.15% of deaths in the Maltese Islands for the year 2014.[1] Plaque fissuring and/or plaque erosion constitute the foundations of the pathogenesis of acute coronary syndromes (ACS) ranging from a spectrum of unstable angina, ST elevation myocardial infarction (STEMI) and non-STEMI.[2]

2015 has been an exceptional year with respect to the progress made in the understanding of ACS. Both the European Society of Cardiology (ESC)[3] and the American College of Cardiology/ American Heart Association[4] published new guidelines on the management of ACS in patients without persistent ST-segment elevation. This article aims to highlight some of the major developments and recommendations that have been put forward.

One of the major recommendations by ESC and the American College of Cardiology/American Heart Association is that, following chest pain onset, ACS can be ruled in or ruled out at 0 and 1 hours if a high sensitivity cardiac troponin test is available. Additional testing at 3-6 hours is required if the first 2 troponin measurements are not conclusive and the clinical scenario is still suggestive of ACS. This was also proposed by Reichlin *et al*[5] who concluded that high sensitivity cardiac troponin T baseline values and absolute changes within the first hour substantially accelerate the management of suspected myocardial infarction (MI) with safe rule-out and accurate rule-in of acute MIs. Another significant finding concerns triglycerides. ESC and the American College of Cardiology/American Heart Association concluded that the relationship of triglycerides to the risk of ACS was independent of LDL-cholesterol. Furthermore, fasting triglycerides predicted long and short term cardiovascular risk. This highlights the role of triglycerides in atherosclerosis, hence pointing out the importance of targeting these in both the prevention and management of ACS.[6]

The role of cardiac magnetic resonance in relation to risk stratification of patients diagnosed with ACS was also studied. Eitel *et al*[7] stated that this is most important if done within 10 days from the index event in patients with persistent STEMI. Furthermore, microvascular obstruction was the only significant predictor in addition to TIMI risk score to provide prognostic value above clinical risk assessment and left ventricular ejection fraction; hence indicating that microvascular obstruction after successful epicardial recanalization by primary percutaneous coronary intervention (PCI) remains an unmet therapeutic target.[7]

The role of thrombectomy in the management of ACS was another controversial topic discussed in the guidelines. The Thrombus Aspiration During Percutaneous Coronary Intervention in Acute Myocardial Infarction (TAPAS) study[8] suggested that the removal of thrombi by manual thrombectomy before coronary stenting has the potential of reducing distal embolization and improving microvascular perfusion hence reducing mortality, whilst improving target vessel revascularisation and MI rates. However, other studies conducted showed that although improvement in ST-segment resolution and distal embolization with thrombectomy were achieved, these did not translate in clinical benefits. In actual fact, these latter studies reported that thrombectomy failed to reduce the development of heart failure or the mortality rate; actually, thrombectomy increased significantly the risk of stroke.[9,10]

An interesting recommendation was the adoption of a radial approach for coronary angiography and PCI rather than femoral access. It was proven that the use of radial access reduced major bleeding and all-cause mortality whilst not increasing the risk of MI or stroke.[11] What is more interesting is that in STEMI patients, repeated cycles of brief inflations of the angioplasty balloon were shown to reduce infarct size and improve the recovery of myocardial contractile function.[12] Another thought-provoking issue is the use of supplemental oxygen in acute MI patients. A study showed that there were no benefits with routine oxygen therapy in uncomplicated normoxic acute MI patients; in actual fact it was found that it increased myocardial injury, increased infarction size on cardiac magnetic resonance, with more recurrent MI and more frequent arrhythmias.[13] Last but not least, the role of aldosterone in acute MI was also looked into. In fact, there is a surge in aldosterone levels shortly after the onset of MI which has a number of deleterious effects such as sodium retention possibly promoting arrythmogenesis (in combination with potassium and magnesium depletion), endothelial dysfunction, increased vascular tone and cardiac remodelling amongst others. In the REMINDER study,[14] patients with acute STEMI without a history of heart failure who received epleranone (aldosterone antagonist) within 24 hours of symptom onset fared much better than patients with placebo with regards to mortality, heart failure, sustained ventricular tachycardia or fibrillation, ejection fraction ≤40% and elevated pro-BNP.

Given the great complexity and vital importance of the cardiovascular system, this area is undoubtedly one of the most researched and studied to date. New developments and milestones are reached daily, altering our clinical practices with the sole aim of improving morbidity and mortality. Prevention is better than cure and it is with this foresight that the medical profession should ascertain that preventive strategies are promoted in an attempt to prevent a number of cardiovascular pathologies.

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ALEXANDER MANCHÉ

CARDIAC SURGERY IN MALTA: PAST, PRESENT AND FUTURE

ABSTRACT

In 1918 neurosurgeon Sir Charles Ballance removed a bullet from the heart of a soldier based in Malta. After WWII cardiac surgeon Mr Lance Bromley and cardiologist Dr Edwin Besterman treated Maltese patients in St Mary's Hospital, London. A visiting consultant service in 1983 was followed by a permanent resident program in 1995, providing a comprehensive adult cardiothoracic service. The future of cardiac surgery depends on evolving technologies and surgeons who are innovators.

Cardiac surgery was inaugurated in Malta on the 16th February 1918 when Sir Charles Ballance, a renowned neurosurgeon and a colonel in the British Expeditionary Forces in Malta, removed a bullet from the heart of 21-year old trooper Robert Hugh Martin.[1] Dr Sarah Marguerite White assisted Ballance and Lt Colonel Shirley administered the anaesthetic. The heart was exposed via a Kochers incision with removal of the left 4th to 6th costal cartilages. Charles Ballance cut into the right ventricle and retrieved the bullet with an artery forceps from the inferior interventricular septum adjacent to the apex of the heart. Significant haemorrhage was stemmed with internal Lembert sutures and a blood transfusion was also administered.[2] This was the third such attempt worldwide but the patient died of sepsis one month post-operatively and the operation never achieved its due recognition. Ballance observed "it is a common experience that bullets frequently lodge in the tissue and induce neither local nor general infection until attempts at removal are made". Ballance recorded his experience in the prestigious Bradshaw lecture, entitled *The Surgery of the Heart*, which he delivered the following year.[3]

The next milestone came in 1947 when Professor Peter Paul Debono operated on 8-year old Iris Magro of Naxxar and successfully ligated her patent ductus arteriosus. The operation was performed on the 27th September at the Bugeja Hospital, Hamrun; the first assistant was Dr Victor Griffiths and the anaesthetist Dr Joseph Darmanin Demajo. The patient was referred by Peter Paul's brother, Professor Josie Debono and by Dr Victor Captur. She complained of weakness and lethargy and had a fever of up to 102°F. Examination revealed a machinery murmur in the pulmonary area and blood cultures were repeatedly positive for *Streptococcus viridans*. A presumptive

CARDIAC SURGERY WAS INAUGURATED IN MALTA ON THE 16TH FEBRUARY 1918 WHEN SIR CHARLES BALANCE REMOVED A BULLET FROM THE HEART OF 21 YEAR OLD TROOPER ROBERT HUGH MARTIN

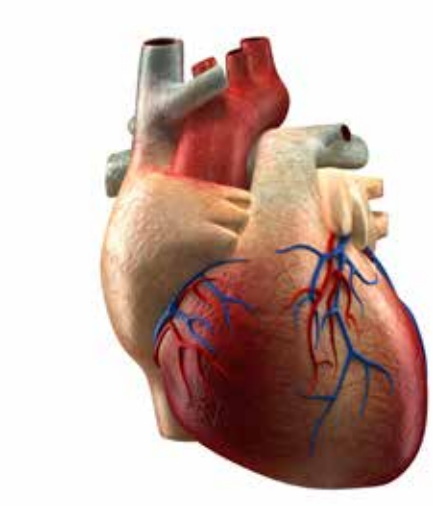
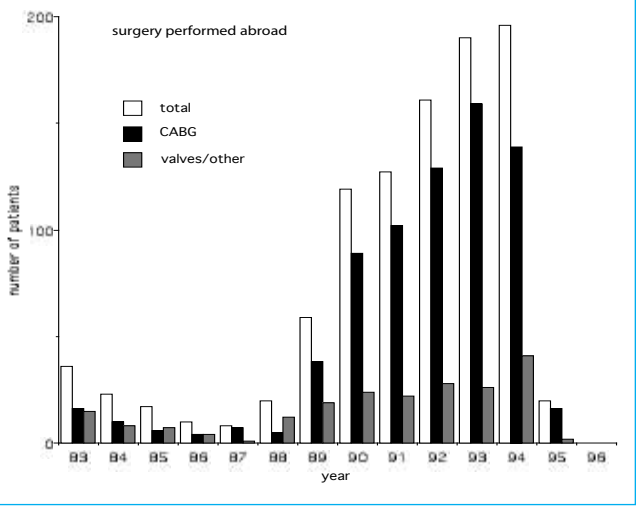


Figure 1: Maltese patients undergoing cardiac surgery in the UK 1983-1996. CABG: Coronary Artery Bypass Graft



diagnosis of infective endarteritis of the patent ductus warranted urgent surgery. At operation the left chest was entered via the second interspace, with division of two adjacent ribs. The ¾ inch ductus was identified and a silk ligature was passed over an aneurysm needle. The ductus was tied on its aortic side using a Ballance knot.[4]

The post-war years saw a consolidation of the links with the United Kingdom in the field of cardiology and cardiac surgery. Visiting consultants from London came to Malta on a regular basis to see patients and advise on treatment. Some of these patients would then be sent to St Mary's Hospital London for further investigation and, in some cases, surgical treatment. Foremost amongst these visitors were cardiac surgeon Mr Lance Bromley and cardiologist Dr Edwin Besterman. Bromley and Besterman reported on their 14-year experience in Malta, performing closed mitral valvotomy at a mean annual rate of 4/100,000 population.[5] Their standard technique, developed at St Mary's Hospital London, involved commissurotomy using a Tubbs dilator. This London series, comprising over 500 patients over a 24-year period yielded excellent clinical results with 94% of patients enjoying full functional capacity, and less than 4% requiring reoperation at 10-year follow-up.[6]

In 1983 Mr Alan Yates performed the first heart operation in Malta and inaugurated a visiting service here. Over the years Maltese patients benefited from the services of UK teams who performed surgery both in the UK (figure 1) and

Figure 2: Maltese patients undergoing cardiac surgery in Malta 1983-1995. CABG: Coronary Artery Bypass Graft

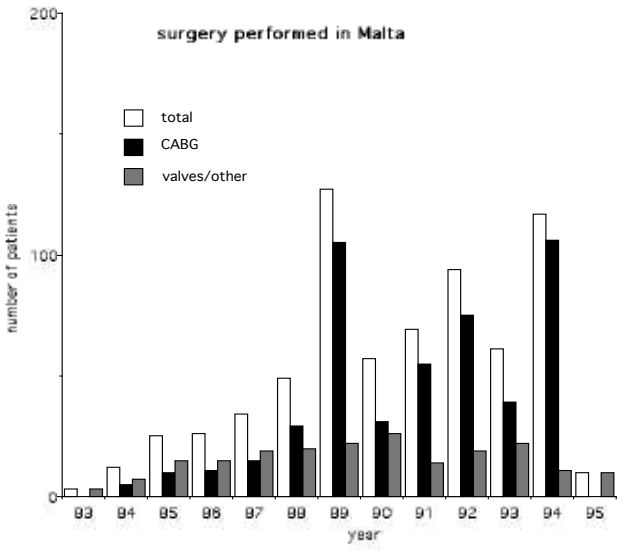


Figure 3: Trends in CABG and PCI 1995-2011

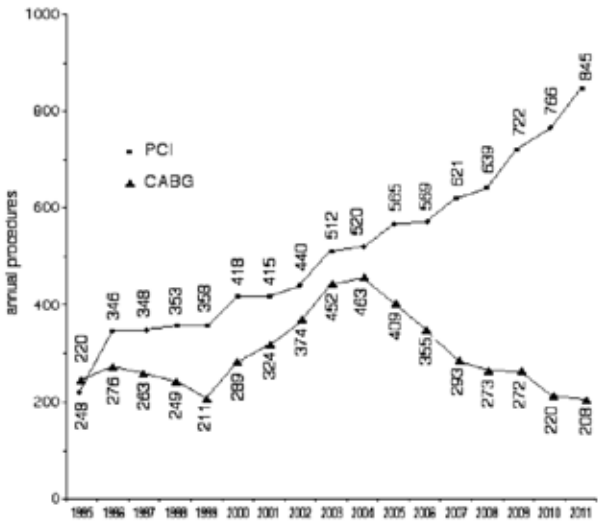


Table 1: Comparison of evolving nature of cardiology services in Malta

Variables	1995	2000	2015
Mean age	60.7		64.9
Mean waiting time (weeks)	38		2
Parsonnet risk	7.6		11.6
EuroSCORE risk⁺		2.7	4.3
Coronary Artery Bypass Grafting	82.7%		44.2%
Aortic Valve Replacement	10.0%		37.2%
Mitral repair	0*		63.2%*
Miscellaneous procedures	1.3%		7.0%
Mean post-op length of stay (days)	6.46		7.51
Post-op Atrial Fribrillation	7.0%		36.4%

*⁺ EuroSCORE was calculated from 2000 onwards; *denotes % of mitral procedures*

in Malta (figure 2). Yates was joined by Mr David Anderson, also from Guy's Hospital. Other teams participating in this program were headed by Mr Rex Stanbridge from St Mary's Hospital, Mr Fik Shabbo and Mr John O'Riordan from the Brook Hospital, Mr Alan Wood from the Royal London Hospital, as well as Mr Brian Fabri from Liverpool. The early 1990's ushered in an expansion in terms of numbers and this provided a catalyst for setting up a permanent local cardiothoracic unit.

The author visited Malta in January 1995 and performed a trial series of 10 patients. Following his appointment as consultant cardiothoracic surgeon, and anticipating the arrival of cardiologist Professor Albert Fenech from the UK, the permanent local program was planned to commence in April 1995. In preparation for a smooth start in Malta, local theatre, intensive care and ward nurses were flown to the Northern General Hospital, Sheffield for clinical training. Major equipment that was purchased around this time included a heart-lung machine with heater/cooler unit, a blood gas analyser, theatre and transfer monitors, a servo ventilator, an intra-aortic balloon pump, syringe drivers, surgical instruments, as well as pump sets, oxygenators and heart valves. Based on the intervention rates in 1993 and 1994, both with regard to angioplasty and surgical operations, and taking into account the size of the Maltese population and the waiting list as it stood in January 1995, it was projected that approximately 350 operations would have to be performed annually in order to provide an effective service.

The early years of the service saw a steady expansion in operative throughput and a consequent fall in waiting times. Theatre time increased from 6 to 11 half-day sessions per week, with 8 of these sessions out of hours. A transplant program was also inaugurated in 1996.[7] Cancellations, due to ITU staff and bed shortages were finally addressed with the opening of a dedicated CICU in 2000. Around this time two further consultants were appointed and annual operations increased from 300 in 1995 to peak at 537 in 2004. The surgical program was consolidated but was later challenged by a relentless expansion in interventional cardiology (figure 3).[8] This has been largely addressed with the setting up of a multidisciplinary Heart Team 2 years ago.

With the steady encroachment of interventional cardiology into the traditional cardiac surgical domain, the size and nature of our practice has evolved, and our current practice bears little resemblance to that of twenty years ago. A number of comparisons are highlighted in table 1. The longer hospital stay and the increased incidence of atrial fibrillation reflect the higher risk profile of our patients.

The future of cardiac surgery in Malta is largely influenced but international trends. Continuing professional development, including conferences, seminars, hands-on hospital visits, proctoring, and most importantly, the training of our future surgeons in large units abroad, will assure the maintenance of a high quality service. Our relatively small unit provides a diverse and comprehensive cardiothoracic service comparable with that in larger countries. The immediate challenges facing our surgeons involve advances in the fields of surgery for atrial fibrillation,[9] more complex mitral valve repair,[10] corrective surgery for annulo-aortic ectasia,[11] and minimally invasive cardiac and thoracic procedures. To guess the evolution of cardiac surgery in the distant future is to venture into the unknown. What is sure is that more collaboration with interventionists is essential, and the future cardiac surgeon must be trained in open as well as percutaneous skills.[12,13]

REFERENCES CAN BE ACCESSED ON THESYNAPSE.NET

THE VALUE OF TROPONIN ASSAYS IN MODERN MEDICAL PRACTICE

KARL CUTAJAR

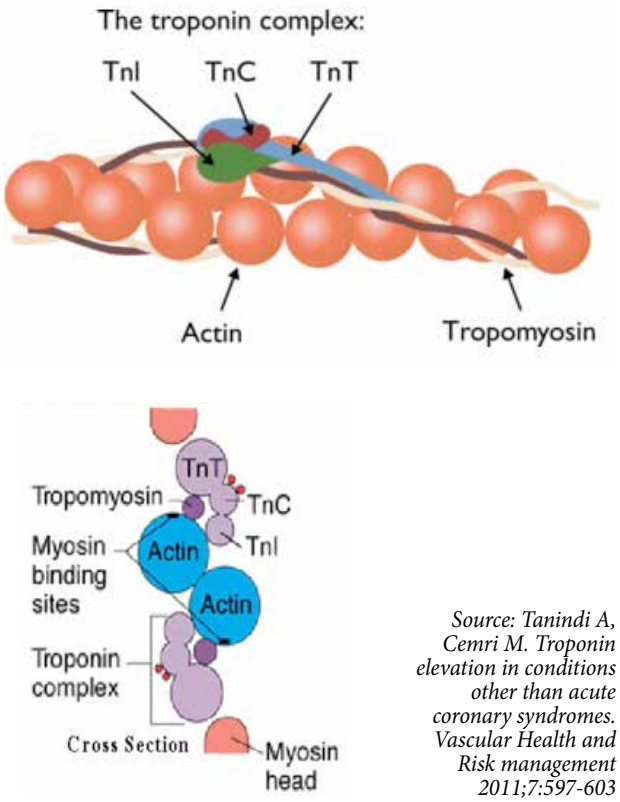
INTRODUCTION

BIOCHEMICAL AND PHYSIOLOGICAL ASPECTS

Cardiac troponins – C, I and T – form part of the troponin complex which is involved in the regulation of the calcium-mediated interaction of actin and myosin in myocytes.[1] Each troponin has a different role in the above mentioned complex. Troponin C is involved in binding calcium, troponin I inhibits interaction of actin to myosin, while Troponin T binds to tropomyosin and facilitates muscle contraction.[1]

Both skeletal as well as cardiac muscle types express troponin C, however the amino acid sequences of troponin I and troponin T are unique to cardiac muscle. It is the specificity of these latter troponins to cardiac muscle that allowed for the development of quantitative assays that detect elevations of troponins in the serum once released by damaged cardiac muscle tissue.[1]

Figure 1: Schematic representation of the thin filament of the muscle myofibrils. *Myosin* is the principal protein from which the *thick filaments* are composed



Source: Tanindi A, Cemri M. Troponin elevation in conditions other than acute coronary syndromes. Vascular Health and Risk management 2011;7:597-603

The majority of Troponin I and C form part of the contractile apparatus of the muscle myofibril. A small fraction of the troponins is however free in the cytoplasm. This fact explains the relatively biphasic rise in serum troponin. The initial rise corresponds to the release of free cytoplasmic troponin. This is subsequently followed by a second rise – that corresponds to the dispersion of the myofibril-bound troponin complexes.[1]

Keeping the above mechanisms in mind, one notes that any form of damage to cardiac muscle may result in the release of the above proteins into the bloodstream. As acute coronary syndromes are the commonest cause of myocardial damage, the detection of elevated levels of troponin levels in the serum are often attributed to such events.[2]

DISCUSSION

TROPONIN: THE IDEAL CARDIAC BIOMARKER

The earliest cardiac biomarkers used to detect myocardial ischemia included aspartate aminotransferase and lactate dehydrogenase isoenzymes, however these biomarkers were found to be poorly specific in view of the fact that they have a wide tissue ditribution.[1] Eventually, creatine kinase (CK)-MB isoenzyme assays were posited as the gold standard investigations in the diagnosis of acute coronary syndromes (ACS).

CK-MB, whilst more specific for cardiac muscle, still constitutes around 1-3% of the CK found in skeletal muscle. It is also present in a small fraction in other organs such as the prostate, uterus and small bowel. Therefore in the setting of major injury to any of the above organs the specificity of CK in detecting myocardial damage is reduced.[1]

CK-MB has gradually been sidestepped by cardiac troponin assays, which have ever since their initial use for the diagnosis of ACS, become more and more sensitive.[3] Nowadays the cardiac troponin testing is the preferred diagnostic test for ACS particularly for non-ST segment-elevation myocardial infarction (NSTEMI). The results from cardiac troponin testing guide the decision for the adequate intervention in patients in whom the diagnosis of ACS is not obvious from the clinical presentation and the findings on ECG.[3]

Troponin I and T, when compared to other biomarkers, have both the highest sensitivity and specificity for cardiac ischemia.[1] Between 1995 and 2007, the limit of detection of cardiac troponins fell from 0.5ng/mL to 0.006ng/mL, accounting for approximately a hundred-fold improvement in analytic sensitivity.[3]

However, whilst the increasing sensivity of troponin assays are allowing us to recognise and treat ACS earlier, the ever increasing

sensitivity of these biomarkers is in itself inevitably associated with a reduction in the specificity of the test.[3]

The value of troponins in the diagnosis of ACS

Acute myocardial infarction (MI) is defined as necrosis of myocardial tissue. The diagnosis nowadays requires that there must be a rise or fall in troponin levels with at least one value above the 99th percentile of the upper reference limit of the normal healthy population as defined by European Society of Cardiology in 2007.[1] In addition, there should be at least one of the following:

1. ECG changes indicative of ischemia (e.g. new ST/T wave changes or new LBBB)
2. Symptoms suggestive of ischemia, e.g. chest pain, diaphoresis, nausea, SOB or loss of consciousness
3. Imaging studies showing evidence of new wall motion abnormalities/loss of viable myocardium.[1]

In the past, the major limitation of cardiac troponins in aiding diagnosis of ACS was the fact that in the first few hours after an MI, plasma troponin levels would still be undetectable – secondary to the delayed increase in circulating levels of cardiac troponins. Generally the diagnosis would depend on monitoring the patient and taking serial blood samples over a 6-12 hour period.[2] Nowadays with the high sensitivity troponin assays which are becoming available, it is recommended that the second specimen can be collected at 2-3 hours from the first specimen taken at presentation.[3] This is a huge improvement as the longer the wait before a diagnosis is made (and any applicable intervention) the greater the morbidity and mortality. However, as mentioned earlier, the greater sensitivity of the troponin assays means that the number of patients with detectable Troponin elevations in the emergency department or other in-hospital settings, will increase as a result. This poses greater challenges on physicians to make a differential diagnosis. Non-ischemic causes of troponin elevation should thus always be kept in mind. One should always refer to the clinical picture, ECG and other available investigations.[2]

Non-ACS causes of elevated Troponins

Many cardiovascular and non-cardiovascular states are associated with elevated troponin levels. Atrial fibrillation, supraventricular tachycardias, heart failure, myocarditis and cardiac contusion are among the non-ACS causes of increased troponin levels.

Increased toponins levels are also noted to be present in conditions such as Chronic obstructive pulmonary disease (COPD) and acute pulmonary embolism. These conditions cause right heart strain which in turn might explain the link with the elevated troponin levels. End-stage renal disease (ESRD) is also commonly associated with an elevated troponin level. In fact, it is thought that if all the patients with ESRD were to have their troponin levels measured, in over 50% of the patients they would be elevated. This is often attributed to the impaired excretion of troponin, however it might also be the result of small areas of clinically silent myocardial necrosis.[2]

Intracranial pathology is another non-cardiac cause of elevated troponin levels. Not uncommonly, patients with intracranial hemorrhages (e.g. subarachnoid haemorrhages) and acute strokes are found to have elevated troponin levels. Furthermore these individuals may also have electrocardiographic changes, such as cardiac rythm disurbances, which may further confuse the picture. One theory for the above is that myocardial ischemia develops pursuant to any pre-existing cardiac tachycardia/hypertension. Howwver, nowadays the most widely accepted explanation is the "cathecolamine hypothesis". It is believed that acute brain injury causes a massive release of cathecolamines (norepinephrine) from sympathetic nerve terminals innervating the myocardium. This subsequently leads to myocyte necrosis and contractile dysfunction resulting in the ECG changes and troponin release into the plasma.[2]

Non-thrombotic causes of elevated troponin levels[1]*.*

1. Direct myocardial damage
   - Cardiac contusions
   - Direct current cardioversion
   - Cardiac infiltrative disorders
   - Chemotherapy
   - Myocarditis
   - Cardiac transplantation (immune-mediated reactions)
2. Myocardial strain
   - COPD
   - CHF
   - Acute pulmonary embolism
3. Chronic renal insufficiency
4. Intracranial pathology (subarachnoid haemorrhages/acute stroke)
5. Demand ischemia (in absence of ACS)
   - Left ventricular hypertrophy
   - Anaemia
   - Hypotension
   - Hypovolaemia
   - Atrial Fibrillation/Supraventricular tachycardia

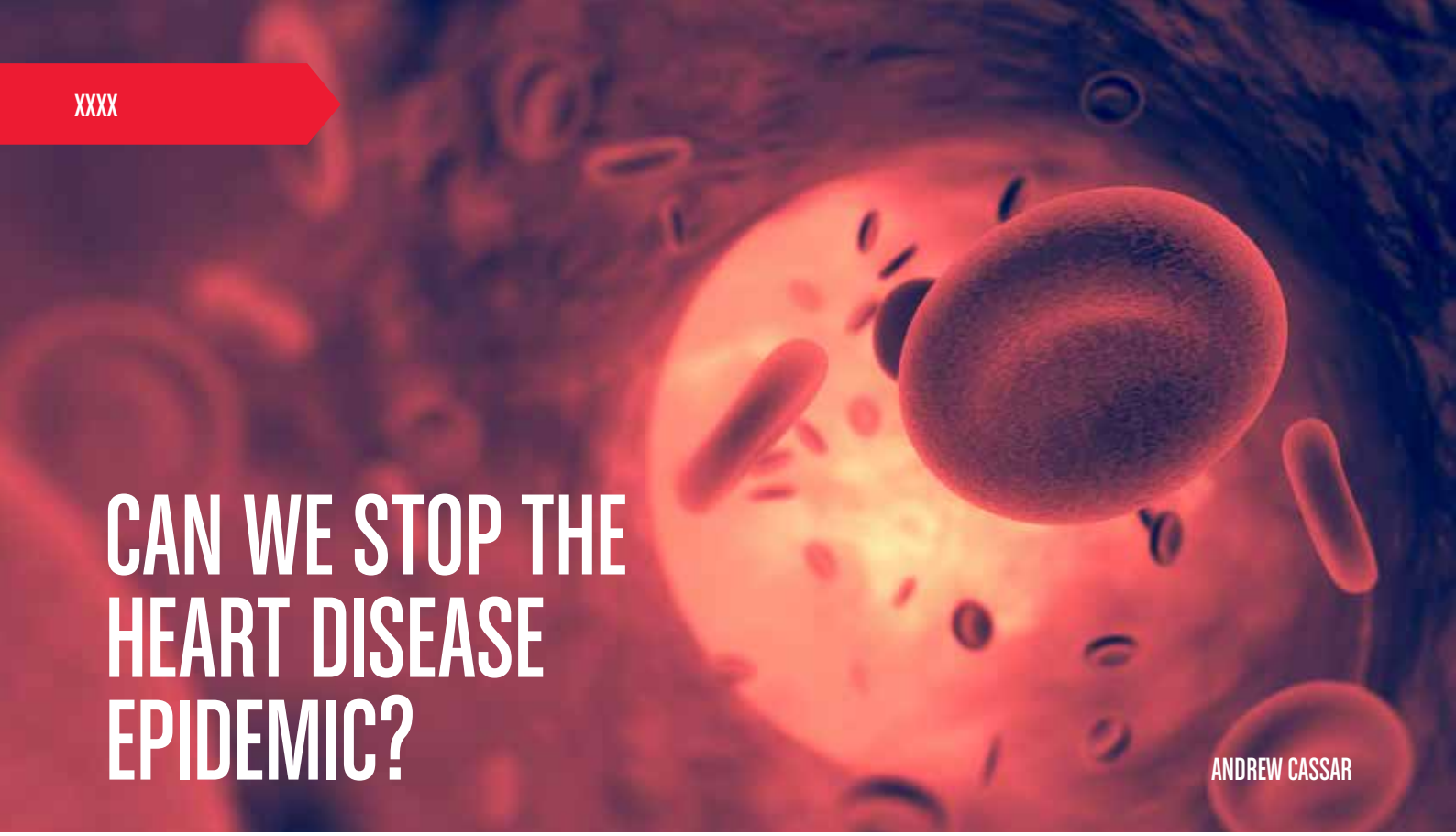
The Prognostic role of Cardiac Troponins

Apart from their diagnostic role, cardiac troponins also yield prognostic information. Patients having clinical evidence of ischemia and high levels of troponin in the circulation tend to have a worse prognosis. Studies have shown that peak troponin T levels in the circulation actually correlate well with the infarct size. The greater the extent of the troponin rise, the poorer the prognosis.[1]

CONCLUSION

Early detection of MI is crucial in ensuring better outcomes. Troponin assays are essential in establishing an earlier diagnosis. However, the ever-increasing sensitivity of these assays is associated with a decrease in their specificity. One should consider the clinical picture as well as other available investigations, and always take at least two serial troponin readings.

REFERENCES CAN BE ACCESSED ON THESYNAPSE.NET



CAN WE STOP THE HEART DISEASE EPIDEMIC?

ANDREW CASSAR

Cardiovascular disease is responsible for around 46% of deaths in Malta, of which more than half are due to coronary artery disease (CAD). What is, however, more important is that CAD is the number one cause for potential years of life lost in those under the age of 65 years with 12.8% of all deaths.[1]

CAD secondary to atherosclerosis is viewed as a disease of developed countries and the characteristic western diets, and is associated with obesity, smoking and lack of exercise. It is also more common in countries having an ageing population, which in itself is a sign of prosperity and associated good healthcare. Notwithstanding these facts, in recent times, we have started experiencing improving rates of age-adjusted cardiovascular mortality in the western world. This is primarily attributed to increased awareness of risk factor modifications for primary prevention, as well as medical advances in treatment. The latter, however, is expensive and less cost effective than primary prevention. In parallel, we are also witnessing an increase in incidence of cardiovascular morbidity and mortality of epidemic proportions in Eastern Europe and the developing countries. From an economic point of view, with the current global economic situation, especially in developing nations, the burden of treatment of cardiovascular disease can overwhelm the already stretched healthcare services.

1. SMOKING

In the US Centres for Disease Control and Prevention's report on smoking-attributable disease, it is estimated that smoking causes 1 in 10 of cardiovascular deaths worldwide.[2] In the US around a third of cardiovascular deaths in those older than 35 years are thought to be caused by smoking. Western countries have enacted legislation and punitive taxes, as well as educational programmes to try to reduce smoking rates.[3] In keeping with this fact, a recent literature review found that smoking reduction alone resulted in a reduction of cardiovascular deaths ranging between 6-56% in various different western countries.[4] As tobacco smoking is an addiction, preventing the initial exposure to smoking is the most cost-effective strategy. Campaigns to motivate smokers to quit are not enough, unless one can give support to the quitting decision, as there is clear evidence that quitting rates are much higher when one follows a smoking cessation programme.[5] Unfortunately, tobacco companies have shifted their marketing tactics to developing countries with their huge population of young people. They have tapped into their vast resources to fight tooth and nail against any legislation targeting tobacco in poor countries (which do not have the financial means to fight back). To this respect, the assistance offered by billionaire philanthropists, such as Bill Gates and Michael Bloomberg, to these countries has been most opportune.

2. HYPERLIPIDAEMIA, DIABETES AND DIET

Changes in diet and the ensuing metabolic diseases are thought to be a major contributor to cardiovascular disease in both the developed and developing world. The prevalence of diabetes, hyperlipidaemias and obesity has increased dramatically in societies as their dietary habits changed with different economic realities. A higher fat and refined carbohydrate content in food, coupled with an increasingly sedentary lifestyle, has produced a metabolic substrate for atherosclerosis in different racial groups. Despite the fact that different races have different genetic susceptibilities to CAD, diet plays a very important role. The proof of this is the French paradox (with the decreased

incidence of CAD when compared to their neighbours despite racial similarities), and increased incidence of CAD in Asian immigrants as they adopt their host country's diet.

Changing dietary habits is extremely difficult. Food is not merely a source of nourishment, but has several psychosocial facets, which is inherently ingrained in our society. It gives us pleasure, comforts us and makes us feel good. Tastes are acquired early on in childhood, and what gives comfort to a Chinese person might not have the same effect on us. To add to that, multi-billion dollar companies are constantly competing with each other to maximise profits and get consumers to buy their food with their aggressive marketing campaigns. Research has shown that it is only through the release of dopamine into the pleasure centres in the brain by high quantities of sugar, salt, and unsaturated fats that customers keep buying the same products again and again. Would the marketing efforts of fast food chains have the same effect if they exclusively sold unflavoured water and salads?

Decades of research by the medical community on dietary habits have produced great awareness throughout the western population. However, this has not been matched with legislative efforts by politicians, as has happened with reasonable success with tobacco. Unfortunately, marketing and labelling of food products can be misleading and is poorly controlled. Taxation of unhealthy food, and restriction of advertising is being proposed in several countries, but this is very complex to legislate as food products are very heterogeneous and loopholes are easily found.

Locally, there is widespread awareness of the importance of serum lipid levels and the associated cardiovascular risk, and checking one's cholesterol levels is popular with health conscious individuals. When dietary modification and exercise is not enough, statin therapy has proven to be highly effective in reducing the risk of atherosclerotic disease with a relatively favourable benefit-risk ratio. Choosing whom to give statins to for primary prevention has become a topic of great debate and research.

3. HYPERTENSION

High blood pressure is an important factor in the development of acquired cardiovascular disease, especially stroke.[6] High levels of salt in processed food is thought to be the main cause of essential hypertension in western societies. Tribes with practically no hypertension incidence have ended up with extremely high rates in a single generation as soon as they were exposed to processed food. The pharmaceutical industry has invested billions of dollars in coming up with a wide variety of effective anti-hypertensive agents. The recently published SPRINT trial has shown that lowering target systolic blood pressure to below 120 mmHg rather than 140mmHg halved the risk of death from cardiovascular disease.[7] The principal challenge with hypertension is not the lack of appropriate treatment, but the large proportion of undiagnosed or undertreated hypertensive patients in the general population.

4. EXERCISE

An increasingly sedentary lifestyle and lack of regular exercise is a well-known problem of the modern world. Most et al have reported that there is a reverse J-shaped relationship between leisure time physical activity and cardiovascular mortality, thus recommending a moderate amount of weekly exercise.[8] Once again, although exercise is regularly recommended by doctors, what is most needed is political action. Sports and exercise should be a priority in our education system, and not just an afterthought. An infrastructure to promote walking, cycling and other physical activity is sorely needed locally.

THE WAY FORWARD

Premature deaths have considerable social and economic effects on society. The fact that its largest contributor, cardiovascular disease, is potentially avoidable makes this disease worth investing in with respect to time and money. Physicians currently limit their role to treating patients who come to them worried about their symptoms, or advising patients who are aware of the need for primary prevention. Unfortunately, persons who do not actively seek doctors for primary prevention are usually the ones who lead an unhealthy lifestyle and have the highest risk. It is saddening and equally surprising when the author meets second-generation arteriopaths, who have had 20 years to stop smoking and correct their cholesterol levels, only for the tragedy of the death of a young father to be repeated again with the son.

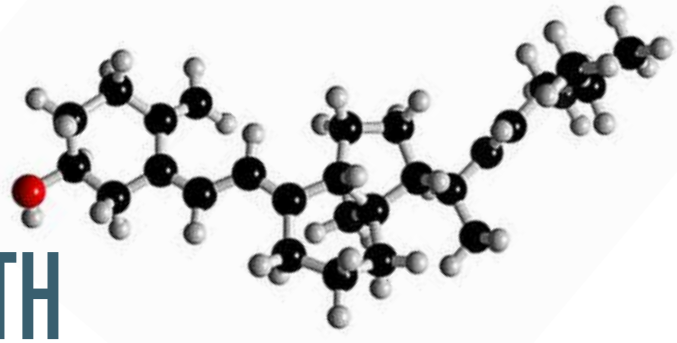
Our current healthcare system does not actively promote primary prevention for heart disease. A system similar to breast and colon cancer screening is feasible without the need of sophisticated and expensive equipment. The nurse-led Cardiac Rehabilitation Unit at Mater Dei Hospital is very effective for secondary prevention, and the response by patients has been overwhelming. A similar approach should be adopted for primary prevention of the whole general population. High-risk families and individuals should be easy to identify. Once this cohort is identified by qualified nurses, lifestyle advice can be given and if need be, these can be referred to physicians for any necessary medical management. Furthermore, IT systems can help standardise processes, and monitor the success or otherwise of any risk factor modifications.

Healthcare professionals should also be on the frontline, lobbying politicians to further educate children and help improve the health of our society. What children eat throughout their childhood will impinge on their future health status. In view of this fact, the government must be especially proactive in promoting healthy nutrition for its younger generations. Teenage smoking is also another aspect government should tackle; it is too easy for 16 year olds to come across cigarettes. Unfortunately, our politicians tend to overlook the future, so it is up to doctors and health care professionals to work tirelessly for those necessary changes which will eventually make early cardiovascular deaths a rare occurrence.

REFERENCES CAN BE ACCESSED ON THESYNAPSE.NET

MARIA BONNICI

VITAMIN D AND CARDIOVASCULAR HEALTH



It is well-known that vitamin D supplementation improves bone strength and deficiency leads to rickets in children and osteoporosis in adults.[1] Through observational studies it was noted that vitamin D deficiency is an independent risk factor for cardiovascular disease.[2,3] In 2008, Giovannucci *et al.,* reported that in The Health Professional Follow-Up Study which was conducted on 50,000 men, those men who were deficient in vitamin D were twice more likely to suffer from a myocardial infarction than those with adequate levels.[4] Additionally, in a cohort of patients, Ford *et al.,* identified a statistically significantly association between low vitamin D levels and obesity, glucose intolerance, metabolic syndrome and hypertension, which all increase the risk of cardiovascular disease.[5] This manuscript will review how vitamin D deficiency may predispose to coronary problems and how adequate vitamin D stores may improve cardiovascular health.

Vitamin D comes in two forms, ergocalciferol (vitamin D2) and cholecalciferol (vitamin D3). Vitamin D2 is found in mushrooms and specific plants e.g. alfalfa, whilst vitamin D3 is primarily found in oily fish. Both can also be found in fortified foods or supplements. Additionally, vitamin D3 can be synthesised cutaneously in humans from irradiation of 7-dehydrocholesterol by ultraviolet B radiation.

The liver converts vitamin D to 25-hydroxyvitamin D [25(OH) D], or calcidol, which is the major circulating metabolite and reflects vitamin D intake and endogenous production. Serum measures of 25(OH)D reflect the true vitamin D status. 25(OH) D is then converted, primarily in the kidneys, to the active form 1,25-dihydroxyvitamin D [1,25(OH)$_2$D] or calcitriol. This hormone maintains bone health and cardiovascular health. One must note that this active form does not correlate with the overall vitamin D status of the person and therefore its assays are not clinically useful.[1] Calcitriol, together with its receptor - present throughout the body including the vascular smooth muscle, endothelium and myocardium - in turn bind to retinoic acid x-receptor and serve as a nuclear transcription factor. This alters gene function including protein synthesis. Indirectly or directly vitamin D has the power to regulate over 200 genes, including those responsible for renin production in the kidney, growth and proliferation of both cardiomyocytes and vascular smooth muscle cells, insulin production in the pancreas and the release of cytokines by lymphocytes.[1]

Experimental studies in vitamin D-deficient animals have shown that they have an increased risk of hypertension, atherosclerosis and left ventricular hypertrophy.[6] In humans it was found that vitamin D inhibits renin gene expression and therefore it lowers down blood pressure through the rennin-angiotensin pathway.[7] Detrimental cardiovascular effects were found with hyperparathyroidism which could be the result of chronic vitamin D deficiency. Vitamin D deficiency leads to decrease in intestinal calcium absorption which in turn triggers parathyroid hormone release and eventually secondary hyperparathyroidism. An increase in parathyroid hormone levels leads to mobilization of calcium from bone, increased renal tubular calcium reabsorption and increased renal production of 1,25(OH)$_2$D. In 2003, Vestergaard and Mosekilde reported that patients who underwent surgical parathyroidectomy due to hyperparathyroidism had approximately 40% lower relative risks of myocardial infarction and stroke.[8] Moreover, an observational study on elderly patients found that those elderly individuals with elevated parathyroid hormone had a doubling-mortality when compared with those elderly with a normal parathyroid hormone.[9] The physiology behind this is that an increased parathyroid hormone level is associated with an increase in both blood pressure and myocardial contractility. This eventually leads to myocardial hypertrophy, apoptosis, and fibrosis of both the left ventricle and the vascular medial smooth muscle.[10] Furthermore, Andersson *et al.* found that in patients with moderate or severe chronic kidney disease, vitamin D deficiency and/or an increase in parathyroid hormone predisposes to calcification of the heart valves and myocardium.[11]

Vitamin D has anti-inflammatory properties;[12] in fact, low vitamin D levels increase systemic inflammation, evidenced by elevated serum C-reactive protein and interleukin-10.[10] Elevated circulating concentrations of pro-inflammatory cytokines could contribute to the pathogenesis of congestive heart failure. On the other hand, a recent double-blind, randomized, placebo-controlled trial has suggested that vitamin D supplementation reduces the inflammatory milieu in congestive heart failure patients.[13]

Who needs testing for vitamin deficiency or vitamin D supplementation?

Testing and supplementation is not recommended for everyone. These may be advised for people who are in long term care, bed-bound, or there is a medical condition which is indicative of vitamin D deficiency such as hypocalcaemia and hypophosphataemia. Patients with a history of bone fracture or osteopenia/osteoporosis should also be investigated for possible supplementation. On the market there are many different vitamin D preparations with the most commonly available being vitamin D2 and vitamin D3. It is recommended to take vitamin D3 when possible because it is the naturally occurring form of vitamin D. Obviously supplementation depends on the severity of the vitamin D deficiency. If the vitamin D levels are <20ng/ml, the treatment usually includes 50,000 IU of vitamin D2 or D3 once or more per week for 6-8 weeks, and then 800-1000 IU of vitamin D daily. If the vitamin D levels are 20-30ng/ml, the recommended treatment is 800-1000 IU daily for a 3 month period. Once normal levels of vitamin D are achieved it is recommended to continue with 800 international units daily. In people who have medical conditions which predispose to low vitamin D levels, the recommended dose of vitamin D will be determined on an individual basis.[1]

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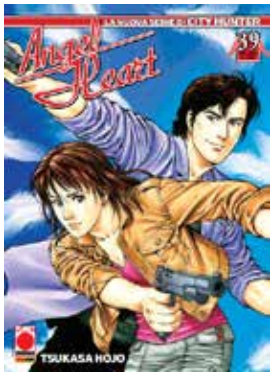

MANGA
Writer: Tsukasa Hojo
Publisher: Shinchosha [1st season], Tokuma Shoten [2nd season]
Magazine: Weekly Comic Bunch [1st season], Monthly Comic Zenon [2nd Season]
Run: 2001 - ongoing

ANIME TV SERIES
Director: Toshiki Hirano
Writer: Sumio Uetake
Network: NTV, Japan
Run: 2005 –2006

THE CONCEPT OF CARDIAC TRANSPLANTATION AND CELLULAR MEMORY - 'ANGEL HEART'

MICHELLE MUSCAT

A manga, animated series and live-action drama named *Angel Heart* based on the work of Tsukasa Hojo, centers on a fascinating and somewhat controversial topic in neurocardiology, that of cellular memory. *Angel Heart* follows a heart transplant recipient as well as Ryo Saeba, also known as the underground sweeper 'City Hunter', who was the partner of the heart donor. Throughout the story some thoughts and memories are seen to resurface within the transplant recipient, in a highly dramatized manner, which were not originally her own. Cellular memory is a somewhat controversial scientific concept, often discussed and disputed, as either fact or fiction.

The series centers on a girl, trained and forced to become a top notch assassin named 'Glass Heart', who tries to take her own life after her most recent assassination mission. Simultaneously another woman, named Kaori, is declared brain dead, and given she had a donor card her organs are harvested. After being transplanted with Kaori's heart, which was revealed to be a very close match upon histocompatibility testing, 'Glass Heart' is haunted by images and thoughts that she never knew she had, and had never encountered before.

This leads to the question if there may be indeed some form of memory transference to individuals who receive a heart transplant or if this is pure science fiction. It has been documented that people who underwent a heart transplant are more likely to exhibit changes in certain personality traits,[1] and certain eminent real life case reports have also illustrated the possibility of cellular memory.[2,3] Quite a few patient-recounted post-heart transplant reports may be found discussing the matter.[4,5] Although skepticism exists around this topic, numerous theoretical explanations have been put forward in order to offer further insight into this phenomenon.[6] For example, one of the hypotheses, 'the neuropeptide theory', envisages that the neuropeptides stored within every single cell could form the basis of a neuroendocrine biochemical mechanism for memory.[7] More research is currently being carried out on different facets of cellular memory.[8-12] Although some aspects of *Angel Heart* appear somewhat unrealistic and are added to increase dramatic tension and rivet the audience's attention, they do bring attention to this concept of 'cellular memory', which, although controversial, does have its roots in stories and hypotheses reported in the literature.

This review is partially funded through the Endeavour Scholarship Scheme.

REFERENCES CAN BE ACCESSED ON THESYNAPSE.NET

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For Gibraltar only: *Seretide 125, 250 Evohaler:* Each dose provides 25 microgram salmeterol xinafoate and 125 microgram or 250 microgram of fluticasone propionate. **Therapeutic Indications:** For Malta and Gibraltar: *Seretide Diskus and Evohaler:* is indicated in the regular treatment of asthma where use of a combination (long-acting beta-2-agonist and inhaled corticosteroid) is appropriate. *Seretide Diskus* is indicated for the symptomatic treatment of patients with COPD with a FEV_1<60% predicted normal (pre-bronchodilator) and a history of repeated exacerbations, who have significant symptoms despite regular bronchodilator therapy. *Seretide 50 Evohaler* is used in patients not adequately controlled with inhaled corticosteroids and 'as needed' inhaled short acting beta-2-agonist or patients already adequately controlled on both inhaled corticosteroid and long-acting beta-2-agonist. For Gibraltar only: *Seretide 125, 250 Evohaler:* is indicated in the regular treatment of asthma where use of a combination (long-acting beta-2-agonist and inhaled corticosteroid) is appropriate. Used in patients not adequately controlled with inhaled corticosteroids and 'as needed' inhaled short acting beta-2-agonist or patients already adequately controlled on both inhaled corticosteroid and long-acting beta-2-agonist. **Dosage and administration:** Seretide is for inhalation use only. ***Seretide Diskus:*** Asthma – Adults and adolescents 12 years and over: one puff twice daily of Seretide 100 or Seretide 250 or Seretide 500 (each containing 50 mcg of salmeterol xinafoate and 100 mcg, 250 mcg or 500 mcg respectively of fluticasone propionate). Patients should be given the strength of Seretide containing the appropriate, lowest fluticasone propionate dosage for the severity of their disease. 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It is important, therefore, that the patient is reviewed regularly and the dose of inhaled corticosteroid is reduced to the lowest dose at which effective control of asthma is maintained. Prolonged treatment of patients with high doses of inhaled corticosteroids may result in adrenal suppression and acute adrenal crises. Rarely, a range of psychological or behavioural effects such as psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression (particularly in children) may develop on prolonged use. Monitor height of children on prolonged inhaled steroid therapy. Transfer from oral steroids: Special care needed. Monitor adrenal function. Consider appropriate steroid therapy during periods of stress or elective surgery. Ritonavir can greatly increase the concentration of fluticasone propionate in plasma, therefore avoid concomitant use. There is also an increased risk of systemic side effects with other potent CYP3A inhibitors. There was an increased reporting of lower respiratory tract infections (particularly pneumonia and bronchitis) in the TORCH study in patients with COPD receiving Seretide compared with placebo; older patients, patients with a lower body mass index (<25kg/m^2) and patients with very severe disease (FEV_1<30% predicted) were at greatest risk of developing pneumonia regardless of treatment. Concomitant use of systemic ketoconazole significantly increases systemic exposure to salmeterol. This may lead to an increase in the incidence of systemic effects (e.g. prolongation in the QTc interval and palpitations). Concomitant treatment with ketoconazole or other potent CYP3A4 inhibitors should therefore be avoided unless the benefits outweigh the potentially increased risk of systemic side effects of salmeterol treatment. **Drug Interactions:** Avoid beta-blockers. Concomitant use with other beta-adrenergic containing drugs can have a potentially additive effect. Potent CYP3A4 inhibitors: Co-administration of ketoconazole (400 mg orally once daily) and salmeterol (50 mcg inhaled twice daily) resulted in a significant increase in plasma salmeterol exposure which may lead to an increase in the incidence of other systemic effects of salmeterol treatment (e.g. prolongation of QTc interval and palpitations) compared with salmeterol or ketoconazole treatment alone. The concomitant administration of ketoconazole should be avoided, unless the benefits outweigh the potentially increased risk of systemic side effects of salmeterol treatment. There is likely to be a similar risk of interaction with other potent CYP3A4 inhibitors (e.g. itraconazole, telithromycin, ritonavir). **Pregnancy and Lactation:** Experience limited. Balance risks against benefits. **Undesirable effects:** *Very Common/Common* - candidiasis of mouth and throat, pneumonia, bronchitis, hypokalaemia, headache, hoarseness/dysphonia, throat irritation (uncommon with Seretide 50 Evohaler), nasopharyngitis, sinusitis, contusions, traumatic fractures, arthralgia and myalgia, muscle cramps (uncommon with Seretide 50 Evohaler). See SPC for information on all adverse events. **Overdose:** *due to Salmeterol:* tremor, headache, tachycardia; *due to Fluticasone propionate:* temporary adrenal suppression.
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Gibraltar: any suspected AEs and medication errors can also be reported via the UK regulatory authority (MHRA): https://yellowcard.mhra.gov.uk/

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2. DeBlic J *et al. Pediatr Allergy Immunol* 2009: 20:763–771
3. Seretide Evohaler (fluticasone propionate/salmeterol xinafoate) Summary of Product Characteristics, Allen & Hanburys Ltd. October 2014.
4. Seretide Accuhaler (fluticasone propionate/salmeterol xinafoate) Summary of Product Characteristics, Allen & Hanburys Ltd. October 2014.

Date of Preparation: **January 2015** ZINC CODE: **MLT_GIB/SFC/0002/15**

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▼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 trifenatate). **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 $beta_2$-agonist and inhaled corticosteroid) is appropriate; and for the symptomatic treatment of adults with COPD with a FEV_1<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 $beta_2$-agonist and inhaled corticosteroid) is appropriate. **Dosage and Method of Administration:** *For Athsma:* 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 $beta_2$-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 $beta_2$-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 mos 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)

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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/adrportal and posted to the Malta Medicines Authority, Post-licensing Directorate, 203, Level 3, Rue D'Argens, Gżira GŻR 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 100/25 mcg compared with fluticasone furoate 100 mcg 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 (FF/VI) 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/FFT/0003/16 Date of preparation: February 2016

gsk

Theravance

AN UPDATE IN BREAST CANCER EPIDEMIOLOGY AND HEALTHCARE SERVICES IN MALTA

JASON ATTARD
MIRIAM DALMAS
KATHLEEN ENGLAND

ABSTRACT

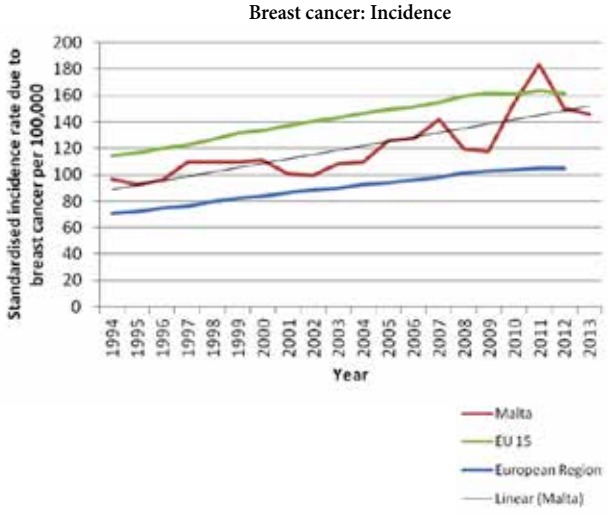
Cancer of the breast is the most common malignancy and the leading cause of cancer-related mortality in women. Over the past 20 years, mortality from breast cancer in Malta has shown a steady decline and survival from this disease has registered marked improvement, despite the fact that incidence continues to increase. Increased awareness as well as the development of specialized breast care health services have resulted in positive outcomes, with local mortality rates approaching that of the EU-15 average.

BACKGROUND

Breast cancer is the most common malignancy in women accounting for about one quarter of all female cancers and is the leading cause of cancer-related mortality in women.[1] On average, 57% of breast cancer cases are diagnosed in women below the age of 65 years.[2] The average 5-year relative survival of European women diagnosed with breast cancer in 1999-2007 was 81.8 (95% confidence interval: 81.6-82.0).[2]

The risk of breast cancer is highest in affluent westernised populations.[1] The Western lifestyle, characterised by a high-caloric diet, rich in animal fat and proteins, together with low physical activity, has been shown to be associated with an increased risk of breast cancer.[3] Women with a higher body mass index are at a higher risk. On the other hand, sustained physical activity throughout the life course protects women by about 20-40%.[4] Furthermore, the excessive consumption of alcohol is associated with a mild increase in the risk of breast cancer with risk increasing linearly with increasing intake.[5]

Figure 1: Breast cancer incidence rate time trends: 1994-2013.[9]
(Annual fluctations in the incidence rate for Malta are often due to small numbers and therefore a linear trend line has been added which depicts the general trend in the incidence rate for Malta)



THE RELATIVE SURVIVAL RATE [OF BREAST CANCER] IN MALTA IS STILL PERSISTENTLY LOWER THAN THE EUROPEAN AVERAGE ...

Also, recent evidence shows a potentially causal relationship between smoking and breast cancer, especially if long-term and heavy and if started at an early age.[6]

Other risk factors include a family history of breast cancer in first degree relatives, late childbirth, no history of breastfeeding, early menarche and late-onset menopause.[7] There is a small increase in the relative risk in women who used combined oral contraception and in those who used hormonal replacement therapy.[7]

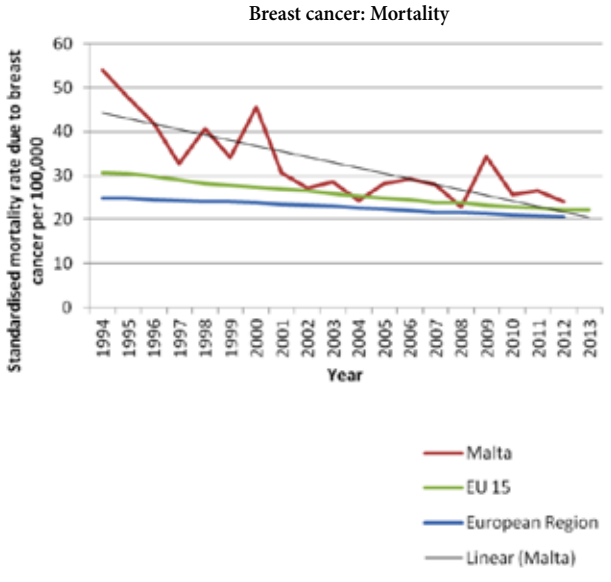
BREAST CANCER EPIDEMIOLOGY IN MALTA

I. INCIDENCE

The Malta National Cancer Registry[8] reports that during the time period 2011-2013, the average annual incidence in Malta amounted to 323 cases per year. The average age at diagnosis was 63.4 years and the age range varied from 17 to 97 years.

In Malta, the incidence rates of breast cancer have been steadily increasing over the past 20 years. Incidence rates for Malta are lower than the average of the EU 15 Member State countries (EU member states pre-2004 accession), but higher than the average of the European Region countries (53 countries under the remit of the WHO Regional Office for Europe) (figure 1).[9] Overall, it is clear that there is a steady upward trend across Europe. Of note, it appears that since 2008, the upward trend for the average EU 15 Member State countries has plateaued (the annual rates show a more flattened pattern).

Figure 2: Breast cancer mortality rate time trends: 1993-2013[8]



II. MORTALITY

During the time period 2011-2013, the average annual mortality attributed to breast cancer in Malta amounted to 82 deaths. The average age at death from breast cancer was 71.1 years and the age range varied from 31 to 96 years.[10]

Time trends for the breast cancer mortality rates for Malta have shown a steep decrease over the past 20 years, approaching the average EU 15 mortality rate. The time trends of standardised mortality rates of breast cancer in the European Region, the EU 15 member states, and in Malta are depicted in Figure 2.[9] The fall in standardized mortality rate over time is due both to an increase in the age at death and improvements in the overall survival from breast cancer.

III. SURVIVAL

The prognosis of breast cancer depends on the stage at diagnosis, the histological type and tumour grade, the immunophenotype (such as the expression of human epidermal growth factor receptor type 2 and oestrogen/progesterone receptor), and the overall health status of the individual.[11] Improvements in survival are the product of health care access, earlier disease detection (for example, through population screening), and advances in treatment. The widespread use of hormonal agents in oestrogen receptor-positive tumours, coupled with effective chemotherapeutic drug regimes have both resulted in a better overall prognsois, including an increase in remission rates and lower recurrence rates.[12]

In Malta, the 5-year relative survival rate has increased from 75.4 years for women diagnosed in 1990-1994,[13] to 75.9 years[14] and 84.4 years[15] for those diagnosed in 1995-1999 and 2000-2007, respectively. Despite this clear improvement in breast cancer outcomes, the relative survival rate in Malta is still persistently lower than the European average (based on 29 European countries grouped into five European regions).[15] This distinction is most discernible when comparing the outcomes for Malta with those of Northern Europe but it is also notable when compared to the average for Southern Europe (see Table 1).

In conclusion, over the past 20 years, mortality from breast cancer in Malta has shown a steady decline, survival from this disease has registered unrelenting improvement, whilst incidence continues to increase. Consequently, the national healthcare services have grown and evolved in parallel to meet the rising and diversifying needs of the Maltese population.

NATIONAL HEALTHCARE SERVICES FOR BREAST CANCER

The Breast Care Unit service was established in 2000 and is currently housed at Mater Dei Hospital. This Unit caters for

the diagnosis and surgical treatment of invasive breast cancer (just over 300 new cases per year), as well as non-malignant breast pathologies. It also offers follow-up services. The cancer care pathways (diagnostic workup and treatment plans) of women diagnosed with breast cancer are discussed at weekly multi-disciplinary team (MDT) meetings. The MDT includes breast cancer surgeons and nurses, pathologists, radiologists, oncologists and managers from the national screening program. The Breast Care Unit was renamed the Agatha Breast Unit in 2015 during celebrations to mark 15 years since its inception. During the celebration program, guidelines for diagnosis, treatment and follow-up, coordinated by the clinic's surgical professionals, were presented and launched. New surgical techniques such as oncoplastic and immediate reconstruction surgery have been introduced to complement the plastic and reconstruction surgery that were already available.

Breast cancer patients are also offered specialized allied healthcare professional services such as occupational therapy, physiotherapy, as well as the services of clinical psychologists and social workers. Physiotherapists also organize a specialized lymphoedema clinic. A number of publications offering information to clients and patients have also been developed and are distributed by the National Screening Unit, the Agatha Breast Unit and the Sir Anthony Mamo Oncology Centre.

Newer health technologies are improving the diagnostic capabilities across the board. In the medical imaging department, two full-field digital mammography machines with stereo-guided equipment, ultrasound equipment equiped with 2D and 3D probes, and a 3 Tesla MRI scanner with dedicated breast software were introduced. Current pathology services are also increasingly relying on immunohistochemistry to test for oestrogen and progesterone receptors, HER2 amplification and other basal biomarkers. The results of these investigations are allowing a more personalised approach to the adjuvant and neo-adjuvant therapy that can be offered to patients.

Oncological treatments, namely chemotherapy, hormone therapy and radiotherapy, and palliative care are managed and delivered at Sir Anthony Mamo Oncology Centre. The new Oncology Centre, which was inaugurated in 2015, is equiped with 3 linear accelerators, planning stations and a large bore CT simulator.

Population-based organised mammography screening was introduced towards the end of 2009 for women aged between 50-60 years. By 2015, this has been extended up to women that are 65 years old. In the Health Interview Survey (2008) that was conducted before the introduction of the organised screening program, 40% of women in the 50-65 year group reported that they had at least one mammography in the preceding three years.[16] During 2013, the screening program performed mammography screening on 9,027 women (58.1% of the women invited for screening during 2013). Of these, 44 women were eventually referred for further investigation and treatment of breast pathology. The breast pathology of 35 of these women was confirmed to be invasive breast cancer while the remaining 9 cases were eventually confirmed to be carcinoma-in-situ.

Table 1: Age-specific and age-standardised relative survival for breast cancers diagnosed in 2000-2007, by European region and overall[15]

		Age-standardised relative survival with 95% confidence intervals in parentheses		
	Number of cases	1-year	5-year	Conditional
Northern Europe	138,062	96.4 (96.2 - 96.5)	84.7 (84.4 - 85.1)	87.9 (87.6 - 88.3)
Ireland and UK	364,027	93.4 (93.3-93.6)	79.2 (79.0 - 79.4)	84.7 (84.5 - 85.0)
Central Europe	318,766	95.7 (95.6 - 95.8)	83.9 (83.6 - 84.1)	87.7 (87.5 - 87.9)
Southern Europe	173,693	95.6 (95.4 - 95.7)	83.6 (83.3 - 83.9)	87.5 (87.2 - 87.8)
Malta	**1,806**	**95.7 (94.4 - 97.1)**	**80.8 (77.3 - 84.4)**	**84.4 (81.0 - 87.9)**
Eastern Europe	121,443	91.0 (90.8 - 91.3)	73.7 (73.2 - 74.1)	80.9 (80.5 - 81.4)
Europe (based on 29 European countries)	1,115,991	94.8 (94.7 - 94.9)	81.8 (81.6 - 82.0)	86.3 (86.1 - 86.5)

CONCLUSION

The comprehensive breast cancer care services which are offered in Malta, have consistently been shown to be continuously improving. The outcomes of these services can be further improved through initiatives to lower incidence through the promotion of healthier lifestyles, and reduce mortality by advancing earlier detection through health education and population screening.

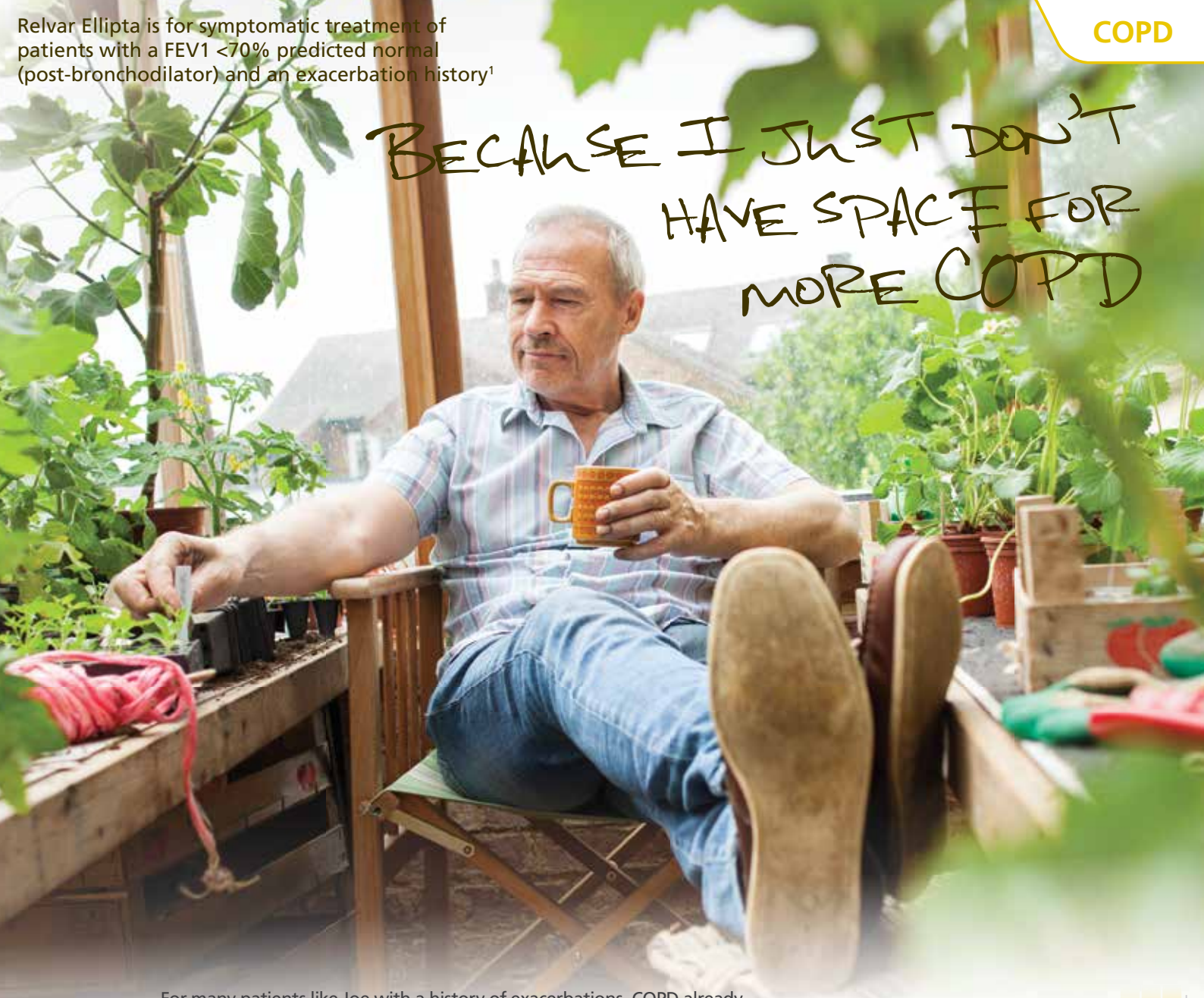
Improvement of the breast care services offered can be more vigorously channeled towards achieving higher quality of these services such as through the introduction of initiatives to help reduce the waiting times between different phases of the breast cancer care pathways. Additional effort needs to be devoted towards achieving more positive patients' experience during the diagnostic and therapeutic phases as well as beyond, through the emerging and important themes of rehabilitation and survivorship. The latter two domains are constantly growing in importance and significance in tandem with achievements in cancer survival.

Acknowledgements: Malta National cancer Registry: Dr Domenic Agius and Ms Rita Micallef

REFERENCES CAN BE ACCESSED ON THESYNAPSE.NET

Relvar Ellipta is for symptomatic treatment of patients with a FEV1 <70% predicted normal (post-bronchodilator) and an exacerbation history[1]

COPD



For many patients like Joe with a history of exacerbations, COPD already takes up too much space in their life, yet they fear losing even more. So, when they need maintenance therapy, choose new Relvar Ellipta:

- The first ICS/LABA combination to deliver continuous 24-hour efficacy[2]
- In a practical, once-daily dose[1]
- Delivered in an easy to use device that patients prefer to their current inhaler[3,4*]

RELVAR® ELLIPTA®

(fluticasone furoate and vilanterol inhalation powder)

Practical efficacy

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.

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MLT_GIB/RESP/0004/16 Date of preparation: Feb 2016

gsk

Theravance

A JOKE A DAY KEEPS THE DENTIST AT BAY

Sitting on the side of an American highway waiting to catch speeding drivers, a policeman sees a car puttering along at 22 miles per hour. He thinks to himself, "this driver is just as dangerous as a speeder!" So he turns on his lights and pulls the driver over.

Approaching the car, he notices that there are five very old ladies, two in the front seat and three in the back - wide-eyed and white as ghosts. The driver, obviously confused, says to him "Officer, I don't understand. I was doing exactly the speed limit! What is the problem?"

"Ma'am" says the officer, "You weren't speeding but you should know that driving slower than the speed limit can also pose a danger to other drivers".

"Slower than the speed limit? No sir, I was doing the speed limit exactly ... 22 miles per hour!" the old woman says, quite proudly.

The policeman, trying to contain a chuckle explains to her that **'22'** was the route number, not the speed limit. A bit embarrassed, the woman grinned and thanked the police officer for pointing out her error.

"But before I let you go Ma'am, I need to ask … is everyone in this car ok? The women at the back seem awfully shaken and they haven't uttered a single word this whole time," he asked.

"Oh, they will be alright in a minute officer, we just got off Route 119".

MENINGITIS

MPSA

JESSICA ZARB
PUBLICATIONS OFFICER

Meningitis is an inflammation of the membranes that cover the brain and spinal cord. Infectious causes include bacteria, viruses and fungi. On the other hand, non-infectious causes include cancers and head injuries. This review will discuss the most common causes, namely bacterial and viral infections.

Bacterial meningitis may be caused by several pathogens, namely Haemophilus influenza, Streptococcus pneumoniae, Listeria monocytogenes and Neisseria meningitides. Different pathogens characteristically affect specific age groups, e.g. Haemophilus influenza generally affects infants and children, whereas Listeria monocytogenes infections are characteristic ofnewborns and the elderly. Bacterial meningitis is usually severe and can cause serious complications, however, most people recover with the aid of antibiotics. Risk factors include age, whereby infants are at a higher risk, and immunosuppression, amongst others. Transmission of the causative agents occurs through the exchange of respiratory and throat secretions; it is not spread through casual contact such as simply breathing the air where a person with meningitis has been. Unlike other bacterial causes of meningitis, infections of Listeria monocytogenes can occur by eating contaminated food. Symptoms of bacterial meningitis may appear suddenly or over several days. Apart from a sudden onset of fever, headache, and stiff neck,signs of the infection include nausea, vomiting, photophobia and confusion. Once diagnosed, the treatment should commence as soon as possible, where treatment is also recommended for close contacts of people suffering from Meningococcal meningitis and Haemophilus influenza infections.

Viral meningitis is less severe than bacterial meningitis, however, infants and immunosuppressed people are more likely to develop a severe form of the illness. Causes of viral meningitis include non-polio enteroviruses, mumps virus, herpes viruses, measles virus, influenza virus and arboviruses, such as the West Nile virus. The symptoms of viral meningitis are similar to bacterial meningitis infections.

Both bacterial and viral meningitis can be diagnosed through specific lab tests on specimens such as cerebrospinal fluid.

Preventive measures primarily include vaccination and avoiding close contact with people who are sick.

HEARD IN THE Grapevine

ZIKA VIRUS STRUCTURE

The Zika virus, discovered in Uganda in 1947, is a type of virus called flavivirus. This genus of viruses include dengue, yellow fever, and West Nile viruses. These are all primarily transmitted to humans through the bite of infected *Aedes aegypti* mosquitoes. The estimated 20% of infected persons who actually get sick usually exhibit mild symptoms which subside within a few days.

Zika virus circulated relatively unnoticed until 2013, when the virus caused an outbreak in the French Polynesia. The first confirmed case of infection in Brazil was reported in May 2015. Since that time, the virus has spread to other territories in Central and South America as well as the Caribbean. The current outbreak provides mounting evidence that the Zika virus can also cause microcephaly in babies born to mothers infected with the virus during pregnancy.

Pursuant to this, a team of investigators examined the structure of a mature Zika virus particle at near-atomic resolution. They used a technique called cryo-electron microscopy. The process involved freezing virus particles and firing a stream of high-energy electrons through the sample to create tens of thousands of images. These 2D images were then combined to yield a detailed 3D view of the virus. Results appeared online on March 31, 2016, in *Science - http://science.sciencemag.org/content/early/2016/03/30/science.aaf5316.*

The surface of the flavivirus is composed of a shell made of 180 copies of both an envelope glycoprotein and 1 of 2 other proteins anchored in a lipid membrane. The researchers found that the Zika virus structure is similar to that of other known flaviviruses, except for one region of the envelope glycoprotein. Flaviviruses may use this glycoprotein region to attach to and enter human cells. The newly identified Zika variation could help explain the virus's ability to attack nerve cells. It might also shed light on Zika's proposed link to microcephaly. If the site on the envelope glycoprotein functions in Zika as it does in related viruses, the detailed structure might help scientists design ways to block viral attachment and entry to human cells.

Source: www.nih.gov

EDITOR'S PICK
FOR BOOKWORMS

VASCULAR ENGINEERING: NEW PROSPECTS OF VASCULAR MEDICINE AND BIOLOGY WITH A MULTIDISCIPLINE APPROACH

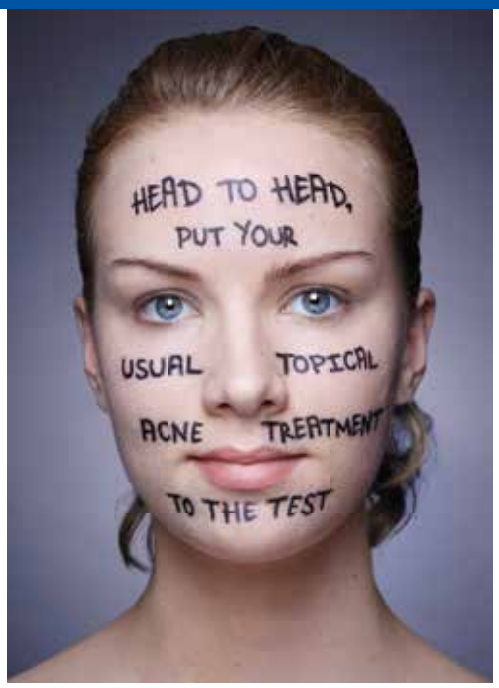
by Kazuo Tanishita & Kimiko Yamamoto (Editors)
Springer; 401 pages; $189.16
Published in April 2016

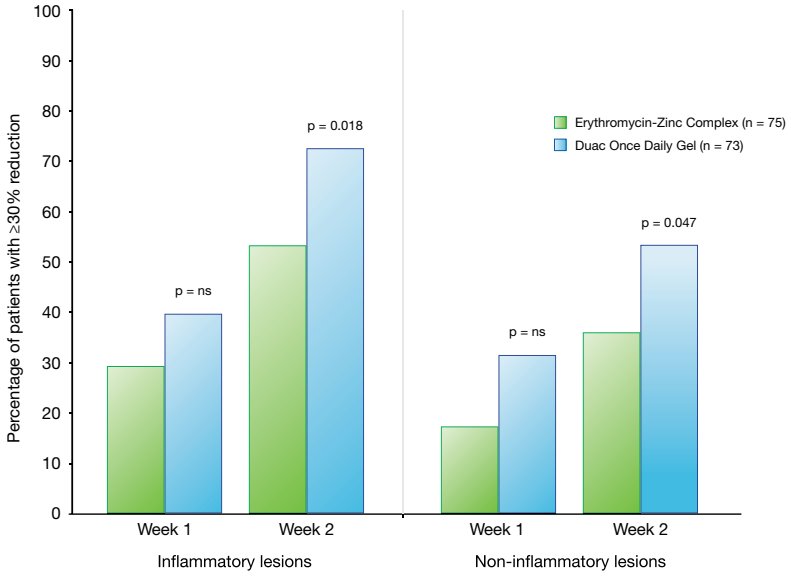
This book describes the fundamental biology and mechanics of the vasculature and examines how this knowledge has underpinned the development of new clinical modalities, including endovascular treatment and vascularization of reconstructed tissue for regenerative medicine. Vascular engineering is a multidisciplinary field integrating vascular biology, hemodynamics, biomechanics, tissue engineering, and medicine. Each chapter offers insights into the dynamics of the circulatory system and explains how the impact of related disease conditions – atherosclerosis, hypertension, myocardial ischemia, and cerebral infarction – has generated a focus on developing expertise to both maintain and treat the vascular system.

As a comprehensive book in this expanding area, Vascular Engineering serves as a valuable resource for clinicians as well as academics and professionals working in biophysics, biomedical engineering, and nano and microrheology. Graduate students in these subject areas will also find this volume insightful.

Source: www.amazon.com

HEAD TO HEAD, DUAC WORKS FASTER THAN ERYTHROMYCIN-ZINC COMPLEX[1]





Graphs adapted from Langner A *et al. JEADV* 2007

- More patients with mild to moderate acne achieved at least a 30% reduction in inflammatory and non-inflammatory lesion counts at week 2 with Duac than Erythromycin-zinc complex[1]
- DUAC demonstrated a faster onset of action, reducing total lesion count in significantly more patients than Erythromycin-zinc complex at just 2 weeks[1]
- Most common side effects include erythema, peeling, dryness, burning sensation, photosensitivity and headache

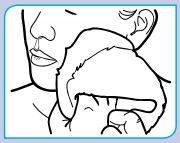
DUAC INDICATIONS & USAGE ADVICE[2]

- Duac Once Daily Gel is indicated for the topical treatment of mild to moderate acne vulgaris, particularly inflammatory lesions in adults and adolescents from 12 years of age and above[2]
- Formulation contains added moisturisers, glycerin and dimethicone, for better tolerability[4]

YOUR EXPERT ADVICE CAN SHOW ON THEIR FACE

Duac comes ready-mixed, and is easy for your patients to use. It is recommended that you offer the following guidance[3]: Once-daily, in the evening, your patients should[2]:

• Thoroughly wash the affected area of skin



• Gently pat dry

• Apply a thin layer of Duac gel on the affected area, not just the individual spots

TIPS[3]

If your patient's skin peels or becomes dry, they can try:
- Using an oil and fragrance-free hypoallergenic moisturiser
- Using Duac less often, or stopping for one or two days before starting again

Duac® Once Daily 10mg/g + 50mg/g Gel Abridged Prescribing Information

**Please refer to the full Summary of Product Characteristics (SPC) before prescribing*

Trade Name: Duac® Once Daily Gel. **Active Ingredients:** Clindamycin phosphate/anhydrous benzoyl peroxide. **Pharmaceutical Form:** 10mg/g + 50mg/g gel. **Indication:** Topical treatment of mild to moderate acne vulgaris, particularly inflammatory lesions in adults and adolescents from 12 years of age and above. **Posology and Method of Administration:** Cutaneous use only. *Adults and Adolescents:* Once daily in the evening. Treatment should not exceed more than 12 weeks. *Elderly:* No specific recommendations. **Contraindication:** Hypersensitivity to active substances, lincomycin and any of the excipients. **Precautions for Use:** Avoid Contact with the mouth, eyes, lips, other mucous membranes or areas of irritated/broken skin. Use with caution in patients with a history of regional enteritis, ulcerative colitis and antibiotic-associated colitis. If significant diarrhoea occurs or patients suffers from abdominal cramps, treatment should be immediately discontinued. *Resistance to clindamycin:* Patients with a recent history are more likely to have pre-existing anti-microbial resistant *Propionibacterium acnes* and commmensal flora. *Cross-resistance:* May occur when using antibiotic monotherapy. **Fertility, Pregnancy and Lactation:** There is no adequate data. Avoid application of the product to the breast area. **Effect on Ability to Drive or Use Machines:** No studies. **Side Effects:** Very Common side effects (at least 1 in 10) include erythema, peeling and dryness. Common side effects (less than 1 in 10) include burning sensation, photosensitivity and headache. **Overdose:** No specific antidote. Treatment should consist of appropriate symptomatic measures or clinically managed.

Local Presentation: 30g gel. **Marketing Authorization Holder:** GlaxoSmithKline UK Ltd., Trading as Stiefel. **Marketing Authorization Number:** MA 300/01401. **Legal Category:** POM.

Date of Preparation: January 2016

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 SPC, WHICH IS AVAILABLE FROM: GSK (MALTA) LIMITED (TEL: 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/adrportal and posted to the Malta Medicines Authority, Post-licensing Directorate, 203, Level 3, Rue D'Argens, Gżira GŻR 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/

References: 1. Langner A *et al.* JEADV 2007; **21**: 311-319. **2.** Duac 5% Summary of Product Characteristics, January 2015. **3.** Duac 5% Patient Information Leaflet, October 2014. **4.** Langner A *et al.* BJD 2008; **158**: 122-129.

Stiefel a GSK company

Duac® once daily gel — *Clindamycin 1% and benzoyl peroxide 5%*

Job no.: MLT_GIB/CBP/0001/15 Date of preparation: January 2016

A DOCTOR OF MANY TALENTS

On the set of *Strada Stretta*, a local Maltese TV production

MEETING DR JOE PACE IN ONE OF THE CLINICS HE ATTENDS, ALLOWS MARIKA AZZOPARDI AN OPPORTUNITY TO DISCOVER MORE ABOUT THIS DOCTOR'S PROFESSION, HIS HOBBIES AND INTERESTS, FROM IT, TO ACTING, SKIING AND MORE.

TS: AS A FAMILY DOCTOR, YOUR WORK TAKES YOU TO VARIOUS PHARMACIES AROUND THE SOUTH OF MALTA, APART FROM CARRYING OUT ROUTINE HOME VISITS, BUT HAS IT ALWAYS BEEN SO?

I became a doctor in 1988 and worked for a few years in primary care. I then spent 16 years working towards computerising the local public health service, during which time I sat for a Master degree in Public Health Medicine (becoming a specialist in this sphere). Indeed, I spent so much time on medical computing, that I relegated my medical practice to a part-time basis. However, I am presently a full-time family doctor again.

TS: WHAT WAS THE PURPOSE OF YOUR WORK IN MEDICAL COMPUTING?

I was involved in introducing computing skills in St Luke's Hospital, Mater Dei Hospital, local health centres and Gozo General Hospital. Our team would implement computing systems purchased by the Government from foreign companies and act as a go-between in order to facilitate the use of these systems within the National Health Service. I sometimes also wrote small computer programs myself to fill in gaps or provide services for areas that were too small for a full-blown formal purchase.

TS: CAN YOU ELABORATE ON THIS?

Yes, for instance, our team worked towards implementing computing systems within the hospital labs, so that results from the analysers could be fed directly to the computer system and sent out in a timely fashion to the clinicians concerned. I also had a paw in the setting up of the 'myHealth' system.

TS: WHAT WERE THE BIGGEST HURDLES AND CHALLENGES?

Most definitely, the business change did bring on great challenges, but mainly these challenges revolved around limited resources, both of the financial and of the human kind. Suffice to say that in Ireland and Portugal for instance, a hospital the size of Mater Dei Hospital has a staff complement of 20-25 IT specialists. In our case, our team included about 10 members of

staff who worked on a nationwide basis. Having few resources, including not enough people was only one of the problems. Another one was the need of twisting a new tool round to adapt to old methods, and of course, the lack of resources did not help us overcome the resistance to change. Our limited IT budget did not grow on an annual basis, but rather remained static or was restricted over time. Having said that, our team was always very positive and managed to do a great deal with what was made available.

TS: WHY DID YOU DECIDE TO LEAVE THE COMPUTING WORLD?

The politics and daily difficulties involved in the massive project of implementing several large software packages all across the Maltese national health scheme eventually wore me out. I decided I needed to change and go back to being a general practitioner as I was not seeing a future for myself nor any future and valid growth for my career. I did take on a job as a CEO for a private company in between, but in the end I did go back to becoming a full-time family doctor.

TS: WHAT ARE YOUR FEELINGS ABOUT THIS CHANGE?

I am indeed surprisingly very happy, since I am once again relating to people and finding some loyalty from my plethora of patients. Apart from my work as a family doctor, I also serve as a private consultant with a company specialising in medical informatics. I am presently working on a project focusing on the elderly and people with a disability. The project aims to support staff members with the necessary tools for easier management of administrative tasks. This should help staff dedicate more time to actually providing care to patients, by relieving them from the administrative workload.

Dr Pace [standing first from right] during his undergraduate studies, with fellow medical students

Award won as best director in the MADC One Act Play FestivalG

Marriage photo

Taking part in a play staged by Narcy Calamatta

TS: WHAT DO YOU DO IN YOUR SPARE TIME, IF YOU HAVE ANY?

I love to ski and one of my most recent travels has been to ski in Bulgaria at an altitude of 2700m. I used to play football but now skiing is my preferred sport. Then again I do a lot of acting. When I had more time, I had been known to take part in three plays in just one season. I have acted in theatre productions for MADC, Maleth, Koperatturi and others. To a certain extent, local theatre companies now accept to work around my availability if they want me to be in their cast.

TS: WHAT IS YOUR PREFERRED ROLE?

I love Shakespearean parts, but my typical roles do not generally show me up as a bad guy. Having said that, comedy is not easy for me due to my physique. Last summer I acted out Trevor Zahra's monologues, and in the past I enjoyed being part of Francis Ebejer plays. But by far, my most favourite role has been Alistair in the play by Oresta Calleja 'Il-Belliegħa fil-Bir'. It was an extremely complicated role about a homosexual man who had to deal with several paternal issues.

TS: ... AND YOU WRITE?

Yes indeed, I have written a novel (Merlin Publishers), called 'It-Tielet Teorija'. My second book is in the works and due to be published later this year. I am turning 53 this May, happily busy and having fun in what I do. I remarried in 2012 and together with my wife, we have four 'grown' kids.

I READ THE SYNAPSE BECAUSE...

Over the many years during which it has been in existence, it has always provided excellent, relevant information for the Maltese healthcare scene.

AZITHRIN

Azithromycin
500mg
film-coated tablets

Fight back with 3 when infection hits

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ULTRASOUND DIAGNOSIS OF COMMON MUSCULO-SKELETAL DISORDERS IN YOUNG ATHLETES – PART II

PIERRE VASSALLO

In part I of this article, we discussed tendonous injuries that tend to limit performance in young athletes. Part II of this article will deal with ultrasound (US) diagnosis of ligamentous injuries.

Ligaments are similar to tendons in that they have an ordered lamellar arrangement of fibers and therefore appear fibrillar and hyperechoic on US. In skeletally immature patients, the ligaments insert into un-ossified bone, which is hypoechoic (Fig 1), while in skeletally mature individuals they insert into hyperechoic cortical bone (Fig 2).

Ligament tears appear as focal or diffuse areas of decreased echogenicity that disrupt the normal fibrillar pattern, or as discontinuity of the ligament. As with tendons, ligaments show anisotropy particularly close to their attachments that may lead to incorrect diagnosis. The most amenable ligaments on ultrasound are the extra-articular ligaments of the knee (medial and lateral collateral ligaments), the lateral ankle ligaments (particularly the anterior fibulo-talar ligament or ATFL) and the ulnar and radial collateral ligaments of the elbow and thumb.

Ligament tears may be better appreciated during dynamic ultrasound imaging rather than on static scans; one example would be to scan the ATFL during the anterior drawer test. The anterior drawer test checks for anterior instability of the ankle and is performed by applying posterior pressure on the anterior aspect of the distal tibia while pulling the posterior aspect of the calcaneus anteriorly.

The ATFL is best visualised in its longitudinal plane that runs from the anterior aspect of the tip of the fibula to the anterior portion of the talus (Fig 3). A tear of the ATFL can appear as loss of its fibrillar pattern, focal thinning of the ligament or a defect in the ligament (Fig 4); these features may become more evident when observed dynamically during the anterior drawer test or when compared with the contralateral normal ligament (Fig 5).

The ulnar collateral ligament (UCL) of the elbow is also well visualised by ultrasound. It has three components, the anterior, posterior and transverse bundles. The anterior bundle of the UCL is one of the main stabilising structure in the medial aspect of the elbow and is best imaged in its longitudinal course (Fig 6). A torn UCL (anterior bundle) usually results from forceful throwing as may occur in pitching (baseball) and may present with loss of the fibrillar pattern, focal thinning and as a defect in the substance of the ligament on US (Fig 7).

The UCL of the thumb is prone to injury during forced adduction as may occur during skiing injuries caused by the ski pole or by a fall on the extended thumb (Fig 8). Scanning along the longitudinal plane of the ligament will demonstrate the defect within the ligament, which is again more evident while dynamically scanning during forced thumb adduction (Fig 9). Scanning of the UCL of the thumb requires a special high resolution US probe frequently referred to as a hockey stick probe.

The medial and lateral collateral ligaments of the knee (MCL and LCL) (Fig 10) are prone to tears resulting from valgus/varus knee strain. Scanning in the longitudinal plain of the ligaments will best depict their integrity. Tears of the MCL or LCL appear as loss of the fibrillar pattern, focal hypo-echogenicity, ligament thinning or as a defect in the ligament (Fig 11).

The literature contains an ever-increasing list of ligamentous structures that are amenable to US evaluation. With the advent of high frequency ultrasound probes ranging up to 22MHz, tiny superficial ligaments can be assessed with accuracy often greater than is allowed by Magnetic Resonance Imaging. Such structures include the tiny ligaments and pulleys retaining the flexor tendons of the fingers as well as ligaments in the wrist and foot that are of vital importance to the stability and function of the related joints. The information delivered by US on ligamentous integrity is of vital importance when providing tailored treatment targeted towards obtaining the best functional outcome.

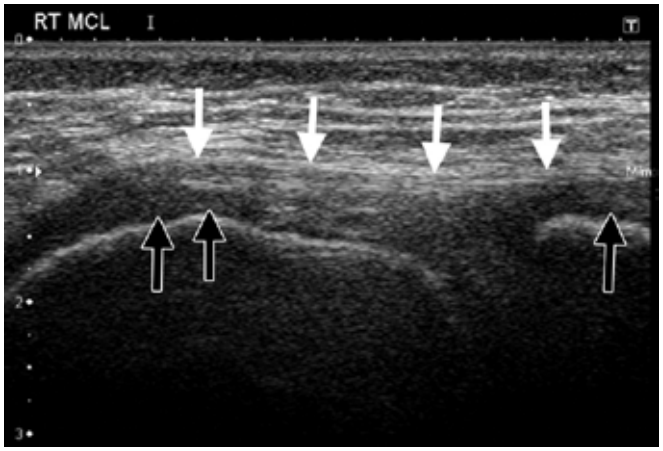


Figure 1. US appearance of a normal medial collateral ligament (MCL) of the knee in a skeletally immature individual. Longitudinal image showing the normal hyperechoic fibrillar pattern of the MCL (white arrows). At the insertions of the MCL, normal thick hypoechoic un-ossified cartilage is seen both at the femur and tibia (black arrows) in this skeletally immature individual

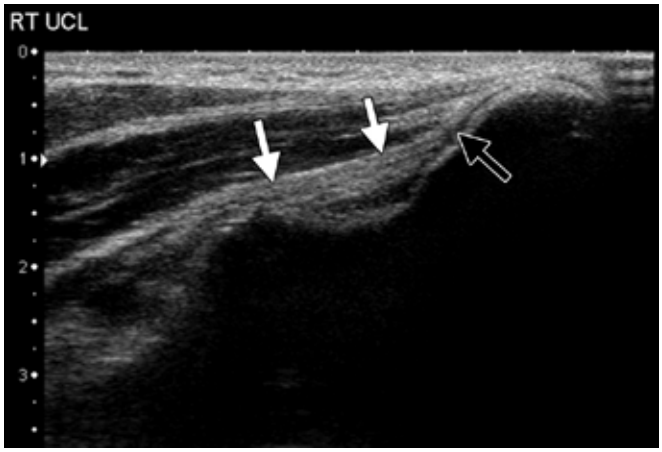


Figure 2. US appearance of a normal ulnar collateral ligament (UCL) (anterior component) in a skeletally mature patient. Note the normal hyperechoic fibrillar pattern of the UCL (white arrows). The fine hypoechoic line at the humeral insertion of the UCL (black arrow) represents the enthesis (or common flexor insertion fibrocartilage)

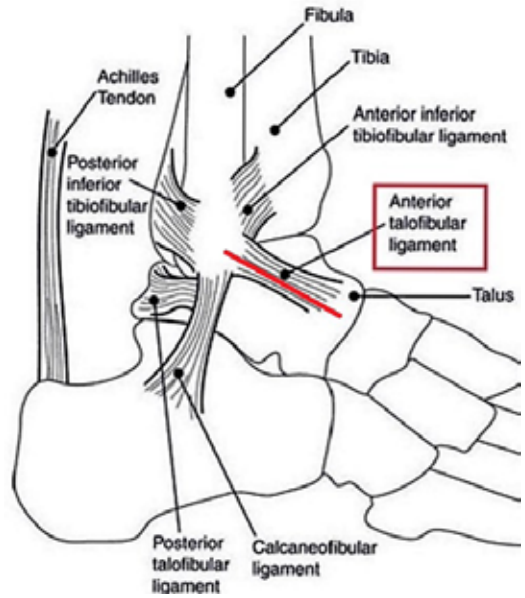


Figure 3. Anatomy of the anterior fibulo-talar ligament (ATFL) and the optimal scanning plane indicated by the red line

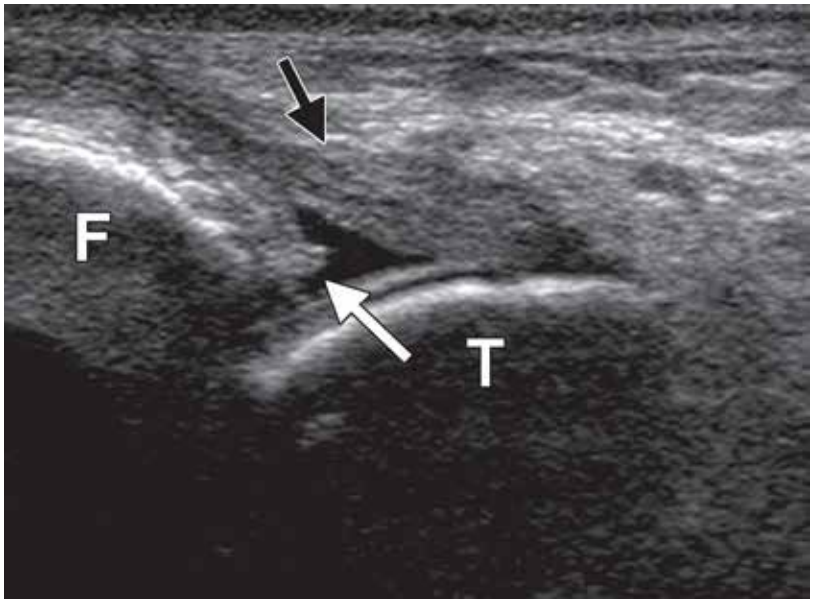


Figure 4. Longitudinal US scan of a torn ATFL shows discontinuity of the ATFL, with a small stub of ligamentous tissue still attached at its fibular footprint (white arrow). The ligament also shows loss of the normal fibrillar pattern, decreased echogenicity, and abnormal tapering near the fibula (F) (black arrow), findings consistent with prior tearing and subsequent degeneration

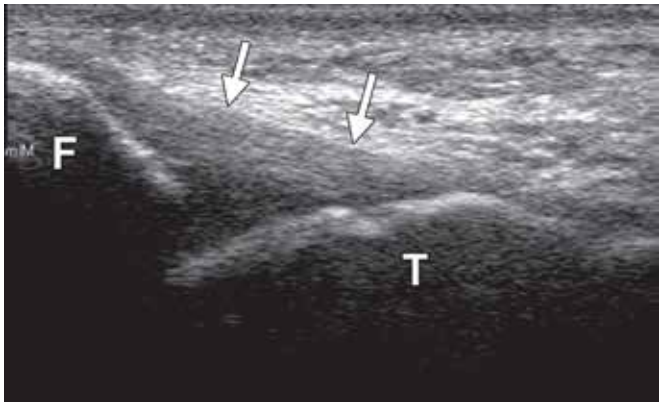


Figure 5. Longitudinal US scan of the contralateral normal ATFL shows a normal hyperechoic ligament with an organized fibrillar pattern (arrows) and a normal insertion onto the footprint of the fibula (F)

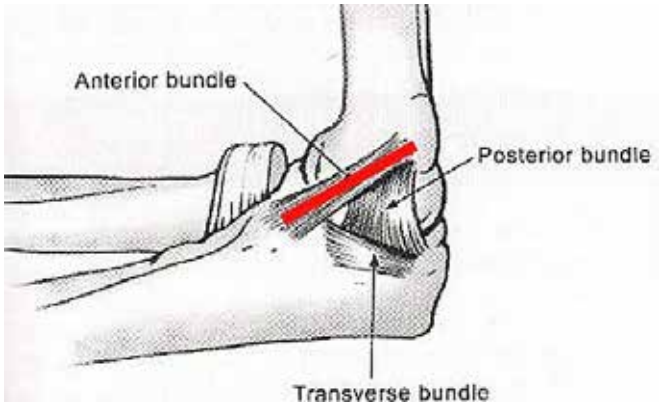


Figure 6. Anatomy of the UCL of the elbow showing three component bundles. The main stabilising structure is the anterior bundle that is best imaged in the longitudinal plane as shown by the red line

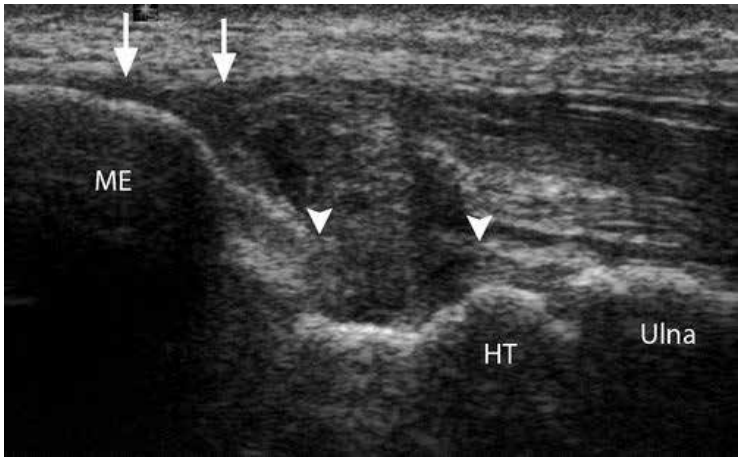


Figure 7. Longitudinal US image shows a tear of the UCL with hypoechoic scar tissue filling the gap between the proximal and distal ends (arrowheads). Dynamic US with application of valgus stress demonstrated the abnormality more clearly. Medial epicondylitis (arrows) is also present. HT = humeral trochlea, ME = medial epicondyle

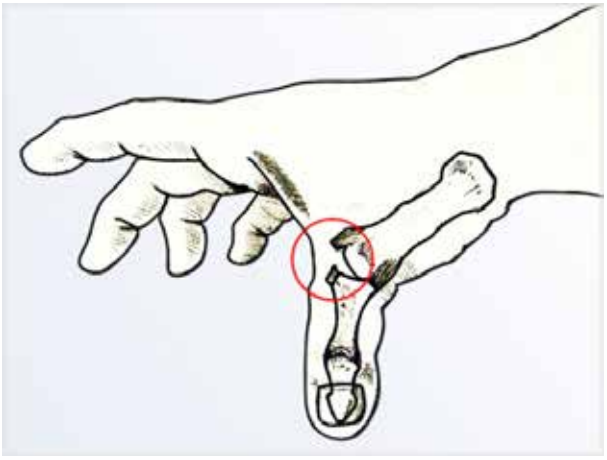


Figure 8. Anatomy and mechanism of injury of the UCL of the thumb

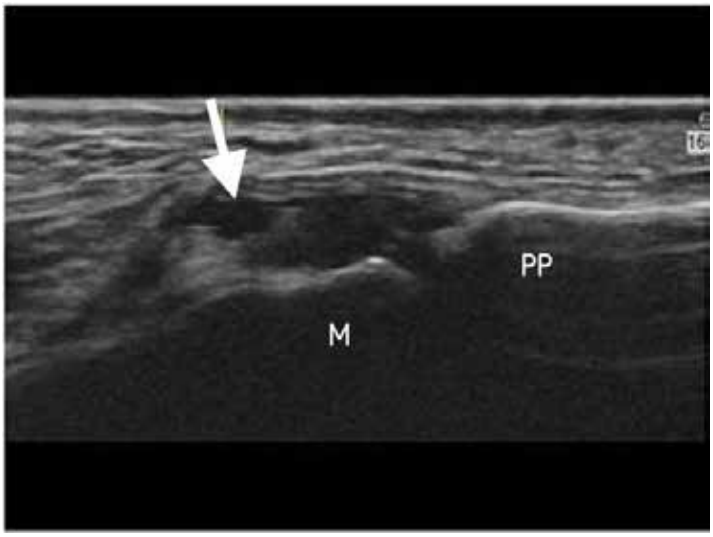


Figure 9. Longitudinal scan of the UCL of the thumb showing a full thickness tear (arrow) that occurred as a result of a fall on the extended thumb. PP = proximal phalanx and M = metacarpal bone

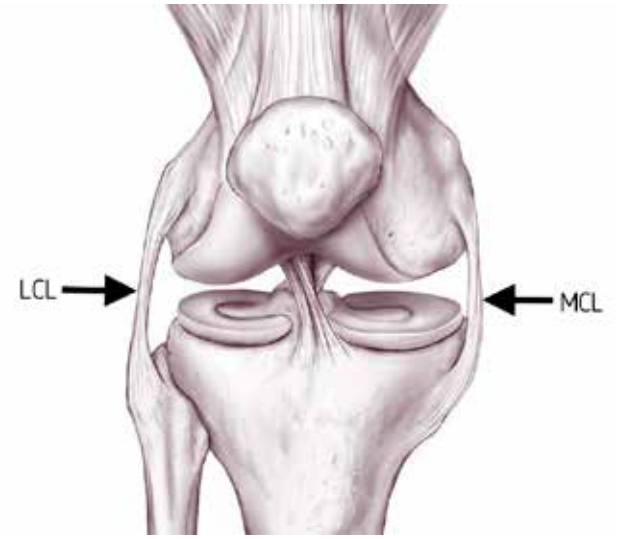


Figure 10. Anatomy of the medial and lateral collateral ligaments of the knee (MCL and LCL). Their function is to prevent excessive knee valgus/varus

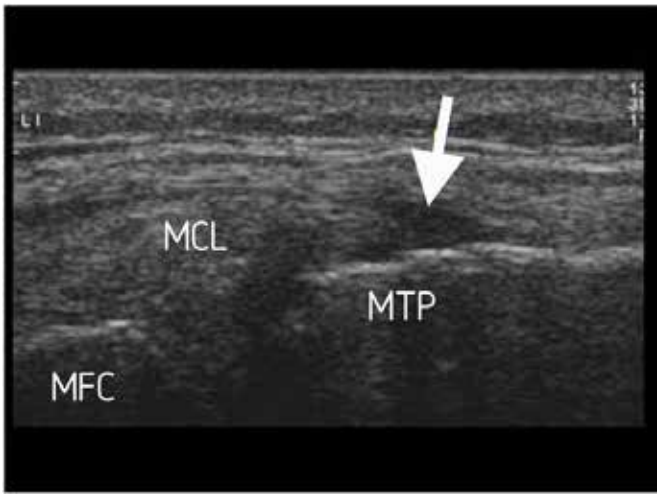
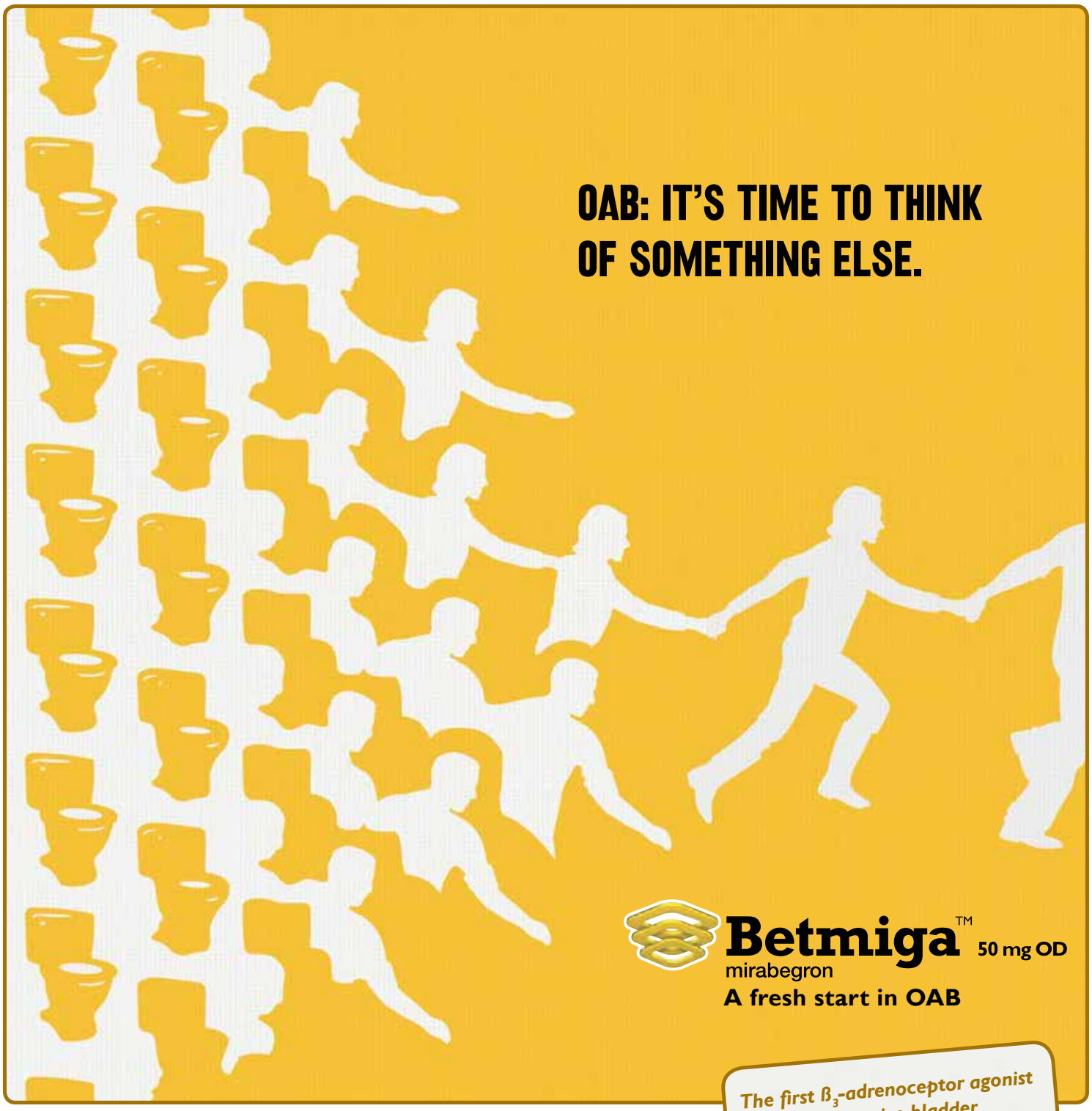


Figure 11. Longitudinal US image of the MCL showing a full thickness tear appearing as a defect (arrow) close to its distal insertion into the medial tibial plateau (MTP). The MCL is shown attaching proximally to the medial femoral condyle (MFC)



astellas

Prescribing Information Presentation: Betmiga™ prolonged release tablets containing 25 mgor 50 mg mirabegron. **Indication:** Symptomatic treatment of urgency, increased micturition frequency and/or urgency incontinence as may occur in adult patients with overactive bladder (OAB) syndrome. **Dosage:** Adults (including the elderly): Recommended dose: 50 mg once daily. Children and adolescents: Should not be used. **Contraindications:** Hypersensitivity to active substance or any of the excipients. **Warnings and Precautions:** Should not be used in patients with end stage renal disease, severe hepatic impairment and severe uncontrolled hypertension. Not recommended in patients with severe renal impairment and moderate hepatic impairment concomitantly receiving strong CYP3A inhibitors. Dose adjustment to 25 mg is recommended in patients with moderate renal and mild hepatic impairment receiving strong CYP3A inhibitor concomitantly. Caution in patients with a known history of QT prolongation or in patients taking medicines known to prolong the QT interval. Not recommended during pregnancy and in women of childbearing potential not using contraception. Not recommended during breastfeeding. **Interactions:** Clinically relevant drug interactions between Betmiga™ and medicinal products that inhibit, induce or are a substrate for one of the CYP isozymes or transporters are not expected, except for inhibitory effect on the metabolism of CYP2D6 substrates. Betmiga™ is a moderate and time-dependant inhibitor of CYP2D6 and weak inhibitor of CYP3A. No dose adjustment needed when administered with CYP2D6 inhibitors or CYP2D6 poor metabolisers. Caution if co-administered with medicines with a narrow therapeutic index and significantly metabolised by CYP2D6. When initiating in combination with digoxin the lowest dose for digoxin should be prescribed and serum digoxin should be monitored. **Adverse Effects:** Urinary tract infection, tachycardia, palpitation, atrial fibrillation, blood pressure increase, leukocytoclastic vasculitis. Prescribers should consult the Summary of Product Characteristics in relation to other side effects. **Pack and Prices:** Country specific. **Legal Category:** POM. Product Licence Number: Betmiga™ 25 mg EU/1/12/809/003; Betmiga™ 50 mg EU/1/12/809/010. **Date of Preparation:** November 2012 **Further information available from:** Astellas Pharma Europe B.V. P.O. Box 344, 2300 AH Leiden, The Netherlands. Betmiga™ is a Registered Trademark. For full prescribing information please refer to the Summary of Product Characteristics. 20140312-UR-BTMA-08

Adverse events should be reported. Report adverse events to E.J. Busuttil Ltd. Tel: +356 21 44 7184

SEROXAT®

The Anxiolytic Antidepressant:[1,2]

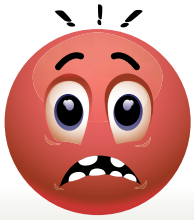
Major Depressive Disorder (MDD)[3]

Generalised Anxiety Disorder (GAD)[3]

Social Anxiety Disorder (SAD)[3]

Post -Traumatic stress Disorder (PTSD)[3]

Obsessive Compulsive Disorder (OCD)[3]



Panic Disorder[3]

Different indications require different dosage regimens. Please refer to the full SPC for more prescribing information.

SEROXAT ABRIDGED PRESCRIBING INFORMATION

Please refer to full Summary of Product Characteristics (SPC) before prescribing.

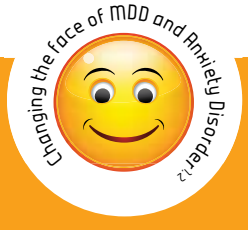
TRADE NAME: SEROXAT. **ACTIVE INGREDIENT:** Paroxetine. **PHARMACEUTICAL FORM:** Film-coated tablets, 20mg. **THERAPEUTIC INDICATIONS:** Major Depressive Episode, Obsessive Compulsive Disorder, Panic Disorder with and without agoraphobia, Social Anxiety Disorders/Social phobia, Generalised Anxiety Disorder, Post-traumatic Stress Disorder. **POSOLOGY AND METHOD OF ADMINISTRATION:** Administer once daily in the morning with food. Refer to full SPC for dosing information for specific conditions. Withdrawal symptoms seen on discontinuation of Paroxetine: abrupt discontinuation should be avoided. ***Elderly:*** maximum dose should not exceed 40mg daily. ***Children and adolescents:*** Should not be used. ***Renal/hepatic impairment:*** Dose should be restricted to lower end of dosage range. **CONTRAINDICATIONS:** Hypersensitivity. Should not be used in combination with MAOIs, thioridazine or pimozide. **PRECAUTIONS FOR USE:** Treatment to be initiated 2 weeks after terminating treatment with an irreversible MAOI or 24 hours with a reversible MAOI. Do not use in children and adolescents under the age of 18 years. Suicidal thoughts or clinical worsening: an improvement may not occur in the first few weeks of treatment. Akathisia. Serotonin syndrome/neuroleptic malignant syndrome may develop rarely: discontinue if such events occur. History of mania, renal and hepatic impairment, diabetes and in epilepsy, narrow angle glaucoma or history of glaucoma, patients with cardiac conditions or at risk of hyponatraemia, concomitant use with oral anticoagulants or drugs that increase risk of bleeding, history of bleeding disorders. Paroxetine may lead to reduced concentrations of endoxifen, one of the most important active metabolites of tamoxifen: concomitant use should be avoided. Withdrawal symptoms may occur on discontinuation of Paroxetine treatment. **DRUG INTERACTIONS:** Caution for use in combination with serotonergic drugs like St John's Wort, L-tryptophan, tramadol, linezolid, methylthioninium chloride, triptans, SSRIs, pethidine and lithium. Concomitant use with MAOI's is contraindicated. Caution with pimozide, anticonvulsants and with drugs metabolised by CYP 2D6. Reduced efficacy of tamoxifen. Caution in patients at an increased risk of bleeding and in patients on oral anticoagulants, NSAIDs, acetylsalicylic acid and antiplatelet agents. Adjust Seroxat dosage if necessary when given with drug metabolising enzyme inducers or with fosamprenavir/ritonavir. Concomitant use of alcohol is not advised. **PREGNANCY AND LACTATION:** ***Fertility:*** SSRIs may affect sperm quality but this is reversible following discontinuation of treatment. ***Pregnancy:*** Use in pregnancy only when strictly indicated (*see full SPC for more detail*). ***Lactation:*** Use during lactation can be considered. **EFFECTS ON ABILITY TO DRIVE AND USE MACHINES:** Patients should be cautioned about their ability to drive a car and operate machinery. **UNDESIRABLE EFFECTS:** ***Very Common (≥ 1/10):*** Nausea, Sexual dysfunction; ***Common (≥ 1/100, < 1/10):*** Increases in cholesterol levels, decreased appetite, somnolence, insomnia, agitation, abnormal dreams (including nightmares), dizziness, tremor, headache, blurred vision, impaired concentration, yawning, constipation, diarrhea, vomiting, dry mouth, sweating, asthenia, body weight gain. Increased risk of bone fractures in patients receiving SSRIs and TCAs. Common withdrawal symptoms include: dizziness, sensory disturbances, sleep disturbances, anxiety and headache. Adverse events from paediatric clinical trials: Increased suicidal related behaviours (including suicide attempts and suicidal thoughts), self-harm behaviours and increased hostility. *Refer to full SPC for the full list of adverse reactions.* **LOCAL PRESENTATION:** Seroxat Tablets (by 30 tablets) **MARKETING AUTHORISATION HOLDER:** SmithKline Beecham Ltd. **MARKERTING AUTHORISATION NUMBERS:** MA172/00201. **DATE OF PREPARATION:** April 2015.

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 SPC, WHICH IS AVAILABLE FROM: GSK (MALTA) LIMITED (TEL: 21238131)

REPORTING ADVERSE EVENTS (AEs):

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)**

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/adrportal and posted to the Malta Medicines Authority, Post-licensing Directorate, 203, Level 3, Rue D'Argens, Gżira GŻR 1368, MALTA, or sent by email to postlicensing.medicinesauthority@gov.mt



Reference: 1. Gelenberg AJ, Freeman MP, Markowitz JC, Rosenbaum JF, Thase ME, Trivedi MH *et al.* Practice guideline for the treatment of patients with major depressive disorder (Third Edition) American Psychiatric Association 2010. 2. Baldwin *et al.* Evidence-based pharmacological treatment of anxiety disorders, post-traumatic stress disorder and obsessive-compulsive disorder: A revision of the 2005 guidelines from the British Association for Psychopharmacology Journal of Psychopharmacology 1–37 2014. 3. Seroxat SPC August 2015.

Job No: MLT_GIB/PXT/0003/16
Date of preparation: March 2016