

## Who's afraid of oral contraceptives for endometriosis?

Conservative surgery is the most popular treatment for ovarian endometriotic cysts. However, excision is followed by a recurrence rate of about 10% per year. The possibility of preventing postoperative recurrences is very important, as the likelihood of conception after secondary surgery seems almost half that after a primary procedure. Ovulation appears crucial in the pathogenesis of endometriomas. Therefore, suppression of ovulation should be protective against cyst relapse after operative laparoscopy.

The results of a recent systematic literature review and meta-analysis suggest that postoperative oral contraceptive (OC) use dramatically decrease the risk of ovarian endometrioma recurrence, especially in women who use OCs regularly and for prolonged periods, with an almost 90% risk reduction compared with never users (Vercellini et al, 2012). Thus, whenever conception seeking is deferred, regular OC use until pregnancy is desired should be suggested. Moreover, prolonged OC use protects also from recurrence of postoperative pain symptoms, and greatly reduces the risk of epithelial ovarian cancer.

When years of treatment with OCs are considered, the issue of their safety becomes preeminent. In particular, the effect of OCs on the risk of thrombosis is frequently of concern for both patients and caring physicians. The results of a large, Danish historical registry based cohort



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study, as well as those of a systematic review and meta-analysis on the risk of thrombosis in OC users have been recently published and deserve mention.

All Danish non-pregnant women aged 15-49 with no history of thrombotic disease or cancer, were followed from 2001 to 2010. The risk of venous thromboembolism (VTE) in, respectively, OC users and in users of non-oral hormonal contraception, as well as risk of arterial thrombosis (thrombotic stroke and myocardial infarction) has been reported in three separate articles (Lidegaard et al, 2011; Lidegaard et al, 2012a; Lidegaard et al, 2012b; Manzoli et al, 2012). In the first report (Lidegaard et al, 2011), the incidence rate of venous thrombosis in non-users of combined OCs was 3.7/10,000 women years. The relative risk (RR) of VTE in current users of OC containing levonorgestrel and 30 µg ethinylestradiol (EE) was 2.19 (95% CI, 1.74 to 2.75). Compared with users of OCs containing levonorgestrel, the risk was about doubled in users of OCs containing desogestrel, gestodene, and drospirenone. Interestingly, a 20-25% reduction in risk was observed in users of OC containing EE 20 µg with respect to those using an OC containing EE 30-40 µg. Progestin only products (norethisterone and desogestrel pills) conferred no increased risk of venous thromboembolism.

In the second, more recent, report, the authors observed a RR of VTE of, respectively, 7.9 (95% CI, 3.5 to 17.7) and 6.5 (4.7 to 8.9) in users of the transdermal patch

### Inside this eJournal

- 1 President's message
- 3 Upcoming meetings
- 4 A word from the editor
- 5 News: You can fight endometriosis
- 6 Centres of excellence or expertise for endometriosis: Idealism and reality
- 8 Obituary: David Healy
- 9 WCE2014

and of the vaginal ring (Lidegaard et al, 2012a). Again, the risk was about doubled compared with users of OCs containing levonorgestrel. The RR was not significantly increased in users of progestin-only subcutaneous implants and in users of the levonorgestrel-releasing IUD.

With regard to arterial thrombosis, the baseline risk in non-users of hormonal contraception was 2.1/10,000 person-years for thrombotic stroke, and 1.0/10,000 person years for myocardial infarction (Lidegaard et al, 2012b). The risk of arterial thrombosis was associated with EE dose more than with the progestin type contained in various OCs. In users of OCs containing EE 30-40 µg, the risk was about doubled, whereas the RR increase was 20-50% in users of OCs containing EE 20 µg. A slightly higher RR was observed with the transdermal patch and the vaginal ring. The use of progestin-only systems, including the levonorgestrel-releasing IUD, did not significantly increase the risk.

Overall, the authors calculated that among 10,000 women using for one year an OC containing 20 µg EE associated with desogestrel, two will develop an arterial thrombosis and seven a venous thrombosis (Lidegaard et al, 2012b). The latter complication is thus three-four times more frequent, but generally much less severe. In addition, the risk is highest in the first year of use and progressively decreases with time.

Manzoli and co-workers reached similar conclusions after their meta-analysis of 16 cohort and 39 case-control studies. Overall, the OR of venous thromboembolism in OC users versus non-users was 3.41 (95% CI, 2.98 to 3.92). In other words, the risk of VTE increased from about 5/10,000 woman-years in non-users to about 15/10,000 woman-year in OC users. Therefore, the use of OC in 1,000 women will cause an additional VTE each year. Considering that mortality from VTE in 20 to 44 years old women is about 1%, OC use would cause one additional death each year every 100,000 users. Mortality from unwanted pregnancies is 12/100,000 births.

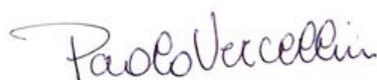
What do the above data teach us? Firstly, we should use the OC with the lowest EE dose possible, as it has been demonstrated that this variable impacts on the risk of both, venous and arterial thrombosis. Secondly, the use of OC containing levonorgestrel is advisable.

However, levonorgestrel may not be the best choice for bleeding control when OCs are used continuously instead of cyclically: it is well known that breakthrough bleeding in women with endometriosis means pain. Thirdly, alternative modalities for estrogen-progestin combinations administration, such as the transdermal patch and the vaginal ring, are by no means less risky than third and fourth generation OCs. Fourthly, progestins appear relatively safe, whether used by the oral, subdermal, or intrauterine route.

More in general, the best modality to reduce the risk of thrombotic events in OCs users appears to be smoking discontinuation, weight loss in overweight patients, and practice of regular physical exercise. Estrogen-progestin combinations should not be used in women with hypertension. The World Health Organization has classified routine thrombophilia screening in women with no familial and personal history of thrombosis as "not appropriate".

Finally, we are not considering the use of OCs or progestins as contraceptive methods, but as an effective treatment for a chronic, inflammatory condition with a natural tendency to recur. The alternative appears to be frequent postoperative pain relapse, serial surgery, and repetitive injury to already damaged gonads. In fact, no other available medication for endometriosis can be used for years with a similar safety profile.

The 40-year follow-up results of both, the Royal College of General Practitioners' Oral Contraception Study (Hannaford et al, 2010) and the Oxford-Family Planning Association contraceptive study (Vessey et al, 2010) consistently confirmed that OC use is associated with a slight reduction in all cause mortality, including that from breast cancer. According to Petitti (2012), "women, their physicians, and the public should be reassured not only by the Danish study but by the vast body of evidence from epidemiologic studies of hormonal contraception that have been done over the past five decades".



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## Upcoming meetings

<b>19th Annual Meeting of the Middle East Fertility Society</b>	<b>3 - 5 October 2012 Dubai, UAE</b>
<b>68th Annual Meeting of the ASRM</b>	<b>20 - 24 October 2012 San Diego, USA</b>
<b>41st Annual Meeting of the AAGL</b>	<b>5 - 9 November 2012 Las Vegas, USA</b>
<b>2nd Asian Conference on Endometriosis</b>	<b>9 - 11 November 2012 Istanbul, Turkey</b>
<b>1st European Congress on Endometriosis</b>	<b>29 November – 1 December 2012 Siena, Italy</b>
<b>2nd International Meeting Principles and Controversies in the Treatment of Deep Infiltrating Endometriosis (DIE)</b>	<b>7 - 8 December 2012 Athens, Greece</b>
<b>The Best of ESHRE and ASRM</b>	<b>6 - 10 March 2013 Paradise Island, Bahamas</b>

## Inspirational discovery

**Did it not happen to you? Did you not wonder, growing up, what discoveries you would witness? Did you not dream of what the future would look like?**

After watching Stanley Kubrick's 2001: A Space Odyssey as a young boy I remember how I worked out how many more years it would be before I could travel to the moon. I sometimes also wondered what it must have been like to live at the time when Sir Isaac Newton and Albert Einstein made their world-changing discoveries.

Before Newton few people had grasped the universal significance of objects falling towards the earth. Newton was the first to understand that earth's gravity is not a unique phenomenon in our little corner of the universe. He understood that it could be used to accurately explain the motions of all the planetary bodies, something that Copernicus and Kepler had described before him with varying degrees of accuracy, but never explained. His law of universal gravitation:  $F = G \frac{m_1 m_2}{r^2}$  goes even further than that, it states that any two bodies, heavenly or not, anywhere in the known universe attract each other proportionally to their respective masses and inversely proportional to the square of the distance that separates them. This was mind-boggling stuff at the time, all from one single genius.

It took more than two centuries before Einstein was able to explain why gravity exists. After he had shown in his theory of special relativity that nothing can move faster than light, he used a brilliant thought experiment to demonstrate that gravity is not a force as Newton assumed. In his thought experiment he imagined that our sun would suddenly and magically disappear and wondered what would happen to the orbit of the earth. Given that no particle and no force can travel faster than light, our planet would not 'feel' that the sun had disappeared for another eight minutes and one would thus have to conclude that the earth would continue to spin in its heliocentric orbit for a little while longer. This nonsensical conclusion led Einstein to develop the concept of four-dimensional space-time distorted by objects with mass. The more massive the object, the more space-time warps and the more other objects are



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influenced by it, which from our perspective translates into gravitational attraction. Again another mind-boggling discovery from a single genius.

On the fourth of July this year, less than a century after Einstein's formulation of the theory of general relativity, I finally have had that special excitement: the knowledge that I have lived to witness a very special discovery. The recent announcement of the (very likely) discovery of the Higgs boson has probably also not escaped your attention. Just like Newton did not explain the nature of gravity, Einstein never explained the nature of mass, although he relied on it heavily (pardon the pun) to explain the warping of space-time. This is why the confirmation of the existence of the Higgs boson is such an important discovery. The Higgs boson is a manifestation of the Higgs field and it is this field that gives other particles, such as protons and electrons, their mass. Imagine the Higgs field permeating space as a thick soup. Some particles have more difficulty travelling through it and have more mass (inertia) and other particles like electrons fly through it and thus have little mass (inertia).

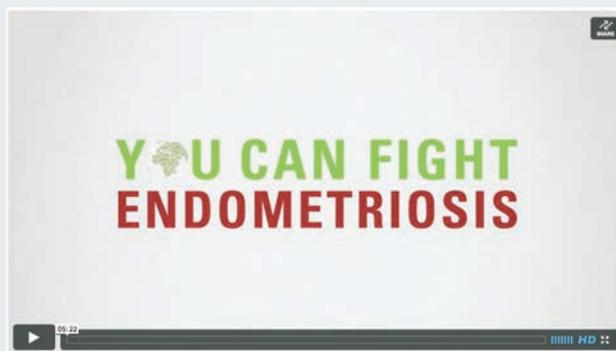
Now here is the beautiful thing. The Higgs particle has been predicted by a number of smart physicists and last month's discovery of the particle at the Large Hadron Collider at CERN, Geneva, involved thousands of researchers from 111 countries. Undoubtedly, this is the new way forward. Large international teams working together to make ground-breaking discoveries. I foresee

that significant discoveries in our field will also come from such large international collaborations. Let the Higgs particle discovery be an inspiration to us all!

Given that WCE 2014 is only another 2 years away, ring up those colleague overseas, put your brains together and “do the other things, not because they are easy, but because they are hard” (JFK). Amaze us in São Paolo!

“

WES’s educational film about endometriosis has now been viewed by more than 50,000 people. The film explains what endometriosis is, how it is diagnosed and treated, what women can do themselves. It refers also to national endometriosis organisations for additional information and support.



Many have chosen to embed the five-minute informative film into their websites to help provide factual information about endometriosis to a lay audience – we encourage you to do the same in our continued quest to get information about endometriosis and its treatment to as many women as possible.

The film is now also available in French, German, Italian, and Spanish. All the films - along with two commentaries by our Past President, Hans Evers, and former MEP, Diana Wallis – are available from: <https://vimeo.com/endometriosis/videos>

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## Centres of excellence or expertise for endometriosis: Idealism and reality

### Alan Lam

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In recent time the concept of “centre of excellence” has been promulgated as the “ideal way” to optimise the care of women suffering from endometriosis (D’Hooghe and Hummelshoj, 2006). Reservations and alternative opinions have been expressed about this concept and what should underpin such centres (Koninckx and Ussia, 2009).

### Excellence vs. expertise

At the WES 2011 Montpellier Consensus Workshop Group, it was suggested that the term “excellence” be replaced by “expertise”.

The proposed change of terminology from “centre of excellence” to “centre of expertise” is an astute move by the WES Consensus Group and should bring to focus the idealism of COE and the reality of what COE can offer women with proven or suspected endometriosis.

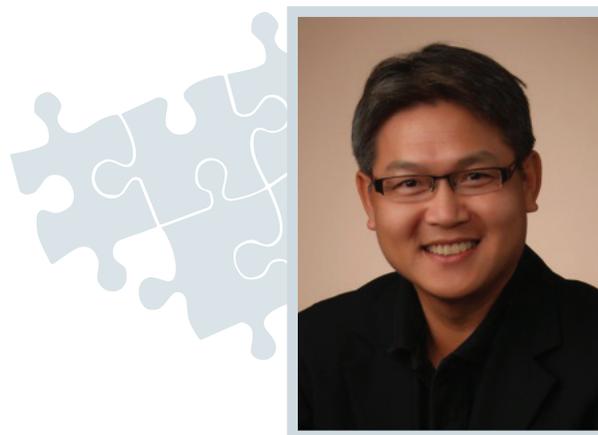
First and foremost, I believe that a centre can aim to offer expertise, but it should not claim to offer “excellence”. Such a claim should be based on open disclosure of regular audit outcomes based on universally accepted criteria.

“Expertise”, according to the Oxford Dictionary, is defined as having special or expert knowledge or skill in a particular subject or activity, while “excellence” is defined as “the quality of being extremely good”.

The ideal of COE is to draw together a network of experts to offer expert, evidence-based and experience-based advice and treatment options.

The reality of our current understanding of this condition and the outcomes from currently available treatment options do not guarantee “excellent” outcomes at all times, no matter how excellent a health professional we think we are.

This distinction is very important in clinical practice



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and should be part of the routine discussion we have with our patients, regardless of whether we work as individual clinician in a remote setting or as a member of a COE in a major teaching institution.

### So, what is the idealism of COE and what is the reality?

Let’s look at laparoscopic excision of endometriosis as a management option for pelvic pain for example. According to Abbott et al (2003), women can expect that, in expert hands, laparoscopic excision can significantly reduce pain and improve quality of life for up to 5 years. However, is the outcome really that “excellent” when the same authors also found that 36% of women may require further surgery for pain in the same follow-up period?

What about reproductive performance, pain recurrence and disease prolapse after conservative surgical treatment for endometriosis? Vercellini, our current president, reported that women can expect a cumulative pregnancy rate of 47%, a cumulative probability of moderate to severe dysmenorrhoea of 24%, and disease relapse of 12% at 3 years from surgery. Further, he found no observed association between endometriosis stage or lesion type and lesion site and the above study outcomes (Vercellini et al, 2003). This study poses more questions than it answers, most fundamentally, it questions the validity of the current predictive value of the current endometriosis classification.

For women seeking surgical treatment for deep infiltrative endometriosis with or without bowel surgery, they often travel long distance to hopefully achieve “excellent” surgical outcomes at a COE. But the reality is that even in expert hands, at recognised COE, the overall major postoperative complication rate for any type of surgery may be around 9% (Kondo et al, 2010). Our own data (unpublished) indicates a similar major complication rate for ultra-low segmental resection in a multi-disciplinary setting, figures which are comparable to those reported by colorectal surgeons elsewhere (Platell et al, 2006). Here, the distinction between expertise and excellence is highlighted by the reality of the challenging nature of surgery for severe endometriosis.

For women seeking treatment for endometriosis-associated infertility, we are told that “*infertility surgery is dead: only the obituary remains?*” (Feinberg, Levens and DeCherney, 2008). But should women be led into believing that they can be guaranteed of a successful live pregnancy outcome from IVF when success rates remain around 30% for each treatment cycle, and furthermore, when many women with endometriosis are in the older above 35 age group?

So, given the currently incomplete understanding of the aetiology of endometriosis, the unclear natural history, the unpredictable pathological behaviour, the often delayed or mistaken diagnosis, the doubtful value of the current classification, the limited effectiveness and associated side-effects of medical and fertility therapies, the potential morbidity and repeated need of surgical intervention, the idealism of COE should be balanced with the reality of what we can offer women.

We should strive for progress but not forget that:

*“If you expect perfection from other people, your whole life is a series of disappointments, grumbling and complaints. If, on the contrary, you pitch your expectations low, taking folks as the inefficient creatures which they are, you are frequently surprised by having them perform better than you had hoped”* **Bruce Barton** (1886 - 1967) American author and politician.

These are my personal views and do not reflect that of WES or the WES 2011 Montpellier Consensus Workshop Group.

## Note

I acknowledge Lone Hummelshoj, WES Secretary General, for her assistance in my research for this topic.

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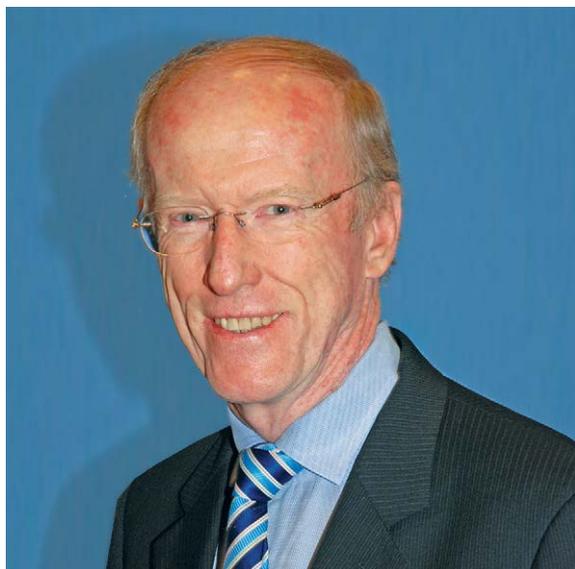


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## Obituary: David Healy

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### David Lindsay Healy

Obstetrician and gynaecologist, IVF researcher, and advocate for women's reproductive rights. Born on Sept 30, 1948, in Melbourne, Australia, he died of cancer in Melbourne on May 25, 2012, aged 63 years.

David Healy was a man who chose his words carefully, and made them count. As a passionate advocate for women's reproductive rights on the international stage, a principled clinician, and a successful academic, he had an uncanny capacity to make things happen: to create important collaborations, inspire colleagues, and advance fertility research. "He was an outstanding diplomat", says his colleague Euan Wallace from Monash Medical Centre in Melbourne, Australia. "He enjoyed bringing apparently disparate groups together and getting them to work together."

Healy had a talent for subtle persuasion that would sometimes leave colleagues mystified as to how they had agreed to a new undertaking, notes Rob McLachlan, from Prince Henry's Hospital in Melbourne. "You would leave the room wondering what had just happened. 'How did he manage to get me involved?'" he laughs. That skill for persuasion perhaps came to fullest fruition after 2010, when Healy took up the presidency of the International Federation of Fertility Societies, a diverse grouping of associations. "He managed very well to bring the societies together, to work with WHO and to make uniform statements about the directions that fertility care should be heading", says Wallace.

Raised in the leafy Melbourne suburb of Murrumbeena, Healy won a scholarship to attend the new medical school

at Monash University. He graduated from there in 1973 and 6 years later completed a PhD on human prolactin physiology, before winning a prestigious NHMRC Applied Health Science Fellowship that carried him overseas—to the US National Institutes of Health and the Medical Research Council's Centre for Reproductive Biology in Edinburgh, UK. Returning home in 1985 he rejoined Monash University and became a specialist for the university's in-vitro fertilisation (IVF) programme and a senior lecturer, as well as taking an appointment as a consultant obstetrician and gynaecologist at Melbourne's Queen Victoria Medical Centre. That same year, he became the first obstetrician and gynaecologist to be awarded a Wellcome Trust Senior Clinical Research Fellowship, an opportunity he used to study antiprogestones, inhibins in reproduction, relaxin in pregnancy, and the GnRH analogues in IVF. The work he led, together with Henry Burger, David de Kretser, Rob McLachlan, and others, provided the foundations for today's successful IVF technology and contributed to Monash's prominent position in the field.

"One of the things he always said to me was that you've got to enjoy coming to work in the morning", remembers Wallace. In 1990, Healy was awarded a Chair at Monash, and in 1994 became chairman of the university's Department of Obstetrics and Gynaecology—a position he held until his death. "He tried to develop a department that was not only successful but was also an enjoyable place to be. It's a friendly place, a warm place, and a place where people look after each other", says Wallace. As well as those successes as an administrator, Healy achieved recognition internationally for his research. But it was his unstinting work as an advocate for women's rights, particularly around fertility and menopause, that is his most outstanding legacy. "He was fundamentally interested in women's reproductive rights, whether they were living in Melbourne or Malawi", says Wallace. "That was most evident in Australia, where among many other things he was involved in bringing in RU-486." In 1992, Healy and colleagues also formed the Jean Hailes Foundation, a not-for-profit organisation dedicated to the physical and emotional wellbeing of Australian women, where he remained a Founding Board Member throughout his life.

The next generation of researchers and clinicians became an increasing focus for Healy. "On the many boards and conference organising committees in which he was involved he would always argue to make room for the new generation", wrote his Monash colleague Luk Rombauts recently. Although his formality, intellect, and high standards could be a little intimidating to those who didn't know Healy well, behind the suit-and-tie exterior lurked a wickedly dry sense of humour, a passion for golf, and an undying love for the Essendon Australian rules football team. Healy's wife, Lyn, died a year before him; they are survived by their children, Ross and Meagan, and one grandchild.

Stephen Pincock

## Thank you for choosing the themes for WCE2014

Dear Colleagues,

In the last issue of the eJournal I invited you to vote for the topics YOU felt should be addressed at the 12th World Congress on Endometriosis.

THANK YOU for doing so!

The choices you made were very clear, and I am delighted to be able to announce that the topics YOU chose for the ten main seminars are:

- Management of pain and infertility in deep disease
- Non-invasive diagnosis
- Mechanism of pain
- Endometriosis and cancer
- New drugs
- Genetics, epigenetics, and hereditary aspects
- Prevention and management of recurrences
- Endometrioma and ovarian reserve
- Adenomyosis
- Immunology and stem cells

I encourage you to prepare your research and be ready to submit abstracts by 3Q 2013. As per established WES procedure the top five abstracts for each of the ten topics will be presented as main seminars at WCE2014.

However, if your topic is not listed – please do not let this stop you! In addition to the main seminars, WES typically features an additional 50 oral presentations and hundreds of posters.

In fact, WES will be generous with its time for free communication and poster sessions in order to cover as many aspects of endometriosis as possible.

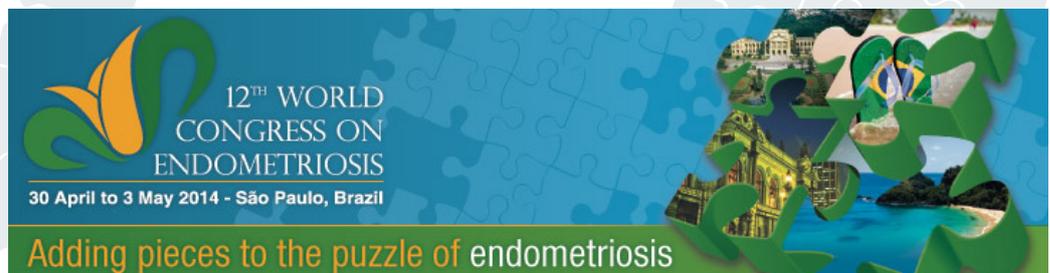
PLEASE keep working with your ideas, hypotheses, and evidence... and be prepared to present YOUR work at WCE2014: the place to be if YOU want to be THE ONE to add more pieces to the puzzle of endometriosis!



Mauricio Abrao  
WCE2014 President



Professor Mauricio Simões Abrão  
WCE2014 President



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